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Hüban ATİLLA
Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye

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CONTENTS

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AT A GLANCE

2025 Issue 4 at a Glance:

Esteemed colleagues,

In its fourth issue of 2025, the Turkish Journal of Ophthalmology contains six original research articles, one review, and three letters to the editor.

In their study titled "Performance of ChatGPT-4 Omni and Gemini 1.5 Pro on Ophthalmology-Related Questions in the Turkish Medical Specialty Exam", Sabaner and Yozgat evaluated the response and interpretation capabilities of two artificial intelligence-based large language models for multiple-choice questions related to ophthalmology in medical specialty exams. Noting that ChatGPT-4o is one step ahead, the authors emphasized that aside from answering correctly, ChatGPT-4o and Gemini 1.5 Pro have the potential to improve ophthalmology medical education by providing detailed explanations (See pages 177-185).

In their study evaluating the outcomes of scleral contact lens compliance in patients with difficult corneal and ocular surface pathologies, Özçelik et al. reported that although scleral contact lenses are difficult and time-consuming to fit and disadvantageous in terms of cost, they offer good visual acuity, comfort, and stability (See pages 186-192).

In their study titled "Macular Telangiectasia Type 2: Long-Term Disease Progression and Management of Complications", Özbek et al. examined the long-term progression of macular telangiectasia type 2 (MacTel) using a standardized classification system and evaluated the incidence and treatment strategies of secondary complications such as macular neovascularization (MNV) and macular hole (MH). The authors concluded that MacTel is characterized by a decrease in visual acuity and progressive deterioration of the retinal anatomy in the long term. They emphasized that although anti-VEGF treatment for MNV provides visual improvement in the short term, its long-term effectiveness is limited, and the development of MH is rare but poses a clinically significant challenge due to the limited functional results (See pages 193-199).

In their study titled "Effect of Ranibizumab in Patients with Treatment-Naïve Retinopathy of Prematurity", Khalid et al. evaluated the effect of intravitreal ranibizumab (IVR) on disease regression and need for rescue treatment in 76 eyes with treatment-naive type 1 ROP and aggressive ROP (AROP). They found that ranibizumab was effective in initial disease regression, but reactivation occurred in all AROP cases and 60% of type 1 ROP cases. The authors emphasized the importance of more frequent follow-up after IVR injection, especially in AROP patients (See pages 200-206).

In their retrospective study titled "Adalimumab in Focus: Evaluating Effectiveness and Safety in Non-Infectious Uveitis at a Tertiary Referral Center in Türkiye", Yargı Özkoçak et al. evaluated the effect of adalimumab (ADA) treatment on visual acuity, number of immunosuppressive treatments, immunosuppressive drug load, and frequency of local treatment in cases of non-infectious uveitis and reported that ADA is a safe option that provides functional benefits in different indications and age ranges, especially reducing dependence on additional treatments (See pages 207-214).

In a study titled "Prevalence and Prognosis of Glaucoma/Elevated Intraocular Pressure in Patients with Uveitis", Esen Barış et al. reviewed the records of 2176 uveitis patients and evaluated 594 uveitic eyes with glaucoma or intraocular pressure elevation. The overall prevalence of glaucoma/elevated intraocular pressure was found to be 20.2%, with glaucoma most common among eyes with anterior uveitis (41.1%) and intraocular pressure elevation most common in intermediate uveitis (71.2%). The authors reported that medical treatment was sufficient for intraocular pressure control in 77.1% of the eyes (See pages 215-220).

The review by Bayraktar et al. discusses oculoplastic problems seen in glaucoma patients, which are frequently encountered in recent years, and the authors presented their clinical findings and treatment approaches with their own experience and original examples (See pages 221-229).

Myopia control glasses are increasingly used to slow the progression of myopia by creating peripheral myopic defocus. In the first letter to the editor, Murat Erbezci emphasized that the use of these glasses may negatively impact critical stages of children's neurovisual development, and long-term follow-up studies on this subject are necessary (See pages 230).

In their letter to the editor, Singh et al. presented a case of Urrets-Zavalia Syndrome (UZS) after posterior chamber phakic intraocular lens implantation. They emphasized that UZS can also develop after refraction surgery, and that early diagnosis and high intraocular pressure and rapid control of anterior chamber inflammation affect optimal visual outcomes (See pages 231-233).

Finally, Arıcı et al. described a patient who presented with bilateral infraorbital mass 10 years after dermal filler injection, which she initially denied receiving. The authors emphasized that with the rising use of fillers, hyaluronic acid dermal fillers can also be included in the differential diagnosis of solid periorbital masses, thus increasing the importance of patient and medical history to avoid unnecessary diagnostic tests (See pages 234-236).

Respectfully on behalf of the Editorial Board,

Nilgün Yıldırım, MD

Original Article

Performance of ChatGPT-4 Omni and Gemini 1.5 Pro on Ophthalmology-Related Questions in the Turkish Medical Specialty Exam

Mehmet Cem Sabaner, Zübeyir Yozgat

Kastamonu University Faculty of Medicine; Kastamonu Training and Research Hospital, Department of Ophthalmology, Kastamonu, Türkiye

Abstract

Objectives: To evaluate the response and interpretative capabilities of two pioneering artificial intelligence (AI)-based large language model (LLM) platforms in addressing ophthalmology-related multiple-choice questions (MCQs) from Turkish Medical Specialty Exams.

Materials and Methods: MCQs from a total of 37 exams held between 2006-2024 were reviewed. Ophthalmology-related questions were identified and categorized into sections. The selected questions were asked to the ChatGPT-4o and Gemini 1.5 Pro AI-based LLM chatbots in both Turkish and English with specific prompts, then re-asked without any interaction. In the final step, feedback for incorrect responses were generated and all questions were posed a third time.

Results: A total of 220 ophthalmology-related questions out of 7312 MCQs were evaluated using both AI-based LLMs. A mean of 6.47±2.91 (range: 2-13) MCQs was taken from each of the 33 parts (32 full exams and the pooled 10% of exams shared between 2022 and 2024). After the final step, ChatGPT-4o achieved higher accuracy in both Turkish (97.3%) and English (97.7%) compared to Gemini 1.5 Pro (94.1% and 93.2%, respectively), with a statistically significant difference in English (p=0.039) but not in Turkish (p=0.159). There was no statistically significant difference in either the inter-AI comparison of sections or interlingual comparison.

Conclusion: While both AI platforms demonstrated robust performance in addressing ophthalmology-related MCQs, ChatGPT-4o was slightly superior. These models have the potential to enhance ophthalmological medical education, not only by accurately selecting the answers to MCQs but also by providing detailed explanations.

Keywords: Artificial intelligence, large language model, ChatGPT-4 Omni, Gemini 1.5 Pro, medical education, ophthalmology, e-learning

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Address for Correspondence: Mehmet Cem Sabaner, Kastamonu University Faculty of Medicine; Kastamonu Training and Research Hospital, Department of Ophthalmology, Kastamonu, Türkiye

E-mail: drmcemsabaner@yahoo.com **ORCID-ID:** orcid.org/0000-0002-0958-9961

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Introduction

"Understanding these marvels of our era, the thinking machines, does not necessitate a diabolical intelligence; rather, simple common sense suffices."[1] Developing thinking machines and effectively integrating them into educational and business environments represents a significant breakthrough for humanity. Artificial intelligence (AI) is exhibiting significant potential across education platforms, notably in the medical sciences.[2,3] AI currently contributes to medicine not only by enhancing educational approaches but also by advancing diagnostic and treatment recommendations in contemporary medical practice.[2,3,4,5,6,7,8,9] Although it is widely assumed that AI can almost never fully replace humans, its potential contributions to medicine and medical education are subjects of considerable interest and curiosity. ChatGPT-4o (omni) and Gemini 1.5 Pro are cutting-edge models designed to provide highly reliable and context-sensitive outputs across a broad range of languages. They are mainly categorized as large language models (LLMs), which are advanced deep learning frameworks trained on extensive datasets to assimilate diverse language characteristics.[3,10] AI-based LLM chatbots are now increasingly utilized in numerous fields, notably in digital education, personalized healthcare, autonomous systems, client support, data science, and software engineering.[10]

AI-driven e-learning is swiftly gaining traction, transforming educational paradigms and practices on a global scale.[10] Tasks such as completing homework, conducting research, answering

multiple-choice questions (MCQs), and even composing academic theses can now be efficiently managed using AI-based LLMs.[11] However, the reliability and efficacy of these AI-driven approaches remain under scrutiny. Previous research has illustrated the potential of AI in addressing MCQs, emphasizing its role in enhancing the acquisition of accurate information.[6] Nonetheless, there is a dearth of studies specifically evaluating the capabilities of AI chatbots in answering ophthalmology-related MCQs.[12,13,14,15,16,17] Consequently, this assessment aimed to reveal critical insights into how chatbots can be effectively utilized for ophthalmology-related MCQs in both English and Turkish. To this end, the study evaluated the responses of these two chatbots to ophthalmology-related MCQs in the Turkish Medical Specialty Exam (MSE).

Materials and Methods

Study Design and Data Collection

This cross-sectional study evaluated the performance of two AI-based LLM chatbot models in answering ophthalmology-related MCQs obtained from past Turkish MSEs. The MSE (known as TUS in Turkish) is a nationwide standardized exam held twice yearly by Türkiye's Student Selection and Placement Centre (ÖSYM in Turkish) for admission to medical specialty training. The MSE consists of two parts, the basic and clinical medical sciences tests.

All questions from a total of 32 exams held in 2006-2021[18] and a specified 10% of the questions from 5 exams held in 2022-2024[19,20,21] are considered works under the Law on Intellectual and Artistic Works that are copyrighted by ÖSYM and available to the public as open access with restrictions on reproduction, distribution, and re-publication. These questions were reviewed in detail by two senior ophthalmologists. Ophthalmology-related questions were identified by consensus and included in this study. These questions were also classified into ophthalmology subtopics.

The evaluation of the chatbots' capacity to answer ophthalmology-related MCQs was conducted using the most current premium versions of Gemini 1.5 Pro (Google, Mountain View, CA) and ChatGPT-4o (OpenAI, San Francisco, CA), accessed via Gemini Advanced and ChatGPT Plus platforms. The overall interaction process, including input prompts and response evaluation, is outlined in Figure 1. Each chatbot session began with a standardized prompt instructing the model to answer MCQs in either Turkish or English following a three-step format: (1) state the correct answer, (2) justify the answer using scientific sources indexed in the Web of Science (WoS) Citation Index and PubMed, and (3) list a minimum of three cited references. For questions containing visual data, the chatbots' image upload features were utilized. The evaluation was conducted in three distinct attempts.

In the first attempt, all selected ophthalmology-related MCQs were presented to the chatbots individually, starting in Turkish. No feedback was given as to whether the responses were correct or incorrect. The same items were then professionally translated into English, followed by back-translation and cross-verification by two researchers. To minimize bias introduced by linguistic structure, answer options were reordered during translation. The English questions were presented to the chatbots individually with no feedback about correctness.

In the second attempt, all previously used questions in both languages were re-entered again without providing feedback.

In the final attempt, chatbot answers that remained incorrect were flagged via the "thumbs down" icon, with the "Not factually correct" reason selected. All questions were then submitted once more for reassessment.

Each attempt was conducted in a separate chatbot session. In each attempt, the correctness of responses was judged solely according to the official answer keys. Selection of the correct option was required for a response to be marked as accurate, regardless of the explanation's quality. Conversely, if an incorrect option was selected—even with a correct explanation—the answer was considered incorrect. For each attempt, the accuracy rate was computed as the percentage of correct answers.

Each explanation generated by the chatbots, including its cited references, was evaluated independently by two senior

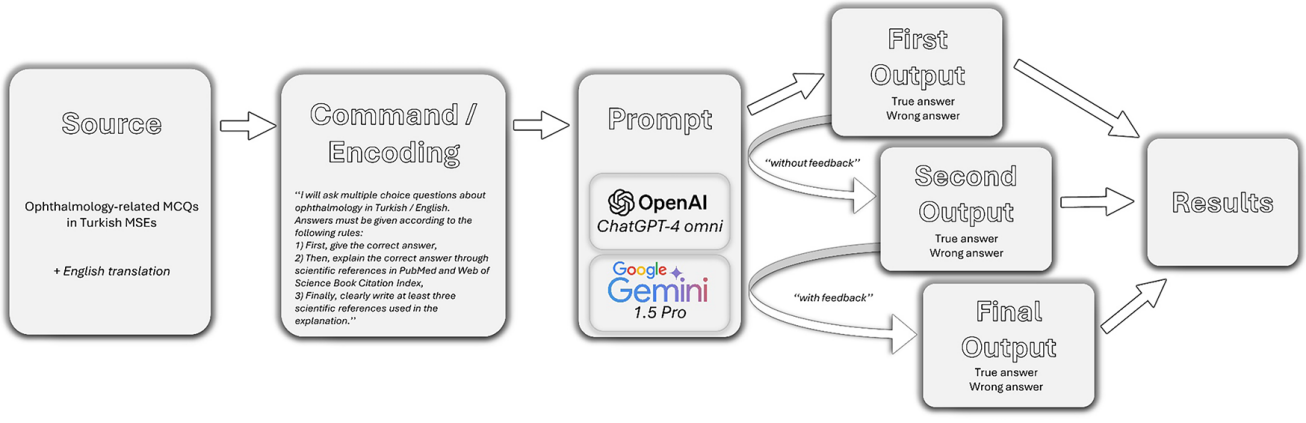

Figure 1. Flowchart of the study
MCQs: Multiple-choice questions, MSEs: Medical Specialty Exams

ophthalmologists. A 4-point Likert scale was employed to assess the relevance of each response to the intended ophthalmic knowledge: 1 = Not relevant, 2 = Somewhat relevant, 3 = Quite relevant, and 4 = Highly relevant. Of the four points, three were designated to assess the scientific soundness of the explanation, while the remaining point focused on the reliability of the cited references. Minor errors such as incorrect publication dates or faulty hyperlinks were not penalized; however, inconsistencies in author names, article titles, or journal sources were considered during scoring. If two or more references were missing or erroneous, point deductions were applied. The item-level content validity index (I-CVI) was determined by calculating the proportion of raters who assigned a score of 3 or 4 to each item.[22] To assess overall validity, average CVI values were calculated by averaging the I-CVI scores across all items for each attempt by both chatbots. An average CVI value ≥0.80 was interpreted as acceptable content validity, following the criteria established by Polit and Beck.[22]

Informed consent and institutional review board approval were not required for this AI-based LLM chatbot evaluation study.

Statistical Analysis

To analyze the data, statistical evaluations were conducted using GraphPad Prism (v10.2.3, San Diego, CA, USA) and IBM SPSS Statistics software (v22.0, Armonk, NY, USA). The Sankey diagram illustrating question flow and categorization was created using the online tool SankeyMATIC. Descriptive statistics were presented as mean ± standard deviation (SD) or median with interquartile ranges (25^{th}–75^{th} percentile), as appropriate. For categorical variables, Pearson's chi-square test was primarily employed. However, Fisher's exact test or Yates' continuity correction was applied when assumptions of expected frequency counts were not met (i.e., expected cell count <5 or 5-25, respectively). In comparisons involving more than four categorical groups, Pearson's chi-square remained the default method. Differences in the word count of explanations between the two chatbot systems were analyzed using the non-parametric Mann-Whitney U test, given the non-normal distribution of the data. To assess consistency across attempts and rater agreement in the Likert-scale evaluations, intraclass correlation coefficients were calculated. Statistical significance was defined as a p value below 0.05, and all analyses were conducted within a 95% confidence interval (CI).

Results

Of the 7312 MCQs reviewed from 37 past Turkish MSEs, a total of 220 questions were identified as ophthalmology-related and selected for further analysis. Detailed information regarding the question selection process and the subspecialty distribution is visualized in Figure 2. Due to ÖSYM's copyright restrictions, the full text of the questions and answers could not be published. However, details about the questions included are provided in the Appendix 1, and Turkish MSE-like questions and chatbot answer examples are presented in the Supplemental Material. Neuro-ophthalmology was the most frequently represented subspecialty (n=72), while glaucoma and uveitis were the least (n=13 each). Across the evaluated exams (32 full exams and the pooled 10% of exams shared between 2022-2024), the average number of ophthalmology questions was 6.47 (SD: 2.91), with a minimum of 2 and a maximum of 13, as illustrated in Figure 3.

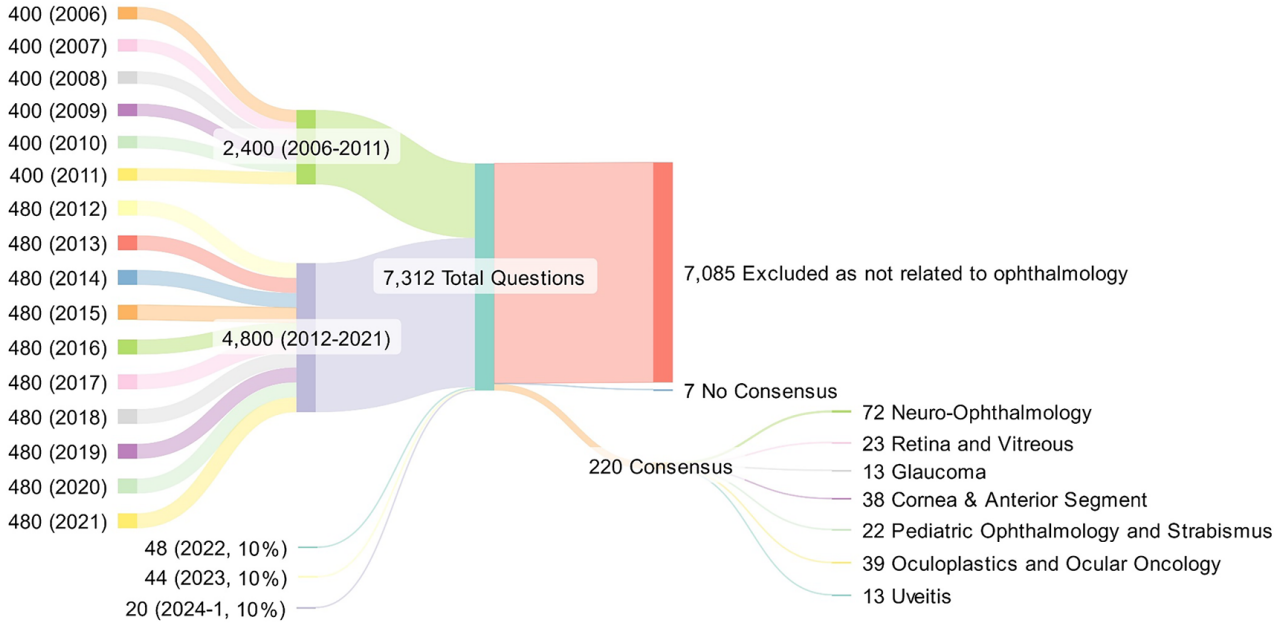

Figure 2. Sankey study diagram illustrating Medical Specialty Exam question selection and subspecialty distribution

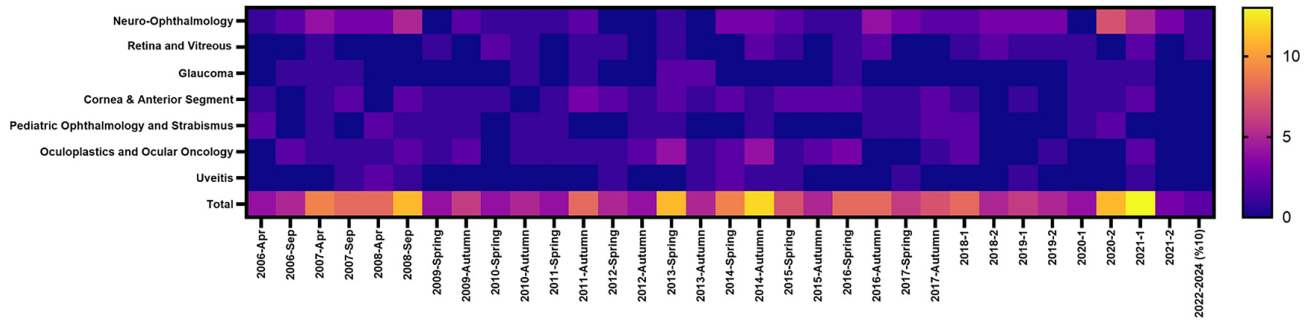

Figure 3. Subspecialty distribution heatmap chart of the Medical Specialty Exam questions according to year.

Detailed accuracy outcomes across all three attempts, stratified by language (Turkish and English) and by AI model, are presented in Table 1. In the final attempt, ChatGPT-4o demonstrated higher accuracy rates in both Turkish (97.3%) and English (97.7%) compared to Gemini 1.5 Pro (94.1% and 93.2%, respectively). This difference reached statistical significance in the English-language comparison (p=0.039), while it did not reach significance in Turkish (p=0.159). Although a progressive increase in accuracy was observed across successive attempts for both models, these changes were not statistically significant (p>0.05). In the overall analysis (n=220), ChatGPT-4o demonstrated superior performance across all attempts in terms of the number of correct responses. In Turkish, ChatGPT-4o achieved 209, 210, and 214 correct answers, while Gemini 1.5 Pro produced 202, 204, and 207, respectively (p>0.05 for all comparisons). In English, this difference reached statistical significance in the final attempt (215 vs. 205; p=0.039), although earlier attempts did not achieve significant differences (p=0.312).

When evaluated across individual ophthalmic subspecialties, no statistically significant differences were observed between the two AI platforms. Furthermore, no statistically significant interlingual variation was noted for either model when answering the same set of questions in Turkish versus English. The detailed distribution of performance according to exam years is provided in Table 2.

Among the evaluated items, only two MCQs included visual content. Notably, both chatbots correctly answered these questions in both languages, suggesting adequate visual interpretation capabilities under the tested conditions.

Content validity, assessed through average CVI values, demonstrated high agreement for both chatbots across all attempts and in both languages, as detailed in Table 3. Despite these high ratings, both models occasionally produced hallucinated or fabricated references. These instances—such as mismatched author names or journal titles—were systematically accounted for during I-CVI scoring.

In terms of explanation length, statistically significant differences were observed between Turkish and English responses for both models. Explanations generated in English were notably longer than their Turkish counterparts (ChatGPT-4o: median 178 vs. 88 words; Gemini 1.5 Pro: median 124 vs. 81.5 words; all comparisons, p<0.001). Furthermore, across both languages, ChatGPT-4o produced longer responses than Gemini 1.5 Pro (p<0.001 for both Turkish and English comparisons).

To assess response consistency across attempts, Cohen's kappa (κ) values were calculated for each AI model. In Turkish, κ values were 0.974 (95% CI, 0.967-0.980) for ChatGPT-4o and 0.967 (95% CI, 0.957-0.975) for Gemini 1.5 Pro. In English, both models achieved a κ value of 1.000, indicating perfect agreement. These results reflect near-perfect repeatability between the first and second attempts, during which no feedback was provided to the chatbots.

Discussion

The present study demonstrates that state-of-the-art LLM chatbots are capable of responding to ophthalmology-related MCQs in both Turkish and English with high levels of accuracy. Notably, ChatGPT-4o outperformed Gemini 1.5 Pro in the final evaluation attempt conducted in English, achieving statistically superior results. Despite this difference, both AI platforms exhibited robust performance across languages and attempts, supporting their potential as supplementary tools in ophthalmology education and assessment.

Due to the unique position and relative isolation of ophthalmology from other medical disciplines, ophthalmological questions can pose significant challenges for healthcare professionals. In parallel, the increasing reliance of healthcare professionals on online resources for up-to-date ophthalmological knowledge underscores the growing importance of AI-based LLMs in medical education. These models are rapidly gaining recognition as transformative tools in digital learning environments, capable of supplementing traditional instruction by providing immediate, structured, and reference-supported responses. Accordingly, AI-driven chatbots have emerged as accessible support mechanisms that can assist learners in interpreting complex MCQs across various languages and contexts.

Table 1. Interlingual and inter-model comparisons of chatbot performance on section questions across multiple attempts

	n	Correct answer count and accuracy (%)												p*			
		ChatGPT-4o						Gemini 1.5 Pro									
		TR			EN			TR			EN			Inter-AI		Interlingual	
		First	Second	Final	First	Second	Final	First	Second	Final	First	Second	Final	TR	EN	ChatGPT-4o	Gemini 1.5 Pro
Neuro-ophthalmology	**72**	67 (93.1)	68 (94.4)	70 (97.2)	66 (91.7)	66 (91.7)	70 (97.2)	65 (90.3)	65 (90.3)	67 (93.1)	64 (88.9)	64 (88.9)	64 (88.9)	0.763 0.745 0.441	0.779 0.779 0.097	>0.99 0.745 >0.99	>0.99 0.779 0.561
Retina and vitreous	**23**	22 (95.7)	22 (95.7)	23 (100)	23 (100)	23 (100)	23 (100)	22 (95.7)	22 (95.7)	22 (95.7)	22 (95.7)	22 (95.7)	22 (95.7)	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99
Glaucoma	**13**	12 (92.3)	12 (92.3)	13 (100)	13 (100)	13 (100)	13 (100)	12 (92.3)	12 (92.3)	13 (100)	12 (92.3)	12 (92.3)	13 (100)	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99
Cornea & anterior segment	**38**	38 (100)	38 (100)	38 (100)	38 (100)	38 (100)	38 (100)	36 (94.7)	36 (94.7)	36 (94.7)	38 (100)	38 (100)	38 (100)	0.493 0.493 0.493	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99	0.493 0.493 0.493
Pediatric ophthalmology and strabismus	**22**	21 (95.5)	21 (95.5)	21 (95.5)	21 (95.5)	21 (95.5)	21 (95.5)	20 (90.9)	20 (90.9)	20 (90.9)	20 (90.9)	20 (90.9)	20 (90.9)	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99
Oculoplastics and ocular oncology	**39**	37 (94.9)	37 (94.9)	37 (94.9)	38 (97.4)	38 (97.4)	39 (100)	36 (92.3)	36 (92.3)	37 (94.9)	37 (94.9)	37 (94.9)	37 (94.9)	>0.99 >0.99 >0.99	>0.99 >0.99 0.494	>0.99 >0.99 0.494	>0.99 >0.99 >0.99
Uveitis	**13**	12 (92.3)	12 (92.3)	12 (92.3)	11 (84.6)	11 (84.6)	11 (84.6)	11 (84.6)	12 (92.3)	12 (92.3)	11 (84.6)	11 (84.6)	11 (84.6)	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99	>0.99 >0.99 >0.99
Total	**220**	209 (95)	210 (95.5)	214 (97.3)	21 (95.5)	210 (95.5)	215 (97.7)	202 (91.8)	203 (92.3)	207 (94.1)	204 (92.7)	204 (92.7)	205 (93.2)	0.249 0.233 0.159	0.312 0.312 **0.039**	>0.99 >0.99 >0.99	0.858 >0.99 0.845

TR: Turkish, EN: English, AI: artificial intelligence, LLM: Large language models. The AI-based LLMs were listed in alphabetical order. The p values of the interlingual and inter-AI comparisons are listed in order for the first, second, and final attempts. *If at least one of the expected frequencies from the quadruple variables was below 5, "Fisher's exact test"; and if it was between 5 and 25, "Yates' continuity corrected chi-square test" was used. $p<0.05$ was considered statistically different in 95% confidence interval

Table 2. Evaluation of ChatGPT-4o and Gemini 1.5 Pro across examination years: language and model comparisons

Year	n	Correct answer count and accuracy (%)										p*			
		TR					EN					Interlingual		Inter-AI	
		ChatGPT-4o			Gemini 1.5 Pro		ChatGPT-4o			Gemini 1.5 Pro		ChatGPT-4o	Gemini 1.5 Pro	TR	EN
		First	Second	Final	First	Second	Final	First	Second	Final	First	Second	Final				
2006	**9**	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)				
2007	**17**	17 (100)	17 (100)	17 (100)	15 (88.2)	15 (88.2)	15 (88.2)	17 (100)	17 (100)	17 (100)	15 (88.2)	15 (88.2)	15 (88.2)				
2008	**19**	19 (100)	19 (100)	19 (100)	18 (94.7)	18 (94.7)	18 (94.7)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)				
2009	**10**	10 (100)	10 (100)	10 (100)	9 (90)	9 (90)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)				
2010	**9**	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)				
2011	**12**	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)				
2012	**9**	7 (77.8)	7 (77.8)	7 (77.8)	8 (88.9)	8 (88.9)	8 (88.9)	8 (88.9)	8 (88.9)	8 (88.9)	8 (88.9)	8 (88.9)	8 (88.9)				
2013	**16**	16 (100)	16 (100)	16 (100)	15 (93.8)	15 (93.8)	15 (93.8)	16 (100)	16 (100)	16 (100)	15 (93.8)	15 (93.8)	15 (93.8)				
2014	**21**	19 (90.5)	19 (90.5)	21 (100)	21 (100)	21 (100)	21 (100)	20 (95.2)	20 (95.2)	21 (100)	19 (90.5)	19 (90.5)	19 (90.5)	>0.99	>0.99	>0.99	>0.99
2015	**12**	11 (91.7)	11 (91.7)	12 (100)	12 (100)	12 (100)	12 (100)	10 (83.3)	10 (83.3)	12 (100)	10 (83.3)	10 (83.3)	10 (83.3)	>0.99	>0.99	>0.99	>0.99
2016	**16**	15 (93.8)	15 (93.8)	15 (93.8)	13 (81.3)	13 (81.3)	13 (81.3)	15 (93.8)	15 (93.8)	15 (93.8)	14 (87.5)	14 (87.5)	14 (87.5)	>0.99	>0.99	>0.99	>0.99
2017	**13**	13 (100)	13 (100)	13 (100)	12 (92.3)	12 (92.3)	13 (100)	12 (92.3)	12 (92.3)	13 (100)	11 (84.6)	11 (84.6)	11 (84.6)				
2018	**13**	13 (100)	13 (100)	13 (100)	11 (84.6)	11 (84.6)	11 (84.6)	13 (100)	13 (100)	13 (100)	12 (92.3)	12 (92.3)	12 (92.3)				
2019	**11**	10 (90.9)	11 (100)	11 (100)	8 (72.7)	9 (81.8)	9 (81.8)	10 (90.9)	10 (90.9)	10 (90.9)	10 (90.9)	10 (90.9)	10 (90.9)				
2020	**15**	13 (86.7)	13 (86.7)	13 (86.7)	14 (93.3)	15 (100)	15 (100)	13 (86.7)	13 (86.7)	13 (86.7)	15 (100)	15 (100)	15 (100)				
2021	**16**	14 (87.5)	14 (87.5)	15 (93.8)	14 (87.5)	14 (87.5)	15 (93.8)	15 (93.8)	15 (93.8)	16 (100)	14 (87.5)	14 (87.5)	15 (93.8)				
2022-2024 (10%)	**2**	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)				

TR: Turkish, EN: English, AI: Artificial intelligence, LLM: Large language models. *Comparison between the years 2016-2024 via chi-square test. The AI-based LLMs were listed in alphabetical order. The p values of the interlingual and inter-AI comparisons are listed in order for the first, second, and final attempts. $p<0.05$ was considered statistically different in 95% confidence interval

Over the past few years, LLM chatbots like ChatGPT and Gemini have attracted growing interest as educational tools in medicine.[5,6,7,8,9] Early versions, such as ChatGPT-3.5 and Google Bard, delivered only moderate performance, with reported accuracies between 50% and 70% across different exam settings including the Turkish MSE, United States Medical Licensing Examination, and dedicated ophthalmology question banks.[15,23,24,25,26] These results, while promising, highlighted clear limitations in reasoning depth, domain-specific precision, and multilingual reliability.

