DUCHNEVIČ, Olgerd, GALASIŃSKA, Iwona, MICHALIK, Beniamin, HAJDUK-MAŚLAK, Katarzyna, SZYPUŁA, Aleksandra, SĘK, Michał and SKÓRA, Adrianna. Recent Advances in the Treatment of Ocular Complications of Rheumatoid Arthritis: A review of current literature. Journal of Education, Health and Sport. 2024;59:102-125. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.59.007
https://apcz.umk.pl/JEHS/article/view/48109
https://zenodo.org/records/10655459

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 15.01.2023. Revised: 08.02.2024. Accepted: 12.02.2024. Published: 13.02.2024.

Recent Advances in the Treatment of Ocular Complications of Rheumatoid Arthritis: A review of current literature

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Abstract

Introduction: Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that often causes ocular complications, of which keratoconjunctivitis sicca (KCS), scleritis and episcleritis are the most common entities. When left untreated, they can adversely affect eye health and cause vision loss in severe cases. Therefore, early and effective treatment of ophthalmic complications may significantly improve visual outcomes in patients with rheumatoid arthritis.

Aim of the study: The aim of the study was to compile and analyze the current literature on the treatment of the most prevalent ocular manifestation associated with RA. Special emphasis was placed on recently approved drugs and those in late-stage clinical trials.

Methods and materials: Publication research was conducted using the PubMed database and Google Scholar with a primary focus on literature from the past 10 years. Firstly, common ocular complications of rheumatoid arthritis were identified, and relevant treatment modalities were extracted for further analysis. Finally, the names of relevant drugs or drug classes were used along with the names of the aforementioned disease entities to discover clinical trials regarding their efficacy and safety. Additionally, references from selected manuscripts were included.

Summary: The landscape of treatment for ocular complications associated with RA offers a promising future for patients and clinicians. Three new therapeutic modalities for dry eye disease have been approved in 2023, and three additional drugs are in late-stage clinical trials. Furthermore, recent advances in biologic therapy have shown considerable promise in treating scleritis, especially in patients refractory to conventional treatment or with severe symptoms of the disease.

Keywords: rheumatoid arthritis; scleritis; episcleritis; ocular inflammation; dry eye syndrome; keratoconjunctivitis sicca; treatment

1.1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes idiopathic inflammation. It is more prevalent in women, occurring two to three times more frequently than in men [1]. The prevalence of active RA is around 0.32% with an annual incidence among women of 48 per 100,000, and 20 per 100,000 for men [2]. Most patients experience periods of exacerbations and remissions, and the most characteristic symptom is pain and swelling of the joints, with morning stiffness of varying duration, usually >1 hour. It usually affects small joints of the hands and feet, but large joints, such as the knee joint, can be affected. Although nonspecific symmetric arthritis is the hallmark of the disease, extraarticular features are not uncommon, with eye-related complications being one of the most significant concerns. Patients with long-standing RA may experience a wide range of ocular signs and symptoms, but ocular manifestations can also precede articular symptoms of RA. A recent meta-analysis investigating ocular complications (OC) in various rheumatic diseases found that approximately 18% of RA patients had ocular involvement, suggesting that the eyes are a frequent extra-articular manifestation of the disease [3]. The predominant ocular symptoms in RA include dryness of the ocular surface, discomfort, redness, pain of varying intensity, and vision disturbances. Studies have shown a higher incidence of anterior eye involvement in patients with RA, with conditions such as keratoconjunctivitis sicca (KCS), episcleritis, scleritis, peripheral ulcerative keratitis (PUK), and anterior uveitis (AU) [4,5]. Keratoconjunctivitis sicca was the most common complication, affecting 16% of patients, while scleritis and episcleritis occurred in 3% and 2% of patients, respectively [3]. Retinal vasculitis is considered to be a rare manifestation. When left untreated, RA may lead to irreversible joint destruction, potentially blinding ocular conditions, other organ damage resulting in severe disability, and in more profound cases – premature death. Early diagnosis and treatment of RA slow the progression of the disease, prevent its complications, and significantly improve patients' quality of life.

1.2. Aim of The Study

The purpose of this review is to explore current treatment options and to highlight the latest advances in the treatment of ocular complications related to rheumatoid arthritis. Emphasis has been placed on recently approved drugs, as well as on therapies for RA-related OC that are currently in advanced stages of clinical research.

