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Ocular Side Effects of Autoimmune Disease Therapies

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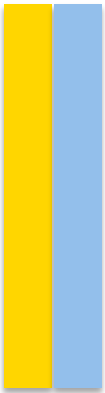

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Ocular Side Effects of Autoimmune Disease Therapies

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À minha família e aos meus amigos por todo o apoio incondicional.

RESUMO

Introdução: Nas últimas décadas, houve avanços notáveis na gestão das doenças autoimunes, o que tem melhorado o prognóstico e a qualidade de vida dos doentes. No entanto, as diversas opções terapêuticas que surgiram têm sido associadas a numerosos efeitos adversos oculares.

Objetivos: O objetivo desta dissertação é realizar uma revisão da literatura sobre a iatrogenia oftalmológica dos tratamentos das doenças autoimunes, a fim de sistematizar o conhecimento atual.

Desenvolvimento: As doenças autoimunes, que podem ser agudas ou crónicas, são caracterizadas por uma resposta patológica contra autoantigénios, causando inflamação, lesão celular ou um distúrbio funcional com consequências clínicas. Estas respostas estão subjacentes a um amplo espectro de doenças, que podem manifestar-se como condições generalizadas, como doenças reumáticas sistémicas (por exemplo, lúpus eritematoso sistémico ou artrite reumatóide) ou doenças específicas de tecidos ou órgãos, tais como a colite ulcerosa e a esclerose múltipla. Apesar de serem condições patológicas, os seus mecanismos são semelhantes às respostas imunológicas típicas do organismo a agentes estranhos.[1] A resposta imune inata é imediata e inespecífica, desencadeada por traumatismo, *stress* ou infeção. Contrariamente, a resposta imune adaptativa é um processo mais lento que pode persistir, desenvolver memória e requer a produção de células B ou T específicas para determinado antigénio. As doenças autoimunes surgem de uma resposta imune adaptativa específica direcionada aos autoantigénios, invalidando os mecanismos de tolerância que evitam reações excessivas. Habitualmente, a abordagem para o tratamento destas doenças envolve atingir o sistema imunitário hiperativo com imunossupressores ou diminuir a inflamação com anti-inflamatórios.[2] Os agentes biológicos surgiram como alternativas terapêuticas eficazes quando os pacientes não respondem adequadamente aos tratamentos comuns. Contudo, os medicamentos tradicionais antirreumáticos, nomeadamente os antimetabolitos, têm sido associados a efeitos secundários oculares como o prurido, a irritação e a secura da conjuntiva. Além disso, a cloroquina e a hidroxicloroquina estão associadas à retinopatia irreversível com possível perda de visão. Em contraste, os agentes biológicos têm sido associados a casos de uveíte e a patologias desmielinizantes. Efeitos colaterais infeciosos destes medicamentos incluem retinite por citomegalovírus, coriorretinite toxoplásmica e endoftalmite.[3]

Conclusão: Através de uma perspetiva interdisciplinar, esta revisão da literatura irá aprofundar a relação multifacetada entre o tratamento de doenças autoimunes e a sua potencial iatrogenia oftalmológica, destacando a importância da deteção precoce, da educação do paciente e de uma abordagem colaborativa entre reumatologistas e oftalmologistas.

Palavras-chave: Foi utilizada uma lista de palavras-chave: Doenças Autoimunes, Terapêutica, Medicamentos Antirreumáticos, Efeitos Colaterais e Reações Adversas Relacionadas a Medicamentos, Iatrogenia, Doenças Oculares.

ABSTRACT

Introduction: The field of autoimmune disease management has witnessed remarkable advancements in recent decades, leading to significant improvements in patient outcomes and quality of life. However, the complex therapeutic arsenal employed in the management of autoimmune diseases has been associated with numerous ocular adverse effects and complications.

Objectives: The purpose of this dissertation is to perform a literature review on the ocular side effects of autoimmune disease therapies to systematise the current knowledge.

Development: Autoimmune diseases, which can either be acute or chronic, are characterized by a pathologic response against autoantigens, causing inflammation, cellular damage, or a functional disturbance with clinical consequences. These responses underlie a wide spectrum of disorders, which can manifest as generalised conditions like systemic rheumatic diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis) or tissue- or organ-specific disorders, such as ulcerative colitis and multiple sclerosis. Despite being pathological conditions, their mechanisms are similar to the body's typical immune response to foreign agents.[1] The innate immune response is immediate and nonspecific, triggered by trauma, stress, or infection. On the other hand, the adaptive immune response is a slower process that can persist, develop memory, and require the production of antigen-specific B or T cells. Significantly, autoimmune diseases arise from a specific adaptive immune response targeting autoantigens, invalidating the usual mechanisms of tolerance that prevent excessive reactions to self-antigens. The standard approach to managing these diseases involves targeting the hyperactive immune system with immunosuppressants or decreasing the inflammation with anti-inflammatories.[2] Biologic agents have emerged as effective therapeutic alternatives when patients do not respond adequately to the usual treatments. However, traditional disease-modifying antirheumatic drugs, namely antimetabolites, have been linked to ocular side effects such as pruritus, irritation, and dryness of the conjunctiva. Also, chloroquine and hydroxychloroquine are associated with irreversible retinopathy with possible vision loss. In contrast, biologic agents have been associated with cases of uveitis and demyelinating conditions. Also, infectious side effects of these medications include cytomegalovirus retinitis, toxoplasmic chorioretinitis, and endophthalmitis.[3]

Conclusion: Through an interdisciplinary lens, this literature review will delve into the multifaceted relationship between autoimmune disease treatments and their potential iatrogenic ophthalmologic complications, highlighting the importance of early detection, patient education, and a collaborative approach between rheumatologists and ophthalmologists.

Keywords: A list of keywords was used, namely: Autoimmune Diseases, Therapeutics, Antirheumatic Agents, Drug-Related Side Effects and Adverse Reactions, Iatrogenic Disease, Eye Diseases.

LIST OF ABBREVIATIONS

CQ - Chloroquine
CMV - Cytomegalovirus
DMARDs - Disease-modifying antirheumatic drugs
FAF - Fundus autofluorescence
GC - Glucocorticoids
HCQ - Hydroxychloroquine
IOP - Intraocular pressure
JAK - Janus kinase
NSAIDs - Non-steroidal anti-inflammatory drugs
PSC - Posterior subcapsular cataracts
RA - Rheumatoid arthritis
RPE - Retinal pigment epithelium
SD-OCT - Spectral-domain optical coherence tomography
SLE - Systemic lupus erythematosus

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METHODOLOGY

A comprehensive literature search was conducted using PubMed, focusing on case reports, case series, review articles, retrospective/prospective studies, and clinical trials obtainable up to January 2024. For each antirheumatic agent, the search strategy comprised the terms "(drug name) AND (adverse effects OR side effects OR adverse) AND (eye diseases OR eye OR ocular OR ophthalmic)." The antirheumatic agents covered in this review are outlined in Table I. After reviewing the titles and abstracts for relevance, full-text manuscripts were found accordingly. In instances where electronic copies were unavailable, attempts were made to procure full-length manuscripts through the Hospital Santo António library. Articles discussing ocular side effects in humans associated with the antirheumatic medication were identified from the search results. Studies were excluded from this review if full-length articles were not accessible, multiple-drug treatments confounded the effects of an individual drug, ocular side effects were unclear, or evidence for causality was ambiguous.