As newer models like ChatGPT-4o and Gemini 1.5 Pro emerged, a marked improvement became evident. Several studies reported significantly higher success rates—often exceeding 70%, and in some cases over 90%—particularly in structured, multiple-choice exam formats and language-specific settings such as the medical proficiency tests for medicine or ophthalmological board assessments.[13,14,16,17,27]

Still, much of the available research has focused on open-ended questions or general medical content. Few have looked closely at ophthalmology—a highly specialized and visually driven field—and even fewer have explored how these models perform across different languages. This study was designed to address that gap by directly comparing ChatGPT-4o and Gemini 1.5 Pro on a bilingual (Turkish and English) set of ophthalmology-related MCQs, using standardized prompts that required scientific justification and citation. In doing so, our aim was not only to assess model accuracy, but also to explore the pedagogical and linguistic dimensions of AI-assisted learning in a focused clinical field. Interestingly, the comparatively high accuracy rates observed in our findings may

Table 3. Validity assessment of explanations generated by chatbots

			Average CVI	ICC (95% CI)
ChatGPT-4o	**TR**	First	0.95	0.849 (0.756-0.901)
		Second	0.96	0.850 (0.774-0.897)
		Final	0.97	0.834 (0.753-0.885)
	EN	First	0.96	0.951 (0.936-0.963)
		Second	0.96	0.942 (0.924-0.956)
		Final	0.98	0.885 (0.850-0.912)
Gemini 1.5 Pro	**TR**	First	0.93	0.862 (0.771-0.911)
		Second	0.94	0.878 (0.820-0.915)
		Final	0.95	0.850 (0.757-0.902)
	EN	First	0.92	0.927 (0.893-0.949)
		Second	0.93	0.925 (0.890-0.947)
		Final	0.93	0.918 (0.877-0.944)

TR: Turkish, EN: English, CVI: Content validity index, ICC: Intraclass correlation coefficient, CI: Confidence interval

be attributed to several methodological strengths. First, we employed the most recent versions of both AI platforms, each incorporating substantial architectural improvements over earlier iterations such as ChatGPT-3.5 or Google Bard. Second, the use of structured prompts that demanded not just correct answers, but also evidence-based reasoning, likely enhanced the quality of model outputs. Third, the bilingual design enabled controlled cross-linguistic comparison, offering valuable insight into model behavior in languages underrepresented during training. This combination of technological currency, prompt rigor, and linguistic breadth distinguishes the present study from prior work and reinforces the relevance of LLMs as adaptable tools in medical education.

Upon evaluating the exams over the years, we noted a lack of inter-AI and interlingual differences, but there was a significant difference in the inter-AI comparison for the total English MCQs in the final attempt. These results should not be viewed as contradictory, as it was likely influenced by the heterogeneous distribution of question types and difficulty levels across examination years.

One of the more intriguing findings in this study was the effect of user feedback on chatbot performance. While neither model truly "learns" in the traditional human sense during testing, both ChatGPT-4o and Gemini 1.5 Pro showed modest improvements in their final attempt after receiving a standardized negative feedback signal for incorrect answers. This raises an important question: to what extent do LLMs adapt their outputs in response to structured cues, even without persistent memory? These observations may reflect the underlying influence of reinforcement learning from human feedback, a core training mechanism that guides how these models prioritize factual consistency and contextual reasoning.[28,29] Although no real-time learning occurs during user interaction, feedback signals—such as rating a response as "factually incorrect"—can temporarily shift the model's focus toward more cautious, evidence-based reasoning patterns.[28,29,30] In practical terms, this suggests that even a simple, well-designed correction can nudge a chatbot toward a more accurate and academically grounded answer, particularly in high-stakes domains like medicine. As previously emphasized by Antaki et al.[15], the educational value of LLMs lies not only in their ability to produce correct answers but also in their potential to facilitate reasoning and reflection. For medical educators and exam designers, this opens up new possibilities. If thoughtfully implemented, controlled feedback mechanisms could enhance the pedagogical role of chatbots—not just as static responders, but as adaptive tools that promote critical thinking and iterative learning.

The validity analysis indicated that both chatbots achieved satisfactory content validity across Turkish and English, as reflected by consistently high expert ratings. Notably, the explanations generated in English were more detailed than those in Turkish for both models, suggesting that users may access richer content when interacting in English. ChatGPT-4o, in particular, provided longer and more comprehensive responses in both languages, making it a potentially preferable tool for learners seeking in-depth justifications. Furthermore, both models frequently included brief comments on why alternative options were incorrect. This practice of addressing distractors may enhance the educational value of chatbot interactions by promoting a deeper understanding of the reasoning process underlying multiple-choice assessments.

AI-based LLM chatbot technology, readily accessible at people's fingertips, continues to evolve rapidly, including in ophthalmology.[31,32,33] For instance, earlier versions of ChatGPT were limited by a knowledge cut-off (September 2021).[34,35,36] However, with the latest updates, ChatGPT has gained the ability to browse the internet and provide up-to-date content, demonstrating the potential for progressively improving accuracy rates. While this advancement is promising for research purposes, it also introduces the disadvantage of rapid publication obsolescence.[35] Additionally, it may lead to accuracy discrepancies between different versions of the same chatbot, posing challenges

for consistent and reliable use in academic and professional settings. Also, despite these significant advancements, chatbots remain prone to generating hallucinations and fabricating references.[35] Therefore, maintaining a supervisory role while utilizing such tools is essential to ensure reliability.

Study Limitations

While this study elucidates critical aspects regarding the benefits of ChatGPT-4o over Gemini 1.5 Pro in addressing ophthalmology-related MCQs in Turkish MSEs, it is not devoid of limitations, including 1) evaluating performance only in Turkish and English languages, 2) the lack of assessment for open-ended question performance, and 3) the use of only two AI-based LLMs, despite the availability of many other models. Another significant limitation of this study is the focus on evaluating the effectiveness of LLMs using MSE questions specifically designed to assess the fundamental ophthalmology knowledge of general practitioners. Consequently, the findings presented here are not comprehensive enough to fully elucidate the potential role of LLMs in ophthalmology education. Further detailed studies focusing on various aspects of ophthalmology are required to better understand and define the utility of LLMs in this field. Also, in our study, only the officially published answer keys and question cancellations were taken into consideration. While rare, there have been instances in such examinations where questions were later contested, with appeals or legal proceedings initiated for their cancellation. However, these questions are typically not reflected in the officially released answer keys and therefore could not be accounted for in analysis. This represents a limitation of the study, as the inclusion of such contested questions might have provided a more comprehensive assessment of the data.

Although extremely rare, it was observed in both AI-based models that the logical explanation was provided but the wrong choice was chosen, or the wrong explanation was given but the correct choice was selected. One should always remember that everyone, including AI, can make errors, so it is always wise to check the results. Furthermore, as chatbots are prone to generating fabricated references and hallucinations, the lack of a dedicated validity analysis specifically aimed at assessing reference accuracy may be regarded as a limitation. Lastly, since accuracy rates of participants for these exams were not known and not publicly available, a comparison between the human accuracy rates and those of the AIs could not be performed.

Even with these flaws, to the best of our knowledge, this is the first AI comparative study to reveal that ChatGPT-4o exhibits a modest performance advantage over Gemini 1.5 Pro in addressing ophthalmology-related MCQs in Turkish MSEs. Additionally, the evaluation of a substantial number of MCQs (n=220) and the inclusion of three consecutive attempts with and without feedback enhance this work. Furthermore, the requirement for scientific explanations from PubMed and the WoS Citation Index may have influenced these results. The use of the most up-to-date AI versions also strengthens the study. Finally, unlike most other studies, questions containing figures were evaluated in this study.

Conclusion

Both AI-based LLMs demonstrated robust performance in answering ophthalmology-related MCQs. They hold promise for improving ophthalmology education by not only accurately identifying the correct answers to ophthalmology-related MCQs but also offering explanations. While both AI platforms prove to be useful, ChatGPT-4o is significantly ahead. Further research on the contributions of AI-driven e-learning, particularly for med students and ophthalmology residents, is essential in this relatively nascent technological field.

Ethics

Ethics Committee Approval: Since this study did not involve human participants or animal experiments, ethics approval and informed consent were not required.

Informed Consent: Patient consent is not required for this article.

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Declarations

Authorship Contributions

Surgical and Medical Practices: M.C.S., Z.Y., Concept: M.C.S., Z.Y., Design: M.C.S., Z.Y., Data Collection or Processing: M.C.S., Z.Y., Analysis or Interpretation: M.C.S., Z.Y., Literature Search: M.C.S., Z.Y., Writing: M.C.S., Z.Y.

Conflict of Interest: All authors certify that they have no affiliations with or involvement in any organization with any financial or non-financial interest in the subject matter or materials discussed in this article. The use of multiple-choice questions was intended for scientific purposes only.

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Original Article

Spectrum of Scleral Lens Fit and Patient Compliance: A Single Center Retrospective Study

Oğuzhan Özçelik, Zeynep Özbek, Canan Aslı Yıldırım, İsmet Durak

Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye

Abstract

Objectives: To discuss the results of scleral contact lens fit in patients with difficult corneal and ocular surface pathologies.

Materials and Methods: This single-center, retrospective case-series included 49 eyes of 34 patients who underwent scleral lens fitting for visual acuity improvement from February 2018 to 2023. All patients underwent Orbscan/Pentacam corneal topography before a complete ophthalmological exam. The first trial lens was chosen according to manufacturer guidelines and topographic parameters. Best corrected Snellen visual acuity was assessed with spectacles before fit and over-refraction after fit and converted to logarithm of the minimum angle of resolution (logMAR). The vault was evaluated both at the slit-lamp and with anterior segment optic coherence tomography when possible.

Results: Twenty-one patients (61.8%) were male and the mean age was 37.4±14.8 years (range: 12-71). Twenty-three eyes (46.9%) had keratoconus, 11 eyes (22.4%) had refractive error after penetrating keratoplasty, 7 eyes (14.3%) had irregular astigmatism due to corneal scar, 4 eyes (8.2%) had advanced stage Steven-Johnson syndrome, 2 eyes (4.1%) had corneal perforation repair, and 2 eyes (4.1%) had severe dry eye. The appropriate lens was determined after 3.7±1.9 trials (range: 1-8 trials.) Although five patients refused scleral contact lenses due to cost, lenses were successfully fitted and used in 39 eyes of 29 patients. The mean daily wear time was 9.3±4.5 hours (range: 2-16) and mean follow-up was 52±49 months (range: 12-180). Mean uncorrected logMAR visual acuity and mean spectacle-corrected logMAR visual acuity was 1.09±0.47 and 0.67±0.50, which improved significantly to 0.13±0.20 after scleral contact lens fitting.

Conclusion: Scleral lens fit is a time-consuming practice for the ophthalmologist and an intimidating task for the patient. However, in addition to their good optical results, they provide very good comfort and stability. Although the large diameter may seem like the major disadvantage during scleral lens trial, the cost becomes more of an issue in developing countries.

Keywords: Irregular astigmatism, keratoconus, keratoplasty, scleral contact lens

Introduction

Scleral contact lenses are large-diameter (over 15 mm) rigid gas-permeable (RGP) lenses that are completely supported by the sclera. They do not contact the cornea and limbus and provide a tear film reservoir between the posterior surface of the lens and the anterior surface of the cornea.[1,2] Although scleral lenses have been in ophthalmology practice for over a century, they have been used more frequently over recent years because of newer high-Dk materials that permit better diffusion of oxygen, reducing the complications seen with older generation scleral lenses.[3,4] Scleral lenses play an important role in the treatment of corneal disease, providing hydration of the ocular surface and protecting it from trauma caused by scarred lid margins and lashes.[5,6] They also provide visual rehabilitation by optical neutralization of corneal surface irregularities.

Studies have recognized the benefits of scleral lenses in the management of various ocular surface diseases, including keratoconjunctivitis sicca, cicatrizing conjunctivitis, neurotrophic keratopathy, exposure keratopathy, and limbal stem cell deficiency.[5,6,7,8,9,10,11] Recent studies have also highlighted their effectiveness in managing severe dry eye and ocular surface irregularities.[12,13,14,15]

In this study, we evaluated the results of scleral lens fitting in patients with irregular corneal astigmatism and difficult ocular surface pathologies.

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Address for Correspondence: Oğuzhan Özçelik, Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye
E-mail: oguzhanozcelik07@gmail.com **ORCID-ID:** orcid.org/0000-0001-9862-7247
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Materials and Methods

This study was approved by the Dokuz Eylül University Hospital Research Ethics Board before data collection and analysis (decision no: 2024/38-22; date: 13/11/2024). This single-center, retrospective case series included 49 eyes of 34 patients who underwent scleral lens fitting mainly for improvement of visual acuity from February 2018 to 2023. Since the study was a retrospective study, an informed consent form was not used. All patients underwent Orbscan (Bausch & Lomb) or Pentacam (Oculus) corneal topography before a complete ophthalmological exam. The first trial lens was chosen according to the manufacturer's suggestions based on topographic parameters. We started with a base curve of 7.80 mm, diameter of 16 mm, and a vault of 300-350 µm for moderate cones and post-surgical eyes, while we chose larger diameters for severe cones or patients with ocular surface diseases such as Stevens-Johnson syndrome (SJS).

Statistical Analysis

The study data were evaluated using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) software. The Kolmogorov-Smirnov test was used to evaluate whether the data showed normal distribution. Parameters before and after scleral lens wear were compared using Wilcoxon test, with a p value <0.05 considered statistically significant.

Fitting and Evaluation

The lens was mounted on the plunger and filled with saline, which was dyed with a fluorescein strip used for evaluating the ocular surface and the tear film. The patient was then told to sit down and bend their head forward until their face was parallel to the ground. The lens was inserted by one of the researchers (Z.Ö. or C.A.Y.) using the plunger, paying attention not to spill the dyed saline. The upper lid was gently pulled back, the superior edge of the lens was placed under the upper lid first, and then the same technique was repeated for the lower lid. Then the patient was asked to sit up. The position of the lens and the tear reservoir was checked with a blue flashlight. If there was no touch or air bubbles and a nice homogeneous fluorescence was observed underneath the lens, the patient was instructed to wait for 30 minutes for the lens to settle.

Snellen best corrected visual acuity (BCVA) was assessed with spectacles before fit, and over-refraction was performed 30 minutes after fitting. Visual acuity values were converted to logarithm of the minimum angle of resolution (logMAR). Success was defined as at least two lines of increase in BCVA.

The lens and tear reservoir were re-evaluated at the slit-lamp. The thickness of the fluorescent reservoir was simply compared to that of the cornea with slit illumination (Figure 1), and vault was considered appropriate when the thickness of the fluorescence beneath the lens was half the corneal thickness, as an average vault of 200-250 µm was advocated. A steeper base curve was selected when there were air bubbles or conjunctivochalasis at the edge of the lens. The landing zone was also evaluated for blanching. Vault was measured quantitatively by anterior segment optical coherence tomography (AS-OCT; Visante OCT, Zeiss) when available (AS-OCT was out of order in 2020, and some patients were evaluated using a temporary demo AS-OCT [Anterion, Heidelberg Engineering]) (Figure 2). Imaging was difficult in some of our patients, such as those with SJS or

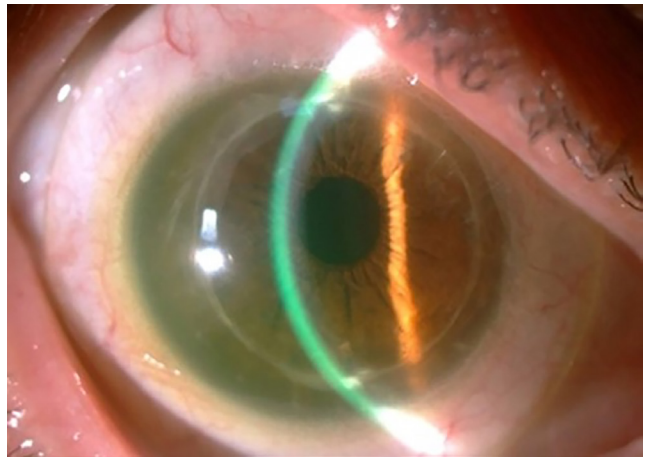

Figure 1. Anterior segment photography of a patient with high astigmatism after penetrating keratoplasty with the scleral lens showing adequate vault

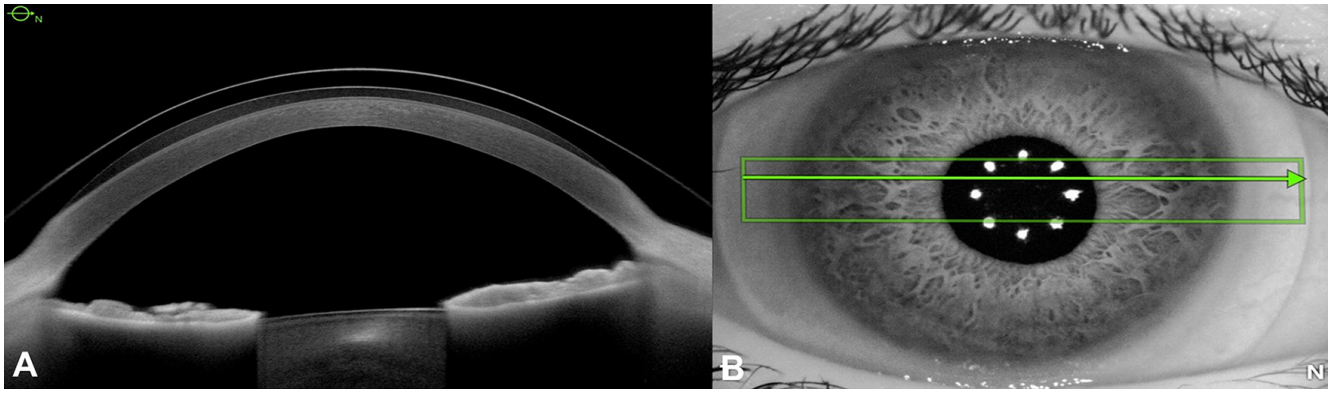

Figure 2. A) Anterior segment optical coherence tomography of a keratoconus patient 30 minutes after fitting scleral lens. B) Infrared image of the same patient 30 minutes after fitting the scleral lens

bilateral corneal perforation (Figure 3). All measurements and examinations were performed by a single researcher (Z.Ö.) to avoid interobserver variability. Vault was increased when touch was observed.

When we decided on the final lens to order, we showed the patient how to put the lens in and take it out and provided an opportunity to practice at the clinic before placing the order. When the lens was delivered, the patient returned to the clinic with the package including the lens, care solution, wetting drops, plunger, and information booklet. After checking the parameters, the package was opened, and we performed the first insertion. We rechecked visual acuity and fit and then taught the patient the insertion and removal once again. Every patient was told to start wearing the lens gradually: for 2 hours on the first day of use, 4 hours on the second, and 6 hours on the third. They were also warned to remove the lens after 4 hours of wear to clean, refill, and reinsert if scleral lens wear was still required, to prevent midday fogging and protein buildup.

Results

Twenty-one patients (61.8%) were male and 13 patients (38.2%) were female. The mean age was 37.4±14.8 years (range: 12-71 years). Twenty-three eyes (46.9%) with keratoconus, 11 eyes (22.4%) with refractive error after penetrating keratoplasty, 7 eyes (14.3%) with irregular astigmatism due to corneal scar, 4 eyes (8.2%) with advanced-stage SJS, 2 eyes (4.1%) with corneal perforation repair, and 2 eyes (4.1%) with severe dry eye were included (Table 1). All patients with keratoconus and grafts had been previously fit with RGP contact lenses but recently were uncomfortable in them. Mean uncorrected logMAR visual acuity and mean spectacle-corrected logMAR visual acuity were 1.09±0.47 and 0.67±0.50, respectively, which improved significantly to 0.13±0.20 after scleral lens fitting ($p<0.05$) (Figure 4). Before ordering the lens, the necessary power adjustment was made considering the vertex distance when over-refraction exceeded 4 diopters. Visual acuity with the scleral lens remained stable without any serious complications during 29.5±14.5 months (range: 12-48 months) of follow-up. All patients reported that they wore their lenses every day for at least 2 hours. Mean duration of wear was 9.3±4.5 hours (range: 2-16 hours) (Table 2). Mean vault height measured by AS-OCT in 23 eyes of 17 patients was 0.21±0.02 mm (range: 0.15-0.26 mm). Twenty-nine patients were successfully fit and all continued wear. Although no scale was used to assess patient comfort, according to information provided by the patients during follow-up visits, all patients stated they were more comfortable with scleral lenses than their previous lenses. However, 5 patients refused to use scleral lenses for financial and practical purposes. Three lenses had to be replaced because one was broken after 3 months of use and the other two patients had changes in refraction while waiting for shipment. Two of our patients continued to use scleral lenses even though they complained of midday fogging. No patient experienced conjunctival blanching, chalasis, or limbal vascularization.

Table 1. Demographic properties

Gender	Male, 21 (61.8%) Female, 13 (38.2%)
Age (years)	37.4±14.8 (range: 12-71)
Indication	**Keratoconus**, 23 eyes (46.9%) **Refractive error after PK**, 11 eyes (22.4%) **Irregular astigmatism (corneal scar)**, 7 eyes (14.3%) **Advanced SJS**, 4 eyes (8.2%) **Corneal perforation repair**, 2 eyes (4.1%) **Severe dry eye**, 2 eyes (4.1%)

PK: Penetrating keratoplasty, SJS: Stevens-Johnson syndrome

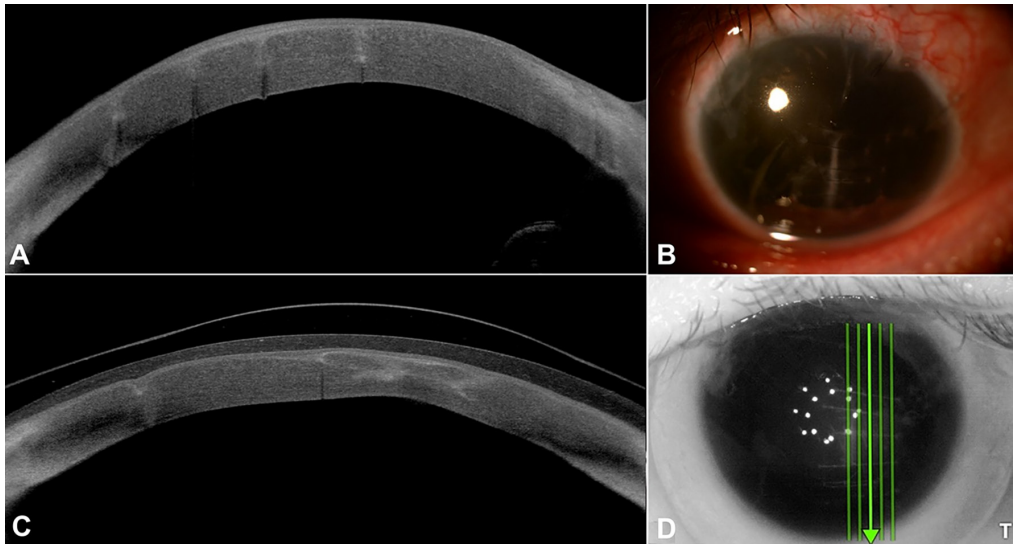

Figure 3. A patient with total aniridia, aphakia, and bilateral corneal perforation repair: A) Anterior segment optical coherence tomography (AS-OCT) before scleral lens fitting. B) Slit-lamp biomicroscopy before fitting. C) AS-OCT 30 minutes after fitting. D) Infrared image 30 minutes after fitting

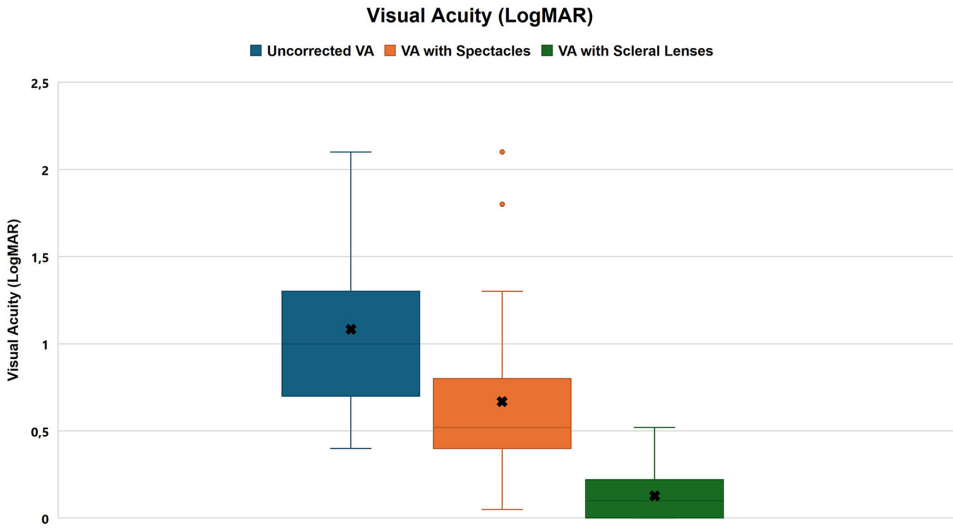

Figure 4. Changes in visual acuity with no correction, spectacles, and scleral lenses
logMAR: Logarithm of the minimum angle of resolution, VA: Visual acuity

Table 2. Characteristics of the patients	
Lens trials (n)	3.65±1.92 (range: 1-8)
Uncorrected VA (logMAR)	1.09*
Spectacle-corrected VA (logMAR)	0.67*
Scleral lens-corrected VA (logMAR)	0.13*
Mean follow-up (months)	52.03±49.04 (range: 12-180)
Mean daily wear time (hours)	9.3±4.5 (range: 2-16)

*p<0.05 (Wilcoxon test), VA: Visual acuity, logMAR: Logarithm of the minimum angle of resolution

Discussion

High and/or irregular astigmatism is the main reason for low vision in patients with keratoconus, pellucid marginal degeneration, keratoglobus, and post-keratoplasty astigmatism. Although soft and RGP lenses may help to improve vision in mild to moderate cases, soft lenses do not work on steeper corneas with advanced disease, and RPG lenses with small diameters simply cannot remain stable on a steep or irregular cornea. They frequently dislocate or bear on the cornea, causing discomfort. Therefore, we may have to offer other alternatives such as piggyback contact lenses, hybrid lenses, and scleral lenses.[11,12,13,14]

Schornack and Patel[12] used Jupiter scleral lenses in the management of keratoconus and reported that median BCVA improved from 20/40 before scleral lens fitting to 20/20 after fitting. They suggested using Jupiter scleral lenses for providing acceptable visual acuity and comfort in patients with keratoconus. Recent studies have also shown the efficacy of scleral lenses in improving vision and quality of life in keratoconus patients. For instance, Marty et al.[13] highlighted the role of scleral lenses in managing irregular corneal conditions, emphasizing their ability to provide superior visual acuity and comfort compared to other contact lens modalities. Our results, show improved visual acuity and better satisfaction with in patients who had previously used RGP and hybrid lenses and were unsatisfied.

Alipour et al.[16] evaluated fitting feasibility, efficacy, and safety of miniscleral contact lenses in correcting vision in patients with corneal grafts. In their study, mean BSCVA before fit was 0.73 logMAR (standard deviation [SD]: 0.50) ranging from 0.09 to 2.00, which improved to 0.17 logMAR (SD: 0.19) with the miniscleral lens. Similarly, Pecego et al.[17] reported positive outcomes using Jupiter scleral lenses in pediatric patients, indicating that scleral lenses can be effectively used across different age groups. In our study, the age of the patients we tested for scleral lenses was between 12 and 71, which supports the literature.