1.3. Materials and Methods

Publication research was conducted using the PubMed database and Google Scholar, focusing on recent literature, spanning January 2014 until January 2024. Firstly, common ocular complications of rheumatoid arthritis were identified by reviewing available meta-analyses and systematic reviews, discovered using a combination of following keywords: “rheumatoid arthritis”, “ocular”, “ophthalmic”, “complications” and “manifestations”. The following keywords were then used to find relevant treatment modalities for further review: “dry eye disease”, “keratoconjunctivitis sicca”, “scleritis”, “episcleritis”, “treatment” and “management”. Finally, the names of relevant drugs or drug classes were used along with the names of the aforementioned disease entities to discover clinical trials regarding their efficacy and safety. Additionally, relevant references from selected manuscripts were included.

2. Keratoconjunctivitis sicca

Keratoconjunctivitis sicca (KCS), also known as “dry eye disease” (DED), is the most common ocular complication of RA that may occur in approximately 16% of RA patients [3]. The Dry Eye Workshop (TFOS DEWS II) defines it as a “multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.” [6]. DED can be classified into two primary subcategories: aqueous-defficient and evaporative (or a combination of the above) [7].

Presenting symptoms include dryness of the eye, discomfort, grittiness, and a burning sensation [8]. Other symptoms include photophobia, stinging, pain, blurred vision [9] and “paradoxical watering” caused by a secondary increase in tear production due to ocular surface irritation [10]. DED significantly degrades patients’ quality of life and the visual performance in many areas of their daily life [11–13].

2.1. General treatment principles of keratoconjunctivitis sicca

Traditional methods of treatment include patient education, lifestyle and dietary modifications, lid hygiene, artificial tear substitutes, and anti-inflammatory therapy. Lubricating drops are the mainstay of pharmacological therapy. A systematic review has revealed that lubricating drops seem to be a safe and effective treatment for ameliorating DED symptoms [14]. In addition to the aforementioned treatment, moderate to severe cases of KCS may require essential fatty acid supplements, anti-inflammatory drugs, corticosteroids, cholinergic agonists, topical mucolytic agents, autologous serum drops, or surgical procedures to ameliorate dry eye symptoms [15].

The modern paradigm of KCS treatment emphasizes causative and targeted therapy over mere symptom alleviation. It is worth noting that due to its multifactorial etiology, the management of DED may require the targeting of multiple pathways.

2.2. Current treatment modalities

The treatment of dry eye disease is an evolving and a fast-paced field characterized by frequent introductions of novel therapeutic modalities – a reflection of our perpetually expanding understanding of DED. Over the past five years, noteworthy additions to the armamentarium of KJS treatment have included Varenicline solution (OC-01) nasal spray (Tyrvaya® nasal spray 0.03 mg; Oyster Point Pharma, Princeton, New Jersey, USA), Loteprednol etabonate ophthalmic suspension 0.25% (EYSUVIS®; Kala Pharmaceuticals, Arlington, Massachusetts, USA, [also known as KPI-121 0.25%]) and Lifitegrast 5% (Xiidra®; Novartis, Basel, Switzerland). In the year 2023 alone, three new drugs have been approved for the treatment of dry eye disease: Cyclosporine 0.1% ophthalmic solution, Perfluorohexyloctane ophthalmic solution and Lotilaner ophthalmic solution. Our study aims to provide a comprehensive overview of the new treatment options while providing a brief description of the treatments currently under investigation.

2.2.1. Cyclosporine 0.1% ophthalmic solution

Cyclosporine A is an inhibitor of calcineurin that blocks T-cell activation, infiltration, and successive release of pro-inflammatory cytokines that serve a key role in the pathogenesis of ocular inflammation [16]. Topical cyclosporine has uses in various eye conditions, including keratoconjunctivitis sicca, but may also be used to prevent graft rejection after keratoplasty.

Cyclosporine A exhibits its therapeutic effect in treating DED by increasing tear production, decreasing ocular inflammation, protecting conjunctival epithelial cells, and improving the density of conjunctival goblet cells and corneal surface integrity [17].

Topical cyclosporine A in ophthalmology has been used since 1980 [18] and several formulations of cyclosporine have been developed (Restasis® [0.05% CsA, Allergan, Irvine, CA] and Ikervis® [0.1% CsA, Santen, Tampere, Finland]), the most recent being CyclASol 0.1%, which we will discuss more in depth.