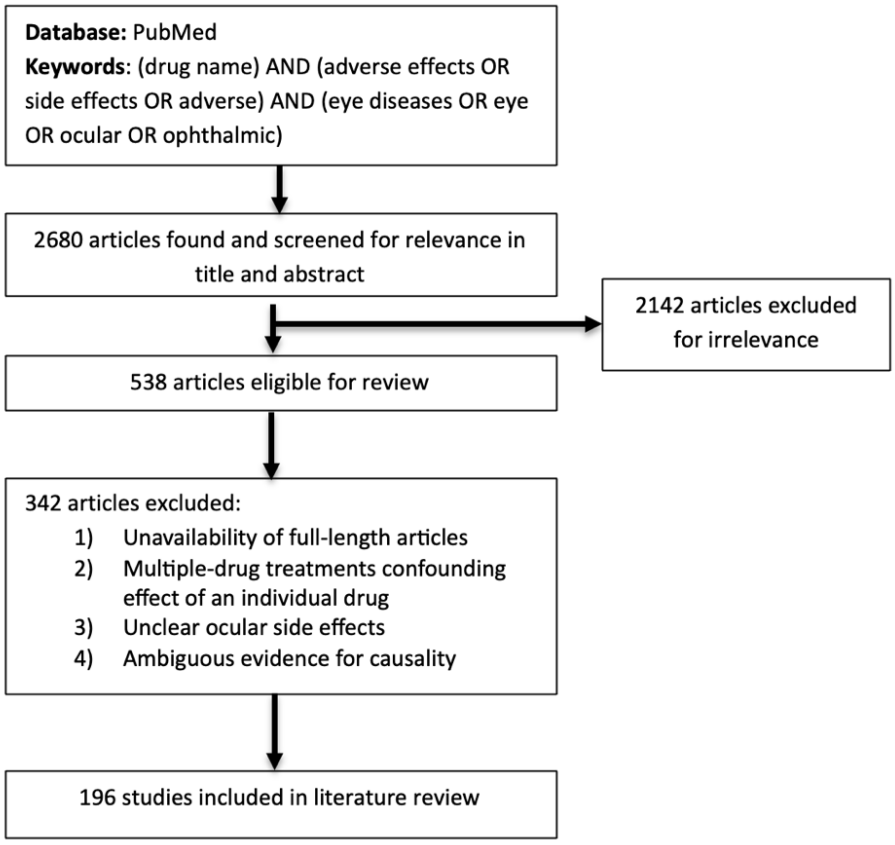

Fig. 1: Study selection flowchart

INTRODUCTION

Autoimmune Diseases

The immune system's primary role is to protect the host from infectious agents. However, this system can also be the source of disease through two mechanisms: immune deficiency and autoimmunity. Autoimmune diseases, which can be either acute or chronic, involve an abnormal immune reaction to the body's antigens, causing inflammation, cellular damage, or a functional disturbance with clinical consequences.[1, 2] Autoimmune disorders encompass a spectrum, from organ-specific diseases with localized antibody and T-cell reactions to non-organ-specific diseases affecting multiple tissues, such as systemic rheumatic diseases like systemic lupus erythematosus (SLE). These indicate a complex immune malfunction that involves various cellular pathways and complicates treatment strategies. Autoimmune diseases can be classified by evaluating their clinical characteristics, serology, and histopathology. Despite advances in the understanding of these diseases, improving their classification and diagnosis, and developing new treatment options, there is still a scarcity of knowledge about their etiology.

Although autoimmune diseases are often perceived as rare, they have a significant impact on global morbidity and mortality, with studies indicating they affect 3-5% of people worldwide. There are approximately 100 disorders, varying in incidence and prevalence, that are influenced by age, sex, ethnicity, and family history. Generally, there is a greater prevalence in first-degree relatives and monozygotic twins and a higher disease frequency in women. Research suggests that both genetic predispositions and environmental factors contribute to the onset of autoimmunity. The identification of specific environmental triggers, such as diet, microbiota, infections, and exposure to certain chemicals like tobacco smoke, remains challenging yet critical to establishing individual susceptibility.[2]

Managing autoimmune diseases typically aims to either replace what the body lacks, such as insulin in type 1 diabetes, or reduce the harmful inflammatory response, usually achieved through immunosuppressive agents namely antimetabolites, corticosteroids, and anti-inflammatory medications. A more recent therapeutic approach involves biological agents targeting specific immune or inflammatory pathways, such as TNF-α inhibitors, which have revolutionized the treatment of systemic rheumatic diseases and inflammatory bowel disease. However, the complex therapeutic arsenal employed in the management of autoimmune diseases has been associated with numerous adverse effects and complications.[1-3]

Ocular Side Effects of Autoimmune Disease Therapies

Traditional disease-modifying antirheumatic drugs (DMARDs) are often the first line of treatment for systemic rheumatic diseases. They include antimetabolites such as azathioprine, methotrexate, mycophenolate mofetil, and leflunomide. Additionally, ciclosporin, a T-cell inhibitor, and cyclophosphamide, an alkylating agent, are also used. Generally, DMARDs have been linked with ocular

side effects like dryness of the conjunctiva, irritation, and pruritis. A more recent category of antirheumatic treatments, biologics, aim at precise immune system targets. These include TNF-α inhibitors, interleukin inhibitors, and anti-lymphocyte drugs, which have been associated with ophthalmological complications such as uveitis and nervous system disorders such as demyelination. Also, adverse effects of these medications may include endophthalmitis, cytomegalovirus retinitis, and toxoplasmic chorioretinitis.[3]

Hydroxychloroquine (HCQ) is progressively being used to treat a range of autoimmune diseases and has been shown to improve survival rates in patients with SLE. Nonetheless, both hydroxychloroquine and chloroquine (CQ) can lead to permanent vision impairment due to retinopathy. The initial effect of these drugs is on the retinal pigment epithelium, potentially progressing to a distinctive 'bull's eye maculopathy', which is characterised by a ring of retinal pigment epithelial loss surrounding the fovea. This critical and irreparable vision loss can be further complicated by cystoid macular edema and epiretinal membrane formation.[4] Additionally, steroids are an essential component in managing various diseases, especially those involving inflammation or immune responses. Their ocular side effects are diverse, encompassing conditions such as glaucoma and cataracts, an increased risk of ophthalmological infections, and delayed corneal healing.[5] Concerning non-steroidal anti-inflammatory drugs (NSAIDs), these rarely present ocular adverse events, but there have been reports of corneal crystal deposition and edema. On the other hand, COX-2 inhibitors may result in conjunctivitis and blurred vision.[3, 6]

Given that this review is qualitative, it's not possible to determine the actual frequency or incidence of the ocular side effects reported, which have been documented mainly from case reports and series and do not establish a definitive cause-and-effect relationship. Therefore, the prevalence of these adverse events is likely higher, and the clinical presentations are more varied than the literature suggests. To conclusively connect the use of a drug to the emergence of these side effects, randomised controlled trials are essential. Due to the extensive potential for ocular side effects from these medications, close collaboration between rheumatologists and ophthalmologists is essential for the early detection and management of these adverse effects.[3, 7]

Current Recommendations

Awareness is growing among doctors about the importance of conducting comprehensive eye exams when assessing patients with autoimmune conditions. Preventing ocular complications in these diseases is best achieved through a coordinated approach involving general practitioners, internists, ophthalmologists, and rheumatologists.[8] Due to the range of therapies used in the treatment of autoimmune diseases and their continuous developments, evidence of their ocular side effects and possible screening methods is still emerging. Most importantly, physicians should remain aware of the potential risk of ocular adverse drug reactions and communicate any instances observed in their patients, to generate stronger evidence for more definitive conclusions.[7] Identifying early symptoms of ocular toxicity, discontinuing the medication, and quick referral to an ophthalmologist can help prevent irreversible damage to the eyes and visual loss.[9]

Hydroxychloroquine and chloroquine have been used for several decades, and guidelines on optimal dosage and screening methods have already been developed due to the substantial evidence on their side effects.[4] The protocols for screening for HCQ-induced retinopathy, including the timing, the identification of patients at risk, and the screening methods, are subjects of ongoing discussion. Recognised risk factors include a daily dosage exceeding 5.0mg/kg of real weight, treatment duration over five years, impaired renal function, or existing retinal disease.[10] Given the possibility of permanent retinal damage, the American Academy of Ophthalmology advises an initial examination of the retina to exclude pre-existing maculopathy and suggests yearly evaluations after five years for those on safe dosages who do not present significant risk factors. Automated visual field testing and spectral-domain optical coherence tomography (SD-OCT) are the recommended primary screening tools. The multifocal electroretinogram can objectively confirm visual field test results, and fundus autofluorescence (FAF) can visually map out retinal damage.[11]

Regarding biologic agents, despite the increasing evidence on the ocular side effects of TNF-α inhibitors, the majority of this information is derived from case reports, which precludes accurate conclusions. These insights do not change the existing guidelines for using biologic therapies. Instead, they highlight the importance of vigilant monitoring of the ocular health of patients undergoing these therapies and of further evidence regarding potential adverse effects.[12]

OCULAR SIDE EFFECTS OF AUTOIMMUNE DISEASE THERAPIES

CORTICOSTEROIDS

Corticosteroids, derived from cholesterol in the adrenal cortex, are steroid hormones. Their synthetic counterpart, corticoids, has gained widespread medical use since the 1850s owing to their anti-inflammatory, anti-allergic, and immunosuppressant properties.[13] Corticosteroids exert their effects by binding to the intracellular corticosteroid receptor, thereby modulating gene expression and influencing protein synthesis. The non-specific suppression of the immune response makes corticosteroids a cornerstone in treating various autoimmune disorders, including rheumatoid arthritis (RA) and systemic lupus erythematous.[14-16] The well-documented ocular side effects associated with both natural and synthetic steroids encompass immunosuppression-related complications, increased infection risk due to decreased tear lysozyme levels, and impaired corneal epithelial wound healing.[17, 18] Compartment-specific toxicities, including anterior (subconjunctival hemorrhages, translucent blue sclera, eyelid hyperemia, and edema) and posterior (retinal embolic events, central serous choroidopathy), have been reported.[19] Neurologic adverse events, such as diplopia, nerve palsies, papilledema, and retinal haemorrhages, have been linked to intracranial hypertension following epidural steroid injection.[20-22] The most extensively documented ophthalmological consequences of corticosteroid use are the induction of cataracts and an increase in ocular pressure leading to glaucoma.