Asena and Altınörs[14] reported the clinical outcomes of scleral Misa lenses for visual rehabilitation in 24 eyes of 12 patients with pellucid marginal degeneration. Mean BCVA improved 3.3 lines with scleral lenses compared to spectacle correction in all patients. Subjective complaints associated with scleral lenses, including discomfort, difficulty with lens insertion and/or removal, and suboptimal quality of vision, were reported by 4 patients (7 eyes, 29%). Rathi et al.[18] discussed recent advancements in scleral lens technology, highlighting improvements in lens materials and designs that enhance patient comfort and visual outcomes.

Parminder and Jacobs[19] evaluated advantages of using scleral lenses for refractive surgery complications in their study and suggested that patients with keratectasia, dry eye syndrome, and corneal neuralgia after refractive surgery benefit from scleral lenses in terms of improved visual acuity and dry eye issues. Additionally, Yuksel et al.[15] successfully fit a patient with corneal exposure secondary to facial nerve palsy with scleral lenses. The spectrum of patients in whom we have tried scleral lenses and had success was diverse; the most common indications

were keratoconus, refractive error after penetrating keratoplasty, irregular astigmatism due to corneal scarring, SJS, dry eye, and postoperative corneal perforation.

Pullum et al.[20] described the current indications for scleral lenses. In their study, 1,560 eyes of 1,003 patients were evaluated, and the total numbers of eyes for each contact lens indication were as follows: primary corneal ectasia, 496 (61.4%); corneal transplant, 150 (18.6%); ocular surface disease, 91 (11.4%); aphakia, 17 (2.1%); myopia, 21 (2.6%); and ptosis, 14 (1.7%). Visser et al.[21] evaluated the subjective performance of modern scleral lenses in 284 eyes of 178 patients. Significantly increased patient scores were noted with the current scleral lens compared to the former correction (78.9% for comfort, 78.2% for visual quality, and 87.7% for overall satisfaction) ($p<0.001$). In the study conducted by Akkaya Turhan et al.[22], the Likert scale was used in patients with keratoconus using mini scleral lenses. A score of 4.69 (range: 4-5) was obtained, which was consistent with the literature. Recent advancements have expanded the indications and improved the outcomes of scleral lens use.[16,18,24,25] Although we did not use any comfort scales, our patients reported satisfaction with their scleral lenses at follow-up visits.

Corneal transplantation (keratoplasty) is widely used for treating corneal diseases such as keratoconus, dystrophy, and corneal scarring. Despite advances in surgical techniques, postoperative astigmatism remains a significant cause of suboptimal visual acuity. Approximately 20% of patients experience high astigmatism after keratoplasty, primarily due to irregularities in the graft-host junction, leading to high-order aberrations.[26,27,28] Suzuki et al.[28] reported that scleral lenses are the most commonly prescribed contact lens type in patients after keratoplasty (61% of 464 eyes studied). Unlike corneal RGP lenses, which rest on the corneal surface, scleral lenses rise above the cornea and rest on the sclera, preventing mechanical pressure at the graft-host junction and reducing the risk of lens-induced trauma.[26,29,30] Scleral lenses provide superior visual rehabilitation after keratoplasty because they mask corneal irregularities. They also provide a protective fluid reservoir that increases ocular surface stability.[28] Studies have reported significant improvement in BCVA with scleral lenses compared with uncorrected visual acuity (UCVA) and conventional BCVA. Barnett et al.[31] reported improved visual acuity from a mean BCVA of 20/50 to 20/25 with scleral lenses compared with spectacles. Kumar et al.[32] reported an improvement from 1.10 logMAR (UCVA) to 0.22 logMAR with scleral lenses. In a study by Penbe et al.[33], visual acuity improved from 1.15±0.26 logMAR (UCVA) and 0.84±0.24 logMAR (with spectacles) to 0.13±0.09 logMAR. Similarly, our postgraft patients had better visual acuity with scleral lenses compared to spectacle correction (0.09±0.10 vs. 0.82±0.64 logMAR).

Subjective comfort levels with scleral lenses were high compared to other types of lenses in postgraft patients. In a study by Lee et al.[34], 82% of patients wore scleral lenses for most or all of their waking hours. Another study found that 75% of patients could wear scleral lenses for more than 10 hours daily.[35] Common complaints of discomfort included difficulty handling the lenses (29%), halos, blurs, or haze (23%), and excessive tear residue in the lens reservoir (23%).[30] In our study, the subjective comfort of postgraft patients was also high, and all of our patients reported better comfort compared other types of lenses.

Some complications were reported in patients wearing scleral lenses after keratoplasty. Corneal graft rejection (5-30%) is a major reported complication.[31,33,35] Although this is a concern, studies suggest that the rejection rate is similar in patients who do not wear contact lenses.[36] Another complication is microbial keratitis (6%).[35,37] Risk factors include overuse, noncompliance with cleaning, and prolonged hypoxia under the lens. The main risk factor for graft edema is low endothelial cell density before lens insertion (6%).[35] However, Penbe et al.[33] found no significant change in endothelial cell density after 6 months of scleral lens use, although caution is advised in patients with preexisting low endothelial cell counts. Our postgraft patients had no complications such as corneal graft rejection or microbial keratitis.

Severe ocular surface disease has been one of the primary indications for large scleral lenses for many years, as they keep the ocular surface moist and protect against dehydration.[16,18,23,24] Alipour et al.[16] reviewed the use of scleral contact lenses in the management of severe ocular surface disease and concluded that they are effective in improving symptoms and ocular surface integrity. The SJS patient in our study reported that in addition to improved visual acuity, she would prefer wearing her scleral lenses just because they significantly alleviated her scratchy and stinging pain complaints due to trichiasis, emphasizing the therapeutic role of scleral lenses in severe ocular surface disease.

Dimit et al.[38] determined the type and distribution of ocular conditions treated in a clinic dedicated to scleral devices and reported the clinical outcomes. The most common reasons for fitting were to relieve symptoms of moderate to severe dry eye syndrome, persistent epithelial corneal defects, SJS, graft-versus-host disease, ocular cicatricial pemphigoid, neurotrophic corneal disease, atopic keratoconjunctivitis, and management of refractive problems with keratoconus.

In our study, the majority of patients experienced significant improvement in visual acuity and comfort with scleral lenses, consistent with findings from recent literature.[14,18,21] The challenges faced by some patients, such as handling difficulties and financial constraints, are also reported in other studies.[14,23] Efforts to improve patient education and reduce costs could enhance the accessibility and acceptance of scleral lenses.

When we review the literature, the follow-up periods of patients who underwent scleral lens trial were reported as 4 to 14 months by Schornack et al.[8], 14.1±3.7 months (range: 8.5-18 months) by Asena and Altınörs[14], 17 months by Schornack and Baratz[9], 22.5 months (range: 3-32 months) by Schornack and Patel[12], and 33.6 months (range: 2-144 months) by Romero-Rangel et al.[11] With a mean follow-up of 29.5±14.5 months (range: 12-48 months), our study has a relatively longer follow-up compared to most of the previous reports, which stands out

as an important aspect.

Two interesting patients in our study group were a woman with SJS and a man who had bilateral corneal perforation after a car accident. He was aphakic and totally aniridic in both eyes. They were both extremely motivated to use scleral lenses despite their poor visual acuity, which caused them extra difficulty in handling. The most striking experience for us was the man who asked if he could have an iris prosthetic aphakic scleral lens. This highlights the potential for customized scleral lenses to address complex ocular conditions, as discussed in recent studies.[25]

Study Limitations

Some limitations of this study are lack of a control group and comfort scale rating for patient feedback, as well as possible selection bias. No control group was included in the study compared to scleral lens users. The study mainly aimed to discuss the results of scleral contact lens fitting in patients with difficult corneal and ocular surface pathologies. At the same time, since it is a single-center study, possible selection bias should not be ignored. In addition, no comfort scale was used to evaluate the comfort results of patients after scleral lenses.

Conclusion

To conclude, scleral lenses are an important option that offer patients comfort and visual rehabilitation. We demonstrated improved vision and better comfort with scleral lenses in patients with keratoconus and grafts as well as patients with severe ocular surface diseases, consistent with recent literature.

Ethics

Ethics Committee Approval: Dokuz Eylül University Hospital Research Ethics Board before data collection and analysis (decision no: 2024/38-22; date: 13/11/2024).

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

Surgical and Medical Practices: Z.Ö., C.A.Y., İ.D., Concept: O.Ö., Z.Ö., Design: O.Ö., Z.Ö., Data Collection or Processing: O.Ö., Analysis or Interpretation: O.Ö., Literature Search: O.Ö., Z.Ö., Writing: O.Ö., Z.Ö.

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Original Article

Macular Telangiectasia Type 2: Long-Term Disease Progression and Management of Complications

Merve Özbek, Özgür Artunay, Rümeysa Koçak, İlker Hoşver, Metehan Şimşek

University of Health Sciences Türkiye, Beyoğlu Göz Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye

Abstract

Objectives: To evaluate the long-term progression of macular telangiectasia type 2 (MacTel) using a standardized classification system and to assess the incidence, progression, and management strategies of complications such as macular neovascularization (MNV) and macular hole (MH).

Materials and Methods: This retrospective study analyzed the medical records of patients diagnosed with MacTel at a tertiary referral center in Türkiye from January 2004 to February 2025. Patients with a minimum follow-up of 3 years and no confounding macular pathologies were included. Data collection included best corrected visual acuity (BCVA), multimodal imaging (optical coherence tomography [OCT], fundus autofluorescence, fluorescein angiography), and demographic variables. Disease severity was classified using the MacTel Classification System developed by Chew et al. Longitudinal changes in BCVA and OCT parameters were statistically analyzed.

Results: A total of 184 eyes from 94 patients (mean age: 63.89±9.98 years; mean follow-up: 79.27±50.69 months) were included. A significant decline in BCVA was observed ($p<0.001$). MNV was present in 29 eyes (15.8%), with 18 receiving intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy (mean injections: 5.89±3.72). While post-treatment BCVA showed improvement ($p<0.001$), long-term visual outcomes were not significantly different from baseline ($p=0.213$). MH formation occurred in 8 eyes (4.3%), with 6 undergoing successful surgical closure. Structural retinal changes, including ellipsoid zone disruption and pigmentation, significantly progressed over time ($p<0.001$).

Conclusion: MacTel demonstrates a progressive decline in visual and structural integrity over extended follow-up. While anti-VEGF therapy offers short-term benefits for MNV, its long-term efficacy remains limited. MH development, though rare, poses a significant challenge, with variable surgical outcomes.

Keywords: Macular telangiectasia type 2, macular neovascularization, macular hole

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Address for Correspondence: Merve Özbek, University of Health Sciences Türkiye, Beyoğlu Göz Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye

E-mail: drmerveyalcin@gmail.com **ORCID-ID:** orcid.org/0000-0002-4280-5718

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Introduction

Macular telangiectasia type 2 (MacTel), also known as idiopathic juxtafoveal telangiectasia, is a progressive bilateral retinal disorder. The condition typically manifests in individuals over the age of 40 and is more prevalent in females.[1] The characteristic retinal pathology of MacTel typically begins in the parafoveal temporal region and progresses superiorly and nasally, often with loss of retinal transparency, discontinuity of the ellipsoid zone (EZ), and the presence of right-angled venules (RAVs). As the disease progresses, complications such as macular neovascularization (MNV), central pigmentation, and full-thickness macular hole (MH) may develop, reflecting the progressive and degenerative nature of the disease.[2,3] Though identified in the 1980s, the natural progression and underlying etiology of MacTel remain poorly understood despite its significant impact on vision. Knowledge regarding the disease's long-term course and causative mechanisms is also limited.[4]

Complications such as MNV and MHs are associated with the progression of the disease. The development of MNV in particular can lead to significant visual loss. While short-term clinical studies have demonstrated the benefit of anti-vascular endothelial growth factor (anti-VEGF) therapies in the treatment of MacTel-associated MNV, the long-term efficacy of these interventions has not yet been fully determined.[5] Meanwhile, the occurrence of MHs, although very rare, poses a significant challenge; considerable heterogeneity in functional and anatomical outcomes has been reported following surgical treatment.[6] Given the slow and long-term nature of the

condition, it is essential that longitudinal studies are conducted to delineate the disease's progression and evaluate the long-term efficacy of therapeutic modalities.

The objective of this study was to examine the natural progression of MacTel over an extended period of time and to propose a management strategy for the associated complications.

Materials and Methods

A retrospective analysis of medical records was performed at a tertiary referral center in Türkiye, with the approval of the Ethics Committee of Hamidiye Scientific Research, University of Health Sciences (approval number 12/4, date: 17.10.2024). The study was executed in accordance with the Declaration of Helsinki. The requirement for informed consent was not applicable to this retrospective study, as it employed anonymized archival data.

Medical records from January 2004 to February 2025 were evaluated. The sample included individuals diagnosed with MacTel with a minimum of 3 years of follow-up data. Patients with concomitant macular pathologies that could interfere with the assessment of MacTel, and those whose diagnosis was uncertain due to overlapping clinical features were excluded from the study. Patients with a history of tamoxifen use were also excluded to avoid potential diagnostic overlap with tamoxifen-associated retinopathy. Additionally, patients with media opacities that impeded the acquisition of high-quality optical coherence tomography (OCT) scans for reliable analysis were not included.

The diagnosis of MacTel was made based on the presence of characteristic clinical features identified through biomicroscopic examination, fluorescein angiography (FA), and OCT. The presence of diabetes mellitus (DM) and hypertension was confirmed by the current use of prescribed medications.

The following data were collected: age, sex, baseline and final best corrected visual acuity (BCVA) measured using Snellen, follow-up time (months), and diagnoses of DM and hypertension. Fundus photography, FA, fundus autofluorescence (FAF), and OCT images from baseline and final visits were assessed. Snellen BCVA was converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. Fundus photographs obtained during routine clinical examinations were captured using the TRC 50DX retinal camera (Topcon, Tokyo, Japan). OCT, FAF, and FA images acquired with the Spectralis HRA system (Heidelberg Engineering, Heidelberg, Germany) were retrospectively analyzed from records.

OCT imaging was employed to evaluate structural features, including pigmentation, hyperreflectivity, the inner limiting membrane (ILM) drape sign, hyporeflective cavities, disruption of the EZ, and measurements of subfoveal choroidal thickness (SFCT) and central macular thickness. SFCT was measured using enhanced depth imaging OCT scans. SFCT was manually delineated from Bruch's membrane to the inner scleral surface beneath the fovea using Heidelberg Spectralis software. FA was employed to evaluate late leakage, while FAF images were analyzed for the presence of focal hypo-autofluorescence—indicative of pigment migration—and increased FAF signal in the foveal area.

The classification of patients with MacTel was based on the MacTel Classification System, developed by Chew et al.[3] as part of the MacTel Project. This standardized 7-grade system was applied to eyes with a confirmed diagnosis using multimodal ocular imaging, including OCT, FAF, FA, and color fundus photography. Disease severity was stratified according to key imaging biomarkers associated with decline in visual acuity, such as EZ loss, pigmentary changes, and OCT hyperreflectivity. Eyes classified as Grade 0 exhibited diagnostic features of MacTel without significant risk factors for vision loss, whereas higher grades (1–6) corresponded to increasing structural disruption and functional impairment. Furthermore, the development of full-thickness MHs and MNV was assessed using OCT, FA, and/or OCT angiography. EZ integrity was assessed using OCT with Heidelberg Eye Explorer software (Heyex, version 6.0.13.0, Heidelberg Engineering). The B-scan traversing the foveal center was selected, and EZ break length was measured in micrometers.

Statistical Analysis

Statistical analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were presented as median (interquartile range). Categorical variables were summarized as frequencies and percentages. Categorical variables were analyzed using the chi-squared or Fisher's exact test, as appropriate. Longitudinal changes in BCVA and OCT parameters were evaluated using the paired t-test for normally distributed data or the Wilcoxon signed-rank test for non-normally distributed data. A p value <0.05 was considered statistically significant.

Results

A total of 184 eyes from 94 patients were analyzed with a mean follow-up period of 79.27±50.69 months. The minimum follow-up duration was 3 years. The male-to-female ratio was 35 (37.2%) to 59 (62.8%). The mean age of the study cohort was 63.89±9.98 years. DM was present in 37 patients (39.4%) and hypertension in 30 (31.9%). Eight patients (8.51%) were identified as having mild non-proliferative diabetic retinopathy (DR). Proliferative DR was not observed in any of the patients.

The mean logMAR BCVA at presentation was 0.47±0.41. The most frequently observed clinical findings were loss of retinal transparency (91.8%) and the presence of RAVs (90.8%) (Figure 1). However, it should be noted that the assessment of retinal transparency was not discernible in a subset of patients due to confounding factors, such as the presence of MNV and pigmentary plaques. Other common clinical findings included the presence of hyporeflective retinal cavities (60.9%), the

ILM drape sign (50%), OCT hyperreflectivity (34.2%), and hyperreflective retinal pigment clumps (23.9%). In 125 of 135 eyes with available FA examinations, leakage was observed in the late stages. A total of 142 eyes were evaluated with FAF imaging. Hypofluorescence was identified in 47.18% (n=67) and hyperfluorescence in 52.82% (n=75) of these eyes.

Table 1 illustrates the classifications of patients at baseline and final visit according to the MacTel Classification System developed by Chew et al.[3] Table 2 compares the clinical and imaging findings obtained at baseline and final visit.

In the baseline examination, 155 (84.2%) of the analyzed eyes exhibited non-proliferative MacTel. Meanwhile, 29 (15.8%)

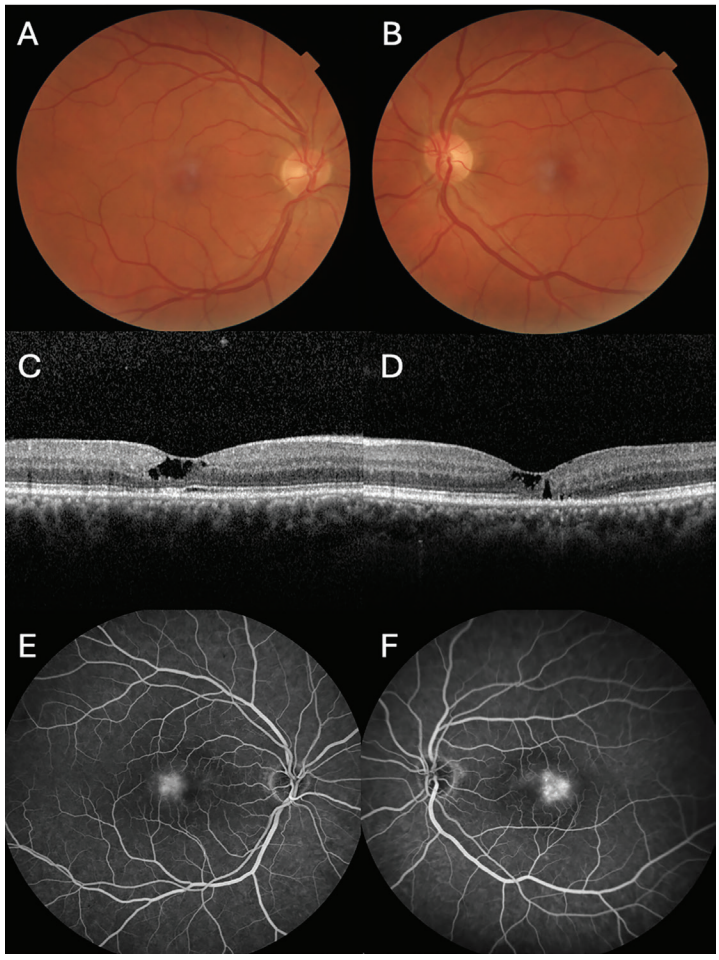

Figure 1. Fundus photographs (A, B), optical coherence tomography (OCT) images (C, D), and fluorescein angiography (E, F) of a patient with macular telangiectasia type 2. The fundus images reveal a loss of retinal transparency temporal to the fovea, accompanied by angiographic leakage. OCT images demonstrate hyporeflective cavities in both the inner and outer retina. A central hyporeflective inner retinal cavity is observed at the foveal center, with an overlying internal limiting membrane drape

Table 1. Distribution of eyes classified according to the MacTel Classification System (Chew et al.[3]) at baseline and final visits

Stage	Classification of macular telangiectasia type 2 (MacTel)	Number of eyes at baseline visit (%)	Number of eyes at final visit (%)
0	No EZ break/no pigmentation/no OCT HR	26 (14.1)	17 (9.2)
1	Non-central EZ break/no pigment/no Oct HR	30 (16.3)	10 (5.4)
2	Central EZ break/no pigment/no OCT HR	62 (33.7)	49 (26.6)
3	Non-central pigment/no, non-central or central EZ loss/no OCT HR	4 (2.2)	8 (4.3)
4	OCT HR/EZ break (either central or non-central)/no pigment	37 (20.1)	29 (15.8)
5	Central pigment/no exudative neovascularization/EZ present or not gradable	9 (4.9)	42 (22.8)
6	Neovascularization (exudative) ± central pigment	16 (8.7)	29 (15.8)

EZ: Ellipsoid zone, HR: Hyperreflectivity, OCT: Optical coherence tomography

presented with MNV, of which 18 had active MNV and 11 had scarred lesions. Of the 18 patients who underwent intravitreal anti-VEGF treatment for active MNV, 7 received bevacizumab (Avastin, Genentech, South San Francisco, CA, USA), 3 received aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, NY, USA), and 8 received ranibizumab (Lucentis, Novartis, Basel, Switzerland). The mean number of injections administered was 5.89±3.72; the mean follow-up period of these patients was 129.17±56.48 months. A comparison of baseline and post-injection visual acuity in the 18 treated patients revealed a statistically significant improvement in BCVA following intervention (baseline: 0.80±0.39; post-injection: 0.61±0.35; p<0.001). However, no significant difference was observed between baseline and final BCVA at the end of the follow-up period (baseline: 0.80±0.39; final: 0.94±0.58; p=0.213).

MH formation was observed in 8 patients during the follow-up period. Surgery was not performed in 2 patients, as visual improvement was deemed unlikely due to the presence of scarring. The characteristics, surgical procedures, and postoperative outcomes of the 6 patients who underwent surgery are presented in Table 3. Following surgery, MH closure was achieved in all patients, with improved BCVA observed in 5 patients. However, at the final follow-up visits, a decline in visual acuity was noted due to progression associated with MacTel. A representative case is presented in Figure 2.

Discussion

The present study presents a large cohort with extended follow-up durations, utilizing a multimodal imaging-based classification to assess MacTel type 2. A significant decline in BCVA was observed in the overall cohort between the baseline and final visits (p<0.001). MNV was present in 15.8% of patients, and notably, MH formation developed in 8 eyes of 8 patients (4.3%) during the follow-up period.

The proposed classification system for MacTel developed by Chew et al.[3] offers several significant advantages over previous models through the incorporation of objective, image-based criteria that directly correlate with disease progression and visual acuity loss. Utilizing SD-OCT findings such as EZ discontinuity, hyperpigmentation, and OCT hyperreflectivity, the system provides a reproducible and quantifiable method for staging. In contrast to the Gass-Blodi classification,[7] which relies primarily on vascular features, the current model emphasizes structural retinal changes that have a direct impact on visual acuity, providing increased clinical relevance. The simplified grading scale further facilitates practical use in routine ophthalmic examinations, enabling earlier detection and more accurate prognostication.[3] Its adoption in recent studies underscores its growing recognition and clinical applicability.[2,8,9]

As demonstrated by Chew et al.[3], the central EZ break is a critical factor contributing to reduced visual acuity. In the present study, 30.4% of patients were classified as stage 0 or 1,

Table 2. Comparison of optical coherence tomography findings and best-corrected visual acuity at baseline and final visits

	Baseline visit	Final visit	p value
Mean logMAR visual acuity (Snellen equivalent)	0.47±0.41	0.64±0.48	**<0.001***
Central macular thickness (μm)	247.93±36.84	243.16±54.66	0.193*
Subfoveal choroidal thickness (μm)	294.84±61.64	290.97±64.44	0.298*
Ellipsoid zone break length (μm)	1087.06±873.35	1514.53±1015.64	**<0.001***
Pigmentation (n, %)	44 (23.9%)	96 (52.2%)	**<0.001¶**
Hyperreflective retinal dots (n, %)	63 (34.2%)	93 (50.5%)	**<0.001¶**
Hyporeflective retinal cavities (n, %)	112 (60.9%)	93 (50.5%)	**<0.001¶**

*Paired t-test, ¶Fisher's exact test, logMAR: Logarithm of the minimum angle of resolution

Table 3. Patient characteristics, surgical procedures, and postoperative outcomes for macular holes associated with macular telangiectasia type 2

Patient ID	Age	Sex	Preop BCVA (logMAR)	Surgery	Postop BCVA (logMAR)	Final BCVA (logMAR)	Final outcome	Follow-up time (months)
1	60	M	0.69	Free ILM patch graft	0.39	1.00	Closed	36
2	80	F	1.00	Temporal inverted ILM flap	0.69	0.69	Closed	42
3	84	F	1.30	Free ILM patch graft	0.69	1.00	Closed	47
4	74	M	0.69	ILM peeling	0.52	0.79	Closed	82
5	62	F	0.52	Free ILM patch graft	0.22	0.22	Closed	180
6	67	F	0.52	Temporal inverted ILM flap	0.52	1.30	Closed	45

F: Female, M: Male, BCVA: Best corrected visual acuity, ILM: Internal limiting membrane, logMAR: Logarithm of the minimum angle of resolution

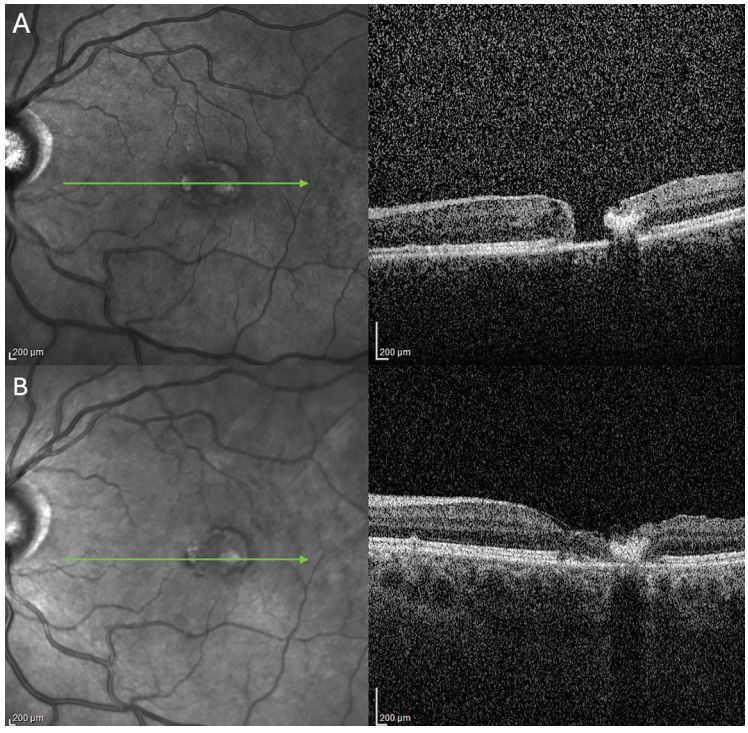

Figure 2. Optical coherence tomography (OCT) images of a macular hole associated with macular telangiectasia type 2. A) Preoperative OCT shows a full-thickness macular hole. B) Postoperative OCT at 6 months following pars plana vitrectomy with a free internal limiting membrane patch graft, demonstrating anatomical closure of the hole

characterized by the absence of central EZ break. Meanwhile, 33.7% of patients were categorized as stage 2, signifying the onset of damage to the central EZ. This distribution suggests that a significant proportion of patients sought medical consultation following the onset of visual impairment. At the final follow-up examination, 14.6% of patients remained in the early stages (stages 0 and 1), while 38.6% had progressed to advanced stages (stages 5 and 6), which are strongly associated with severe visual loss.[3]

Recent studies have reported a high prevalence of DM among patients with MacTel.[10] In our cohort, DM was identified in 37 patients (39.4%). Additionally, mild, non-proliferative DR was observed in 8 patients (8.51%), while no cases of proliferative DR were detected. Similarly, van Romunde et al.[10] reported DM in 50 patients (49%) in their MacTel sample, with mild DR observed in 22 eyes (11%). Notably, no cases of severe or proliferative DR were identified in their cohort. Sauer et al.[11] also found the rate of diabetic patients to be 35%. While previous studies have reported similar incidences, it remains unclear whether this association is coincidental or influenced by lead-time bias from routine ophthalmic screening in diabetic patients. The MacTel Project 3 addressed this issue by including age-matched controls and confirmed a significantly higher prevalence of DM among MacTel patients. Despite potential biases, current evidence increasingly supports a relationship between DM and MacTel.[10,12]

The most common clinical findings in this cohort were loss of retinal transparency (91.8%) and the presence of RAVs (90.8%). Müller cells are essential for preserving the blood-retinal barrier and providing trophic support to surrounding neurons. As these cells envelop neurons, supply nutrients, and maintain close interactions with retinal blood vessels in the outer plexiform layer, the neurodegenerative theory of MacTel proposes their dysfunction as a key factor. The resulting nutritional deprivation may play a significant role in the loss of retinal transparency frequently observed in MacTel.[13]

According to the Gass and Blodi[7] clinical staging system, the presence of RAVs in fundoscopy is associated with advanced MacTel (stages 3-5). However, this classification relies exclusively on morphological findings from fundoscopy and FA, without incorporating insights from advanced imaging techniques such as OCT or OCT angiography. Tzaridis et al.[14] demonstrated that multimodal imaging, particularly OCT angiography, has the capacity to detect vessels exhibiting RAV characteristics at earlier stages (1-2), thus suggesting that vascular abnormalities may manifest earlier than previously thought. Their findings also highlight the value of advanced imaging in the early detection and understanding of MacTel progression.[14] In contrast, Chung et al.[15] associated inner retinal disorganization, outer retinal cavities, and EZ disruption on OCT with the presence of RAVs, indicating a more advanced disease stage. Chandran et al.[16] further showed that multicolor imaging, particularly green

reflectance, has higher sensitivity and negative predictive value in detecting RAVs compared to traditional imaging. The authors noted that Chung et al.'s[15] reliance on fundus photography and FA may have limited early-stage detection.[16] In line with the data discussed above, RAV was one of the most common findings in our study.