CyclASol 0.1% (Vevye™ cyclosporine ophthalmic solution 0.1%; Novaliq GmbH, Cambridge, Massachusetts, USA) is a novel, non-aqueous cyclosporine solution, free of surfactants, oils, and preservatives, which has received the US Food and Drug Administration (FDA) approval in 2023. The formulation leverages the new EyeSol technology based on semifluorinated alkanes, developed for better ocular tolerability, local bioavailability, and faster onset of action [19]. The ESSENCE-2 Randomized Clinical Trial (ClinicalTrials.gov identifier: NCT04523129) demonstrated a profound improvement in total corneal fluorescein staining (tCFS) in 71.6% of the participants allocated to the cyclosporine group compared to the vehicle group after 4 weeks of treatment. Symptoms such as ocular dryness, blurred vision, difficulty looking at screens, and difficulty driving at night were significantly reduced regardless of treatment [20].

2.2.2 Perfluorohexyloctane ophthalmic solution (PFHO)

Perfluorohexyloctane ophthalmic solution (Miebo™ ; Bausch + Lomb; Vaughan, Ontario; [formerly NOV03]) is a preservative-free ophthalmic solution containing a semifluorinated alkane perfluorohexyloctane that reduces water evaporation of the ocular surface by rapidly forming a layer at the tear film-air interface. PFHO has been commercially available in Europe since 2015 (marketed as EvoTears® (Ursapharm Arzneimittel GmbH, Saarbrücken, Germany) and was recently approved by the FDA in 2023. Perfluorohexyloctane is the first FDA-approved drug to treat DED by directly addressing evaporation.

Two Phase III clinical trials (GOBI [ClinicalTrials.gov identifier: NCT04139798] and MOJAVE [ClinicalTrials.gov identifier: NCT04567329]) have shown a consistent improvement of two primary endpoints (tCFS and dryness scores), demonstrating a safety profile similar to that of hypotonic saline solution [21,22]. The most recent phase III open-

label extension study (KALAHARI [ClinicalTrials.gov identifier: NCT04140227]), revealed that improvement in both tCFS and dryness scores was maintained in the PFHO group and the drug was deemed safe [23]. Other studies further corroborate its efficacy in ameliorating DED symptoms with satisfactory tolerability and excellent patient satisfaction [24,25].

2.2.3 Lotilaner ophthalmic solution

Lotilaner ophthalmic solution 0.25% (XDEMVY™; Tarsus Pharmaceuticals, Inc.; Irvine, CA, USA) is a non-competitive gamma-aminobutyric acid (GABA)-gated chloride channel inhibitor selective for mites that causes a paralytic action in the target organism, subsequently leading to its death. Lotilaner ophthalmic solution 0.25% received FDA approval in 2023 and is the FDA-approved treatment for Demodex blepharitis and Demodex-induced meibomianitis [26]. A phase III Saturn-2 trial (ClinicalTrials.gov identifier: NCT04784091) has demonstrated a substantially higher proportion of study subjects with complete collarette cure (56% vs. 13%), clinically significant collarette reduction (89% vs. 33%), substantial eradication of mites (52% vs. 15%), resolution of erythema (31% vs. 9%) and composite cure (19% vs. 4%) when treated with lotaliner, compared to the control group treated with a vehicle formulation without lotilaner. Moreover, the drop regimen had high compliance and was well tolerated by patients [27].

2.3. The Future of Dry Eye Disease Treatment

Three more encouraging drugs – reproxalab, SkQ1 and selenium sulphide ointment – are currently being investigated for their efficacy and safety in treating KJS.

Reproxalap (ADX-102; Aldeyra Therapeutics Inc, Lexington, MA, USA) is a small-molecule inhibitor of reactive aldehyde species (RASP) that are believed to play an essential role in the pathogenesis of DED and allergic conjunctivitis, although the exact mechanism remains unknown. A phase IIb clinical trial revealed a significant improvement in ocular dryness scores and nasal region fluorescein staining after 12 weeks of therapy with reproxalap compared to vehicle [28]. Notably, patients with seasonal allergic conjunctivitis, who were treated with reproxalap, achieved a greater reduction in ocular itching and redness, compared to the placebo group in the phase III INVIGORATE Trial (ClinicalTrials.gov identifier: NCT04207736) [29]. Dry eye disease and ocular allergy exhibit a symptomatic crossover with similarities in the pathological mechanisms that lead to dysregulation of tear film homeostasis

[30]. Given these points, reproxalap may be especially effective for patients in whom a differential diagnosis between both entities is difficult due to overlapping signs or symptoms.