In 1960, *Black et al.* were the first to propose a link between systemic steroid use and posterior subcapsular cataracts (PSC), as their study described this association in patients with rheumatoid arthritis treated with corticoids.[23] Cataracts are defined by the presence of opacity in the ocular lens, leading to a subjective decline in visual acuity. While it commonly results from the natural aging process of the lens, instances of premature onset and progression are frequently associated with various medical conditions, including diabetes, hypertension, obesity, smoking, excessive alcohol consumption, previous ocular damage or ophthalmological surgeries, and prolonged use of a diverse range of drugs such as corticosteroids. These can be administered systemically or through subconjunctival, periocular, intraocular, or intravitreal injections, as well as inhalation sprays and topical medications.[13] Steroid-induced PSC closely resembles other forms of PSC, such as those observed in diabetic patients.[24-26]

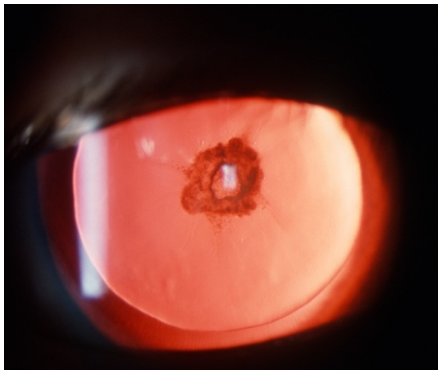

Fig. 2: Posterior subcapsular cataract due to chronic steroid use. Extracted from: Aggarwal S, Ta B, Photographer: James Gilman C, FOPS, Moran Eye Center. Ocular Side-Effects of Corticosteroids. University of Utah: Moran Eye Center; 2018 [Available from: https://morancore.utah.edu/basic-ophthalmology-review/ocular-side-effects-of-corticosteroids/.] [27]

Steroid-induced cataract pathogenesis may involve multiple mechanisms, including the formation of covalent adducts between the steroid molecule and lens particles, resulting in opacities. Inhibition of the sodium-potassium pump in the lens epithelium and subsequent water accumulation within lens fibres have also been proposed. Other theories implicate elevated glucose levels, increased cation permeability, inhibition of glucose-6-phosphate dehydrogenase, inhibition of RNA synthesis, and loss of lens ATP. The complexity of PSC development suggests the involvement of multiple mechanisms.[28-30]

Determining a safe daily dose and duration of corticosteroid use remains challenging due to varying diagnostic criteria, steroid potencies across studies, different patient sensitivity, and genetic predisposition.[31] The risk of developing posterior subcapsular cataracts (PSCs) is influenced by both cumulative and average daily doses of glucocorticoids (GCs), though considerable variability exists among individual patients.[9, 32] A prednisone-equivalent dose of 10mg/day for over one year is associated with the initiation of cataracts in approximately 75% of patients. Even a daily dosage of 5mg for a duration as short as 2 months may trigger PSC onset in susceptible individuals.[23, 26] Notably, steroid therapy tends to exert a more pronounced impact on children, leading to a faster onset of PSC at lower dosages compared to adults.[33]

Patients should be informed about the potential ophthalmological complications of corticosteroids, emphasising the asymptomatic nature of many complications and the need for vigilant monitoring. Systemic steroids pose greater risks with oral use, while nasal administration appears to have fewer concerns, even with prolonged use. The occurrence of cataract development extends beyond the realm of systemic steroid use, as the topical application of steroids commonly employed in treating anterior ocular infections and trauma has been associated for decades with the formation of posterior subcapsular cataracts.[5, 33, 34] Additionally, inhaled steroids, often prescribed for asthma, have been associated with PSC formation. Follow-up examinations, timing, and frequency depend on the doses and duration of treatment; however, monitoring for cataract formation is recommended every 6 months. The discontinuation of medication seldom results in the regression of lens opacities, so treatment involves the surgical removal of steroid-induced PSC. This procedure is conducted using the usual technique of phacoemulsification, coupled with the insertion of an artificial intraocular lens.[7, 33]

Steroid-induced ocular hypertension refers to elevated intraocular pressure (IOP) resulting from the use of glucocorticoids (GCs) in the eye. Failure to address significant IOP elevation can lead to the development of steroid-induced glaucoma. The progression of glaucoma is commonly characterised by loss of the visual field, optic disc cupping, and atrophy of the optic nerve with increased intraocular pressure.[35, 36] Individuals exhibiting increased IOP in response to GCs are identified as "steroid responders," with a commonly accepted definition being an IOP increase > 10mmHg over baseline with clinical significance. In both healthy subjects and glaucomatous patients who are steroid responders, a rise in IOP occurs over 3-6 weeks of continuous eye drop administration, returning to normal values within 2 weeks after therapy cessation, if irreversible trabecular meshwork changes are absent. Rarely, an acute IOP increase can occur within hours of intensive topical dexamethasone treatment initiation.[37-39] Steroid-induced glaucoma can be induced by exogenous GC administration through various routes and, exceptionally, by excess endogenous glucocorticoid production in specific endocrine diseases. The formulation of steroids contributes to IOP rise, with lipophilic steroid acetates, such as dexamethasone acetate 0.1%, penetrating the cornea more effectively than hydrophilic derivatives like phosphates.[40-42]

Glucocorticoids play a direct role in increasing aqueous humour outflow resistance, similar to the pathophysiology of primary open-angle glaucoma.[43, 44] Evidence indicates that GCs alter protein turnover in the trabecular meshwork, leading to increased extracellular matrix protein deposition and trabecular meshwork dysfunction due to cell migration, phagocytosis, retraction, and contractility.[45] Inhibition of metalloproteinases facilitates extracellular matrix deposition, accompanied by the observation of fibrillary-like material, type IV collagen, elastin, heparin sulfate proteoglycan, and fibronectin deposits.[46]

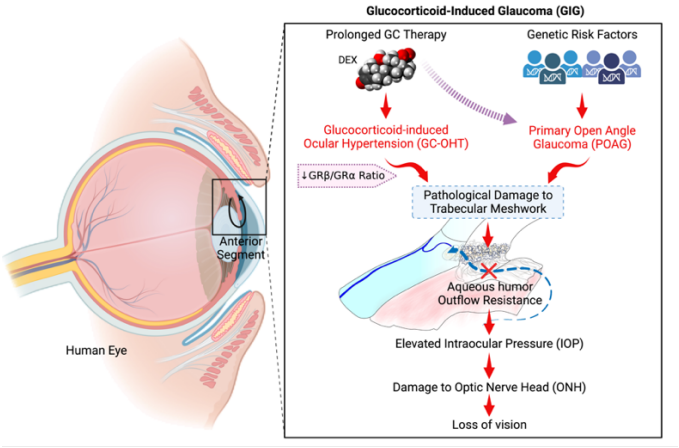

Fig.3: Mechanism of glucocorticoid-induced glaucoma. Glucocorticoids damage the trabecular meshwork, a tissue that regulates aqueous humour outflow and intraocular pressure, inducing ocular hypertension. Trabecular meshwork cells derived from primary open glaucoma eyes have a lower expression of GRβ, a dominant negative regulator of GC activity, compared to those from control eyes. Hence, these cells have an increased pathological response to GCs. The endogenous expression of GRβ in the trabecular meshwork may relate to differences in the development of GC-ocular hypertension in the normal population. Extracted from: Patel PD, Kodati B, Clark AF. Role of Glucocorticoids and Glucocorticoid Receptors in Glaucoma Pathogenesis. Cells 2023;12(2452). [47]

The prevalence of glaucoma associated with steroid use is unclear, but steroid responsiveness varies in the normal population. Approximately 61-63% are non-responders, 33% show a moderate response, and 4-6% are highly responsive to GCs. Elevated IOP in response to GC therapy is more frequent in patients with primary open-angle glaucoma, especially in older subjects.[37, 48] Children may experience earlier, more severe, and rapidly progressing IOP elevation and potential glaucomatous damage.[49, 50] First-degree relatives of primary open-angle glaucoma patients have a higher risk of GC-induced IOP elevation. Connective tissue disease, high myopia, type I diabetes mellitus, and angle-recession glaucoma are reported risk factors.[51-54] Furthermore, supporting evidence suggests a genetic basis for certain instances of steroid-induced glaucoma. Specifically, mutations identified in the gene responsible for encoding a trabecular meshwork protein known as TIGR, appear to predispose a subgroup of individuals using steroids to an increased risk of developing open-angle glaucoma.[55]