Krivosic et al.[17] reported the incidence of MNV in MacTel patients to be 14%. In the present study, 29 eyes (15.8%) exhibited MNV, of which 18 had active MNV and 11 had scarred lesions in the baseline examination. Anti-VEGF injections have been reported as beneficial for short-term treatment of secondary MNV associated with MacTel. However, there is a lack of conclusive data regarding their long-term efficacy and outcomes.[5,18,19] Although we observed early improvement in visual acuity following treatment, no significant gain in BCVA was noted after approximately 10 years of follow-up, likely reflecting the progressive neurodegenerative course of the disease. Overall, our findings suggest that anti-VEGF therapy provides short-term visual benefit and may help mitigate vision loss due to MNV over the long term.

MacTel-associated MHs are rare, and their surgical management remains controversial due to inconsistent functional outcomes despite high anatomical success. In our study, MH formation occurred in eight patients, six of whom underwent surgery. Notably, MH closure was achieved in all surgically treated cases, and five patients demonstrated initial BCVA improvement. However, the long-term outcomes were adversely affected by disease progression, as indicated by a decline in BCVA at the final follow-up (ranging from 36 to 180 months). These findings are in line with previous reports indicating that ILM techniques, including inverted and free flaps, achieve high closure rates but offer limited and often inconsistent visual recovery. Our data showed that surgery achieved anatomical closure, but visual acuity improvements were not sustained, likely due to the progression of MacTel.[6,20,21]

Study Limitations

A notable limitation of this study is its retrospective design, which inherently limits the ability to control for confounding variables. In addition, due to the rarity of MacTel-associated MHs and MNV, our study includes a relatively small number of patients who underwent surgery or injection treatments. Nonetheless, this study provides significant contributions through its use of a modern, imaging-based classification that links structural changes to functional outcomes. This framework enhances clinical decision-making and supports future research into the pathophysiology of the disease and potential therapeutic interventions. With its large cohort and long follow-up period, the study also offers valuable data on secondary complications and their management, offering insight into the long-term outcomes of therapeutic interventions in MacTel.

Conclusion

While MacTel is a slow-progressing disease, only 15% of patients remain in the early stage with minimal visual loss. However, 70% of patients seek medical consultation during the later stages, which is characterized by significant visual loss. The frequent co-occurrence of DM underscores the importance of systemic evaluation in these patients. Early diagnosis, along with timely management of complications, may help delay further visual decline and improve long-term outcomes.

Ethics

Ethics Committee Approval: Ethics Committee of Hamidiye Scientific Research, University of Health Sciences (approval number 12/4, date: 17.10.2024).

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

Surgical and Medical Practices: M.Ö., Ö.A., M.Ş., Concept: M.Ö., Design: Ö.A., M.Ş., Data Collection or Processing: M.Ö., R.K., İ.H., Analysis or Interpretation: Ö.A., R.K., İ.H., Literature Search: M.Ö., Ö.A., R.K., İ.H., M.Ş., Writing: M.Ö.

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Original Article

Effect of Ranibizumab in Patients with Treatment-Naïve Retinopathy of Prematurity

Hina Khalid[1], Tayyaba Gul Malik[1], Arooj Amjad[1], Iqra Khalid[1], Shahid Muhammad[2]

[1]Post-Graduate Medical Institute/Lahore General Hospital, Clinic of Ophthalmology, Lahore, Pakistan
[2]Post-Graduate Medical Institute/Lahore General Hospital, Clinic of Pediatric, Lahore, Pakistan

Abstract

Objectives: To determine the effect of intravitreal ranibizumab (IVR) in patients with treatment-naïve retinopathy of prematurity (ROP) in terms of disease regression and need for rescue therapy.

Materials and Methods: This study evaluated disease regression and rescue therapy requirement in treatment-naïve ROP cases treated with IVR. Among 188 screened patients, 80 had ROP. Thirty-eight patients (76 eyes) with type 1 ROP and aggressive ROP (AROP) were included. Treatment involved a single dose of 0.2 mg ranibizumab injected under aseptic conditions. Patients were monitored post-treatment for up to 6 months. Recurrence of disease was managed with argon laser photocoagulation targeting the peripheral avascular retina. Data analysis utilized t-tests for continuous variables and χ^2 tests for categorical data, with a significance threshold of $p<0.05$.

Results: The study included 19 males and 19 females, with 56 eyes having AROP and 20 eyes with type 1 ROP. All AROP cases required rescue therapy, with a mean interval of 3.43±0.84 weeks between treatments. Sixty percent of type 1 ROP eyes also needed laser therapy. While type 1 ROP cases had slightly higher gestational age and lower birth weight compared to AROP, these differences were not statistically significant ($p=0.081$ and $p=0.27$, respectively). However, the interval between treatments was significantly longer in type 1 ROP than in AROP ($p=0.0016$).

Conclusion: Ranibizumab demonstrated effectiveness in initial disease regression but was linked to reactivation in all AROP and 60% of type 1 ROP cases, highlighting the importance of more frequent follow-ups after ranibizumab injection, particularly for AROP patients.

Keywords: Ranibizumab, retinopathy of prematurity, bevacizumab, anti-vascular endothelial growth factor

Introduction

The foundation for using intravitreal bevacizumab in the treatment of retinopathy of prematurity (ROP) was established by the "Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity" (BEAT-ROP) trial.[1] More recent evidence on the use of intravitreal ranibizumab (IVR) comes from the "Ranibizumab Compared with Laser Therapy for the Treatment of Infants Born Prematurely With Retinopathy of Prematurity" trial.[2] In 2019, ranibizumab was approved by the European Medicines Agency at a dose of 0.20 mg for the treatment of ROP. Since then, the treatment approach has continued to evolve due to the varying disease patterns observed across different regions worldwide. Literature indicates that anti-vascular endothelial growth factor (anti-VEGF) treatment tends to result in recurrence.[3] Additionally, in developing countries, ROP has been reported in infants with higher birth weights and gestational ages (GA), highlighting disease patterns that differ from those in the developed world.[4] This underscores the need for data from these regions to better understand how the disease responds to treatment in these areas. This study aimed to evaluate the efficacy of IVR in treatment-naïve ROP patients from a tertiary care center in a developing Southeast Asian country.

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Address for Correspondence: Tayyaba Gul Malik, Post-Graduate Medical Institute/Lahore General Hospital, Clinic of Ophthalmology, Lahore, Pakistan
E-mail: tayyabam@yahoo.com **ORCID-ID:** orcid.org/0000-0003-1040-7114
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Materials and Methods

This quasi-experimental study was conducted in the ophthalmology department of Lahore General Hospital from July to December 2024. Ethical approval was obtained from the Lahore General Hospital Review Board (IRB number: LGH/297/24, dated: 09.07.2024). The study strictly followed the Declaration of Helsinki, and verbal informed consent was obtained from the parents of all patients before examination and at the start of examination and treatment. Of 188 preterm infants screened during the study period, 80 infants had ROP. For preterm infants born at or before 32 weeks of gestation, oxygen concentration was kept between 91% and 95%.

Based on an ROP prevalence of 27% among preterm infants in a local study,[5] an 80% confidence interval, and 5% margin of error, the required sample size was determined using the formula $n=Z^2\ p\cdot(1-p)/d^2$, where Z = Z-score corresponding to the desired confidence level (for 80% confidence, Z=1.28), p = Estimated prevalence (27% or 0.27), and d = Margin of error (5% or 0.05). According to the result of this calculation, the minimum number of infants to screen was 129.

We screened 188 infants to address dropouts. Out of these, 80 infants were diagnosed with ROP. Screening was conducted following the Pakistan Retinopathy of Prematurity Education and Research Alliance protocols, which include all premature infants born at ≤35 weeks of GA or weight ≤2000 grams. Disease staging was performed using an indirect ophthalmoscope with a 20 D lens and RetCam. Dilating drops were prepared by mixing 0.5 cc of 10% phenylephrine (Mediphrine, Medipak, Pakistan), 1 cc of 1% cyclopentolate (Cyclopen, Ethical, Pakistan), and 3.5 cc of artificial tears (Tears Plus, Allergan, Pakistan). Type 1 ROP was defined as:

- Zone I: any stage ROP with plus disease
- Zone I: stage 3 ROP without plus disease
- Zone II: stage 2 or 3 ROP with plus disease

Treatment-naïve preterm infants with type 1 ROP or aggressive posterior ROP (AROP) defined were included. AROP was defined according to the International Classification of ROP 3rd edition (ICROP3).[6]

Patients with systemic disease, sepsis, and unstable respiratory status were excluded. All patients with type 1 ROP or AROP received IVR within 72 hours of the diagnosis. Strict aseptic protocols were followed in a standard ophthalmic operating room. A drop of 5% of povidone-iodine (Pyodine, Brookes Pharmaceutical Labs [Pvt] Ltd, Pakistan) was instilled in the conjunctival sac. The eye was stabilized using toothed forceps, and the injection was administered 1.5 mm posterior to the limbus, while carefully avoiding injury to the lens. A dose of 0.2 mg/0.02 mL ranibizumab (Patizra, Novartis Pharmaceuticals) was injected. After the injection, a moxifloxacin antibiotic eye drop (Vigamox, Alcon, Pakistan) was instilled and the speculum was removed. Moxifloxacin eye drops (Vigamox) were prescribed four times a day for 5 days. Indirect ophthalmoscopy was performed to assess the perfusion of the central retinal artery and to check for iatrogenic retinal tears or vitreous hemorrhage. Patients were followed up on day 1 post-treatment and subsequently at weekly intervals, depending on their response, for up to 6 months.

The primary outcome measures included disease regression with resolution of neo-vessels and disappearance of the ridge; recurrence of ROP; and any associated complications. Regression and reactivation were defined as per ICROP3.[6] Regression was considered when the disease showed signs of involution and resolution, whereas reactivation was defined as recurrence of the features of acute phase.

The criteria for rescue therapy were:

- New vessels at the junction of vascularized and avascular retina, or in the vitreous.
- Vascular dilation and tortuosity of the posterior pole vessels.
- Fibrous tissue growth, often at the border of vascular and avascular retina.
- Localized traction due to new fibrovascular proliferation.
- A large area of the peripheral retina remains avascular and ischemic.

In cases of disease reactivation, argon laser photocoagulation to the peripheral avascular retina was performed as secondary treatment.

Statistical Analysis

Data collection was conducted using RetCam software, an Excel spreadsheet, and a form designed specifically for this study. Variables with a normal distribution were analyzed using t-tests, while categorical variables were assessed using chi-square tests. Quantitative data was evaluated in terms of percentages and frequencies, with a p value of <0.05 considered statistically significant.

Results

During the study period, 188 patients were screened and 80 infants had ROP. Among these, 28 infants (56 eyes) had AROP and 10 (20 eyes) had type 1 ROP (total 76 eyes). There were 19 males and 19 females. The mean GA was 31.56±2.64 weeks (range, 20-37). Mean birth weight was 1487.85±394.75 g (range, 700-2500) and the first injection was given at a mean GA of 36.86+2.5 weeks (range, 29-41). Rescue therapy was given at 41.41±2.79 weeks (range, 32-46).

Laser treatment was performed as rescue therapy in eyes with incomplete regression after IVR. All patients with AROP needed rescue therapy, with a mean interval between the two therapies of 3.43±0.84 weeks (range, 2-6). Sixty percent of eyes with type 1 ROP also required rescue therapy. Figure 1 shows regression of AROP 4 weeks after IVR. Figures 2 and 3 show premature infants with type 1 ROP. Clinical and treatment details are given in Table 1.

A comparison between the eyes with AROP and type 1 ROP revealed a slightly higher average GA in the type 1 ROP group, but the difference was not statistically significant (p=0.081). Similarly, the average birth weight was slightly lower in the type 1 ROP group, but not significantly (p=0.27). Notably, the interval between the two therapies was significantly longer in the type 1 ROP cases compared to the AROP group (p=0.0016).

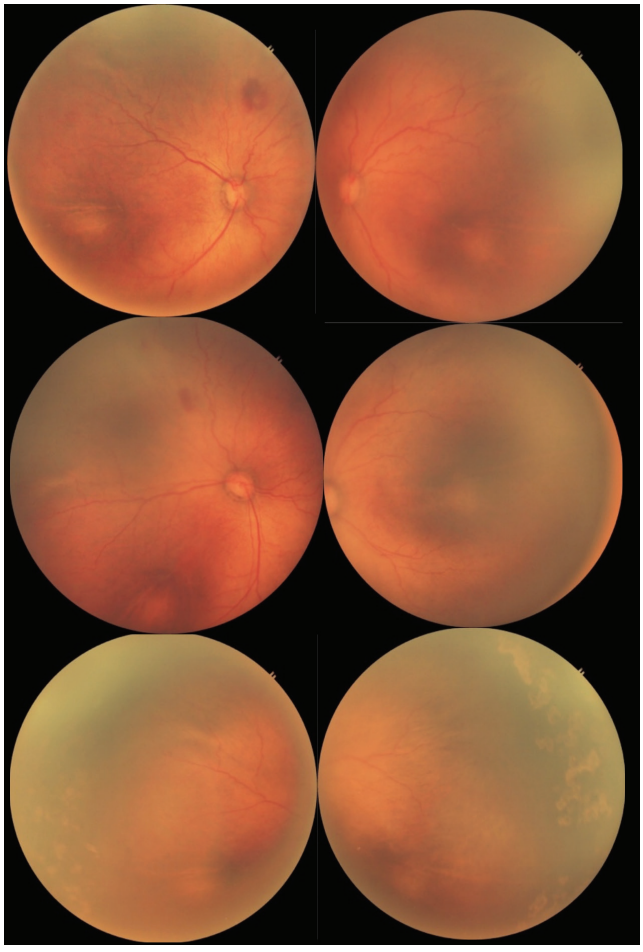

Figure 1. Top, first visit of an infant born at 32 weeks of gestation and 1200 grams, showing aggressive retinopathy of prematurity. Middle, image enhancement. Bottom, regression 4 weeks after intravitreal ranibizumab in both eyes

Discussion

Our results demonstrated that patients receiving IVR for ROP required rescue therapy in 100% of AROP cases and 60% of type 1 ROP cases. These findings are consistent with the previous literature, which highlights disease reactivation as a common occurrence. For instance, Stahl et al.[3] reported late reactivation in 14% of infants treated with two initial injections.

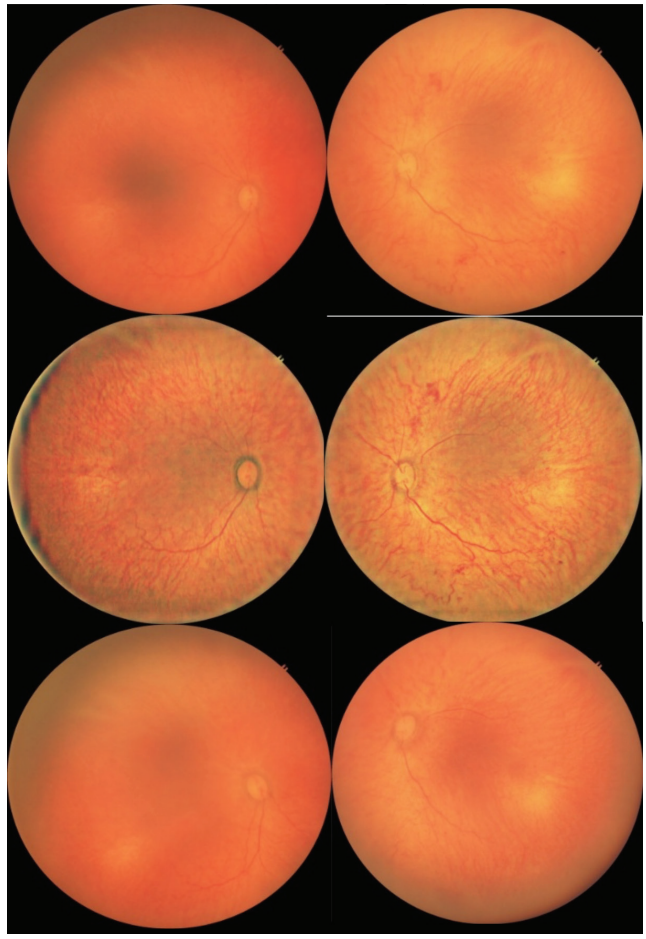

Figure 2. Top, first visit of a premature infant born at 1100 grams and 27 weeks of gestation, exhibiting zone 2, stage 3 with plus disease. Middle, incomplete regression after intravitreal ranibizumab. Bottom, appearance after laser treatment for reactivation

Table 1. Comparison of clinical and treatment characteristics between patients with AROP and type 1 ROP

Parameter	AROP (n=56) (range)	Type 1 ROP (n=20) (range)	p value
Mean gestational age (GA) at birth, weeks	30.71±3.57 (20-34)	32.4±1.71 (30-37)	0.081
Mean birth weight, grams	1535.7±433 (700-2500)	1440±356.5 (1000-2000)	0.27
Mean GA at first injection, weeks	35.71±2.84 (29-39)	38±2.2 (36-41)	0.014*
Mean GA at rescue therapy, weeks	39.14±2.69 (32-41)	43.67±2.88 (40-46)	0.0004*
Mean interval between initial and rescue therapy, weeks	3.43±0.84 (2-4)	4.67±1.03 (4-6)	0.0016*
Percentage of eyes requiring laser	100%	60%	0.0033*

*p<0.05, ROP: Retinopathy of prematurity, AROP: Aggressive retinopathy of prematurity

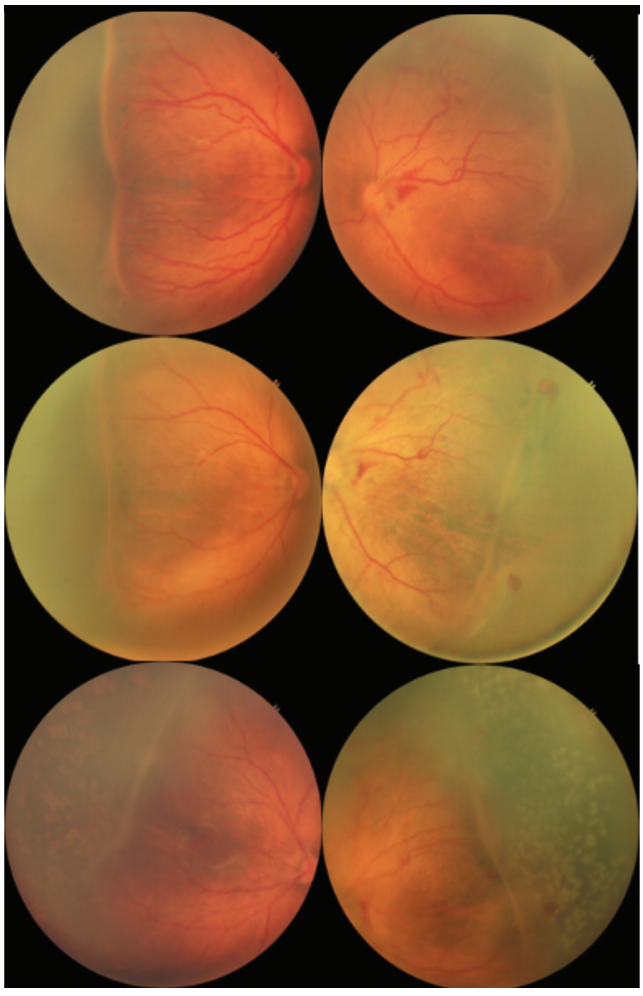

Figure 3. Infant with birth weight of 1800 grams and gestational age of 29 weeks, exhibiting zone 2 posterior, stage 3 disease. Top, before intravitreal ranibizumab injection. Middle, post-injection. Bottom, appearance after laser treatment to the avascular retina due to incomplete regression

Disease regression was observed by week 5 post-injection, but reactivation occurred at week 6, necessitating re-treatment. After subsequent treatments, the disease remained inactive for 8 weeks but reactivated again at week 10. A third injection administered 17 weeks after the initial injection showed slower regression, although the treated eyes displayed no signs of ROP. In contrast, our patients showed initial regression for 3.43±0.84 weeks in AROP and 4.67±1.03 weeks in type 1 ROP. After that we had to opt for rescue therapy in the form of laser photocoagulation. As the disease reactivated within a few weeks, we avoided a second injection owing to the systemic absorption of ranibizumab, which could result in cumulative systemic effects.

The management of ROP has evolved significantly with the advent of anti-VEGF therapies, which offer targeted regression of abnormal vascular proliferation. In this case, IVR has demonstrated substantial efficacy in inducing initial regression of ROP, with studies reporting regression rates exceeding 75% in treated eyes. In our study the initial regression was seen in all patients, but the effect was not long lasting. Thus, we find that recurrence remains a notable concern. While some studies observed recurrence rates as high as 41.5%, others, like Bassiouny et al.[7], reported a significantly lower recurrence rate of 2.3%. The variability in recurrence rates can be attributed to differences in inclusion criteria, dosage, and follow-up protocols. For example, Wong et al.[8] found that recurrence with IVR typically occurred between 41 and 42 weeks of postmenstrual age (PMA), emphasizing the need for vigilant follow-up during this critical period.

A retrospective review by Sahinoglu-Keskek et al.[9] analyzed 15 eyes of 8 premature infants with AROP treated initially with IVR. Reactivation occurred at a median of 5 weeks post-injection, and only two eyes required a second IVR injection. These findings align with our study, which highlighted shorter reactivation intervals in AROP. However, laser photocoagulation for recurrence provided favorable outcomes in our cases.

Extended follow-up is needed after IVR as late recurrence is shown up to 35 weeks after anti-VEGF injection or 69 weeks PMA.[10,11] Longer follow-up is particularly crucial in high-risk cases, such as those with zone I ROP, low Apgar scores, and multiple births.

Our cases of AROP had 100% recurrence. However, Ling et al.[12] reported a recurrence rate of 20.8% in the IVR group and an 8.3±1.6-week mean interval to recurrence.

With the advent of new anti-VEGF drugs, comparative studies of different anti-VEGF indicate that conbercept and ranibizumab are both effective for treating ROP, but conbercept is associated with less recurrence and longer intervals between treatments.[13] On the other hand, in a multicenter prospective trial, recurrence rates were similar between conbercept (16.67%) and ranibizumab (23.34%).[14] However, the interval to reactivation was longer than in our cohort.

Initial regression was seen in all patients in our study. However, Xu et al.[15] reported a failure rate of 11%, with management involving repeat injections, laser therapy, vitrectomy, or combinations thereof. The most common manifestations of treatment failure included recurrent plus disease and stage 3 ROP. Aflibercept has demonstrated longer efficacy with lower recurrence rates than ranibizumab, as observed in studies by Süren et al.[16] and Lee et al.[17] Bevacizumab, with its longer half-life, also showed a lower recurrence rate but raised concerns about systemic side effects.

Recent studies emphasize the need for individualized treatment strategies based on the initial therapy used.[18,19] While IVR is favored for its refractive benefits and anatomical outcomes, repeated use for recurrence should be carefully weighed against the risks of systemic VEGF suppression.

With so many options currently available, the choice of agent often depends on disease severity, the retinal zone involved, and individual patient risk factors. Some studies have compared different doses of IVR in terms of need of re-treatment. Ahmed et al.[20] used low-dose IVR and showed promising results, with complete retinal vascularization and no need for retreatment, though further large-scale studies are required to validate its efficacy and safety.

Although complication rates are higher in laser therapy due to peripheral retinal ablation, the interval between treatment and retreatment is significantly longer than with anti-VEGF agents.[21] On the other hand, the faster action of anti-VEGF agents compared to laser therapy makes them preferable for aggressive cases, especially before 36 weeks of PMA, when laser therapy is associated with higher short-term retinal detachment rates.[22] Higher reactivation risks have been associated with early PMA at treatment and with AROP.[8,23] This holds true to some extent in our study, as patients with AROP had lower GA compared to those with type 1 ROP. Similarly, multivariate analyses identified PMA ≤35 weeks at anti-VEGF therapy and AROP as significant predictors of reactivation.[24]

Optimal timing for adding laser therapy in conjunction with anti-VEGF treatment remains a topic of debate. Kim et al.[25] reported using an 810-nm diode laser within 0 to 8 days post-injection (median 3 days) and observed good outcomes. Others opting for laser intervention in cases of recurrence performed the procedure between 4 and 14 weeks post-injection.[26]

Determining the ideal interval between injection and laser is complex, influenced by factors such as the disease's response to the drug, recurrence patterns, vascular growth into the retina beyond zone 1, infant weight, PMA, systemic conditions, and follow-up compliance. This challenge is particularly pronounced in rural settings, where follow-up compliance can be limited.

Although laser therapy or repeat anti-VEGF injections are valid options, the rationale for delaying laser ablation after anti-VEGF treatment is to allow vascularization to extend beyond the critical zone 1 region. In some cases, vascular growth progresses into more peripheral zones before halting, recurring, or worsening. In our study, we applied laser to the peripheral retina after 4 weeks and spread the laser sessions over multiple visits to allow normal vessels to grow as far as possible.

In a study by Parchand et al.[27], infants with posterior zone I ROP were treated with immediate IVR and zone I-sparing laser ablation at 4 weeks. Combined IVR and zone I-sparing laser ablation were effective in these cases.

Gangwe et al.[28] compared early versus deferred laser therapy in infants with AROP initially treated with IVR. Early laser was performed at 1 week (Group 1), while deferred laser was applied at 6 weeks or earlier if recurrence occurred (Group 2). Structural outcomes were comparable between groups, but deferred laser required fewer spots. In severe cases like AROP, combining IVR with laser therapy has shown promising outcomes. Studies by Kim et al.[25] and Dudani et al.[29] reported successful regression of fibrovascular proliferation and reduced recurrence with this combined approach. However, the timing of laser therapy post-IVR remains critical, as delayed intervention may result in unfavorable outcomes.

One of the benefits of repeated injections is complete vascularization of the retina, which cannot be achieved with laser therapy as described by Xia et al.[30] They found that 54.3% of patients achieved complete vascularization after repeated injections, with GA over 29 weeks being a significant predictor of complete vascularization.

The shorter systemic half-life of ranibizumab compared to other anti-VEGF agents, such as bevacizumab, contributes to its higher recurrence rate. Despite this, IVR's effectiveness in achieving complete retinal vascularization after subsequent injections underscores its utility as a primary and secondary treatment modality.

A significant challenge in ROP management is addressing persistent avascular retina (PAR), a condition observed in 22-38% of eyes treated with anti-VEGF therapy. PAR poses long-term risks, including retinal detachment and vascular abnormalities. Thus, long-term follow-up is imperative for infants treated with IVR to monitor for late recurrences and vascular changes.

Study Limitations

This study highlights the clinical outcomes, challenges, and therapeutic strategies associated with IVR in ROP treatment, supported by evidence from various other studies. The limitations include a short follow-up, which does not address long-term outcomes and the possibility of delayed reactivation of the disease beyond six months. Considering the systemic absorption of the drug, only a single injection was given in this study, and rescue therapy consisted of laser therapy instead of repeat IVR. Lack of a control group and patients from a single center limits the study's generalizability to different populations or healthcare settings. These limitations suggest that while ranibizumab may show promise for initial disease regression in ROP, further research with larger, more diverse populations and longer follow-up periods would be required to establish its long-term effectiveness and safety in treating ROP.

Conclusion

IVR offers a powerful option for managing ROP, particularly in zone I disease and AROP. Despite challenges like recurrence and PAR, its benefits in terms of anatomical outcomes make it a cornerstone in ROP treatment. Continued advancements in anti-VEGF therapies and combination strategies hold promise for improving outcomes in this vulnerable population.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Lahore General Hospital Review Board (IRB number: LGH/297/24, dated: 09.07.2024).

Informed Consent: Informed consent was obtained from the parents of all patients before examination and at the start of examination and treatment.

Declarations

Authorship Contributions

Surgical and Medical Practices: H.K., T.G.M., A.A., I.K., S.M., Concept: H.K., T.G.M., A.A., I.K., S.M., Design: H.K., T.G.M., Data Collection or Processing: H.K., T.G.M., A.A., I.K., S.M., Analysis or Interpretation: H.K., T.G.M., Literature Search: H.K., T.G.M., Writing: T.G.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Adalimumab in Focus: Evaluating Effectiveness and Safety in Non-Infectious Uveitis at a Tertiary Referral Center in Türkiye

Berru Yargı Özkoçak[1], Çiğdem Altan[1], Burcu Kemer Atik[1], Berna Başarır[2]

[1]University of Health Sciences Türkiye, Beyoğlu Eye Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[2]Eye Protection Foundation, Bayrampaşa Eye Hospital, İstanbul, Türkiye

Abstract

Objectives: To evaluate the indications, efficacy, and safety of adalimumab (ADA) in treating active non-infectious uveitis (NIU) in the Turkish population in a real-world setting.