SkQ1 (Visomitin®; Mitotech Pharma, Luxembourg, Luxembourg) is an ophthalmic solution of a small molecule mitochondria-targeted antioxidant SkQ1. It has been shown to effectively modulate the electric potential of mitochondrial membranes, reduce cell destruction and damage caused by excess concentrations of reactive oxygen species, and decrease inflammation of the ocular surface [31].

Selenium sulphide ointment (AZR-MD-001; Azura Ophthalmics Ltd, Tel Aviv, Israel) is a keratolyic and keratostatic agent that stimulates sebum production. The postulated mechanism of action of selenium sulphide involves the disruption of disulfide bonds, thus clearing the orifices of meibomian glands and reducing the viscosity of secretions [32]. Meibomian gland dysfunction (MGD) is a well-established risk factor for DED, thereby making selenium sulphide a possible candidate for KJS treatment [6]. A phase II clinical trial revealed that patients treated with AZR-MD-001 had a significantly greater increase in the number of open meibomian glands and the self-reported ocular surface symptoms score compared to vehicle. The treatment protocol was well tolerated and was considered safe [32].

3. Scleritis

Scleritis is a relatively uncommon, yet potentially devastating inflammatory condition of the sclera. It usually presents with severe pain, redness, and swelling of the sclera, tearing, photophobia, decreased visual acuity, and may potentially lead to blindness if left untreated. Compared to episcleritis, scleritis occurs more often in individuals with underlying systemic disease [33,34], most commonly rheumatoid arthritis (8–15% of patients with scleritis) [33–35].

Scleritis is usually categorized into four subtypes: diffuse anterior, nodular anterior, necrotizing, and posterior [36], of which diffuse and necrotizing forms are more common in patients with RA [34,35]. Patients may develop RA-related scleritis many years after the diagnosis of RA, with mean duration of rheumatic disease before scleritis occurred being approximately 15 years [37].

3.1. General treatment principles of non-infective scleritis

Treating acute scleritis primarily involves systemic NSAIDs and steroids, which have proven effective in numerous research studies [38]. Several authors have proposed a step-by-step treatment approach, starting with systemic non-steroidal anti-inflammatory drugs (NSAIDs), followed by systemic administration of corticosteroids, and subsequently the deployment of systemic non-corticosteroid immunomodulatory drugs [39,40].

3.1.1. Non-steroidal anti-inflammatory drug therapy

Non-steroidal anti-inflammatory drug (NSAID) therapy is recommended primarily for patients with diffuse and nodular subtypes of anterior scleritis. In a retrospective analysis involving 392 individuals diagnosed with non-necrotizing anterior scleritis, Sainz de la Maza et al. reported a 36.7% positive response to oral NSAIDs, including indomethacin, diflunisal, naproxen, ibuprofen, piroxicam, diclofenac, meloxicam, and celecoxib [41]. There are reports of the use of flurbiprofen administered orally for this purpose [42]. Watson and Hayreh showcased the efficacy of NSAIDs, suggesting oral indomethacin as the initial treatment choice [36]. Some researchers suggest that indomethacin may be more effective than other available NSAIDs [41]. On the other hand, Jabs et al. reported a 30% response rate to NSAIDs among scleritis patients who were treated with indomethacin [43].

3.1.2. Oral corticosteroids

Systemic corticosteroids therapy is often required in refractory scleritis. The routine dose is 1 mg/kg/day [44]. Steroid pulses can be used if there is an increased risk of scleral perforation. A pivotal study by McCluskey and Wakefield established the effectiveness of corticosteroids in the treatment of scleritis. In their group of 14 patients, all showed improvement with pulsed methylprednisolone. However, 6 individuals (43%) needed additional immunosuppression to reach a state of complete inactivity [45].