Steroid-induced glaucoma, an iatrogenic form of secondary open-angle glaucoma, necessitates early detection to prevent blindness. Monitoring IOP during steroid treatment is crucial, with baseline measurements before initiation and subsequent measurements every 2 weeks for the first 2-3 months. The frequency may vary based on the route of administration. High-risk patients, such as glaucoma patients and children, require diligent follow-up. If the drug has been utilised for less than a year, there is reversibility of the ocular hypertension upon discontinuation of the therapy. Following the cessation of steroids, intraocular pressure usually returns to baseline levels within 2-4 weeks. However, in cases where steroid therapy has been prolonged for $\geq$18 months, the elevation may endure.[42, 56] Management includes interrupting therapy, using lower concentrations or weaker steroids, and considering IOP-lowering medications. These include beta-blockers, alpha-2 agonists, and carbonic anhydrase inhibitors. In cases

where patients do not tolerate or respond to these drugs, medical laser trabeculoplasty is recommended, particularly when there is an imminent risk of optic nerve injury. Alternatively, trabeculectomy is reserved for patients who are unresponsive to both medical and laser treatments or are anticipated to undergo additional treatments involving glucocorticoids. Future treatments may involve tissue plasminogen activator and gene therapy.[7, 35]

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) constitute a chemically diverse group of agents that have analgesic, antipyretic, and anti-inflammatory properties, useful for alleviating pain and inhibiting inflammation in certain autoimmune diseases, such as systemic lupus erythematous. Despite their widespread and long-term use, ophthalmic complications associated with NSAIDs are infrequent and inadequately documented.[9, 57]

Recognised for its potency among NSAIDs, indomethacin has been linked with cases of corneal opacities, particularly during prolonged use. The related symptoms include blurred vision and light sensitivity, which can be mild or evolve into noticeable photophobia. Under slit lamp examination, these changes emerge as thin stromal speckled opacities or display a whorl-like distribution reminiscent of the *cornea verticillata* pattern of hydroxychloroquine keratopathy. When indomethacin is discontinued, the corneal alterations may subside or, more rarely, disappear within 6 months.[7, 9, 58, 59] Furthermore, NSAIDs have been linked to cases of retinopathy. Evidence suggests that these agents, particularly indomethacin, can cause retinal pigmentary changes leading to blurred vision. Specifically, the lesions involve pigment scattering of the perifoveal retinal pigment epithelium and fine-depigmented areas around the macula. The electroretinogram and electrooculogram may be altered in accordance with the extent of retinal involvement.[60-62]

There are increased bleeding tendencies with the use of a variety of NSAIDS, including ibuprofen, piroxicam, oxaprozin, and naproxen, which are also associated in some cases with blurred vision, photophobia, and central vision changes. Acetylsalicylic acid, commonly known as aspirin, may result in conditions such as subconjunctival haemorrhage and hemorrhagic retinopathy if used in high doses or over a long period of time, due to its anticoagulant properties. Such agents should be averted before or after surgery, following trauma, and in cases of hyphema.[63-65]

The anti-inflammatory effects of NSAIDs are accomplished by inhibition of cyclooxygenase-1 and cyclooxygenase-2 enzymes; however, rofecoxib, celecoxib, valdecoxib, lumiracoxib, nimesulide, and etodolac selectively inhibit only cyclo-oxygenase (COX)-2. These COX-2 inhibitors are associated with different ocular side effects such as conjunctivitis and blurred vision, especially with rofecoxib and celecoxib. Nevertheless, these symptoms typically resolve upon therapy cessation with no lasting impact.[6]

TRADITIONAL DMARDs

HYDROXYCHLOROQUINE

Antimalarials have played a pivotal role in managing rheumatic diseases for many decades. Introduced in 1953, chloroquine (CQ) was succeeded by hydroxychloroquine (HCQ) in 1955, with the latter surpassing CQ due to its decreased ophthalmological risks. Despite this, HCQ is linked to various established side effects, encompassing myopathy, neuropathy, cardiac myotoxicity, and ocular toxicity; specifically, lens opacities, outer retinal damage, keratopathy, and retinal toxicity.[10, 66]

Characterised as a lipophilic base, hydroxychloroquine easily penetrates cell membranes. Its actions include destabilizing lysosomes, inhibiting antigen presentation, decreasing prostaglandin and cytokine production, and affecting toll-like receptor signaling and leucocyte activation.[67] These mechanisms result in immunosuppressive, antiproliferative, antithrombotic, and photoprotective events. Although it is primarily administered for rheumatoid arthritis and systemic lupus erythematosus, diverse autoimmune diseases such as Sjogren´s syndrome and antiphospholipid syndrome also benefit from this drug. HCQ tends to deposit in tissues with high melanin content, such as the skin, ciliary bodies, and the retinal pigment epithelium. Studies suggest HCQ affects lysosomal function, potentially impeding phagocytosis and autophagy in the retinal pigment epithelium.[4, 10] In vitro studies on cultured RPE cells indicate altered lysosome pH, leading to increased lipofuscin levels associated with photoreceptor degeneration. The unique hydroxyl group in HCQ limits its ability to cross the blood-retinal barrier, contributing to its lower toxicity compared to CQ.[68, 69]

Cornea verticillata, or vortex keratopathy, is a reversible epithelial change caused by HCQ and CQ, creating a whorl-like pattern after drug precipitation. This alteration has a negligible visual effect and is less frequent with HCQ in comparison with CQ.[70]

Retinopathy, albeit rare, poses a considerable concern, potentially leading to irreversible central vision loss. Detecting the condition early is challenging due to its asymptomatic nature and the absence of discernible changes on fundoscopy, which emphasises the need for screening.[71] The initial signs of HCQ retinopathy are slight alterations in the macula, characterized by pigmentary stippling and the absence of the foveal reflex. The paracentral origin of the functional changes prevents symptoms. Gradually, this retinopathy develops into a symptomatic paracentral and central scotoma, featuring a distinctive bull's eye maculopathy (BEM) with a depigmented perifoveal area. Assymmetrical differences may be perceived between the eyes, and peripheral observations may show choroidal outlines and subtle granularity of the retina. In rarer instances, severe damage can cause segmental constriction of arterioles in the retina with optic disc pallor.[71] Cystoid macular edema can occasionally arise, and in advanced instances, there is extensive atrophy of the RPE and the retina, leading to diminished visual acuity, and peripheral and nocturnal vision loss.[72] Symptoms such as photopsia, metamorphopsia, and reduced colour vision have also been described.[4, 70, 73]

Recent imaging techniques, such as SD-OCT, have shown structural alterations in the initial period, unveiling thinning of outer retinal layers, a lack of the parafoveal photoreceptor inner segment/outer segment junction, and preservation of the central fovea.[74, 75] While the locus of toxicity is predominantly parafoveal, Asian patients frequently exhibit extramacular injury. Early changes can be reversed, as evidenced by the recovery in functional and morphological abnormalities.[76-78] However, treatment cessation does not guarantee immediate stabilisation, with adverse effects persisting for up to 7 years, including the potential progression to bull's eye maculopathy. The late presentation could signify a gradual decompensation of cells that underwent metabolic injury during the drug exposure period.[11, 79, 80]

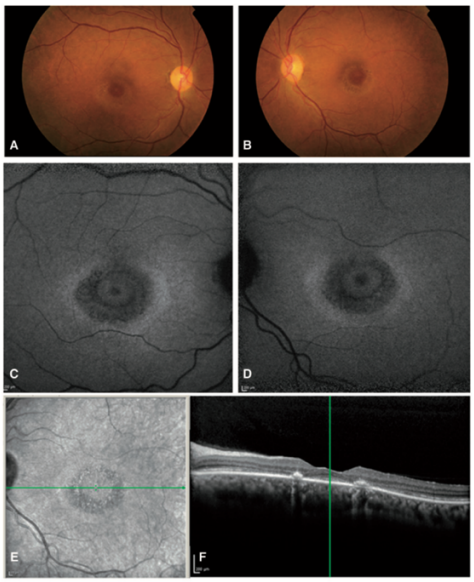

Fig.4: Ocular findings of hydroxychloroquine retinopathy by different imaging techniques. A 53-year-old female patient was diagnosed with HCQ retinopathy after taking HCQ for 12 years at a daily dose of 400mg. Bilateral bull´s eye maculopathy was visible clinically on fundal photographs A and B. Symmetrical high signal haloes in the right eye (C) and left eye (D) are revealed by FAF and by the infrared reflectance image (E). Thinning of the inner retinal layers with loss of the parafoveal photoreceptor zone and central foveal spearing is demonstrated by SP-OCT (F). Ding HJ, Denniston AK, Rao VK, Gordon C. Hydroxychloroquine-related retinal toxicity. Rheumatology (Oxford). 2016;55(6):957-67.