Materials and Methods: This retrospective observational study included patients diagnosed with NIU treated with ADA on-label. The study assessed the impact of ADA treatment on best corrected visual acuity (BCVA), number of immunosuppressive therapies (IST), immunosuppressive drug load, and the frequency of required local treatment. BCVA was monitored at baseline and subsequent months to determine the onset of functional efficiency of ADA treatment.

Results: A total of 289 eyes of 146 patients (60 females, 86 males) diagnosed with NIU and treated according to the ADA protocol were included in the study. The mean age was 37.6±14.4 years (range, 4-73) and the median follow-up was 30 months (interquartile range, 18-57). The most common indication for ADA was panuveitis, with a diagnosis of Behçet's uveitis. The use of ADA reduced the number of IST, immunosuppressive drug load, and need for local treatment ($p<0.001$, 0.002, and <0.001, respectively). Corticosteroids could be discontinued in all but one patient. Following ADA, a significant improvement in BCVA was observed from the first month ($p<0.001$ for baseline vs. month 1) and stabilization occurred after the sixth month ($p=0.751$ for month 6 vs. 12). Side effects were reported by 55.2% of patients during IST, while only 8 patients (5.5%) experienced ADA-related side effects. At the end of the follow-up period, 8.9% of patients switched to a weekly dosing schedule. Patients who switched to a weekly regimen required more local treatment before and after ADA treatment ($p=0.02$ and 0.001, respectively), and the number of concomitant IST and drug load were higher during standard-dose ADA use ($p<0.001$ and $p=0.025$, respectively).

Conclusion: This study, the largest single-center investigation in Türkiye, reveals ADA to be a safe option with functional benefits across diverse indications and age ranges. Notably, ADA minimizes reliance on additional therapies.

Keywords: Adalimumab, Behçet uveitis, immunosuppressive drug load, non-infectious uveitis, TNF-α antagonist

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Address for Correspondence: Berru Yargı Özkoçak, University of Health Sciences Türkiye, Beyoğlu Eye Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
E-mail: byargi@hotmail.com **ORCID-ID:** orcid.org/0000-0002-6801-6178
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Introduction

Non-infectious uveitis (NIU) can be a significant cause of visual impairment. It accounts for approximately 70% of all uveitis and is the most common etiology of uveitis in the Turkish population.[1,2] This condition often affects individuals during their most productive years, leading to profound personal, social, and economic consequences.[3]

The current treatment algorithm for NIU is in the form of "step-ladder treatment".[4,5] Nevertheless, immunosuppressive therapies (ISTs) sometimes fail to control inflammation without increasing corticosteroids (CS) in resistant cases, or severe side effects limit the use of IST.[6] There is also a significant economic burden from the increasing number of drugs used.[7] Therefore, biologics may provide a targeted, relatively safe, and effective option for the management of NIU.[8,9]

Tumor necrosis factor-alpha (TNF-α) is a potent pro-inflammatory cytokine.[10] TNF-α antagonist monoclonal antibodies are effective in treating uveitis.[9,11,12] TNF-α inhibitors have become the first-line treatment for many inflammatory diseases, including NIU.[8,13,14] The efficacy of adalimumab (ADA) treatment has been demonstrated in the literature on NIU treatment.[15,16,17,18] Authorized for the treatment of NIU by the U.S. Food and Drug Administration in 2016, ADA is

the only TNF-α antagonist monoclonal antibody approved for this purpose (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125057s410lbl.pdf). ADA has been officially approved for NIU treatment in Türkiye since 2018. Positive outcomes of ADA treatment for different autoimmune diseases, including NIU, have been reported in Türkiye.[19,20,21]

The main objective of this study was to present our experience with ADA in patients with active NIU and to analyze the indications, long-term efficacy, and safety of ADA in the Turkish population.

Materials and Methods

Study Design and Patient Population

This retrospective observational study was conducted at a tertiary referral uveitis center. Consecutive patients diagnosed with NIU who received ADA (Humira®; AbbVie, Chicago, IL, USA) treatment for at least 6 months between October 2018 and March 2023 were included. The inclusion/exclusion criteria are presented in Supplementary Information S1.

The study was performed with ethics approval obtained from the Ethics Committee of the University of Health Sciences Türkiye, Hamidiye Scientific Research (decision number: 7/24, date: April 07, 2023) and complied with the tenets of the Declaration of Helsinki.

Outcome Measures

Medical records were systematically analyzed for demographic characteristics, anatomical classification of uveitis, etiology of uveitis, complete ocular examination findings, best corrected visual acuity (BCVA), tuberculin skin test (purified protein derivative [PPD]) and/or interferon-γ test (QuantiFERON) results, isoniazid (INH) prophylaxis status, duration of disease before ADA, number of medications used and immunosuppressive drug load at the time of ADA indication and concomitant with ADA, duration of standard-dose ADA usage, ADA-related adverse events, and reason for ADA discontinuation if applicable.

BCVA was assessed at baseline (at the time of first ADA injection) and at 1, 3, 6, and 12 months after the initiation of ADA therapy. The number of ISTs, immunosuppressive drug load, and number of required periocular steroid treatments before and after ADA therapy were recorded. BCVA was assessed using the Snellen chart and converted into logarithm of the minimum angle of resolution (logMAR) for analysis. Immunosuppressive drug load was evaluated with a weighted semiquantitative scale for each medication as described previously by Nussenblatt et al.[22]

Response to ADA therapy was evaluated in all patients within a period of 3 to 6 months following the initiation of treatment. The definitions of inactive disease/non-response/recurrence and the treatment modifications made accordingly are presented in Supplementary Information S2.

The effectiveness of ADA was assessed in terms of change in BCVA, number of ISTs, immunosuppressive drug load, and the frequency of required periocular steroid due to cystoid macular edema (CME) or uncontrolled inflammation. In patients switched to weekly ADA dosing due to non-response or recurrence, the time to transition from standard to weekly dosing was recorded and the same parameters were recorded after weekly dosing.

Treatment Protocol

All patients were in the active phase. The clinic adheres to international guidelines, although the preferred treatment regimen may vary depending on the disease. ADA is the preferred first-line therapy for Behçet uveitis (BU) with vision-threatening posterior segment involvement, as recommended by the European League Against Rheumatism.[13] This is also the preferred option when a patient has a condition that limits steroid usage or a systemic condition that limits IST usage.

ADA (Humira®; AbbVie, Chicago, IL, USA) is administered by subcutaneous injection. Adult patients received 80 mg ADA as an initial dose, followed by 40 mg 1 week later and continuing with 40 mg every 2 weeks thereafter. Children weighing less than 30 kilograms were started on 20 mg ADA once every 2 weeks. As recommended by the Turkish Ministry of Health, patients were screened by a pulmonologist/infectious disease specialist and internal medicine/rheumatology specialist for serious infections, especially tuberculosis (TB) and hepatitis B, and malignancies. In terms of intermediate uveitis, neurologist approval should also be sought due to the risk of demyelination with ADA. For patients with ankylosing spondylitis, ADA was initiated with approval from the rheumatology department. According to the results of PPD/QuantiFERON and pulmonologist's consultation, INH prophylaxis or anti-TB therapy (ATT) was started. INH was initiated at least 4 weeks prior to ADA and maintained for 9 months. Nevertheless, INH prophylaxis was initiated concurrently with ADA in a subset of patients with the authorization of the infectious diseases department, taking into account the patient's clinical status.

If ADA was initiated as first-line therapy, oral or intravenous steroid and at least one IST was also initiated concomitantly with ADA. If ADA was preferred as a second-line treatment, ADA was added to the existing IST regimen. Following the addition of ADA, other treatment agents are adjusted based on the patient's clinical condition.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics for Mac version 23.0 (IBM Crop., Armonk, NY, USA). The data distribution was evaluated using the Kolmogorov-Smirnov normality test. Categorical data are presented as frequency (n) and percentage (%), and numerical variables are presented as mean ± standard deviation or median and interquartile range (IQR). The chi-square test was used to compare categorical variables. Comparisons of subgroups based on diagnoses were conducted using either the independent-samples t-test or the Mann-Whitney U test. For comparison of more than two independent variables, the Kruskal-Wallis test (non-parametric ANOVA) was used. Changes in BCVA, immunosuppressive drug load, and periocular steroid injection requirement between baseline and final follow-up were examined by paired t-test or

Wilcoxon signed-rank test. The generalized estimating equation approach was used to adjust for the pool effect between the right and left eyes of the same patient for BCVA alterations. The statistical significance level was regarded as 0.05.

Results

The medical records of 146 patients (289 eyes) treated with ADA were evaluated. Table 1 presents the baseline demographic and clinical characteristics of the whole cohort.

ADA treatment was initiated as first-line therapy in 12 patients at a standard dose every 2 weeks. The patients were diagnosed with BU (6 patients), Vogt-Koyanagi-Harada disease (VKH; 2 patients), tubulointerstitial nephritis and uveitis syndrome (2 patients), ocular sarcoidosis (1 patient), and spondyloarthropathy (SpA)-associated uveitis (1 patient).

Seventy-four (55.2%) of 134 patients who received IST before ADA reported adverse events, with azathioprine (AZA) being the most frequently reported. Table 2 summarizes the side effects of ISTs used before ADA.

According to PPD/QuantiFERON results, latent TB was detected in 77 patients and INH prophylaxis was initiated as recommended in the Tuberculosis Diagnosis and Treatment Guideline of Türkiye. Additionally, 3 patients received quadruple ATT before ADA treatment. Two patients were diagnosed with TB-related uveitis and received ATT at presentation. One patient diagnosed with serpiginous choroiditis had a history of TB-meningitis, yet the standard duration of ATT was not clearly defined. Therefore, ATT was initiated before ADA.

Steroid treatment was discontinued in all patients except one patient who continued to use steroids at a dose of 16 mg/day for BU. Despite weekly ADA doses, inflammation persisted on angiography in this patient.

The preferred treatment option was ADA monotherapy in 18 patients. The majority of these patients were diagnosed with SpA-associated uveitis (55.5%), followed by BU (22.2%). Among the ISTs used concomitantly with ADA, AZA was the most frequently chosen (48.7%), followed by cyclosporine (27.4%), methotrexate (25.3%), and mycophenolate mofetil (1.4%). Furthermore, 21 patients received combined IST. The number of agents used, immunosuppressive drug load, and the frequency of local treatments were significantly reduced with ADA treatment ($p<0.005$, Wilcoxon signed-rank test, Table 3). A subsequent comparison of these parameters in terms of treatment line revealed no significant differences between first-line and second-line ADA use ($p=0.848$, 0.166, and 0.612, respectively, Mann-Whitney U test).

ADA-related adverse events occurred in 8 patients (5.5%). These included skin rash in 3 patients, cervical lymphadenopathy (LAP) in 2 patients, localized psoriasis in 2 patients, and pulmonary TB in 1 patient. Ultrasonography and tissue biopsy performed to investigate the cervical LAP revealed no malignancy. The symptoms of psoriasis regressed after discontinuing ADA and did not recur after resuming ADA. The patient diagnosed with pulmonary TB had bilateral progression of serpiginous

Table 1. Baseline demographic and clinical features

Number of patients/eyes, N/n	**146/289**
Age, mean ± SD (range), years	37.6 ± 14.4 (4-73)
<18 years, N (%)	8 (5.5)*
>60 years, N (%)	6 (4.1)**
Sex, N (%)	
Female	60 (41.1)
Male	86 (58.9)
Localization of uveitis, N (%)	
Anterior uveitis	17 (11.6)
Intermediate uveitis	8 (5.5)
Posterior uveitis	26 (17.8)
Panuveitis	95 (65.1)
Uveitis etiology, N (%)	
Behçet's uveitis	53 (36.3)
Sarcoidosis	28 (19.2)
Vogt-Koyanagi-Harada disease	18 (12.3)
Spondyloarthropathy-associated uveitis	12 (8.2)
Serpiginous choroiditis	7 (4.8)
Pars planitis	6 (4.1)
Juvenile idiopathic arthritis-associated uveitis	5 (3.4)
Ampiginous choroiditis	4 (2.7)
Idiopathic uveitis	4 (2.7)
Tubulointerstitial nephritis and uveitis syndrome	3 (2.1)
Sympathetic ophthalmia	3 (2.1)
Tuberculosis-related uveitis	2 (1.4)
Posterior scleritis***	1 (0.7)
Previous systemic steroid, N (%)	
None	109 (74.7)
<10 mg/day	12 (8.3)
16 mg/day	5 (3.4)
32 mg/day	9 (6.2)
48 mg/day	2 (1.4)
64 mg/day	9 (6.2)
Previous IST/immunomodulatory/biologics**, N (%)**	
None	12 (8.2)
Azathioprine	57 (39.1)
Methotrexate	37 (25.3)
Mycophenolate mofetil	1 (0.7)
Cyclosporine	51 (34.9)
Etanercept	6 (4.1)
Certolizumab	1 (0.7)
Interferon-α	18 (12.3)
Line of ADA, N (%)	
First-line therapy	12 (8.2)
Second-line therapy	134 (91.8)
Interval between diagnosis and initiation of ADA treatment, median (IQR), months	13.5 (7-36)
Duration of ADA treatment; median (IQR), months	12 (9-24)

N, Number of patients, n: Number of eyes, SD: Standard deviation, IST: Immunosuppressive treatment, ADA: Adalimumab, IQR: Interquartile range
*Patients started on ADA before the age of 18 years were diagnosed with juvenile idiopathic arthritis-associated uveitis (4 patients), tubulointerstitial nephritis and uveitis syndrome (2 patients), pars planitis (1 patient), and sympathetic ophthalmia (1 patient)
**Among patients over 60 years of age, ADA was initiated in one patient due to Vogt-Koyanagi-Harada and in the remaining five patients due to ocular sarcoidosis
***Posterior scleritis is included under posterior uveitis in the uveitis localization section.
****Some patients received combined ISTs

choroiditis despite treatment with AZA and ADA. This patient had a positive QuantiFERON test during the previous screening. However, the pulmonologist did not recommend ATT because a detailed assessment showed no evidence of active TB. They instead recommended only INH prophylaxis before ADA. Following re-evaluation by the pulmonologist due to progression under treatment, the patient was diagnosed with active pulmonary TB. ADA was stopped and quadruple ATT was started.

Table 2. Reported side effects associated with treatment agents used prior to adalimumab

Agents with side effect*, N (%)	Reported side effect*, N
Azathioprine, 22 (15.1)	Anemia, 2 Lymphopenia, 4 Fatigue, 6 Renal function test impairment, 2 Liver function test impairment, 9
Steroid, 20 (13.7)	Cushing syndrome, 5 Acne, 1 Osteoporosis, 4 Neuropathy/myopathy, 2 Steroid-responder glaucoma, 9 Central serous chorioretinopathy, 1
Cyclosporine, 17 (11.6)	Fatigue; 1 Renal function test impairment, 2 Neuropathy/myopathy, 8 Hirsutism, 3 Gingival hypertrophy, 3
Interferon-α, 13 (8.9)	Lymphopenia, 3 Fatigue, 4 Liver function test impairment, 2 Alopecia, 3 Weight loss, 3 Depression, 1
Methotrexate, 10 (6.8)	Anemia, 1 Nausea, 4 Liver function test impairment, 4 Shingles (herpes zoster), 1
Etanercept, 6 (4.1)	Paradoxical uveitis, 6

N: Number of patients
*Overlapping side effects in the same patient and/or different side effects to the same agent. The most common side effect against the agent is written in bold type

Table 3. Alternation of treatment with ADA (patients diagnosed with spondyloarthropathy-associated uveitis were excluded)

	Prior to ADA	Concomitant with ADA	p value
The number of agents, mean, median (IQR)	1.4 1 (1-2)	1.1 1 (1-1)	**<0.001**
Immunosuppressive drug load, mean, median (IQR)	6.7 6.5 (4-10)	5.6 5 (4-7)	**0.002**
The number of local treatments, mean, median (IQR)	1.1 0 (0-1)	0.3 0 (0-0)	**<0.001**

Wilcoxon signed-rank test. IQR: Interquartile range, ADA: Adalimumab. Significant p values written in bold

At the end of the median (IQR) follow-up period of 30 (18-57) months, 83.6% of patients (122 patients) continued to receive the standard bi-weekly treatment. Thirteen patients (8.9%) were escalated to weekly ADA treatment after a median (IQR) of 24 (12-36) months on standard bi-weekly ADA usage. Among the 13 patients (4 females/9 males) switched to weekly treatment, 4 received ADA for BU, 2 for VKH, 1 for sympathetic ophthalmia, 1 for TB-related uveitis, and 1 for idiopathic posterior uveitis.

Comparing the patients who had to be switched to weekly dosing with those who continued to receive ADA bi-weekly, the number of ISTs used and the immunosuppressive drug load during standard ADA usage were statistically significantly higher in the weekly dosing group ($p<0.001$ and $p=0.025$, respectively), although there was no difference before ADA indication. Patients who switched to weekly dosing had statistically significantly higher number of required local treatments before and after ADA indication ($p=0.02$ and 0.001, respectively).

A total of 11 patients (7.5%) discontinued ADA treatment. In one patient receiving ADA for sympathetic ophthalmia, syphilis infection was diagnosed during treatment despite a previous negative VDRL/TPHA (venereal disease research laboratory/reflex *Treponema pallidum* hemagglutination) test result. ADA was discontinued and the patient was referred to the infectious diseases department for 21-day intravenous penicillin therapy. Five patients achieved remission and ceased ADA treatment. Four patients experienced adverse events during the course of their treatment with ADA and discontinued the treatment. One other patient declined to continue ADA treatment for other reasons (Figure 1).

The BCVA (logMAR) results showed a statistically significant improvement at all time points compared to baseline ($p<0.001$ for all). Additionally, significant BCVA improvement was observed between all time points except months 6 and 12 (Figure 2). The change in BCVA did not differ statistically according to whether ADA was used as first- or second-line treatment ($p>0.05$).

The most prevalent indication was BU (36.3%). Consequently, the approach to BU was the dominant factor in the general approach. Specific analyses of the BU population are presented in Supplementary Information S3.

Discussion

The study analyzed large and heterogeneous patient data to investigate the efficacy and safety of ADA in the various subtypes of NIU. Previous studies have demonstrated the efficacy of ADA treatment in achieving better control of ocular inflammation, improving visual acuity and reducing the use of CS in patients with NIU.[16,17,18] The efficacy of ADA treatment was demonstrated in this single-center study involving a Turkish population. To the best of our knowledge, this is the largest single-center real-life experience of ADA use in NIU in the Turkish population.

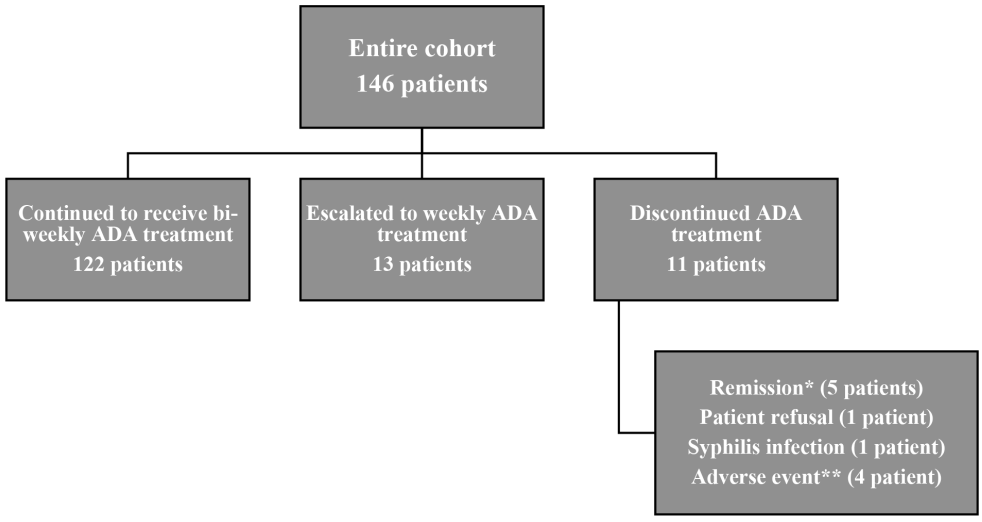

Figure 1. Adalimumab (ADA) use status of patients
**Remission was diagnosed in three patients with Behçet's uveitis, one with sarcoidosis and one with Vogt-Koyanagi-Harada (VKH) disease*
***ADA treatment was discontinued in 2 patients with serpiginous choroiditis due to skin rash, 1 patient with serpiginous choroiditis due to pulmonary tuberculosis and 1 patient with VKH due to lymph adenopathy. The symptoms of dermatological conditions that manifested during ADA administration abated with the cessation of ADA and did not recur upon the resumption of ADA*

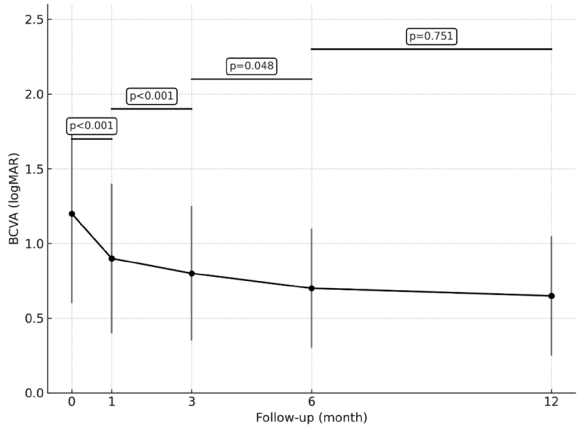

Figure 2. Changes in the mean best corrected visual acuity (BCVA). Patients diagnosed with spondyloarthropathy-associated uveitis were excluded (Wilcoxon signed-rank test)
logMAR: Logarithm of the minimum angle of resolution

The most common indications for ADA were panuveitis, in line with previous studies.[23,24,25] The most common diagnosis was BU. This observation is consistent with the unique epidemiological characteristics of our country. Similarly, BU was the most common NIU subtype in another study by Çam and Celiker[21] evaluating the efficacy of ADA in NIU in the Turkish population.

The most prevalent diagnosis in the pediatric cohort was juvenile idiopathic arthritis (JIA)-associated uveitis, also consistent with the existing literature, and no adverse events were observed. The effectiveness and safety of ADA in pediatric patients have been demonstrated in previous studies.[26,27] A study conducted in Türkiye has demonstrated the efficacy of ADA treatment in pediatric NIU.[28] However, the most common diagnosis in that series was pars planitis, while JIA-associated uveitis was the second most common diagnosis. This discrepancy may be attributed to the relatively low number of pediatric patients in the present clinical data (8 patients), which was a consequence of the absence of interdisciplinary clinical collaboration (e.g., with pediatric rheumatology or internal medicine).

An important outcome evaluated in our study was the efficacy of ADA in both first-line and second-line treatment settings. The impact of treatment line on prognosis remains controversial. The number of patients who received ADA as first-line treatment was limited, and no significant differences were observed between the first- and second-line treatment groups in terms of visual prognosis, number of immunosuppressive drugs used, immunosuppressive drug load, or need for local therapy. It is important to note that the statistical power of this comparison is limited due to the imbalance in sample sizes. However, these findings support the growing trend towards the use of ADA early in the disease course, especially when conventional therapies such as CS and IST are contraindicated or insufficient.

As demonstrated by previous studies, the potential of ADA as a first-line agent is evident, particularly in the context of BU and other forms of sight-threatening uveitis.[13,16,18]

Adverse effects were recorded for more than half of the patients using IST before ADA. However, only 5.5% of patients developed side effects with ADA. In this population with long-term drug use, adverse effects reduce patient compliance, increased visit numbers, and exacerbate the burden on the healthcare system. Considering these disadvantages of IST, early ADA treatment is a feasible option. Previous comparative studies have indicated that the use of ADA has the potential to facilitate a more prompt and efficacious treatment regimen with a comparable safety profile to conventional ISTs.[29,30,31] This is particularly important in the management of NIU subtypes resistant to conventional therapies or in patients who cannot tolerate these treatments.

Adverse events observed during ADA treatment included a skin rash, cervical LAP without evidence of malignancy, localized psoriasis, and pulmonary TB. As TB is endemic in our country, it is unclear whether the pulmonary TB in this patient was the result of the reactivation of latent TB or the development of primary TB. The estimated probability of developing TB during ADA use is 0.4-0.69%.[32,33] Similarly, the incidence of TB in this study was 0.68%. The relatively low adverse event rate in the present study suggests that ADA is generally well-tolerated. However, the risk of latent TB remains a concern, particularly in endemic countries like Türkiye, emphasizing the need for cautious pretreatment screening and monitoring.

In the presented cohort, one patient developed syphilis infection during ADA treatment, despite having a negative VDRL/TPHA test prior to ADA treatment. ADA was discontinued, and the patient was referred to the infectious diseases department, where intravenous penicillin therapy was prescribed. This underscores the broader risk of opportunistic infections in patients undergoing ADA therapy. Screening for syphilis and other infections is a standard approach in the diagnostic workup of NIU. Prior to the initiation of biologic drugs, it is imperative to undertake repeated general serologic tests. As described in several reports in the literature, cases of syphilis have emerged under IST, particularly in patients with dermatological and rheumatological conditions.[34,35,36] The overlapping symptoms of these conditions can delay diagnosis. Patel et al.[37] reported three cases of ocular syphilis under IST. However, baseline serological data were unavailable in these cases. The case in our study is noteworthy due to the documented seroconversion during ADA therapy, suggesting a likely new infection rather than a missed latent case. This finding is particularly important in the context of the global resurgence of syphilis.[38] Given these rising trends and potential diagnostic delays, especially in asymptomatic or latent stages, we believe syphilis serology may be considered as part of the routine infectious disease monitoring, similar to TB, in patients receiving ADA therapy.

A comparison of the pre-indication parameters of patients receiving bi-weekly and weekly ADA treatment demonstrated a statistically significant increase in the number of ISTs used and immunosuppressive drug burden due to insufficient response in patients switched to weekly dosing. The required number of local treatments was statistically significantly higher in patients who switched to weekly dosing, both before and after the indication of standard-dose ADA. The transition to a weekly dosing regimen was necessitated by the presence of uncontrolled inflammation and the increased need for local treatment (persistent CME and uncontrolled inflammation with systemic treatment). In view of the absence of prognostic distinction between first-line and second-line ADA patients, it is conceivable that ADA therapy could be initiated as a first-line therapy at an earlier stage in patients requiring a greater number of local treatments, and the transition could be made to a weekly regimen without insisting on a bi-weekly regimen. Although the clinical characteristics of patients transitioned to weekly dosing were analyzed in this study, follow-up data after the switch were not included in the scope of the analysis. Existing studies have demonstrated that the inflammation was effectively managed in patients transitioned to a weekly regimen with comparable indications.[21,28,39,40,41]

ADA was observed to significantly reduce the need for additional IST and local therapies, in line with previous studies.[23,42,43] Minimizing the use of CS and other IST is of crucial importance, as it reduces the long-term risk of side effects and complications associated with these therapies. This reduction in medication use not only reduces the potential for side effects but also improves patient compliance and overall quality of life. Diminished complications can also enhance patient productivity and healthcare costs. This is a pivotal consideration, given that a considerable proportion of NIU patients are in their most economically productive working years. In a study investigating cost-effectiveness, ADA was found to be a more cost-effective option than conventional treatment, particularly in cases of active uveitis threatening vision.[44] One of the most clinically noteworthy findings of this study was the rapid improvement observed in BCVA in patients treated with ADA. Visual improvement was observed during the first month of treatment, with continued gains until month 6, followed by stabilization through month 12. The rapid recovery of visual function is of vital importance in order to prevent long-term vision loss and to improve patients' quality of life. These findings are consistent with those obtained in previous studies that similarly reported early and sustained improvements in visual acuity with ADA, thereby further confirming its role in rapidly controlling ocular inflammation and restoring visual function.[25,28,45] In terms of the close follow-up of BCVA recovery, the initial weeks could not be evaluated in this study. Nevertheless, in studies conducted with shorter intervals, the rapid control of both anterior and posterior uveitis was observed in all eyes as early as the second week.[27,46]

The approach to BU was the dominant factor in the overall approach taken in the study, since BU was the most common NIU subtype in the present cohort. AZA was the most preferred IST agent in conjunction with ADA. This was mainly because AZA is the first choice of IST for the treatment of BU, in conjunction with CS. In a recently published study evaluating

the approaches of uvea specialists in Türkiye, CS+AZA was identified as the preferred initial treatment, with ADA added in cases of treatment failure. In instances of persistent inflammation unresponsive to standard doses of ADA, treatment was switched to weekly doses, as demonstrated in the presented study.[47] Upon analysis of the BU subgroup, it was observed that despite a notably higher number of IST drugs and need for local treatments, the immunosuppressive drug load did not differ. This is due to the preference for AZA from among the disease-modifying antirheumatic drugs as concomitant to ADA in the treatment regimen. In the chart presented by Nussenblatt et al.[22], which is employed in the calculation of the immunosuppressive drug load, the unit drug load of AZA is notably high. Notwithstanding its inclusion in the Nussenblatt chart, no patient in the study used AZA. It is possible that the AZA unit load may have been overestimated.