Oral corticosteroids have long been a cornerstone in the treatment of scleritis. However, recent findings suggest the effectiveness of steroid injections under the conjunctiva or in the sub-Tenon’s space for patients with localized, non-infectious, and non-necrotizing scleritis. A study involving 68 eyes treated with up to 40 mg of subconjunctival triamcinolone acetonide showed a 97% positive response rate, with 67% of patients remaining in remission after 24

months [46]. Another retrospective study involving 38 eyes found that 36 eyes achieved resolution within six weeks after injection [47].

3.2. Conventional immunosuppressants

In cases refractory to treatment with NSAIDs or systemic corticoids (patients who have not shown signs of clinical improvement), immunosuppressive drugs may be necessary. The most commonly used immunosuppressants are methotrexate (MTX), mycophenolate mofetil (MMF), and cyclophosphamide. The use of salazosulfapyridine and azathioprine in non-infective scleritis has been described, but the data regarding their efficacy are limited [48].

3.2.1. Methotrexate

Methotrexate (MTX) is an antimetabolite that exhibits its therapeutic effect by reducing cell proliferation, promoting T cell apoptosis, increasing endogenous adenosine levels, and modifying cytokine production along with humoral responses [49].

In a retrospective cohort study involving 384 patients with non-infectious inflammatory eye disease, including 56 with scleritis, who were treated with methotrexate as a single non-corticosteroid immunosuppressive drug, complete control and cessation of inflammation lasting 28 days or more were achieved in 56.4% of subjects within 6 months and 71.5% after one year of treatment. Moreover, a corticosteroid sparing effect (<10 mg/day) was observed in 37% of cases after 6 months and in 58% after 12 months of treatment. However, treatment had to be discontinued in 16% of the patients due to adverse effects, primarily associated with the gastrointestinal and hematological systems [49].

In another retrospective study by Hiyama et al., involving 57 patients (88 eyes) diagnosed with non-infectious scleritis, 17 underwent treatment with MTX, where the median maximum dose was 16 mg/week (ranging from 8 to 16 mg). Scleritis was effectively controlled in nearly 80% of patients treated with a combination of MTX and systemic corticosteroids at 5 mg/day or less. MTX-related adverse effects occurred in 47.1% of patients undergoing this therapy. Nevertheless, in the majority of instances, the treatment plan was well tolerated or improved after dosage adjustment [50].

3.2.2. Mycophenolate mofetil

Mycophenolate mofetil is an immunosuppressive drug that reversibly blocks inosine-5-monophosphate dehydrogenase involved in the purine synthesis pathway and selectively hampers T and B lymphocytes reproduction, leading to a suppression of the immune response [51].

A retrospective cohort study conducted by Daniel et al. involving 236 study subjects, of whom 14% were diagnosed with scleritis, assessed the efficacy of MMF combination therapy with prednisone. Complete control of the inflammatory condition lasting 28 days or more was observed in 53% and 73% of the patients, within 6 months and 1 year of treatment, respectively. After 1 year of treatment with MMF, the dose of systemic corticosteroids could be reduced to 10 mg or less of prednisone in 55% of patients, while maintaining sustained control of inflammation. Twelve percent of patients discontinued MMF treatment within the first year due to adverse effects [52].

A systematic review, comprising 4 studies (905 patients), comparing the efficacy of MMF and MTX in the treatment non-infectious ocular inflammatory disease, found no significant differences between the MMF and MTX groups in terms of overall treatment success (OR = 0.97, p = 0.96) and treatment failure (OR = 0.86, p = 0.85) [53].

3.2.3. Cyclophosphamide

Cyclophosphamide is classified as an alkylating agent that induces a cytotoxic effect on rapidly dividing cells by modifying nucleophilic groups on DNA bases, specifically, the 7-nitrogen position of guanine. This process induces cross-linking among DNA bases, irregular pairing of bases, or breakage of DNA strands, causing damage during cell division. This mechanism profoundly hampers the activity of both T cells and B cells, resulting in a broad suppression of the immune system [54].

In a retrospective cohort study by Pujarin et al. involving 215 patients, including 48 with scleritis, a treatment regimen with cyclophosphamide as the only non-corticosteroid immunosuppressive drug, allowed sustained inflammation control (for 28 days or more) in 49.2% of patients within 6 months and in 76% of patients within 12 months of treatment [54].