The precise estimation of HCQ retinopathy incidence is complicated due to variations in study designs and definitions of retinopathy. Current recommendations by the American Academy of Ophthalmology for screening CQ and HCQ retinopathy, recommend a maximum daily HCQ use of 5.0mg/kg of real weight, correlating better with risk than ideal weight. Major risk factors include high dose, prolonged use, concomitant renal disease, and tamoxifen use.[10, 11] Renal disease increases the risk due to impaired drug clearance, while tamoxifen raises the toxicity risk significantly through an uncertain mechanism. Also, patients with underlying retinal disease may be at higher risk.[10, 81] Nonetheless, retinal toxicity can occasionally occur in low-risk individuals, suggesting the contribution of genetic or other unrecognised risk factors. Significantly, bull's eye maculopathy, a characteristic phenotype observed in HCQ retinopathy, has been associated with genetic variants, particularly in the ABCA4 gene.[82]

The recommended screening schedule involves a baseline fundus examination, with annual screening after 5 years of treatment for patients on adequate doses without major risk factors. Primary screening tests include automated visual fields and spectral-domain optical coherence tomography. Fundus autofluorescence and multifocal electroretinogram provide additional corroboration.[11] Humphrey´s visual field and multifocal electroretinogram reveal functional changes, while SD-OCT and FAF show morphological alterations. Even though each method provides valuable insights, none are entirely sensitive, requiring their complementary use for comprehensive assessment.[83, 84] The reliability of current screening methods depends on accurate interpretation. SD-OCT is a common objective test for HCQ toxicity, but early detection of subtle features remains challenging even for experts; therefore, clinician expertise currently guides interpretation due to the absence of quantitative metrics. Advancements in machine learning and image analysis offer promising possibilities for automated screening and diagnosis techniques in this area. Particularly, studies have already investigated the quantitative assessment of outer retinal layers and ellipsoid zone mapping in HCQ retinopathy, revealing substantial differences compared to normal controls.[85] More recently, machine learning-based classification models were developed and tested for automated detection of HCQ toxicity and prediction of progression in eyes without baseline toxicity. These tools have exhibited a high sensitivity to detect toxicity, making them a reasonable complement for clinical decision-making. Although the sensitivity for predicting progression to toxicity was lower, it serves as a valuable indicator to monitor for additional abnormalities in concurrent testing.[86] There are also novel technologies such as adaptive optics imaging for structural evaluation and microperimetry for functional assessment, which are still primarily research tools lacking widespread availability and validation for screening purposes. Additionally, patient counselling is critical for understanding toxicity risks, appropriate dosing, and the need for annual screening.[4, 11]

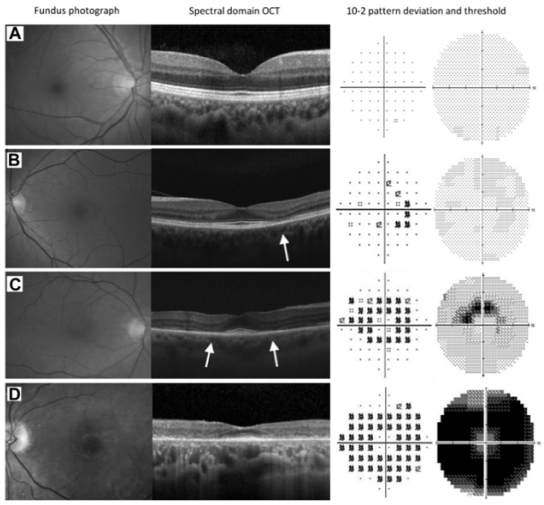

Fig.5: Progression of changes in HCQ retinal toxicity for European patients. (A) Normal eye; (B) early damage with temporal SD-OCT thinning and slight field loss; (C) moderate damage with no fundus changes or RPE loss but more severe SD-OCT and field changes; (D) severe retinopathy with a prominent bull´s eye maculopathy, RPE damage on SD-OCT, and a dense ring scotoma. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol 2014;132:1453–60.

Despite its well-known side effects, hydroxychloroquine remains a crucial element in the treatment of autoimmune diseases. Cautious screening to prevent irreversible visual loss, understanding of risk factors, utilisation of diverse screening methods, and ongoing research are fundamental to optimize patient care and prevent negative outcomes.

ANTIMETABOLITES

Antimetabolites are analogues of natural compounds that disrupt their production or use, thereby hindering vital metabolic processes. Azathioprine, a purine analogue, undergoes conversion to its active metabolites, thereby suppressing nucleic acid synthesis.[87] Due to its cytotoxic effects, it notably reduces antibody and B-cell production and attenuates T-cell-mediated responses. This medication is used in neoplastic and autoimmune diseases, such as rheumatoid arthritis and inflammatory bowel disease.[88, 89] Regarding the treatment of inflammatory bowel disease, there have been cases of cytomegalovirus (CMV) retinitis and reactivation of toxoplasmosis in association with the use of this drug, owing to its immunosuppressive properties.[3, 90]

Functioning as a folate antagonist, methotrexate modulates immune cell infiltration and inhibits the synthesis of purines and pyrimidines by targeting both dihydrofolate reductase and thymidylate synthase. As a result, it possesses anti-proliferative, anti-metabolic, and anti-inflammatory properties that lead to a substantial reduction in pro-inflammatory cytokine levels. Although its initial purpose was for neoplastic diseases, methotrexate has become the first-line disease-modifying anti-rheumatic drug (DMARD) for conditions like rheumatoid arthritis, juvenile idiopathic arthritis, and psoriasis. Its versatility extends to the treatment of inflammatory bowel disease, multiple sclerosis, vasculitis, systemic lupus erythematosus, and other connective tissue diseases.[91, 92] In a cohort of 13 patients subjected to intermittent high-dose methotrexate (30–250 mg/kg), documented symptoms included pruritus, burning sensations, irritation, and blurred vision.[93] Also, patients undergoing methotrexate as part of their chemotherapy for postmolar gestational trophoblastic neoplasia presented with conjunctivitis, dry eyes, and blepharitis.[94] Another reported case involved a young man with internuclear ophthalmoplegia after the administration of intrathecal methotrexate for lymphoma treatment.[95] Since 1992, there have been four noteworthy reports of papilledema and visual field defects, suggestive of optic neuropathy associated with methotrexate use.[96-99] While some cases suggested a correlation between treatment with methotrexate and the development of lymphoma, a large observational study disproved this.[100] Reports have also detailed retinal cotton wool spots following intravitreal or systemic methotrexate, as well as corneal epitheliopathy after intravitreal injection of methotrexate for intraocular lymphoma.[101, 102]

By employing noncompetitive, reversible inhibition of inosine monophosphate dehydrogenase, mycophenolate mofetil effectively hinders purine nucleotide synthesis and diminishes the production of both B and T lymphocytes.[103, 104] Initially used for transplant patient care, it has since found application in treating a spectrum of autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, vasculitis, inflammatory bowel disease, and uveitis. A comprehensive search failed to reveal any documented ocular side effects. However, notably, lower cell viability in human retinal pigment epithelium has been demonstrated in in vitro experiments.[105]

Leflunomide is a non-biologic DMARD with anti-inflammatory and immunomodulatory characteristics, making it useful in the treatment of rheumatoid arthritis.[106] Following the conversion of leflunomide to teriflunomide, it has the capacity to inhibit the enzyme dihydroorotate dehydrogenase, impeding the synthesis of the pyrimidine ribonucleotide necessary for DNA and RNA synthesis.[107] In 2004, a case report documented bilateral cystoid macular edema in a patient after two weeks of leflunomide treatment. As per the report, discontinuation of leflunomide resulted in the resolution of the symptoms.[108]

OTHER TRADITIONAL DMARDs

Ciclosporin serves as an immunosuppressive agent utilised primarily for treating organ rejection following transplantation. It also finds application in autoimmune disorders such as rheumatoid arthritis and psoriasis as a second-line treatment option.[109] Acting as an inhibitor of T-cell-mediated responses, ciclosporin binds to cytoplasmic proteins known as cyclophilins, forming a complex that inhibits calcineurin, thereby reducing cytokine activation.[110] In relation to its ocular side effects, a case report has described CMV anterior uveitis following the use of topical ciclosporin A 0.05% ophthalmic emulsion for dry eyes.[111] Also, a study involving 51 subjects compared the ophthalmic complications of various immunosuppressive medications after renal transplant, including steroids + ciclosporin, steroids + azathioprine, or steroids + azathioprine + ciclosporin, and found no statistically significant difference in macular hyperpigmentation or cataracts.[112] On the other hand, a separate study in 2003 involving 140 subjects advocated that ciclosporin may exacerbate steroid-induced cataracts. The addition of ciclosporin allowed a reduction in the total steroid dose, but still, more subjects in the ciclosporin group exhibited higher levels of steroid-induced cataracts.[113] In Behcet's disease, treatment with ciclosporin A was associated with increased central nervous system manifestations, including internuclear ophthalmoplegia and diplopia. A retrospective study of 117 patients with Behcet's disease identified six patients experiencing new-onset neurological symptoms while on ciclosporin A maintenance therapy.[114] In a case report from 2001, a patient receiving ciclosporin after allogeneic bone marrow transplantation exhibited diplopia and bilateral eye abduction weakness, with these symptoms resolving two days after discontinuation of ciclosporin.[115]