Study Limitations

The present study provides valuable insights into a large and heterogeneous group of NIU patients. However, the retrospective nature of the study represents a limitation in terms of evaluating the impact of ADA on inflammatory processes. The discrepancy between the recorded times of inflammation parameters and the times of ADA injections may result in a biased representation of the effect of ADA on inflammation. Therefore, intraocular inflammation parameters such as anterior chamber cell grading, vitreous haze, fluorescein angiography, or optical coherence tomography findings were not systematically evaluated, which may influence outcome interpretation. This limits the ability to quantify the direct impact of ADA on structural markers of inflammation. Furthermore, the broad range of uveitis etiologies and the inclusion of both pediatric and adult patients (aged 4-73 years) introduce heterogeneity that may affect direct comparisons between subgroups. However, this diversity reflects real-world clinical practice and highlights the broad applicability of ADA across different NIU subtypes and age groups. Moreover, clinical follow-up after switching to weekly ADA dosing was not evaluated in the current study, and TNF-α antibody levels could not be assessed in patients requiring escalation. Prospective studies with standardized inflammatory assessments and structured follow-up are needed to further clarify these findings.

Conclusion

The findings suggest that ADA is an effective and safe treatment option for various types of NIU in a wide age range in Turkish patients. Furthermore, it has been demonstrated to markedly decrease the encountered side effects and need for adjunctive IST and local therapeutic modalities. It also provides early and sustained visual improvement. These results suggest the potential for ADA to enhance patient outcomes by simplifying the treatment regimen and reducing the risk of complications.

Ethics

Ethics Committee Approval: The study was performed with ethics approval obtained from the Ethics Committee of the University of Health Sciences Türkiye, Hamidiye Scientific Research (decision number: 7/24, date: April 07, 2023) and complied with the tenets of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

Surgical and Medical Practices: B.Y.Ö., Ç.A., B.K.A., B.B., Concept: B.Y.Ö., Ç.A., Design: B.Y.Ö., Ç.A., Data Collection or Processing: B.Y.Ö., Analysis or Interpretation: B.Y.Ö., Literature Search: B.Y.Ö., Writing: B.Y.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Prevalence and Prognosis of Glaucoma/Elevated Intraocular Pressure in Patients with Uveitis

Mine Esen Barış, Halil Ateş, Suzan Güven Yılmaz

Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye

Abstract

Objectives: To evaluate the prevalence and clinical course of elevated intraocular pressure (EIP) and glaucoma in different types of uveitis.

Materials and Methods: A retrospective chart review was performed for patients who were treated for any kind of uveitis at Ege University Ophthalmology Department between January 2003 and January 2023. Patients with transient/persistent increase in intraocular pressure (IOP), who were already under treatment with antiglaucoma medications at the initial examination, or who were diagnosed with glaucoma during follow-up were included. Demographic features, uveitis type, time between uveitis and glaucoma/EIP diagnoses, topical and systemic treatments for uveitis, and antiglaucoma medications and surgeries were recorded.

Results: A total of 2176 patient files (1206 anterior uveitis [AU], 247 intermediate uveitis [IU], 165 posterior uveitis [PU], 558 panuveitis [PanU]) were reviewed and 594 eyes of 440 (20.2%) patients (205 female, 235 male) were included in the study (292 eyes with AU, 80 eyes with IU, 44 eyes with PU, and 178 eyes with PanU). Glaucoma was observed in 220 eyes (37.0%) and EIP in 374 eyes (63.0%). Glaucoma was present in 120 eyes with AU, 23 eyes with IU, 13 eyes with PU, and 64 eyes with PanU. IOP was controlled with medical treatment in 458 eyes (77.1%) while glaucoma surgery/laser was needed in 113 eyes (19.0%). No treatment was required for 23 eyes (3.9%).

Conclusion: The prevalence rate of glaucoma/EIP was 20.2%. Glaucoma was most observed in eyes with AU (41.1%), while EIP was most common with IU (71.2%).

Keywords: Behçet's disease, glaucoma surgery, uveitic glaucoma

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Address for Correspondence: Mine Esen Barış, Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye
E-mail: mine.baris@yahoo.com **ORCID-ID:** orcid.org/0000-0003-1341-6737
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Introduction

Uveitis is characterized by inflammation of the uveal structures (iris, ciliary body, choroid). However, the current definition of uveitis also includes inflammation of the retina, vitreous, and optic nerve.[1] Inflammation of these ocular structures might result from various diseases. Uveitis-related elevated intraocular pressure (EIP) is associated with an intraocular pressure (IOP) above 21 mmHg, while uveitic glaucoma is associated with high IOP and optic nerve damage and/or visual field defects.[2]

The mechanism of increased IOP in uveitis can vary. Trabeculitis, peripheral anterior synechia, posterior synechia resulting in pupillary block, corticosteroid exposure, or obstruction of the trabecular meshwork by inflammatory cells might lead to the elevation of IOP in uveitis patients.[3]

The mean annual incidence rate of EIP in adults with non-infectious uveitis is 14.4%.[4] Since uveitis has highly heterogeneous etiologies, the prevalence and mechanism of EIP and its progression to glaucoma depends heavily on the etiology and the localization of the inflammation. Anterior uveitis was reported to be the main cause of elevated IOP in many studies.[5,6] However, there are also reports suggesting no significant difference between anterior and posterior uveitis.[7,8]

The current study aimed to investigate the prevalence and course of EIP and glaucoma in various types of uveitis and evaluate the treatment outcomes of uveitic glaucoma.

Materials and Methods

A retrospective chart review was carried out for uveitis patients who were examined at the Uvea Department of Ege University between January 2003 and January 2023. Patients with an IOP above 21 mmHg in any of the follow-up visits and/or were diagnosed with uveitic glaucoma were included in the study. Ethics committee approval was obtained from the Ege University Ethics Committee for Medical Studies (decision no: 24-9T/9, date: 05.09.2024). Written informed consent was obtained from all patients for the use of data from their medical files.

In the current study, EIP was defined as an IOP measurement above 21 mmHg using Goldmann applanation tonometer. Glaucoma was defined as the presence of glaucomatous optic nerve damage (detected by fundus examination, peripapillary retinal nerve fiber layer thickness analysis using optical coherence tomography, and/or visual field tests) associated with the increase in IOP. All patients with transient or persistent IOP elevation, patients who were already taking antiglaucoma medications at the first visit, and patients diagnosed with uveitic glaucoma were included in the study. Patients who were followed up for less than 3 months and patients with incomplete data were excluded.

For uveitis screening, all patients underwent basic tests including complete blood count, erythrocyte sedimentation rate, C-reactive protein levels, chest X-ray, and interferon gamma release assay, along with serological tests for *Treponema pallidum* and human immunodeficiency virus. Additional tests such as tissue type classification for HLA-B27 and HLA-B51, sacroiliac joint X-ray, and serological tests for *Toxoplasma gondii, Brucella,* or *Bartonella henselae* were performed when appropriate.

Uveitis was classified as acute or chronic. Acute uveitis was defined as the sudden or gradual start of inflammation with complete resolution with treatment, with or without recurrences. Chronic uveitis was defined as persistent inflammation lasting more than 3 months and/or relapsing within 3 months after the termination of therapy.[9]

Age, gender, localization of uveitis, presence of any associated systemic diseases, exposure to corticosteroids, ophthalmological examination findings pertaining to the iridocorneal angle, IOP, best corrected visual acuity (in decimal), the course of the IOP increase, treatment of EIP and glaucoma, number and type of antiglaucoma medications used, and glaucoma surgeries and complications were recorded and analyzed.

Statistical Analysis

The Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.) was used for statistical analyses. Descriptive statistics are presented as mean, standard deviation, median, range, and percentage values. The Shapiro-Wilk test was used to test the normality assumptions of the quantitative data. Chi-square test was used for the comparison of categorical variables. The statistical significance value was defined as $p<0.05$.

Results

The medical records of 2176 patients were reviewed and 594 eyes of 440 patients (20.2%) were included in the study. Gender distribution, mean age, mean follow-up time, and ophthalmological findings are summarized in Table 1.

In 334 eyes (56.2%), either IOP was increased at the first visit or the patient had already been started on antiglaucoma medications by another ophthalmologist due to high IOP identified with uveitis. The mean duration between the first diagnosis of uveitis and IOP elevation was 299.7±849.5 days (range: 0-8030). A total of 41 patients (9.3%) were under 18 years of age at the time of EIP or glaucoma diagnosis.

The presence of any associated systemic and ocular diseases and treatment of uveitis are summarized in Table 2.

Acute uveitis was present in 145 patients (33.0%), while chronic uveitis was found in 295 patients (67.0%). An IOP

Table 1. Demographic features and clinical findings of all study eyes

Total number of patients	440
Female, n (%)	205 (46.5)
Male, n (%)	235 (53.1)
Total number of eyes	594
Age, years, mean ± SD (range)	48.9±20.5 (7-104)
Follow-up period, months, mean ± SD (range)	62.09±88.3 (3-192)
IOP, mean±SD, mmHg (range)	35.6±10.9 (22-60)
BCVA, first visit, logMAR, mean ± SD (range)	0.29±0.3 (2.28-0)
BCVA, last visit, logMAR, mean ± SD (range)	0.26±0.31 (2.28-0)
Iridocorneal angle, eyes, n (%)*	
Open	509 (85.7)
Peripheral anterior synechia	61 (10.3)
Pupillary block	28 (4.7)
Uveitis localization, eyes, n (%)	
Anterior	292 (49.2)
Intermediate	80 (13.5)
Posterior	44 (7.4)
Panuveitis	178 (30.0)

*Eyes could be included in multiple categories.
BCVA: Best corrected visual acuity, IOP: Intraocular pressure, SD: Standard deviation

Table 2. Associated systemic and ocular conditions

Etiology - systemic, patients, n (%)	
Spondyloarthropathies	57 (12.8)
Behçet's disease	82 (18.5)
Undifferentiated connective tissue disorders	8 (1.8)
JIA	17 (3.8)
Sarcoidosis	14 (3.1)
TINU	2 (0.4)
Vogt-Koyanagi-Harada syndrome	5 (1.1)
Multiple sclerosis	2 (0.4)
Etiology - ophthalmic, eyes, n (%)	
Herpetic uveitis	32 (5.3)
Fuchs uveitic syndrome	5 (0.8)
CMV uveitis	2 (0.3)
Posner-Schlossmann syndrome	4 (0.7)
Toxoplasmosis/toxocariasis	11 (1.8)
Uveitis treatment, eyes, n (%)	
Topical corticosteroids	594 (100)
Systemic treatment	
Corticosteroids	358 (60.3)
Conventional immunosuppressives	98 (16.4)
Anti-TNFα agents	87 (14.5)
Intravitreal dexamethasone implant	34 (5.7)
Anterior	2 (0.3)
Intermediate	7 (1.2)
Posterior	4 (0.7)
Panuveitis	21 (3.5)

JIA: Juvenile idiopathic arthritis, TINU: Tubulointerstitial nephritis and uveitis syndrome, CMV: Cytomegalovirus, TNF: Tumor necrosis factor

increase of at least 10 mmHg over baseline was observed in 88 eyes (14.8%) after the initiation of systemic/topical/intravitreal corticosteroids. These eyes were defined as "steroid responders".

EIP was identified in 374 eyes (63.0%), while glaucoma was identified in 220 eyes (37.0%). The incidence of EIP and glaucoma according to the localization of uveitis and the applied treatments are summarized in Table 3. Glaucoma was most frequently associated with anterior uveitis (41.1%), but the relationship did not reach statistical significance (p=0.057). EIP was most frequently associated with intermediate uveitis compared to the other uveitis locations (p=0.03). Surgical and/or laser treatment were required in 113 eyes (19.0%) while medical treatment was adequate for the control of IOP in 458 eyes (77.1%). The treatment modality (surgery/laser/medication) and incidence of surgery did not differ significantly between the patients (p=0.3). Pupillary block was observed in 28 eyes and laser iridotomy was applied to all of them in addition to medical treatment. No treatment was applied to 23 (3.9%) eyes. Thirty-one eyes (5.2%) were found to be legally blind (visual acuity ≤20/200 and/or visual field smaller than the central 20 degrees) at the first visit. At the last visit (median 72 months), 77 eyes (13.0%; 37 medically treated and 40 surgically treated eyes) were found to be legally blind. The incidence of blindness was lower in the medical treatment group compared to the surgically treated group (8.0% vs. 35.4%, p=0.03). In total, 17 eyes (2.9%) underwent vitrectomy. Vitreoretinal surgery was carried out for diagnostic purposes in 2 eyes, tractional membranes/tractional retinal detachment in 2 eyes, vision-reducing dense vitreous membranes/opacities in 3 eyes, macular hole in 2 eyes, and rhegmatogenous retinal detachment in 8 eyes.

The number of antiglaucoma medications used, surgeries performed, and number of surgeries are shown in Table 4. The complications and numbers of eyes requiring revision and repeat surgeries are summarized in Table 5.

Table 3. Frequencies of EIP and glaucoma and applied treatments according to uveitis localization

	Anterior, n (%)	Intermediate, n (%)	Posterior, n (%)	Panuveitis, n (%)	Total, n (%)
Glaucoma	120 (41.1)	23 (28.8)	13 (29.6)	64 (36.0)	220 (37.0)
EIP	172 (58.9)	57 (71.2)	31 (70.4)	114 (64.0)	374 (63.0)
Treatment					
Surgery/laser	60 (20.2)	13 (16.2)	11 (25.0)	29 (16.3)	113 (19.0)
Medical	216 (74.3)	62 (77.5)	32 (72.7)	148 (83.1)	458 (77.1)
None	16 (5.4)	5 (6.3)	1 (2.3)	1 (0.6)	23 (3.9)

EIP: Elevated intraocular pressure, n: Number of eyes

Table 4. Number of antiglaucoma medications and number of performed surgeries

	Anterior n (%)	Intermediate n (%)	Posterior n (%)	Panuveitis n (%)	Total n (%)
Number of antiglaucoma medications					
0	18 (6.1)	40 (50.0)	19 (43.2)	89 (50)	166 (27.9)
1	15 (5.1)	1 (1.25)	3 (6.8)	3 (1.6)	22 (3.6)
2	76 (25.6)	21 (26.2)	7 (15.9)	48 (26.7)	152 (25.4)
3	160 (54.7)	10 (12.5)	14 (31.8)	27 (15.2)	211 (35.5)
4	21 (7.1)	6 (7.5)	1 (2.3)	9 (5.0)	37 (6.3)
5	2 (0.7)	2 (2.5)	0	2 (1.1)	6 (1.1)
Surgical treatment					
Trabeculectomy	32 (10.8)	4 (5)	10 (22.7)	6 (3.4)	52 (46)
Trabeculectomy+phacoemulsification	3 (1)	-	-	2 (1.1)	5 (4.4)
Deep sclerectomy	3 (1)	4 (5)	-	6 (3.4)	13 (11.5)
Ex-Press/XEN glaucoma implant	3 (1)	4 (5)	-	3 (1.7)	10 (8.8)
Glaucoma drainage devices	7 (2.4)	3 (3.7)	-	1 (0.5)	11 (9.7)
GATT	2 (0.7)	2 (2.5)	1 (2.3)	1 (0.5)	6 (5.3)
Cryo-cyclodestruction	2 (0.7)	-	1 (2.3)	3 (1.7)	6 (5.3)
Number of surgeries					
1	35 (11.8)	4 (5)	8 (18.1)	10 (5.6)	57 (50.4)
2	7 (2.4)	1 (1.2)	-	1 (0.5)	9 (7.9)
>3	5 (1.7)	5 (6.2)	2 (4.6)	4 (2.2)	16 (14.1)
Laser treatment					
Laser iridotomy	12 (4)	3 (3.7)	1 (2.3)	12 (6.7)	28 (24.8)
Selective laser trabeculoplasty	5 (1.7)	-	-	2 (1.1)	7 (6.2)

GATT: Gonioscopy-assisted transluminal trabeculotomy, n: Number of eyes

Table 5. Complications and revisions related to glaucoma surgeries (n=113)				
Glaucoma surgery	**n (%)**	**Related complications**	**n (%)**	**Eyes needing revisions/ reoperations, n (%)**
Trabeculectomy with MMC	57 (50.4)	Hypotony Choroidal detachment Hyphema Bleb encapsulation	16 (28.1) 3 (5.2) 3 (5.2) 7 (12.3)	11 (19.3)
Deep sclerectomy	13 (13.5)	Bleb encapsulation	1 (7.7)	3 (23.1)
XEN-45 implantation	5 (4.4)	None	0	5 (100.0)
Ex-Press mini shunt	5 (4.4)	None	0	3 (60.0)
GATT	6 (5.3)	Hyphema	2 (33.3)	0
Ahmed glaucoma valve implantation	11 (9.7)	Hypotony Bleb encapsulation	2 (18.2) 2 (18.2)	2 (18.2)
Cryo-cyclodestruction	6 (5.3)	None	0	0
MMC: Mitomycin C, GATT: Gonioscopy-assisted transluminal trabeculotomy, n: Number of eyes				

Discussion

Uveitic glaucoma was first described in 1813 by Beer.[10] Since then, many studies have evaluated and reported on this condition, adding to our knowledge. It is now known that the etiology of uveitis plays a major role in the increase in IOP, with various mechanisms contributing towards EIP in uveitis. Herpetic uveitis and Posner-Schlossman syndrome are most associated with uveitic glaucoma/EIP, while for non-infectious uveitis, juvenile idiopathic arthritis is one of the most common etiologies.[11] In the current study, the prevalence of EIP/glaucoma was 20.2% among eyes with any type of uveitis. In a multicenter study, the prevalence of uveitic EIP/glaucoma was reported to be 15.8% with an annual incidence rate of 14.4%.[4] In another study, the incidence rate of glaucoma/EIP in uveitis patients was reported to be 6.5% in 1 year and 11.1% in 5 years.[5] Additionally, the prevalence of glaucoma/EIP in uveitis patients was reported as 20% in England,[12] 47.7% in Thailand,[13] 8.8% in Germany,[14] 16.4% in the USA,[15] 8.4% in Taiwan,[16] and 25.4% in Japan.[17] Incidentally, a study from the UK reported the prevalence of uveitic glaucoma as 41.8%, which is higher compared to most of the other published reports.[18]

The prevalence of EIP/secondary glaucoma in childhood uveitis was observed to be 35% in a 5-year prospective study[19] and 8.8% in another report.[13] In our study, 9.3% of the affected patients were under 18 years old. Sharon et al.[20] reported that 41.2% of the patients with high IOP were under 16 years old.

The high variations in the prevalence rates in the reported studies might result from differences in the duration of exposure to corticosteroids and/or the dosage used, as well as the differences in etiologies. Our study encompasses a period before the newer treatment options (such as anti-tumor necrosis factor alpha drugs) were available; therefore, corticosteroids were more commonly used for longer durations. Additionally, since the current study was conducted at a university hospital, which is a tertiary referral center that serves a very large population, our results are strongly affected by the severity of the cases.

The most common disease associated with uveitic glaucoma in the current study was Behçet's disease, followed by spondyloarthropathies. Behçet's disease is already known to be one of the most common etiologies for uveitis in Türkiye (32%),[21] which is also supported by the current study. In another study from Türkiye, the most common localization was anterior (43.6%) and Behçet's disease was the second most common etiology (26%).[22] Although infectious uveitis with herpesviruses, Posner-Schlossman syndrome or Fuchs uveitis syndrome are known to have the highest risk for increase in IOP, Behçet's disease has also been reported to be commonly associated with uveitic glaucoma.[13,17]

In the current study, 63% of uveitic eyes with high IOP had only EIP, whereas 37% of them had glaucomatous degeneration of the optic nerve associated with high IOP. In contrast to our results, Pathanapitoon et al.[13] reported that 61.4% of uveitic eyes with high IOP had glaucoma whereas 38.6% had EIP without any glaucomatous findings. The same study reported that the prevalence of glaucoma in all uveitic eyes was 29%.[13] Heinz et al.[14] reported a very low prevalence (8.8%) of high IOP in uveitic eyes, although 71.5% of the eyes evaluated had glaucomatous degeneration. Similarly, Merayo-Lloves et al.[15] reported that 58.2% of uveitic eyes with high IOP had glaucomatous findings.

Anterior uveitis was the most common type of uveitis among all study patients in the current study (49.2%) and glaucomatous degeneration was most observed in eyes with anterior uveitis (n=120, 41.1%), followed by panuveitis (n=64, 36.0%). The frequency of glaucoma in intermediate and posterior uveitis was 28.8% and 29.6%, respectively. Supporting this, Kanda et al.[17] reported that anterior uveitis was the most common type with EIP (34.6%). Interestingly, these authors did not observe EIP/glaucoma in any of the eyes with posterior uveitis, which may be related to the relatively low number of samples with posterior uveitis (only 23 eyes). Supporting our findings, Pathanapitoon et al.[13] reported that most patients with glaucoma had anterior uveitis (61%) or panuveitis (25%). Herbert et al.[18] also reported that anterior uveitis was the most common type associated with high IOP (38%). Sharon et al.[20] reported that 83% of their

patients with uveitic EIP had anterior uveitis. Contrary to these data, Neri et al.[5] reported that there was no significant difference in the prevalence of EIP between anterior, intermediate, and posterior uveitis.

Since the use of corticosteroids is an unavoidable part of uveitis treatment, corticosteroid-induced EIP is commonly reported.[4] Friedman et al.[23] reported that an IOP increase of at least 10 mmHg was observed in 65% of uveitis patients who received fluocinolone acetonide implants and 24% of those treated with systemic corticosteroids. Glaucomatous optic nerve damage was reported in 26% of patients in the implant group, compared to 6% in the systemic treatment group.[23] Shrestha et al.[24] reported that corticosteroids were the main cause of EIP in most of the new uveitic cases with high IOP (65%) within the first 6 weeks of treatment.

In our study, 60.3% of eyes were treated using systemic corticosteroids during the follow-up period and only 5.7% received intravitreal dexamethasone implants. Feng et al.[25] reported that intravitreal dexamethasone implants did not cause any significant IOP increase when used as combination with phacoemulsification cataract surgery in pediatric uveitis patients. The results of a systematic review and meta-analysis indicated that intravitreal dexamethasone implants cause EIP and increase the number of antiglaucoma medications needed but do not increase the need for glaucoma surgery.[26] It is not always possible to differentiate steroid-induced ocular hypertension from an increase in IOP secondary to the inflammation in uveitis patients. However, we observed an increase in IOP immediately after the initiation of topical/systemic/intravitreal corticosteroid treatment in almost 15% of eyes, which were classified as "steroid responders". An IOP reduction after steroid cessation was not considered a criterion for steroid responsiveness. This is because it is not always possible to completely stop treatment in uveitic patients and IOP does not always decrease when exposure to steroids ends, possibly due to irreversible changes in the trabecular meshwork.[24]

Spondyloarthropathies were the second most common associated systemic condition in this study. Although spondyloarthropathy-associated uveitis is known to result in a decrease in IOP, pupillary block and chronic corticosteroid exposure combined with the inflammatory damage to the trabecular meshwork might cause EIP and/or glaucoma.

In the current study, only 23 eyes (3.9%) did not require treatment of any kind. Most of the eyes with EIP needed antiglaucoma medications at least temporarily. Almost 20% of the eyes in our cohort needed glaucoma surgery/laser treatment. Previous studies have reported the incidence of surgery in this patient group to be approximately 30% (Pathanapitoon et al.[13]), 47% (Merayo-Lloves et al.[15]), 23.2% (Neri et al.[5]), and 30.3% (Herbert et al.[18]). Jones[12] reported that glaucoma surgery was needed mostly in eyes with chronic anterior uveitis, corresponding to 32% of the eyes that underwent glaucoma surgery. The need for glaucoma surgery in the current study was the highest in eyes with posterior uveitis (25%). This may be related to a more extensive systemic exposure to steroids or the severity of the uveitis itself.[27]

The iridocorneal angle was open in most eyes (85%), and two or more topical anti-glaucoma medications were being used on most eyes (67.8%) at the time of surgery in the current study. Postoperative complications were mostly observed after trabeculectomy (50.8%), and bleb encapsulation was common after trabeculectomy, deep sclerectomy, and Ahmed glaucoma valve implantation. Hypotony (15.9%) was the most common postoperative complication, as in previous reports in the literature.[28] Theoretically, deep sclerectomy and XEN-45/Ex-Press mini-shunt implantations are expected to provide better outcomes with fewer complications and more stable IOP.[28,29] In the current study, the incidence of complications was significantly lower with these surgeries, as expected, with no hypotony observed. However, the need for revisions or repeat surgeries was also higher compared to trabeculectomy with mitomycin C and Ahmed glaucoma valve implantation.

Study Limitations

The main limitations of this study are its retrospective design and the heterogeneity of uveitis etiologies. A very important factor in EIP and glaucoma is corticosteroid exposure, which varied between patients and eyes in this study.

Conclusion

In conclusion, we report that high IOP was relatively common in all types of uveitis (~20%). Almost 40% of these cases developed glaucomatous neurodegeneration, with approximately 20% requiring glaucoma surgery. Only about 4% of these eyes required no treatment of any kind. IOP elevation can be seen even years after the initial diagnosis of uveitis, therefore IOP measurements should be carried out at each visit. As children comprise a considerable proportion of patients with uveitis, the extra effort needed for reliable IOP measurements should not be avoided.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ege University Ethics Committee for Medical Studies (decision no: 24-9T/9, date: 05.09.2024).

Informed Consent: Written informed consent was obtained from all patients for the use of data from their medical files.

Declarations

Authorship Contributions

Surgical and Medical Practices: M.E.B., S.G.Y., H.A., Concept: M.E.B., H.A., Design: M.E.B., H.A., Data Collection or Processing: M.E.B., Analysis or Interpretation: S.G.Y., Literature Search: M.E.B., Writing: M.E.B., S.G.Y.

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Oculoplastic Challenges in Patients with Glaucoma

Serdar Bayraktar[1], Kübra Serbest Ceylanoğlu[2], Emine Şen[3]

[1]University of Health Sciences Türkiye, Ankara Etlik City Hospital, Clinic of Ophthalmology, Ankara, Türkiye
[2]Ankara Bilkent City Hospital, Clinic of Ophthalmology, Ankara, Türkiye
[3]Dünyagöz Hospital, Clinic of Ophthalmology, Ankara, Türkiye

Abstract

Glaucoma is typically a disease that occurs in advanced age, requiring lifelong monitoring and treatment with topical medications, laser procedures, or surgery. Patients with glaucoma may also experience oculoplastic issues due to the natural aging process or as a result of glaucoma treatment or surgery. Eyelid surgery in these individuals can lead to complications and undesirable results. Therefore, it is crucial for oculoplastic surgeons to be aware of the incidence and risk factors associated with oculoplastic problems specific to glaucoma patients. Understanding these potential complications is essential for taking necessary precautions and achieving successful surgical outcomes. The purpose of this review is to raise awareness among ophthalmologists specializing in oculoplasty and glaucoma and to contribute to the quality of life of glaucoma patients.

Keywords: Ectropion, eyelid surgery, glaucoma, oculoplastic problems, periorbitopathy, prostaglandin analog, punctum stenosis

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Address for Correspondence: Serdar Bayraktar, University of Health Sciences Türkiye, Ankara Etlik City Hospital, Clinic of Ophthalmology, Ankara, Türkiye
E-mail: drsbayraktar@yahoo.com **ORCID-ID:** orcid.org/0000-0001-6521-9984
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Introduction

Glaucoma is a chronic, progressive optic neuropathy that usually occurs later in life, characterized by irreversible vision loss due to damage to retinal ganglion cells.[1,2] With global population aging, the prevalence of glaucoma is expected to increase.[2] Age-related anatomic and functional changes in the eyelids and orbital region are often accompanied by oculoplastic problems that can occur as a result of both medical and surgical glaucoma treatments.[3,4]

This review aims to comprehensively examine the oculoplastic complications that can arise iatrogenically during the treatment of glaucoma, as well as oculoplastic problems that may occur in glaucoma patients as a natural result of the aging process. Another aim was to guide physicians in their clinical practice by presenting current approaches to the diagnosis, follow-up, and treatment of these issues. Oculoplastic problems specific to glaucoma patients can be grouped under four main headings: (1) oculoplastic problems resulting from medical treatments, (2) iatrogenic oculoplastic problems resulting from surgical treatment, (3) glaucoma-related conditions developing after oculoplastic surgeries, and (4) appropriate treatment of involutional oculoplastic problems in patients with glaucoma.

Oculoplastic Problems Associated with the Medical Treatment of Glaucoma

Currently, the first-line treatment of glaucoma is primarily medical treatment with topical antiglaucoma agents, as indicated by international guidelines.[5,6] Therefore, good knowledge of the changes to the eyelid and orbit that can result from the use of antiglaucoma medications is important for the early recognition and appropriate management of potential oculoplastic problems.