3.3. Biologic Treatment Options

3.3.1. Anti-TNFα therapy

Tumor necrosis factors (TNFs) are cytokines that are believed to be the primary modifiers of the inflammatory reactions responsible for scleral and corneal damage in severe scleritis [55]. The introduction of biological treatment with anti-TNFα agents has meaningfully improved the treatment of many chronic immune and inflammatory diseases, including severe ocular inflammatory conditions, such as refractory scleritis.

The most widely used anti-TNF-α antibodies in the treatment of scleritis are infliximab, adalimumab, and cetrolizumab. Retrospective studies suggest that these TNF alpha inhibitors might effectively treat scleritis that does not respond to other treatment options [48]. In a retrospective study involving 19 patients (28 eyes), five of whom had previously been diagnosed with RA, a significant improvement in scleritis severity was observed between the initial and last follow-up visit. The number of scleritis recurrences decreased considerably over the 12-month period before and after biological therapy. The average corticosteroid dosage decreased from the initial value (19.00±13.56 mg) to the last follow-up visit (7.59±5.56 mg) [56]. Etanercept has proven to be less effective in the treatment of ocular inflammation [57–59].

It is worth noting that despite their therapeutic efficacy, there have been reports of a paradoxical effect in which TNF inhibitors, especially etanercept, caused the onset or recurrence of ocular inflammation [60].

3.3.2. Anti-CD-20 therapy

Rituximab (RTX) is a chimeric monoclonal antibody against the CD20 antigen, which is found on the surface of B cells, which allows targeting and promotion of lysis in this type of cells. It is a widely used biologic agent for the treatment of RA that has proven effective in ophthalmology, particularly in the treatment of non-infectious scleritis that is unresponsive to systemic corticosteroids and one other systemic immunosuppressant. To our knowledge, the only prospective trial showcased the efficacy of rituximab and tolerance by showing a decrease in eye inflammation in 6 months for 9 of 12 patients suffering from non-infectious recalcitrant scleritis, although 7 patients required additional RTX infusions to maintain control of inflammation. In addition, treatment was well tolerated by the study subjects [61].

In their 2021 review article, Ng et al. examined a total of 31 studies on rituximab-treated uveitis and 36 studies on rituximab-treated scleritis. The scleritis population consisted of 121 patients with non-infectious scleritis that was associated with RA in 12.4% of cases. A positive therapeutic response after RTX treatment was reported in 100% of patients, with 20% of patients experiencing a subsequent relapse. RTX treatment was well tolerated and 72.7% of patients did not experience adverse events. The three recorded adverse reactions attributed to RTX were hypotension with infusion, itching with infusion, and acute retinal necrosis [62].

3.3.3. Anti-IL-6 therapy

Tocilizumab (TCZ) is a humanized, recombinant monoclonal antibody against the IL-6-receptor. It inhibits downstream signaling, which leads to a decrease in cytokine production that play a substantial role in intraocular inflammation [63].

In a retrospective study involving a group of 17 patients with conventional immunotherapy-resistant inflammatory eye disease resistant to conventional immunotherapy, intravenous tocilizumab at a dose of 4 to 8 mg/kg/month showed promising results, with 50% of subjects in the scleritis subgroup achieving remission of inflammation and corticosteroids sparing control after 9 months of treatment. However, treatment was discontinued in 4 patients due to TCZ-related adverse events [63]. Other studies have also reported a remission of non-infectious scleritis secondary to rheumatic diseases after treatment with intravenous TCZ [64,65].

3.3.4. Anti-IL-1 Therapy

The interleukin 1 (IL-1) family is a group of cytokines that contribute significantly to the pathogenesis of inflammatory and degenerative eye diseases. IL-1 blocking agents may be a viable treatment option in scleritis and episcleritis secondary to rheumatic conditions [66].

Anakinra is a recombinant human interleukin-1-receptor antagonist. A study conducted by Bottin et al. included ten patients with severe and treatment-resistant scleritis treated with anakinra, of whom one patient had scleritis secondary to rheumatoid arthritis. For this patient, an improvement was achieved in one month, allowing a total discontinuation of corticosteroids. However, the patient had developed a local reaction to anakinra and an ocular relapse has been described at 8 months of follow-up [67].