Cyclophosphamide is widely employed as both an anticancer and immunosuppressive agent due to its high potency, making it useful in the management of organ-threatening autoimmune conditions like vasculitis and lupus nephritis. As an alkylating agent, it disrupts DNA replication, triggering cellular apoptosis.[3, 116] Various reports indicate instances of blurred vision in cancer patients treated with cyclophosphamide, lasting until 14 days.[117] The combination regimen of cyclophosphamide, methotrexate, and 5-fluorouracil was commonly employed in breast cancer treatment and was associated with conjunctivitis, with tearing and pruritus occurring in up to 42% of cases.[118] Another study in 2001 revealed patients experiencing ocular soreness, grittiness, dryness, and increased lacrimation due to this therapy. Furthermore, following the second round of treatment, one patient developed bilateral punctal stenosis.[119] Additionally, a study of 61 patients evaluated the ophthalmological adverse effects of the combination treatment of 5-fluorouracil, epirubicin, and cyclophosphamide for breast cancer and found an association with blepharitis, conjunctival hyperemia, abnormalities of the eyelid margin, and punctate epithelial keratopathy. Patients should undergo a thorough ocular evaluation to aid in the prevention,

early detection, and efficient treatment of established ocular complications associated with these chemotherapy regimens.[120, 121]

Sulfasalazine is approved for treating autoimmune diseases, namely rheumatoid arthritis and ulcerative colitis. For conditions such as axial spondyloarthropathy, mild to moderately active Crohn's disease, psoriasis, and psoriatic arthritis, it is also used off-label.[122] Although its mechanism of action remains incompletely understood, sulfasalazine is metabolized by bacteria in the colon into sulfapyridine and 5-aminosalicylic acid, potentially inhibiting nuclear factor-kappa B or tumor necrosis factor-alpha (TNF-α).[123, 124] A single case of transient myopia with a decline in visual acuity was documented in 2003 following the introduction of sulfasalazine for rheumatoid arthritis at a daily dose of 2g for three weeks. Upon therapy cessation, the myopia improved, and vision remained stable.[125]

Janus kinase (JAK) inhibitors present a novel therapeutic approach for auto-immune conditions, constituting a class of targeted synthetic drugs with an expanding repertoire of molecules. Tofacitinib, a second-generation selective JAK inhibitor, specifically targets the JAK1 enzyme involved in the immune responses underlying certain inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis, for which it is used.[126] Despite limited global experience with these agents, documented side effects primarily associated with tofacitinib include pancytopenia, dyslipidemia, cardiovascular events, venous thromboembolism, lower respiratory tract infections, and reactivation of the herpes zoster virus.[127] In relation to the ocular complications, a study involving 4789 rheumatoid arthritis patients reported that 239 developed tofacitinib-associated HZ, including 2 patients with ophthalmic herpes zoster, and, in an extensive review, six additional cases of ocular herpes zoster were described.[128, 129] Usually, treatment with intravenous and then oral valacyclovir can lead to gradual symptomatic improvement, although decreased visual acuity may persist as a long-term complication.[7]

BIOLOGIC DMARDs

Biologic disease-modifying antirheumatic drugs emerged in the early 1990s and are typically prescribed when there is ongoing disease activity or clinical or radiological disease progression, despite treatment with traditional DMARDs. This class of drugs encompasses monoclonal antibodies, chimeric humanized fusion antibodies, receptors fused with a portion of human immunoglobulin, or small molecules that exhibit high specificity, targeting precise immune mechanisms. Their key functions consist of interfering with cytokine function or production, inhibiting T-cell activation, eliminating B-cells, or inhibiting factors that activate B-cells.[130]

TNF-α INHIBITORS

Tumour necrosis factor-alpha plays a pivotal role in initiating and perpetuating immune responses. Inhibitors targeting TNF-α treat a spectrum of conditions, including rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, and axial spondyloarthropathy, despite increasing susceptibility to infections and malignancies. Concerning their molecular composition, etanercept constitutes a soluble TNF receptor fusion protein, whereas infliximab, adalimumab, golimumab, and certolizumab are recognized as monoclonal antibodies. Notably, uveitis is a common ocular side effect, characterized by

the paradoxical reaction of anti-TNF agents, wherein the treatment may induce or worsen a condition it typically alleviates. Research indicates TNF inhibitors effectively reduce uveitis flares in Behcet's disease, juvenile idiopathic arthritis, spondyloarthropathies, inflammatory bowel disease, and sarcoidosis.[131, 132] However, the initiation of anti-TNF therapy, particularly with etanercept, has been associated with cases of new-onset uveitis. Notably, a population-based cohort analysis, described 31 cases of uveitis in patients with axial spondyloarthropathy, psoriatic arthritis, rheumatoid arthritis, and juvenile idiopathic arthritis treated with TNF inhibitors, the majority occurring due to etanercept.[133] Sarcoid uveitis, sarcoid-like granulomatosis, and scleritis are other paradoxical reactions associated with these agents.[134-139]

Moreover, these medications have been linked to central and peripheral demyelination diseases like Guillain-Barre and Miller-Fisher syndrome.[140] This was described in the case report of a woman who was undergoing infliximab therapy and presented with worsening diplopia, mild ophthalmoparesis, pupillary unresponsiveness, eyelid twitches, and elevated anti-GQ1b antibodies. The diplopia was managed with occlusion, resulting in complete symptom resolution within 10 weeks.[141] Another demyelinating disorder commonly reported in association with TNF inhibitors is optic neuritis. However, the large-scale multi-institutional SABER study in 2013 revealed optic neuritis to be rare among individuals initiating anti-TNF therapy, occurring at rates comparable to those receiving conventional DMARD therapy. These results contrasted with the numerous cases of optic neuritis documented in existing literature, underscoring the importance of considering such evidence when evaluating the adverse effects of TNF inhibitors.[142, 143] Additional neurological side effects associated with TNF inhibition include internuclear ophthalmoplegia, homonymous hemianopia, visual field defects, scotomas, nystagmus, and diplopia.[144-147] The elevated risk of rheumatoid arthritis patients developing uveal melanoma due to treatment with TNF inhibitors was described by a Swedish population-based cohort study, particularly relevant for individuals with prior diagnoses of choroidal nevi or chronic diffuse scleritis.[148, 149] The structure, mechanism, indications, and ocular adverse effects of TNF-α inhibitors are summarised in table II.

Adalimumab, in particular, has been associated with varied ocular side effects in case reports. For example, while receiving adalimumab as a treatment for Crohn’s disease, a woman experienced diffuse bilateral retinopathy, which caused visual field loss for six months in spite of therapy cessation.[150] Bilateral peripheral corneal infiltrates after injection with this agent have also been documented in a patient treated for Crohn’s disease, with recurrences observed after subsequent treatments over the following weeks even with the use of topical corticosteroids.[151] Another case involved a patient with refractory psoriasis who developed central retinal vein occlusion following the fifth dose of adalimumab. Despite discontinuation of adalimumab, the patient developed neovascular glaucoma with vision loss.[152] Similarly, there is a case report of acute retinal necrosis in a patient receiving treatment for psoriasis who regained visual acuity seven years later due to treatment with intravenous acyclovir and prophylactic laser barricade.[153] In relation to infectious complications, a woman experienced a severe necrotizing periorbital infection while receiving adalimumab. She recovered fully after antibiotic therapy.[154]

Another ophthalmological complication of etanercept is the occurrence of periorbital angioedema in the treatment of adult-onset Still’s disease.[155] The association between the administration of etanercept and orbital myositis has been documented by two distinct case reports, resolving with therapy cessation and

high-dose steroid treatment.[156, 157] Additionally, the immunosuppressive properties of etanercept increase the risk of primary intraocular lymphoma, as evidenced by a 50-year-old woman who was effectively managed with intravitreal methotrexate injections and systemic chemotherapy.[158] Several cases of tuberculosis uveitis, bilateral candida, and toxoplasmic chorioretinitis are reported, highlighting the immunosuppression secondary to etanercept therapy.[159-161]

The causality between infliximab therapy and retinal vein thrombosis has been suggested because of the timing of numerous reports documenting the onset of thrombosis in patients undergoing infliximab treatment for Crohn's disease, ulcerative colitis, and plaque psoriasis.[162-164] Also, there is a case report of a patient with a history of acne rosacea of the skin who experienced bilateral rosacea-like keratopathy upon initiation of infliximab therapy for rheumatoid arthritis, improving upon discontinuation of the medication.[165] Infections such as CMV retinitis, toxoplasmic chorioretinitis, orbital cellulitis, and endogenous endophthalmitis have also been associated with infliximab use.[166-168] Notably, a 71-year-old patient treated with infliximab for surgically induced necrotizing scleritis developed Purpureocillium lilacinum endophthalmitis, which was resolved with a vitrectomy and a course of antibacterial and antifungal therapy.[169] Scleritis results in scleral thinning, which could heighten the risk of endophthalmitis. *Jin et al.* proposed that TNF-α inhibitors might facilitate the migration of cilia into the ocular globe, contributing to the development of endophthalmitis.[170]