Prostaglandin-Associated Periorbitopathy

Prostaglandin analogues (PGAs) are often preferred as the first choice in the medical treatment of glaucoma due to their potent intraocular pressure (IOP)-lowering effects, ease of once-daily use, and lower systemic side effect profile.[1,5,6,7,8,9]

However, PGA use can lead to various local side effects that affect the patient's facial appearance and may reduce life comfort, such as iris and periorbital hyperpigmentation, eyelash elongation and discoloration, deepening of the upper eyelid sulcus (DUES) due to orbital adipose tissue atrophy, and enophthalmos with upper eyelid ptosis—conditions collectively referred to as prostaglandin-associated periorbitopathy (PAP) (Figures 1, 2).[3,8,9,10,11,12,13,14,15,16]

Peplinski and Albiani Smith[8] first described DUES in patients using bimatoprost unilaterally. DUES was also reported to develop in fellow eyes in which bimatoprost treatment was initiated and regress after discontinuing bimatoprost, with authors emphasizing the possibly of overlooking DUES in patients using a PGA bilaterally.[8,10,11] Later reports also documented the occurrence of DUES with other PGAs.[3,11,12] Its incidence was found to be highest with bimatoprost, intermediate with travoprost, and lower with latanoprost.[11,13,14]

Lipolysis and reduced collagen fibers in the levator complex caused by PGAs and levator aponeurosis dehiscence due to fibrosis have been implicated as causes of DUES and ptosis associated with PGA use.[3,11,12,14,15] However, the regression of DUES after PGA discontinuation suggests that the pathogenesis cannot be fully explained by Müller muscle fibrosis and that aponeurotic and deep orbital adipose tissue atrophy play a more important role in this process.[14,17] Lipoatrophy of the eyelid and subsequent enophthalmos were also found to be associated with fibroblast apoptosis resulting from inflammatory changes in the orbital extracellular matrix due to PGA use.[3,14,17]

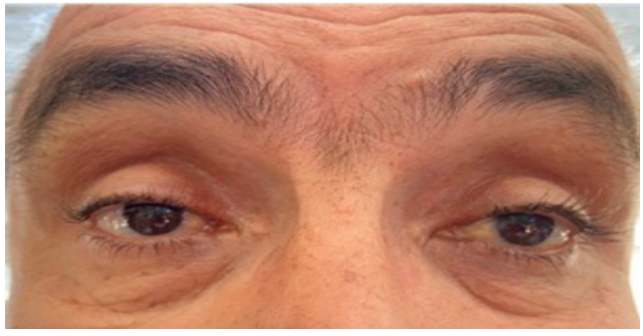

Figure 1. Male patient after bilateral prostaglandin analogue use exhibiting significant bilateral deepened upper eyelid sulci, eyelash elongation, ptosis, and associated pronounced horizontal forehead creases secondary to compensatory frontal muscle use

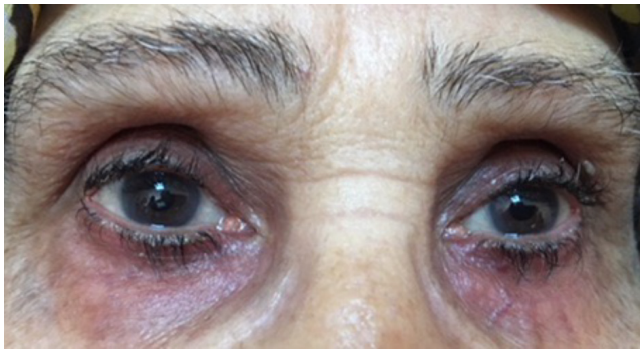

Figure 2. Female patient with significant prostaglandin-associated periorbitopathy secondary to prostaglandin analogue use. Deepening of the upper eyelid sulci, prominent periorbital fat atrophy, and hyperpigmentation in the periorbital region are observed

PGA use also leads to certain changes in the lower eyelid.[10,12,13] On examination, the first symptom of PAP in the lower lid is periorbital fat pad loss, which is especially common in older patients.[13,18] In Hertel exophthalmometer measurements of PAP patients using bimatoprost, Kucukevcilioglu et al.[13] detected enophthalmos due to loss of the periorbital fat pads, but did not find the same results with other PGAs. Fat atrophy and enophthalmos as a result of unilateral bimatoprost use have also been demonstrated by magnetic resonance imaging.[18,19] The onset of DUES and orbital fat atrophy may occur immediately after PGA initiation, or it may occur after a year of treatment.[8,20]

Prostaglandins are known to be potent stimulators of melanogenesis.[21] The increased pigmentation in the eyelid skin, lashes, and iris resulting from PGA use has been attributed to its stimulation of melanogenesis in the lid skin.[2,21] Hyperchromatic changes in iris pigmentation appear to be more permanent than pigmentary changes in the periorbital skin or eyelashes.[2] In the literature, it is reported that eyelid pigmentation occurs least with the use of latanoprost (0-5.9%), while rates of 2.9-15.4% and 1.6-25.9% have been observed with travoprost and bimatoprost, respectively.[9]

PGA-associated hypertrichosis of the eyelid and surrounding skin with thickening and elongation of the eyelashes were described in a series of 43 cases using unilateral latanoprost.[22] It was later noted that the rate of these eyelid changes observed in different studies varied widely for all PGAs (0-77%).[9] All hair follicles in the body, including the eyelid hairs and eyelashes, go through repeated cycles of regression and growth. PGAs are thought to stimulate the transition to the anagen phase, which is the active growth phase of this cycle, thus leading to eyelash hypertrophy and increased number.[2] This hypothesis is also supported by a case in which hypertrichosis associated with travoprost was unexpectedly observed in a graft obtained from the inner surface of the upper arm due to basal cell carcinoma.[23] In addition to the eyelashes and lid, increased hair growth on the upper cheek has also been reported with travoprost use (Figure 3).[24]

DUES and other PAP findings were reported to regress within 1-12 months of PGA discontinuation.[2,3,16,19,24,25] In a series of 25 patients who initially received latanoprost and did not have DUES, Sakata et al.[26] reported that DUES occurred in 15 (60%) of the patients when they switched to bimatoprost for greater IOP reduction and completely resolved in 11 of 13 patients who subsequently switched back to latanoprost. In addition, in two different studies, it was reported that PIP findings such as DUES and periocular pigmentation decreased and patient satisfaction increased after treatment with omidenepag isopropyl, a selective prostaglandin-EP2 agonist, in patients who developed PAP while using conventional prostaglandin F2α analogue drugs.[27,28]

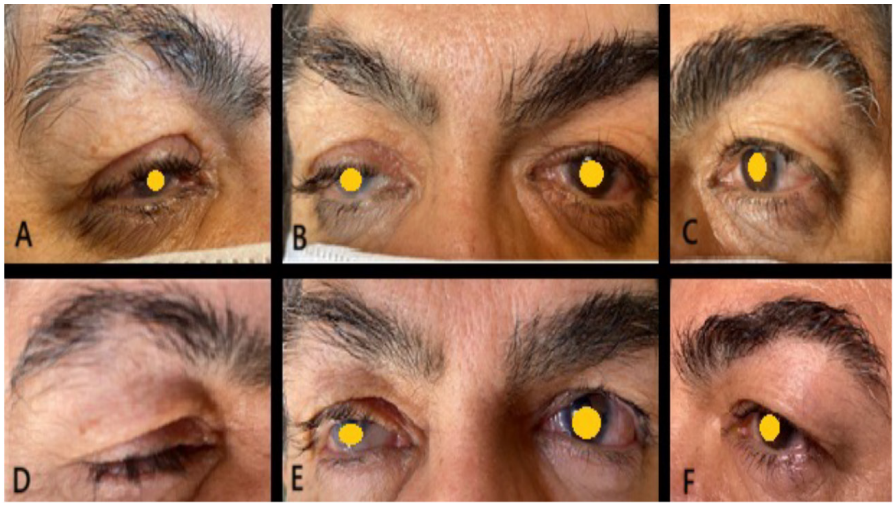

Figure 3. A patient using bilateral travoprost exhibits significant eyelash elongation and hypertrichosis in the periorbital region (A, B, C). Significant reduction in periorbital hypertrichosis was observed at 6 months after treatment discontinuation (D, E, F)

Punctum and Lacrimal System

Topical antiglaucoma drugs can cause inflammatory and fibrotic changes in the ocular surface.[29,30,31] These changes may be related to the active ingredients of the medications, as well as the preservatives used in commercial formulations or the duration of use.[29] The occurrence of similar inflammatory and fibrotic changes in the epithelial and subepithelial tissue of the lacrimal drainage system can lead to narrowing and occlusion of the lumen of the nasolacrimal system.[29,30] Obstruction associated with the use of topical antiglaucoma medications can occur in any part of the lacrimal drainage system.[30,32,33,34] Fourteen cases of punctal and canalicular stenosis were first reported in patients using long-term timolol maleate, betaxolol, and pilocarpine for the treatment of glaucoma, and were attributed to the cicatrizing effects of these agents resulting from the inflammatory changes they induce.[32] Seider et al.[33] determined that 23% of patients scheduled to undergo surgery for symptomatic nasolacrimal duct obstruction had a history of medical treatment for glaucoma. Quinn et al.[34] emphasized in a large-scale population-based study that the use of topical antiglaucoma agents increased the need for surgery to address stenosis in the punctum and other parts of the lacrimal canal. It was also noted that these patients had a higher frequency of entropion and trichiasis. Ulusoy et al.[35] also reported a relationship between the use of topical antiglaucoma agents and the prevalence of punctal stenosis. However, they provided no detailed information about the active ingredient or duration of use in their study.[35] Kashkouli et al.[30] found that punctal obstruction was more common in patients using fixed combination dorzolamide/timolol (26/130, 20%) compared to controls (24/280, 8.6%). Their study also showed that timolol/dorzolamide combination therapy had a more negative effect on the lacrimal duct system compared to monotherapy. Moreover, the authors noted a significantly higher incidence of upper canalicular system obstruction, which they suggested may be attributable to the closer proximity of the upper lacrimal system to the conjunctiva and the fornix, resulting in greater exposure to the inflammatory effects of topical drugs compared to the lower lacrimal system.[30] For this reason, the upper lacrimal system should also be examined in detail in glaucoma patients presenting with epiphora.[30]

Ectropion, Entropion, and Trichiasis

Prolonged use of topical antiglaucoma medications can cause entropion, ectropion, and trichiasis as a result of inflammation and cicatrization of the eyelid and ocular surface caused by both the active ingredients and the preservatives in these medications.[29,34,36,37] In this patient group, which is already predisposed to lid changes due to age-related involutional alterations, chronic antiglaucoma medication use and frequent scratching due to contact dermatitis caused by the drug increase lower lid laxity.[37,38] Cicatrizing changes in the eyelid also cause shortening of the anterior lamella of the lower lid, creating conditions suitable for ectropion.[29,34,36,37] Cases of entropion, ectropion, and trichiasis associated with different antiglaucoma agents have been reported in the literature. In the past, the development of drug-induced ectropion was attributed to agents that are no longer widely used, such as dipivefrin[39] and apraclonidine,[40] whereas cases of entropion, ectropion, and trichiasis are now frequently reported in association with dorzolamide,[29,38] brimonidine,[38,41] and timolol.[37] Altieri and Ferrari[42] compared lid changes between three different PGAs and a control group and indicated that lid laxity did not occur after two years of PGA use. However, there have been reports of entropion, ectropion, and trichiasis due to PGA use.[37,43,44] Among 644 eyes presenting for entropion or ectropion, Serbest Ceylanoğlu and Malkoç Şen[36] reported glaucoma in 2.2% (14 eyes total, 10 entropion/4 ectropion). Golan et al.[37] observed a higher rate (13.2%) in their study, but their inclusion of only lid malposition cases requiring surgery may explain the difference.

In addition, the high number of antiglaucoma medications (2.7 on average) used by these patients indicates the important role of these drugs in the development of lid malpositions.

Ectropion associated with topical drops is known to improve clinically after discontinuing the drug, thus reducing the need for surgery.[36,37] In contrast, entropion and trichiasis are more likely to require surgical correction.[34] Hegde et al.[38] reported regression after drug discontinuation in a series of 13 patients who developed ectropion due to antiglaucoma therapy. However, success rates are low for lid surgery performed without discontinuing or changing the topical antiglaucoma drop causing inflammation and allergy (Figure 4).[36,37,38] In multidrug regimens, inflammation and cicatrization may regress if the antiglaucoma medication causing lid malposition is identified and discontinued and treatment is continued with appropriate topical drops (preferably preservative-free antiglaucoma medications) and short-term topical steroids.[36,38] Alternative treatment options such as laser trabeculoplasty may also be considered.[34] However, patients should be informed that lid and glaucoma surgery may still be required.

Oculoplastic Problems Associated with the Surgical Treatment of Glaucoma

Upper Eyelid Ptosis

As with other anterior segment surgeries, ptosis is a possible complication of filtering or seton surgery that impacts patients' visual function and reduces their quality of life (Figure 5).[15,45,46,47,48,49] While some studies reported that the rate of ptosis development was higher in patients who underwent seton surgery with glaucoma drainage implant (GDI) compared to trabeculectomy and cataract surgery,[50,51] another study showed no significant difference in the frequency of ptosis after GDI surgery (13.7%) and trabeculectomy (10.5%).[52] In a study investigating the incidence of ptosis in patients who underwent trabeculectomy using an antimetabolite, the rate of ptosis at 6 months following surgery was reported as 19%.[45] In another study that included a 2-year follow-up period, 11 (6.7%) of 163 patients who underwent trabeculectomy developed ptosis, 9 of whom required surgical treatment.[46] Authors have emphasized that in cases where trabeculectomy and cataract surgery were combined, the incidence of ptosis was not higher than in patients who underwent cataract surgery alone.[15,47,48] Song et al.[47] stated that the development of ptosis was independent of whether trabeculectomy was performed before or after cataract surgery or combined with phacoemulsification, and was not affected by the size of the conjunctival flap or whether it was limbus- or fornix-based. Koh et al.[48] reported that in addition to bleb morphology and total bleb area, factors affecting the prevalence of postoperative ptosis included the type of anesthesia used during glaucoma surgery, the temporary suture placed in the limbus or upper rectus for eye fixation during surgery, and levator aponeurosis dehiscence resulting from the lids being held open by the speculum over a prolonged surgical time. Fukushima et al.[15] stated that the most important risk factor for ptosis after filtering surgery was the presence of DUES preoperatively, whereas the type of glaucoma, the number of glaucoma drugs used, or the need for postoperative needling were not significant in terms of ptosis development. On the other hand, some studies have emphasized that the risk of ptosis increases in patients who need postoperative needling, undergo external bleb massage, and have frequent eye itching due to ocular surface allergy caused by antiglaucoma agents and preservatives.[45,49]

Although ptosis may resolve spontaneously after glaucoma surgery, it is sometimes persistent. In a series of 339 eyes that underwent trabeculectomy, Malkoç Şen and Serbest Ceylanoğlu[49] reported transient ptosis in 30 eyes (8.8%) and persistent ptosis in 5 eyes (1.5%). Ptosis after glaucoma surgery is considered persistent if it lasts longer than 6 months, and surgical intervention can be planned accordingly.[3] Transient postoperative ptosis mostly occurs due to eyelid edema, hematoma, inflammation, or the effect of anesthetic agents on the oculomotor nerve branches and levator muscle.[3,53] Persistent ptosis usually occurs as a result of levator aponeurosis dehiscence. Age-related soft tissue and orbital fat atrophy and structural changes such as DUES occurring as a result of long-term PGA use before surgery are other contributing factors. Additionally, bleb needling, prolonged lid speculum and fixation suture use with extended surgical time, and a history of eye scratching due to antiglaucoma drug allergy may trigger levator aponeurosis dehiscence and pose a risk for the development of ptosis.[3,48,49,53,54]

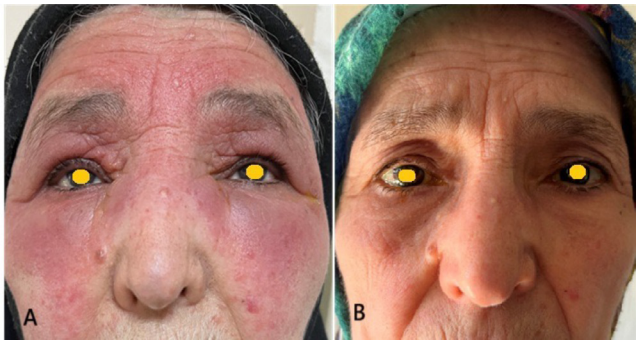

Figure 4. A) Allergic reaction spreading to the periorbital region and face following the use of brinzolamide/brimonidine tartrate fixed combination. B) Regression of the allergic findings was observed after discontinuing treatment

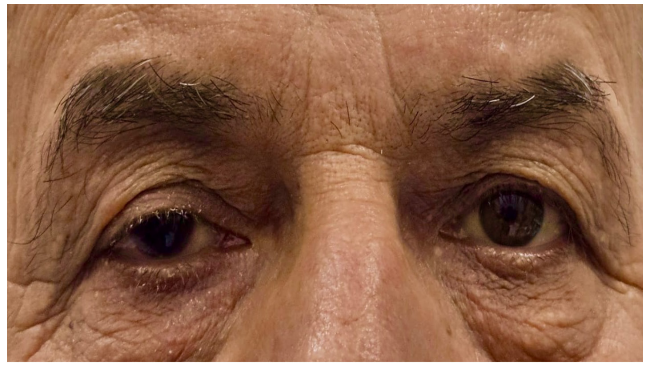

Figure 5. Ptosis following trabeculectomy surgery in the right eye. Marginal reflex distance 1 was 1 mm in the right eye and 4 mm in the left eye

When evaluating the visual field in patients with ptosis before or after surgery, it is important not to ignore the effect of the upper eyelid on the visual field.[3,4] For example, in a patient with an inferior arcuate visual field defect, concomitant ptosis or blepharochalasis may mimic a superior arcuate defect, inadvertently leading to a diagnosis of advanced glaucoma.[49] In such cases, repeating the visual field test while lifting the upper eyelid may demonstrate that ptosis surgery can significantly improve the patient's quality of life. Similarly, new ptosis developing after glaucoma surgery can create the false impression that disease progression continues postoperatively. Repeating the test after eliminating the eyelid's effect on the visual field will also provide guidance in terms of correct treatment management in these cases.

There are some important points to consider in the correction of persistent postoperative ptosis:

• The antimetabolites used during filtering surgery lead to a thinner and avascular bleb structure postoperatively.[55] Therefore, excessive correction should be avoided when planning ptosis surgery in these patients.[3] Otherwise, lagophthalmos may occur and the risk of serious complications such as blebitis and endophthalmitis will increase because the bleb is not adequately protected by the lid.

• Anterior or posterior conjunctival approaches may be preferred in the surgical treatment of ptosis after glaucoma surgery.[56,57,58] Song et al.[56] reported similar results with levator surgery via an anterior approach and Müller muscle resection via a conjunctival approach. Ben Simon et al.[57] stated that this method may be preferrable because there is less need for revision and more satisfactory cosmetic results with the conjunctival approach. However, when applying this technique, caution should be exercised during eyelid inversion to avoid potential iatrogenic traumas that may adversely affect bleb function.[3] The main purpose of surgical correction in patients who develop ptosis after filtering surgery should be to provide aesthetic and functional improvement without compromising bleb function.[3] In fact, Yunoki et al.[58] demonstrated that levator surgery performed via anterior approach in cases of new ptosis following trabeculectomy is completely safe in terms of filtration bleb function. In contrast, Putthirangsiwong et al.[59] stated that the conjunctivomullectomy method applied with the posterior approach may be an effective and safe option but reported that bleb failure occurred in 10.3% of patients with this method, emphasizing the need for caution.

Eyelid Retraction

Compared to ptosis, upper eyelid retraction following trabeculectomy is a very rare complication.[60,61] Therefore, all other neurogenic, myogenic, and mechanical causes that may cause retraction should be ruled out, especially thyroid orbitopathy.[60,61,62,63] First described by Putterman and Urist[64] in 1975, several cases have been subsequently reported by different authors.[60,61,62,63] Lid retraction may occur within 1 week after trabeculectomy[61] or after 20 years.[62] A large and cystic filtration bleb is an important risk factor for the development of lid retraction (Figure 6).[60] However, the fact that the retracted lid returns to its original position when pulled down and the development of unilateral lid retraction following bilateral trabeculectomy indicate that the pathogenesis cannot be explained by mechanical factors alone.[60,61,64] Nevertheless, Putterman and Urist[64] hypothesized that adrenergic substances in the aqueous lead to lid retraction by causing Müller muscle hyperactivation, while Awwad et al.[61] proposed that mitomycin C used during trabeculectomy has a toxic effect on the Müller muscle, leading to fibrosis in the long term. These mechanisms may help at least partially elucidate the pathogenesis of lid retraction in these patients.

The treatment approach to lid retraction following filtering surgery should be individualized according to the patient's symptoms.[60] Cases with mild retraction and bleb dysesthesia can be managed with artificial tears and bleb-related interventions. Mechanical closure at night, topical steroids, and sympatholytic agents may also alleviate retraction. However, these approaches provide symptomatic and temporary relief.[60] The "graded full-thickness anterior blepharotomy" method described by Elner et al.[65] can be implemented in these patients. Shue et al.[62] pointed out that for the surgical correction of lid retraction, methods such as Müller muscle surgery via posterior approach or "full-thickness anterior blepharotomy" may impair bleb function, as in ptosis surgery.[56,58] Aiming to reduce this risk, they modified these techniques and reported that a higher success rate with fewer complications could be achieved with the "conjunctiva-sparing anterior blepharotomy" method they described.[62] In a patient with lid retraction following trabeculectomy who already underwent transconjunctival mullerectomy, Vásquez and González-Candial[63] reported that filling with hyaluronic acid injection provided temporary anatomical and functional improvement and reduced the need for repeated surgery due to recurrent retraction. Clark et al.[66] used mathematical vector analysis to determine the forces affecting upper eyelid position in patients with blebs and showed that injection of botulinum toxin A into the upper lid inhibited retraction.

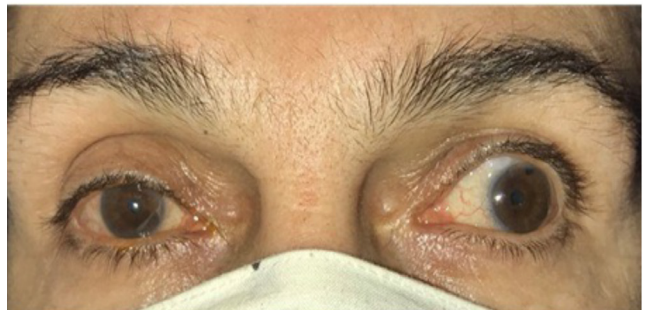

Figure 6. Female patient with mechanical upper lid retraction due to a large cystic bleb located in the superonasal region of the left eye, which also exhibits marked exotropia

Lacrimal Gland Changes Due to Glaucoma Drainage Implants

A GDI is usually implanted in the superotemporal region, near the lacrimal gland. In a study examining the effect of GDIs on lacrimal gland position with magnetic resonance imaging, lacrimal gland measurements in the unoperated orbit were similar to those of the normal population in terms of size and volume, whereas the lacrimal glands on the GDI side had significantly smaller volume, flatter morphology, and more posterior placement.[67] These findings may be directly due to the mechanical pressure caused by the GDI, as well as the gradual development of lacrimal gland atrophy. However, no significant relationship was found between lacrimal gland size and clinical symptoms of dry eye in patients with GDI.[67] Gobeka et al.[68] also reported that lacrimal gland volume was smaller in eyes with GDI compared to trabeculectomized eyes in their high-resolution computed tomography study. Additionally, they observed that lacrimal gland volume was lower in the eyes with GDI compared to unoperated side, as expected. However, lacrimal gland volume in the trabeculectomized eyes was surprisingly higher than in the unoperated eyes. The authors also emphasized that intraoperative mitomycin C application had no effect on lacrimal gland volume or size.[68]

Glaucoma Drainage Implant Exposure

One of the main complications of GDIs is exposure resulting from gradual erosion of the conjunctival tissue over the tube or implant plate, often due to inadequate or incorrect placement (Figure 7).[69,70] This undesirable situation can occur immediately after surgery or over the course of years, leading to serious infectious complications such as orbital cellulitis and endophthalmitis.[70] Tamçelik et al.[71] developed the "Tenon advancement and reproduction technique" to prevent GDI exposure. This technique can reduce the risk of implant exposure by performing it with a short scleral tunnel, as described by the authors,[71] or with a long scleral tunnel[72] or scleral flap.[73] The scleral tunnel technique has been reported to be more advantageous than the scleral flap in patients with GDIs.[74] In addition, various graft materials such as lyophilized pericardium, fascia lata, lyophilized sclera, dura mater, amniotic membrane, and cornea are also used to prevent GDI exposure.[70]

Phthisis Bulbi/Enophthalmos

In the long term, some complications that develop after glaucoma surgery may lead to irreversible ocular conditions such as phthisis bulbi and enophthalmos (Figure 8).

Evisceration and Prosthesis Requirement

Eyes that are completely blind and painful due to uncontrolled IOP despite using all available medical and surgical options for glaucoma treatment may require evisceration and a removable ocular prosthesis. The primary goal in these patients is to relieve chronic and severe ocular pain rather than aesthetic concerns.

Glaucomatous Conditions Following Oculoplasty Surgery

In addition to oculoplastic problems that may develop as a result of medical and surgical glaucoma treatment, there are also glaucomatous conditions that occur following oculoplastic surgery. This phenomenon is an important point that is often overlooked and warrants caution. For example, Osaki et al.[75] reported a statistically significant increase in IOP after upper lid blepharoplasty surgery. The results of their study indicate that the possible risks in terms of glaucoma after blepharoplasty must be carefully evaluated in glaucoma patients and glaucoma suspects. Publications in the literature about the development of acute angle closure following blepharoplasty are also noteworthy.[76,77,78] A common feature of these cases is reports of pupil dilation after surgery. In fact, a study conducted by Koçer and Sen[79] with automatic pupillometry in patients who underwent blepharoplasty surgeries demonstrated significant changes in static and dynamic pupil measurements postoperatively. Although there is still uncertainty regarding the role of other factors that contribute to pupil dilation, such as anxiety, pain, postoperative eye closure, or the pharmacological effects of anesthetic agents, the risk of angle closure after oculoplastic surgery is important.[79] A complete preoperative ophthalmological examination in which the anterior chamber is also evaluated is necessary for all patients undergoing oculoplastic surgery.

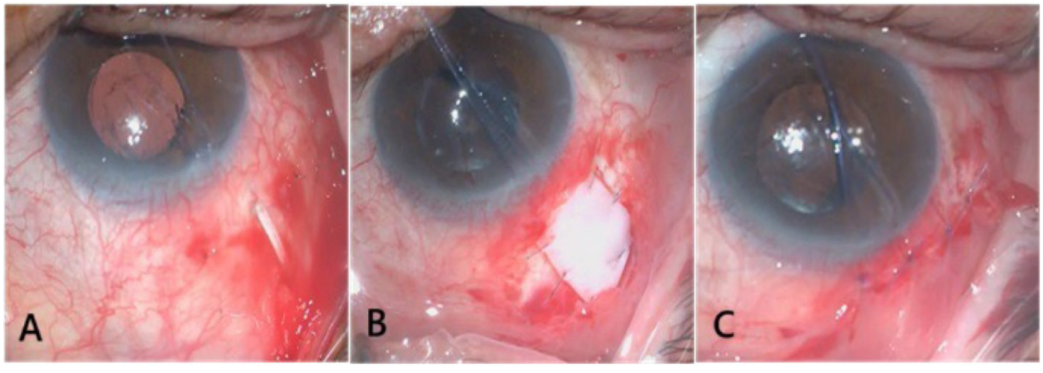

Figure 7. A) Conjunctival dehiscence and subsequent tube exposure in an eye with an Ahmed FP7 glaucoma valve. B) Lyophilized bovine pericardium was fixed over the exposed area using 10-0 nylon suture. C) The conjunctiva was closed primarily

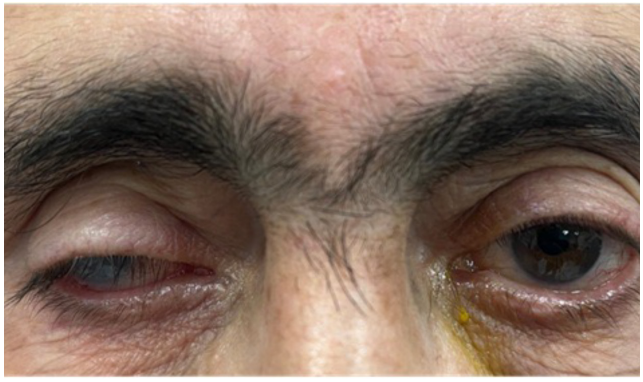

Figure 8. Enophthalmos of the right eye due to absolute glaucoma and phthisis bulbi

Appropriate Treatment of Oculoplastic Problems in Patients with Glaucoma

Beyond the oculoplastic complications associated with glaucoma treatment, it is also important to careful select treatment for glaucoma patients who already have oculoplastic problems. For example, knowing the patient's history of PGA use when planning blepharoplasty or ptosis surgery can be decisive in determining the surgical approach.[3,4] While PAP can be diagnosed more easily in patients using PGAs unilaterally, conditions such as DUES can be overlooked in patients with bilateral use. In such cases, DUES and lipoatrophy that may occur in the present or future due to PGA use should also be taken into account when planning blepharoplasty in addition to age-related periorbital volume loss. A more conservative approach is also recommended, as PGA treatment may accelerate orbital adipose tissue atrophy. In this context, it is prudent to protect the fat pads and minimize the skin excision compared to standard practices. Otherwise, there may be undesirable aesthetic consequences such as a sunken eye appearance after surgery.[3,4]

Concomitant glaucoma is among the important points for oculoplastic surgeons to consider in cases of eyelid malposition. With aging, the incidence of both glaucoma and eyelid malpositions such as ptosis, entropion, and ectropion increases.[3] Therefore, it is critical in treatment planning to distinguish whether lid changes in these patients are a result of age-related physiological mechanisms or a side effect of the topical glaucoma drugs used.[36] In addition, the mechanical effect exerted when instilling topical medication may exacerbate the existing horizontal and vertical lid laxity in these patients. Epiphora is another potential side effect that may cause skin irritation, chronic inflammation, and eventually scarring due to frequent eyelid wiping. Early recognition of side effects related to medical therapy in cases of eyelid malposition allows the timely termination of topical agents before irreversible fibrotic changes, thereby facilitating treatment without surgery and increasing success when surgery is required.