Gevokizumab is a monoclonal antibody against anti-interleukin 1β. Its efficacy in the treatment of active, non-infectious, non-necrotizing anterior scleritis has been evaluated in a phase I/II clinical trial, where one patient had RA-associated scleritis in both eyes. Despite meeting the primary outcome for the right eye (greater than or equal to a 2-step reduction or reduction to grade 0 of scleral inflammation), the more profoundly affected left eye did not improve with treatment and was not continued in the extension phase of the study [68].

3.3.5. JAK inhibitor therapy

Tofacitinib (Xeljanz®; Pfizer, Inc; New York City, NY) is an oral medication used for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis [69–72]. Tofacitinib is a small-molecule inhibitor of Janus kinases (JAKs) that predominantly targets JAK1 and JAK3 proteins, thus blocking signal transduction of multiple inflammatory cytokines, responsible for the pathogenesis of ocular inflammatory disease.

Several individual case reports [73,74], including a case of necrotizing scleritis [75], have documented a resolution of scleral inflammation and a significant reduction in inflammation after treatment with tofacitinib [76]. These findings suggest that JAK inhibitors may be a viable option for patients with scleritis recalcitrant to oral glucocorticosteroids or immunomodulatory drugs, although more research is required. On the other hand, this management protocol should be treated with caution because a significant increase in ophthalmic herpes zoster infections has been reported in patients treated with tofacitinib, compared to patients treated with other DMARDs [77].

4. Episcleritis

Episcleritis is an inflammation of the episcleral tissue, the outermost layer of the sclera. In most cases, it is a self-limiting disease with sudden onset. Unlike scleritis, only a third of patients with episcleritis have an underlying systemic condition, such as rheumatoid arthritis [78,79]. It is estimated that around 2% of patients with RA will develop episcleritis [3]. The disease usually resolves spontaneously after 1 to 2 weeks, with no treatment required in most cases. Pharmacological treatment regimens for episcleritis include oral non-steroidal anti-inflammatory drugs (NSAIDs) and/or topical steroids, topical NSAIDs, and artificial tears [48]. Severe, recurrent, or refractory cases may require periocular steroid injections, oral steroids, or, in rare cases, disease-modifying antirheumatic drugs (DMARDs), such as

hydroxychloroquine, leflunomide, or methotrexate [37]. A recent case report demonstrated a complete resolution of symptoms in a patient with steroid-resistant nodular episcleritis treated with topical 0.1% tacrolimus eye drops [80]. Due to a benign course of the disease and a relatively small fraction of patients who require treatment, the therapeutic options remain mostly unchanged.

5. Conclusions

Rheumatoid arthritis is an inflammatory autoimmune disease that often manifests with ocular complications, of which keratoconjunctivitis sicca, scleritis and episcleritis are the most common entities. When left untreated, they can be potentially blinding, leading to severe disability and a decrease in the quality of life. Early and effective treatment of said complications can substantially improve patients' visual outcomes. In recent years, numerous treatment discoveries have been made, offering a promising future for patients and clinicians. Three new therapeutic modalities for dry eye disease have been approved in 2023 and three additional drugs are in late-stage clinical trials. The novel mechanism of action of several new drugs will broaden the current armamentarium, allowing for a more personalized management of dry eye disease. Moreover, the constant evolution and improvement of biologic therapy shows considerable promise in the treatment of scleritis, especially in patients who are refractory to conventional treatment or with severe symptoms of the disease. Although treatment advances are encouraging, further research, particularly randomized controlled trials and prospective studies with larger sample sizes, to comprehensively assess the efficacy and safety of these emerging treatment modalities.

6. Disclosure

Supplementary materials

Not applicable.

Authors contribution:

Conceptualization, Olgerd Duchnevič, and Iwona Galasińska; methodology, Beniamin Michalik; software, Katarzyna Hajduk-Maślak; check, Olgerd Duchnevič, Iwona Galasińska and Aleksandra Szypuła; formal analysis, Michał Sęk and Beniamin Michalik; investigation, Adrianna Skóra; resources, Michał Sęk; data curation, Aleksandra Szypuła; writing - rough

preparation, Iwona Galasińska; writing - review and editing, Olgerd Duchnevič; visualization, Adrianna Skóra; supervision, Olgerd Duchnevič; project administration, Katarzyna Hajduk-Maślak; All authors have read and agreed with the published version of the manuscript.

Funding Statement

The authors did not receive funding for this project.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Acknowledgements

Not applicable.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Data Availability Statement

The data presented in this study are available upon request from the correspondent author.

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