More recent TNF-α inhibitors, golimumab and certolizumab, have limited data available regarding their potential ocular adverse effects. In the SABER study, researchers documented five cases of optic neuritis associated with the use of golimumab or certolizumab.[143] Additionally, a case report described the development of eyelid Merkel cell carcinoma in a patient undergoing treatment with golimumab for rheumatoid arthritis. After six months of treatment, the tumour surfaced and required extensive treatment, including radical tumour excision, eyelid reconstruction, and radiation therapy.[171]

INTERLEUKIN INHIBITORS

Interleukins are key regulators of growth, differentiation, and activation during inflammatory and immune responses. They form a diverse group of proteins that trigger various biological reactions by binding to high-affinity receptors on cell surfaces.[172] Anakinra, an antagonist of the interleukin-1 receptor, is used to treat conditions like rheumatoid arthritis and neonatal-onset multisystem inflammatory disease. A cohort study tracking the 5-year outcomes of 26 patients with this disease treated with anakinra daily for at least 3 years showed two patients on high-dose treatment that developed nystagmus. Adverse effects observed included ocular edema, glaucoma, and blurred vision with low doses, while higher doses led to blepharospasm and ophthalmic pruritus.[173]

Sarilumab, targeting the interleukin-6 receptor, is indicated for moderate to severe rheumatoid arthritis. Its efficacy and safety in treating posterior segment non-infectious uveitis were evaluated in the phase II SATURN study. This revealed worsening uveitis and retinal infiltrates as the most frequent side effects and showed that vitreous haze was decreased by subcutaneous administration.[174]

Tocilizumab also inhibits the IL-6 receptor and is prescribed for conditions such as rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritis. A significant ocular side effect of this agent was described in a case report of a patient undergoing tocilizumab treatment for 9 months who developed an ophthalmic herpes zoster virus infection affecting the right ophthalmic region with vesicles on the nose and lesions on the anterior part of the left shoulder. Treatment with valacyclovir improved the symptoms, but these recurred after each tocilizumab injection, leading to therapy cessation.[175] In another study, tocilizumab administration led to the recurrence of HTLV-1 uveitis and tropical spastic paraparesis, with improvement upon steroid-based therapy. The substitution to abatacept also worsened symptoms, prompting caution in using biologics in patients with HTLV-1 infections.[176] A multicenter study on tocilizumab for juvenile idiopathic arthritis-associated uveitis reported a case of viral conjunctivitis and bullous impetigo, demanding therapy discontinuation temporarily.[177] Moreover, bilateral papilledema in a child with steroid-dependent systemic juvenile idiopathic arthritis undergoing tocilizumab treatment has also been documented. Vision was restored in one eye and partially recuperated in the other, following urgent unilateral optic nerve sheath fenestration.[178]

Ustekinumab functions by inhibiting IL12 and IL23 and is used in the treatment of plaque psoriasis, psoriatic arthritis, and severe Crohn's disease. In relation to its ocular side effects, only a case of ophthalmic herpes zoster was noted in its safety information.[179] Secukinumab, a monoclonal antibody blocking IL17A, is employed in the treatment of psoriatic arthritis, plaque arthritis, and axial spondyloarthropathy. It was considered a potential predisposing factor for endophthalmitis in a case report of a diabetic patient who developed osteomyelitis and unilateral endogenous endophthalmitis after receiving secukinumab therapy.[180, 181]

ANTI-LYMPHOCYTES

Rituximab is an anti-CD20 monoclonal antibody that induces B-cell depletion, and is useful in the management of autoimmune diseases such as rheumatoid arthritis.[182] The most severe ocular side effect that has been associated with rituximab therapy is acute retinal necrosis, documented in a patient with scleroderma and rheumatoid arthritis undergoing this treatment.[183] Another patient with microscopic polyangiitis experienced progressive outer retinal necrosis after receiving rituximab and cyclophosphamide treatment.[184] Transient bilateral conjunctivitis has also been noted during infusion therapy for bronchial-associated lymphoma.[185] Additionally, two patients with refractory granulomatosis with polyangiitis receiving rituximab developed cystoid macular edema.[186] Regarding infectious complications, there was a higher incidence of CMV retinitis in patients undergoing rituximab and fludarabine-containing regimens simultaneously. In such cases, treatment demanded both intravitreal and systemic ganciclovir/foscarnet therapy, resulting in secondary retinal atrophy in all patients and eventual blindness in 86% of affected eyes.[187] Although the majority of adverse effects stem from systemic treatment, intravitreal rituximab injections may cause a temporary increase in intraocular pressure and iridocyclitis with mutton-fat keratic precipitates, particularly evident in the management of primary vitreoretinal lymphoma.[188]

Abatacept is also an anti-lymphocytic agent that functions by attaching to CD80/CD86 proteins found on antigen-presenting cells, thereby halting T-cell activation. Typically, it is recommended following the ineffectiveness of initial treatment for individuals with moderate to severe rheumatoid arthritis.[189] In terms of ophthalmic complications, abatacept was linked to the development of an infectious corneal ulcer in a study examining its effectiveness and safety in Sjogren's syndrome related to rheumatoid arthritis.[190]

INTERFERONS

Interferons are proteins released in response to viral infections and are extensively used in clinical settings to combat viral infections such as hepatitis C, cancers like non-Hodgkin's lymphoma, and autoimmune diseases like multiple sclerosis. The administration of IFN-α to Behcet's disease patients, particularly those with severe uveitis, has been advocated.[191, 192] Nonetheless, this agent can induce retinopathy, potentially leading to severe optic nerve damage.[193] Instances of episcleritis have been linked to IFNα-2b treatment for mucosal melanoma.[194] Moreover, reports indicate occurrences of optic neuromyelitis, retinal vein thrombosis, retinopathy, non-arteritic anterior ischemic optic neuropathy, cystoid macular edema, Vogt-Koyanagi-Harada disease, optic neuritis, abducens palsy, oculomotor nerve palsy, and glaucoma in patients receiving IFN-α therapy.[195-208]

CONCLUSION

In conclusion, the management of autoimmune diseases often involves a spectrum of medications with the potential for ocular side effects, ranging from steroids to traditional DMARDs to biologic agents. While these therapies are essential for controlling disease activity and improving patient outcomes, their ocular complications highlight the critical need for preventive measures and vigilant monitoring.

First and foremost, proactive steps can be taken to mitigate the ocular risk. Physicians must adhere to established guidelines for dosing and screening, particularly for medications like hydroxychloroquine and glucocorticoids where substantial evidence on risk factors, dosage, and side effects is already available.[11] Additionally, patient education plays a pivotal role in fostering awareness of potential consequences and the importance of regular ophthalmic monitoring for early detection and management of adverse effects. Collaboration between rheumatologists and ophthalmologists guarantees comprehensive patient care, facilitates holistic management approaches, enables timely intervention, and minimises the risk of irreversible vision loss.[8]

As this review is qualitative, it does not ascertain the frequency or incidence of the ocular side effects documented, primarily derived from case reports and series that do not establish definitive causality. To prove these associations and establish the actual incidence, longitudinal studies and randomised controlled trials are imperative. The diverse array of ocular adverse events associated with various therapeutic agents highlights the complexity of managing these conditions and the need for individualised treatment strategies. In the future, research endeavours should prioritise precision medicine within this domain, considering the diverse genetic, socio-environmental, and lifestyle factors present across subpopulations. By doing so, researchers can tailor treatment strategies more effectively, mitigating the risk of undesirable side effects.[209]

Currently, a comprehensive understanding of ocular side effects, diligent preventive measures, regular ophthalmologic monitoring, patient education, and interdisciplinary collaboration are paramount in optimizing patient outcomes and enhancing the quality of care in autoimmune disease management. By prioritising ocular health and advancing research efforts, we can strive towards minimising the burden of ocular complications and improving the overall well-being of patients with autoimmune diseases.

APPENDIX

Table I: List of Antirheumatic Agents

Drug Names	
Corticosteroids	
NSAIDs: indomethacin, ibuprofen, piroxicam, oxaprozin, naproxen, acetylsalicylic acid, rofecoxib, celecoxib, valdecoxib, lumiracoxib, nimesulide, etodolac	
Traditional DMARDs	Hydroxychloroquine
	Antimetabolites: methotrexate, mycophenolate mofetil, leflunomide
	Ciclosporin
	Cyclophosphamide
	Sulfasalazine
	JAK inhibitors: tofacitinib
Biologic DMARDs	TNF-α inhibitors: adalimumab, etanercept, infliximab, golimumab, certolizumab
	IL-inhibitors: anakinra, sarilumab, tocilizumab, ustekinumab
	Anti-lymphocytic agents: rituximab, abatacept
Interferons	

Table II: Structure, mechanism, indications, and ocular adverse effects of TNF-α inhibitors. Adapted from: Nicolela Susanna F, Pavesio C. A review of ocular adverse events of biological anti-TNF drugs. J Ophthalmic Inflamm Infect. 2020;10(1):11.