However, in glaucoma patients with ectropion, the oculoplastic surgeon may overlook this effect. If lid surgery is performed while topical drug treatment is ongoing, surgical failure and recurrence are inevitable because of persistent drug-induced inflammation.[4] Therefore, topical antiglaucoma drugs should be discontinued, inflammation should be controlled with low-potency steroid drops, and the desired IOP reduction should be managed with oral acetazolamide before surgical planning. In patients with severe allergic symptoms, oral antihistamines may be added to treatment. It should also be noted that these patients may need trabeculectomy.[4] In patients with entropion accompanied by glaucoma, the use of preserved topical drops in particular may increase corneal exposure and cause serious ocular surface diseases. Therefore, correcting the entropion with an appropriate surgical method and in a timely manner is essential to avoid interrupting glaucoma treatment.

As discussed above in the relevant section, the frequency of punctal obstruction was found to be higher in patients using dorzolamide/timolol fixed combination.[30,31] It would be a rational approach to avoid these drugs in patients who have developed punctal obstruction for any reason and undergone surgery for its correction. On the other hand, in patients with nasolacrimal duct obstruction and/or lacrimal sac abscess, the presence of a cystic, avascular bleb resulting from the use of antimetabolites during trabeculectomy may significantly increase the risk of blebitis and endophthalmitis. Therefore, the risk of infection should be carefully considered during surgical planning for such patients.

Conclusion

Oculoplastic problems and other complications that may occur due to medical and surgical treatment in glaucoma patients can affect eye health not only in terms of function, but also in terms of aesthetics and comfort. Awareness of these problems and careful management with consideration of risk factors are critical both in terms of medicolegal aspects and treatment success. During the glaucoma treatment process, regular oculoplastic evaluation and early diagnosis of possible complications contribute significantly to both vision and quality of life. It should be noted that glaucoma patients may present unique and challenging surgical conditions compared to other oculoplastic cases. When planning oculoplastic surgery in those who have undergone filtering surgery, the primary focus should be to not disrupt bleb function, and attention should be paid to the risks of blebitis and endophthalmitis in the presence of cystic bleb. It is important to increase the awareness of oculoplastics complications among clinicians planning glaucoma surgery and to determine multidisciplinary management strategies.

Ethics

Informed Consent: Patient consents have been obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: E.Ş., S.B., Concept: E.Ş., S.B., Design: S.B., K.S.C., Data Collection or Processing: E.Ş., S.B., Analysis or Interpretation: E.Ş., S.B., K.S.C., Literature Search: S.B., K.S.C., Writing: S.B., K.S.C.

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Neurovisual Developmental Considerations with Myopia Control Spectacles

Murat Erbezci

Private Practice, İzmir, Türkiye

Dear Editor,

I would like to raise concerns regarding the use of myopia control glasses, such as Defocus-Incorporated Multiple Segments, Miyosmart (HOYA, Tokyo, Japan), Highly Aspherical Lenslets Technology, and Stellest (Essilor, Charenton-Le-Pont, France), in children. While these glasses are effective in slowing myopia progression by creating peripheral myopic defocus, their introduction during critical periods of neurovisual development warrants careful consideration.

A child's neurovisual system undergoes significant development up to around seven years of age,[1] but recent evidence suggests that certain forms of plasticity can persist even in older children and adults, particularly in response to specific interventions or therapeutic protocols.[2,3] During this period, disruptions in visual input can alter the maturation of essential visual functions like binocular vision, contrast sensitivity, and visuo-motor coordination. Myopia control glasses alter visual input, which might interfere with these developmental processes. Specifically, these lenses may affect reading acquisition—a task heavily dependent on visual acuity, binocular vision, and visuo-motor coordination. Given that children often begin learning to read during this sensitive developmental window,[4] the optical modifications of these glasses could hinder reading skills by reducing contrast sensitivity, disrupting binocular alignment, and potentially affecting ocular dominance, which plays a role in binocular coordination and reading fluency. Moreover, myopia control lenses intentionally induce peripheral blur to slow axial elongation, which could impair peripheral visual function and contrast sensitivity. These factors are vital for reading and other academic tasks, potentially contributing to difficulties in reading fluency, comprehension, and word recognition.[5] Additionally, the altered visual input might influence the development of the visual cortex and other neurodevelopmental processes that support cognitive tasks such as spatial awareness and pattern recognition. To mitigate these potential risks, I urge further research into the long-term neurovisual effects of these lenses. Longitudinal studies assessing both refractive outcomes and neurovisual development, particularly in relation to reading acquisition, are essential. In conclusion, while myopia control glasses show promise in reducing myopia progression, their impact on children's neurovisual development, especially in terms of reading, must be thoroughly evaluated. Until such data is available, I recommend a cautious approach to their use, particularly in children at crucial stages of reading development.

Ethics

Informed Consent: This article does not require patient consent.

Declarations

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Address for Correspondence: Murat Erbezci, Private Practice, İzmir, Türkiye
E-mail: muraterbezci@gmail.com **ORCID-ID:** orcid.org/0000-0003-2163-2157
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Urrets-Zavalia Syndrome After Posterior Chamber Phakic Intraocular Lens Implantation: An Unusual Complication

Mamta Singh[1], Alok Ranjan[2], Noor Husain[3]

[1]All India Institute of Medical Sciences, Department of Ophthalmology, Rajkot, India
[2]Patna Medical College and Hospital, Department of Ophthalmology, Patna, India
[3]Indira Gandhi Institute of Medical Sciences, Department of Pharmacology, Patna, India

Dear Editor,

Urrets-Zavalia syndrome (UZS), also known as Castroviejo syndrome, is characterized by a fixed dilated pupil and is a recognized complication of various anterior segment surgeries, including cataract surgery, deep anterior lamellar keratoplasty, Descemet stripping automated endothelial keratoplasty, trabeculectomy, iridoplasty, goniotomy, C3F8 injection into the anterior chamber (AC), and phakic intraocular lens (P-IOL) implantation.[1,2] The reported incidence in the published literature ranges from 0% to 17.7%, depending on the type of surgery performed and numerous intraoperative and postoperative factors.[1] The pathophysiology of UZS involves iris ischemia causing sphincter muscle atrophy or damage to the radial parasympathetic fibers that innervate the pupil constrictor muscles. Neuronal injury can result from direct trauma or alteration in the acetylcholine mechanism leading to parasympathetic dysfunction. Atrophy of the iris sphincter muscle may be due to surgical injury, use of mydriatic agents, AC inflammation, and raised intraocular pressure (IOP) which can be secondary to retained viscoelastic material or intracameral gas injection.[1,3,4] This report presents a case of unilateral UZS in a young patient after posterior chamber P-IOL surgery. The unusual presentation and its significant educational value make this case particularly noteworthy. It highlights the need for awareness of this potential complication, in light of the growing popularity of refractive surgeries, to optimize management strategies. Prior to publication, written informed consent was obtained from the patient for the use of his clinical history and images for academic purposes in established medical journals.

A 25-year-old male patient presented with high myopic astigmatism seeking refractive surgical correction. Subjective correction was –12.00 diopters (D)/-2.25 D × 180° in his right eye (OD) and -7.00 D/- 2.00 D × 180° in the left eye (OS), with a best-corrected visual acuity of 6/6 bilaterally. Keratometry readings were 40.25 D @ 171° and 42.25 D @ 81° for OD and 40.75 D @ 176° and 42.5 D @ 86° for OS. Corneal thickness, white-to-white distance, and AC depth measured 529 µm, 12.12 mm, and 3.33 mm in OD and 526 µm, 12.16 mm, and 3.33 mm in OS. Anterior and posterior segment evaluations were unremarkable for both eyes.

Based on these parameters, implantation of the Eyecryl phakic toric aspheric IOL (Biotech Vision Care; Ahmedabad, India) was planned, with the OD operated on first. The surgery was uneventful, and the patient achieved a visual acuity of 6/6 on the first postoperative day. A week later, the OS was operated without any complications. However, within an hour of surgery, the patient reported increasing pain in the OS. IOP was measured at 40 mmHg (applanation tonometry), and slit-lamp evaluation showed corneal edema, a grade 3+ AC reaction, and a mid-dilated, fixed pupil unresponsive to light. Posterior segment evaluation was normal, with no sign of inflammation. An initial diagnosis of toxic anterior segment syndrome (TASS) was made. The patient was prescribed systemic prednisolone (1 mg/kg

Keywords: Phakic intraocular lens, Urrets-Zavalia syndrome, intraocular pressure, anterior chamber inflammation

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Address for Correspondence: Mamta Singh, All India Institute of Medical Sciences, Department of Ophthalmology, Rajkot, India
E-mail: academicsmamta@gmail.com **ORCID-ID:** orcid.org/0009-0007-3358-2747
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body weight; Omnacortil tablet, Macleods Pharmaceuticals Pvt Ltd, Mumbai, India), acetazolamide (250 mg every 8 hours; Diamox tablet, Sun Pharmaceutical Industries Ltd, Mumbai, India), and homatropine eye drops (twice daily; Homide 2% ophthalmic drops, Indoco Remedies Ltd, Mumbai, India), along with the standard postoperative regimen, which included a combination of topical moxifloxacin (Moxicip ophthalmic drops, Cipla Ltd, Mumbai, India) and prednisolone acetate (Pred Forte ophthalmic suspension, Allergan India Pvt Ltd, Mumbai, India) with lubricating drops. On the first postoperative day, OS visual acuity was limited to counting fingers close to the face, IOP was 24 mmHg, and grade 3+ AC inflammation persisted. The pupil was mid-dilated, irregular, nasally deviated, and nonreactive to light. On the second postoperative day, anterior segment optical coherence tomography was performed to assess the vault and rule out any inadvertent iris capture. The P-IOL was positioned correctly, with a vault of 650 µm, and the AC angle was wide open. Pentacam tomography (Oculus Optikgeraete GmbH; Wetzlar, Germany) confirmed these findings (Figure 1). Given the tomographic finding of an open angle and absence of pupillary block, AC inflammation or retained viscoelastic material were considered the likely causes of the elevated IOP.

With continued topical and systemic treatment, AC inflammation resolved by the seventh postoperative day, and visual acuity improved to 6/9. IOP was 12 mmHg with twice-daily topical timolol (Timolet ophthalmic drops, Sun Pharmaceutical Industries Ltd, Mumbai, India) as the sole antiglaucoma medication. The pupil was mid-dilated, slightly deviated nasally, and sluggishly reactive to light. The patient reported photophobia and night-time glare. On the 14th day, topical pilocarpine (Pilocar 2% ophthalmic drops, FDC Ltd, Aurangabad, India) eye drops were administered every 15 minutes for 1 hour as a trial application, but the pupil remained unresponsive. Surgical mechanical manipulation of the iris followed by intracameral pilocarpine (Carpinol injection, Sun Pharmaceutical Industries Ltd, Mumbai, India) was attempted to restore a regular pupil shape, but the effect was temporary.

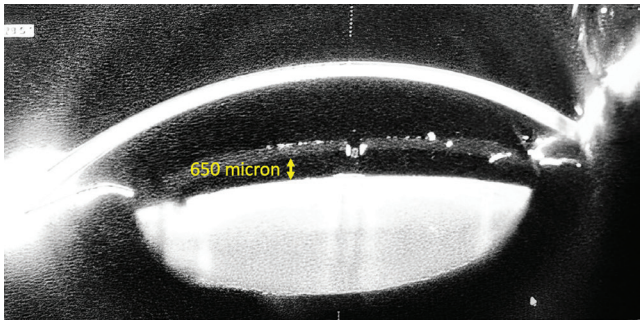

Figure 1. Pentacam tomography (Oculus Optikgeraete GmbH; Wetzlar, Germany) image showing the phakic posterior chamber intraocular lens

By the following day, the pupil had returned to its mid-dilated, nasally deviated position.

A provisional diagnosis of UZS was made. As IOP was within normal range (12-14 mmHg) and baseline glaucoma evaluation showed normal results, the timolol eye drop was stopped and the other postoperative medications were gradually tapered and ceased as per standard protocol. The patient was counselled about the prognosis, and with regular follow-up, symptoms improved significantly. Although the pupillary dilation improved slightly, the pupil maintained a more dilated, nasal configuration. Atrophic patches were seen on the iris, along with pigment dispersion on the P-IOL (Figure 2).

The occurrence of UZS following posterior chamber P-IOL implantation has been sparsely reported in the literature,[4,5,6,7,8] particularly in cases associated with TASS. Potential pathogenic mechanisms for the development of UZS include genetic predisposition to iris tissue injury due to mechanical, neurological, or inflammatory processes.[2] Iris fluorescein angiography in affected patients suggests areas of ischemia and nonperfusion.[9] Although UZS usually manifests unilaterally, rare cases affecting both eyes have been documented, suggesting a potential underlying anatomical predisposition in these eyes.[1,10,11,12] The exact mechanism causing its unilateral or bilateral presentation remains unclear.

In this case, an uneventful surgery was followed by TASS and raised IOP. Both inflammatory and IOP-induced damage have been linked to UZS.[4,8] The association between TASS and UZS in cataract patients has been reported by Nizamani et al.[13] and Ganesan et al.[14], with the latter suggesting that TASS may represent an aborted form of ischemic damage preceding UZS. The clinical events and the P-IOL used in this case closely resembled those reported by Balparda et al.[8] However, unlike their cases, where surgeries were performed at different centers with possible variations in sterilization and handling procedures, the surgeries

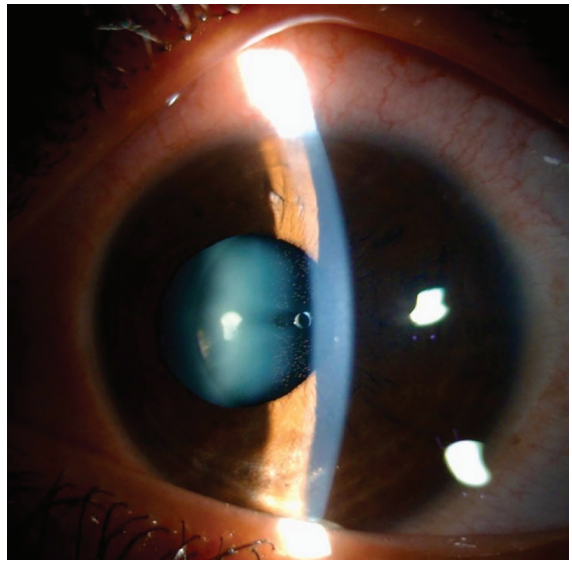

Figure 2. Mid-dilated, nasally shifted pupil, iris atrophic patches, and iris pigment dispersion on the phakic intraocular lens

in this case were performed by the same surgeon at a single center. Early systemic and topical corticosteroid administration controlled the inflammatory cascade by the seventh day in our case. In contrast, cataract formation, endothelial damage, and UZS in their case were likely due to delayed resolution of corneal edema and AC inflammation.

A similar case report of TASS following P-IOL implantation suggested that the etiology may involve viscoelastic residues or an idiosyncratic inflammatory response to intracameral pilocarpine.[7]

Topical pilocarpine has been reported to have a therapeutic role in the UZS pupil, causing its constriction and restoration of light reflex.[4] However, in this case, the pupil did not respond to topical pilocarpine. Given the significant improvement in the patient's subjective symptoms two months post-surgery, any further intervention was temporarily postponed. Pupillary recovery following UZS possibly depends on the spectrum of muscular damage. Patients with marked atrophy of both the anterior and posterior layers of the iris present with irreversible mydriasis. Between one-third and two-thirds of patients with milder damage recover partial pupillary activity within 1 to 18 weeks.[1]

UZS after P-IOL implantation is an uncommon but potentially vision-impairing complication. With the growing popularity of refractive surgeries, it is important to be aware of this clinical entity as a potential complication. Optimal visual outcomes in such cases are dependent on early diagnosis and prompt control of IOP and AC inflammation.

Ethics

Informed Consent: Written informed consent for publication obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: M.S., A.R., Concept: M.S., Design: M.S., A.R., N.H., Data Collection or Processing: A.R., Analysis or Interpretation: M.S., A.R., Literature Search: M.S., N.H., Writing: M.S., A.R., N.H.

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Bilateral Asynchronous Infraorbital Masses in a Patient Denying Dermal Filler Injection

Ceyhun Arıcı[1], Batuhan Aksoy[1], Mehmet Serhat Mangan[2]

[1]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Haydarpaşa Numune Training and Researc Hospital, Sadık Eratik Eye Clinic, İstanbul, Türkiye

Dear Editor,

Filler injections for facial volume restoration, especially with hyaluronic acid (HA) fillers, have surged in the past decade. The infraorbital area is a frequent target to correct volume loss and improve under-eye hollows. Although generally safe, dermal fillers can lead to complications long after treatment, including atypical infections, inflammation, migration, scarring, and foreign body granulomas.[1,2]

Very late-stage orbital mass formation following lower lid injection of HA filler has been reported in only one study.[2] As far as we know, there has been no study reporting very late-stage orbital mass formation bilaterally and asynchronously secondary to HA filler injection into the inferior eyelid. We hereby present a case of a palpable mass in the right infraorbital region 10 years after filler injection in a patient who underwent orbitotomy due to concern about a potential orbital tumor. This diagnosis was confirmed histopathologically. Forty months after the operation, the same clinical situation occurred in the left medial infraorbital area. This time, the lesion regressed with corticosteroid treatment. This case is reported in accordance with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act and with the patient's written consent.

A 43-year-old otherwise healthy woman presented with a 5-week history of a gradually enlarging palpable mass in the right inferior medial orbit (Figure 1A). She had no history of allergies, pain, lacrimation, nasal obstruction, hemorrhage, or prior trauma or surgery. The anterior segment and fundus of both eyes appeared normal, and intraocular pressure was 14 and 15 mmHg in the right and left eyes, respectively, as measured by non-contact tonometer. Periocular examination revealed a firm, non-tender, mobile mass located in the tear trough area of the right orbit. There were no complaints related to the left orbit, and examination was normal. Complete blood count, biochemistry, erythrocyte sedimentation rate, and thyroid hormone values were all normal.

Magnetic resonance imaging (MRI) of the orbit showed a soft tissue mass isointense to muscle on T1-weighted sequences and with a poorly-defined border on T2-weighted sequences, with diffuse enhancement after injection of contrast material (Figure 1B).

A subciliary incision was made 2 mm below the lower eyelid margin. Dissection was carried out deep into the orbicularis oculi and superficial to the orbital septum to expose the infraorbital rim. The periosteum was incised and elevated to access the anterior orbit. Orbital fat was gently retracted to identify the mass, which was carefully dissected from the surrounding structures using blunt and sharp techniques, preserving the infraorbital nerve and extraocular muscles. The mass was excised en bloc and submitted for histopathological analysis.

According to the histopathology report, microscopic examination of hematoxylin and eosin stained sections revealed a granulomatous inflammatory reaction characterized predominantly by the presence of foreign body-type multinucleated giant cells. These giant cells were observed surrounding amorphous, mucoid, basophilic foreign material dispersed within the tissue. The surrounding stroma

Keywords: Filler, granuloma, hyaluronic acid, hypersensitivity, orbital mass

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Address for Correspondence: Ceyhun Arıcı, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Türkiye
E-mail: ceyhundr@gmail.com **ORCID-ID:** orcid.org/0000-0002-7962-8911
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demonstrated a mild lymphocytic infiltrate indicative of a chronic inflammatory response. Additionally, there was evidence of vascular hyperemia, reflecting increased blood flow and local tissue reaction (Figure 1C).

Despite repeated inquiries, the patient did not disclose any history of prior filler injections during the initial ophthalmic examination. Following surgical excision of the mass and the results of pathologic examination, she admitted that she had once received an injection of HA filler bilaterally in the lower eyelids 10 years earlier but had not wanted to disclose this information because she underwent the procedure despite her family's disapproval. At postoperative 2 years, ocular and periocular examination findings were normal and the patient had no complaints (Figure 1D).

Over 3 years after her initial presentation (approximately 13.5 years after HA filler), the patient presented again with the same clinical picture in the left medial lower infraorbital area (Figure 2A). An MRI scan with contrast showed left inferior medial orbital rim soft tissue thickening with enhancement in coronal T2-weighted sequences (Figure 2B). This time, the lesion regressed with cortisone treatment (oral prednisolone tablet [Mustafa Nevzat, İstanbul, Türkiye] started at 32 mg, tapered to discontinuation in 6 weeks) (Figure 2C).

The periorbital area is the first to show signs of aging due to genetic and physiological changes, such as thinning skin, loss of collagen and elastic fibers, and soft tissue and bone reduction. Because of its delicate anatomy, rejuvenation procedures are challenging and may cause side effects.[3]

HA filler injections are popular for treating periorbital defects. The outcomes are generally uncomplicated, although in rare cases, complications such as a granulomatous infection causing mass effect can occur. Mosleh et al.[4] presented a case report of a 63-year-old woman with a mass in the orbit due to migration of dermal filler. This can make it hard to link the mass to the filler. Histopathological confirmation is often necessary to avoid overlooking new pathologies. Qiu and Xiang[5] presented a case report of a 51-year-old woman with persistent swelling after HA dermal filler. A biopsy showed a granulomatous reaction. The patient was treated with intravenous and oral corticosteroids and antihistamines.

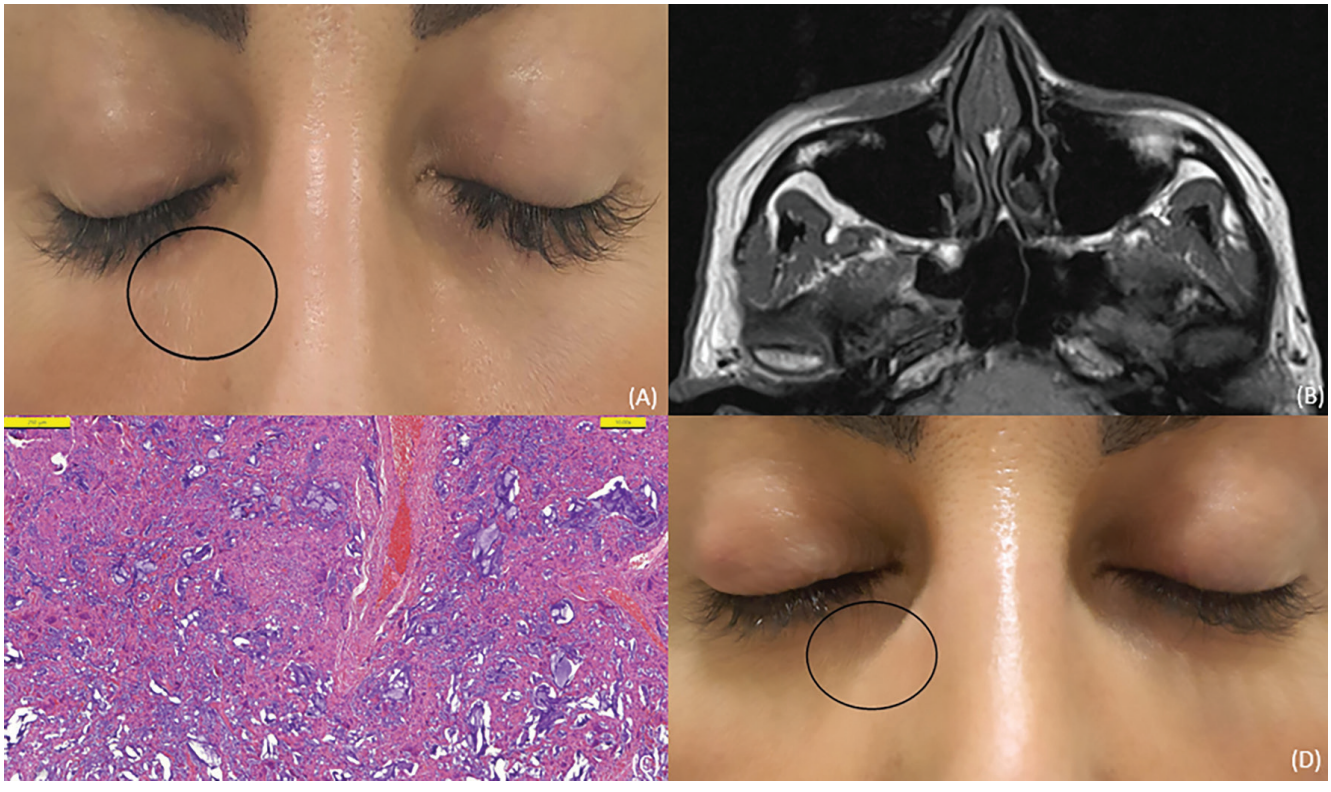

Figure 1. A) Right inferomedial orbital rim mass (circle). B) Pre-contrast axial T1-weighted magnetic resonance image showing soft tissue mass effect in the right infraorbital rim. C) Foreign-body giant cell reaction surrounding amorphous, mucoid basophilic foreign material, mild lymphocytic infiltration, and hyperemia (hematoxylin and eosin, ×100). D) 24 months after surgical removal of right inferior orbital rim mass

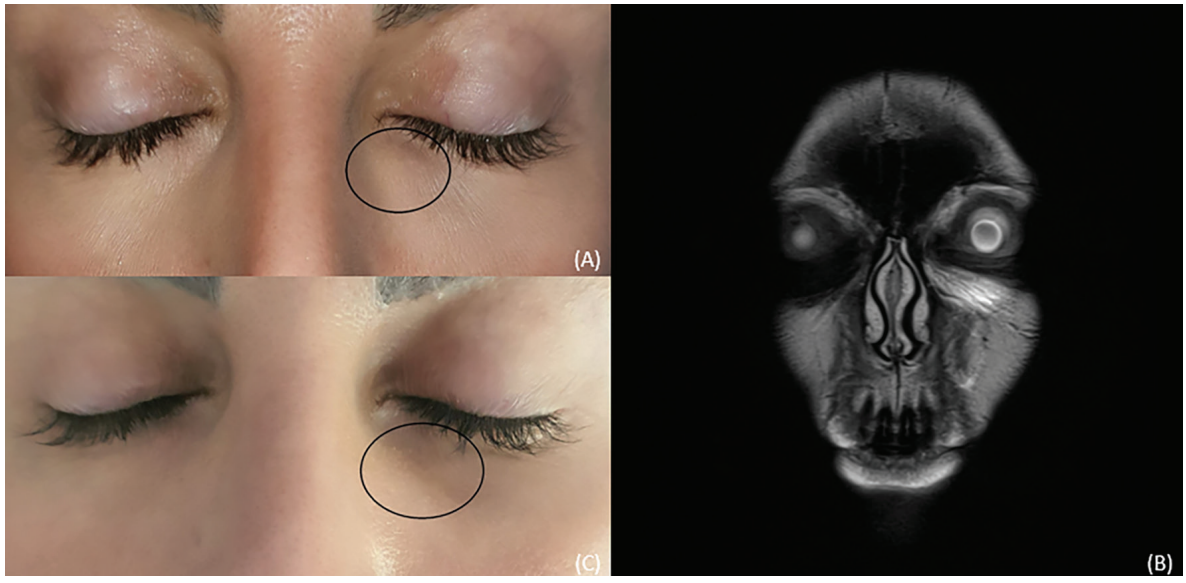

Figure 2. A) Left inferomedial orbital rim soft tissue involvement (circle). B) Post-contrast coronal T2-weighted magnetic resonance image demonstrating inferomedial diffuse contrast enhancement. C) Regression of soft tissue involvement 6 weeks after cortisone treatment

The complications of dermal fillers may have early, late, or delayed onset. Bruising, ischemic changes, and dermal necrosis are acute. Severe vaso-occlusions and wound infections are rare early complications. Later complications include early resorption, persistence, atypical infection, inflammation, and delayed granuloma formation.[1] The specific cause of these reactions is unknown, but one of several theories involves the formation of biofilms around the filler. Biofilms are bacterial communities that have become integrated into a matrix of extracellular polymeric substances, thus enabling the compound to adhere to the tissue surrounding it and evade antibiotics and culture tests.[6] Another theory is that with the persistence of the HA material, delayed inflammation may occur due to degradation products of the cross-linking procedure or product contaminants.[7]

Nathoo et al.[8] reported three cases of periocular mass lesions in which none of the patients recalled or reported undergoing dermal filler treatment in the periorbital area. Physicians should always ask patients about dermal fillers.

In the present case, a mass was found in the right infraorbital region of the patient and a biopsy showed granulomatous inflammation caused by dermal filler. As far as we know, this is the longest time between HA filler injection and the formation of bilateral asynchronous granuloma. Progression of left infraorbital swelling 40 months after surgery was treated with anti-inflammatory therapy without the need for surgery.

In conclusion, clinicians should consider HA dermal fillers in the differential diagnosis of patients presenting with solid periorbital masses. The delayed onset of these masses highlights the significance of prolonged follow-up and patient education regarding potential complications. As in our case, patients may deny having had HA dermal fillers despite persistent questioning because of personal reasons. To avoid unnecessary diagnostic procedures, a history of dermal fillers should be highlighted in the patient history.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Declarations

Authorship Contributions

Surgical and Medical Practices: C.A., Concept: C.A., B.A., M.S.M., Design: C.A., Data Collection or Processing: C.A., B.A., Analysis or Interpretation: C.A., B.A., Literature Search: C.A., B.A., M.S.M., Writing: C.A., B.A., M.S.M.

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