Agent	Adalimumab	Etanercept	Infliximab	Golimumab	Certolizumab
Structure and Mechanism	Fully humanized IgG1 that binds TNF-α	TNFR2 ectodomain fused to IgG1 binds TNF-α and TNFβ	Chimeric murine-human IgG1 that binds TNF-α	Fully humanized IgG1 that binds TNF-α	Humanized PEGylated Fab that binds TNF-α
Indications	RA, psoriatic arthritis, axial spondyloarthropathy, juvenile idiopathic arthritis, uveitis, plaque psoriasis, hidradenitis suppurativa, ulcerative colitis, and Crohn's disease	RA, psoriatic arthritis, plaque psoriasis, axial spondyloarthropathy, and juvenile idiopathic arthritis	RA, psoriatic arthritis, plaque psoriasis, axial spondyloarthropathy, idiopathic pulmonary fibrosis, ulcerative colitis, and Crohn's disease	RA, psoriatic arthritis, axial spondyloarthropathy, and ulcerative colitis	RA, psoriatic arthritis, axial spondyloarthropathy, and Crohn's disease
Ocular Adverse Effects	Uveitis, optic neuritis, endophthalmitis, corneal infiltrates, retinal toxicity, ophthalmoplegia	Uveitis, scleritis, optic neuritis, ocular myositis, tuberculosis uveitis, bilateral candida and toxoplasmic chorioretinitis	Uveitis, optic neuritis, endophthalmitis, retinal vein thrombosis, CMV retinitis, toxoplasmic chorioretinitis, orbital celullitis	Optic neuritis	Optic neuritis

BIBLIOGRAPHY

1. Noel RR. Autoimmune Diseases: Tracing the Shared Threads. Hospital Practice. 1997;32(4):147-54.
2. Wang L, Wang F-S, Gershwin ME. Human autoimmune diseases: a comprehensive update. Journal of Internal Medicine. 2015;278(4):369-95.
3. M. Castillejo BC, Ding Y, Kenol B, Hendershot A, Meara AS. Ocular side effects of antirheumatic medications: a qualitative review. BMJ Open Ophthalmol. 2020;5(1):e000331.
4. Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. Eye (Lond). 2017;31(6):828-45.
5. Renfro L, Snow JS. Ocular Effects of Topical and Systemic Steroids. Dermatologic Clinics. 1992;10:505-12.
6. Fraunfelder FW, Solomon J, TJ M. Ocular Adverse Effects Associated With Cyclooxygenase-2 Inhibitors. Archives of Ophthalmology 2006;124:277-9.
7. Dammacco R, Guerriero S, Alessio G, Dammacco F. Natural and iatrogenic ocular manifestations of rheumatoid arthritis: a systematic review. Int Ophthalmol. 2022;42(2):689-711.
8. Lubon W, Lubon M, Kotyla P, Mrukwa-Kominek E. Understanding Ocular Findings and Manifestations of Systemic Lupus Erythematosus: Update Review of the Literature. Int J Mol Sci. 2022;23(20).
9. Peponis V, Kyttaris VC, Chalkiadakis SE, Bonovas S, Sitaras NM. Ocular side effects of anti-rheumatic medications: what a rheumatologist should know. Lupus. 2010;19(6):675-82.
10. Ding HJ, Denniston AK, Rao VK, Gordon C. Hydroxychloroquine-related retinal toxicity. Rheumatology (Oxford). 2016;55(6):957-67.
11. Michael F. Marmor, Ulrich Kellner, Timothy Y.Y. Lai, FRCOphth, Ronald B. Melles, William F. Mieler. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology. 2016;123:1386-94.
12. Nicolela Susanna F, Pavesio C. A review of ocular adverse events of biological anti-TNF drugs. J Ophthalmic Inflamm Infect. 2020;10(1):11.
13. Kačmař J, Cholevík D. Corticosteroid Induced Posterior Subcapsular Cataract. Cesk Slov Oftalmol. 2019;74(6):226-32.
14. Chrousos GP. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. N Engl J Med. 1995;332:1351–62.
15. Rousseau GG, Baxter JD, Tomkins GM. Glucocorticoid receptors: relations between steroid binding and biological effects. J Mol Biol 1972;67:99–115.
16. Rhen T, Cidlowski JA. Antiinflammatory Action of Glucocorticoids — New Mechanisms for Old Drugs. The new england journal of medicine. 2005;353(16):1711-23.
17. Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. Current Opinion in Ophthalmology. 2000;11(6):478–83.
18. WATERBURY L, KUNYSZ EA, BEUERMAN R. Effects of Steroidal and Non-Steroidal Anti-Inflammatory Agents on Corneal Wound Healing. Journal of Ocular Pharmacology and Therapeutics. 1987;3(1):43–54.

19. Haimovici R, Gragoudas ES, Duker JS, Sjaarda RN, Eliott D. Central Serous Chorioretinopathy Associated with Inhaled or Intranasal Corticosteroids. Ophthalmology. 1997;104(10):1653–60.
20. Purdy EP, Ajimal GS. Vision Loss After Lumbar Epidural Steroid Injection. Anesthesia & Analgesia. 1998;86(1):119–22.
21. Ling C, Atkinson PL, Munton CG. Bilateral retinal haemorrhages following epidural injection. British Journal of Ophthalmology. 1993;77(5):316–7.
22. VICTORY RA, HASSETT P, MORRISON G. Transient blindness following epidural analgesia. Anaesthesia. 1991;46(11): 940–1.
23. Black RL, Oglesby RB, Von Sallmann L, Bunim JJ. Posterior Subcapsular Cataracts Induced by Corticosteroids in Patients with Rheumatoid Arthritis. JAMA 1960;174:166–71.
24. Dluhy RG. Effect of inhaled beclomethasone dipropionate and budesonide on adrenal function, shin changes and cataract formation. Respir Med. 1998;92:15–23.
25. Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. Am J Med. 1995;98:196–208.
26. Urban RCJ, Cotlier E. Corticosteroid-induced cataracts. Surv Ophthalmol 1986;31(2):102–10.
27. Aggarwal S, Ta B, Photographer: James Gilman C, FOPS, Moran Eye Center Ocular Side-Effects of Corticosteroids University of Utah: Moran Eye Center; 2018 [Available from: https://morancore.utah.edu/basic-ophthalmology-review/ocular-side-effects-of-corticosteroids/.
28. Chylack LT. Cataracts and inhaled corticosteroids. N Engl J Med 1997;337:46–8.
29. Karim AK, Jacob TJ, Thompson GM. The human lens epithelium; morphologic and ultrastructural changes associated with steroid therapy. Exp Eye Res 1989;48:215–24.
30. Shun-Shin GA, Brown NP, Bron AJ, Sparrow JM. Dynamic nature of posterior subcapsular cataracts. Br J Ophthalmol 1989;73:522–7.
31. Skalka HW, Prchal JT. Effect of Corticosteroids on Cataract Formation. Archives of Ophthalmology. 1980;98(10):1773–7.
32. Wilson JC, Sarsour K, Gale S, Pethö-Schramm A, Jick SS, Meier CR. Incidence and risk of glucocorticoid- associated adverse effects in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2019;71(4):498–511.
33. Jobling AI, Augusteyn RC. What causes steroid cataracts? A review of steroid-induced posterior subcapsular cataracts. Clinical and Experimental Optometry. 2002;85(2):61-75.
34. Costagliola C, Cati-Giovannelli B, Piccirillo A, Delfino M. Cataracts associated with long-term topical steroids. British Journal of Dermatology. 1989;120(3):472–3.
35. Roberti G, Oddone F, Agnifili L, Katsanos A, Michelessi M, Mastropasqua L, et al. Steroid-induced glaucoma: Epidemiology, pathophysiology, and clinical management. Surv Ophthalmol. 2020;65(4):458-72.
36. Tripathi RC, Parapuram SK, Tripathi BJ, Zhong Y, Chalam KV. Corticosteroids and glaucoma risk. Drugs Aging. 1999;15:439–50.
37. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics. Arch Ophthalmol. 1963;70:492-9.
38. Pleyer U, Ursell PG, Rama P. Intraocular Pressure Effects of Common Topical Steroids for Post-Cataract Inflammation: Are They All the Same? Ophthalmology and Therapy. 2013;2(2):55–72.

39. Yamamoto Y, Komatsu T, Koura Y, Nishino K, Fukushima A, Ueno H. Intraocular pressure elevation after intravitreal or posterior sub-Tenon triamcinolone acetonide injection. Can J Ophthalmol. 2008;43(1):42-7.
40. Jones Rr, Rhee DJ. Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. Curr Opin Ophthalmol. 2006;17:163-7.
41. Marcus MW, Müskens RPHM, Ramdas WD, Wolfs RCW, De Jong PTVM, Vingerling JR, Jansonius NM. Corticosteroids and Open-Angle Glaucoma in the Elderly. Drugs & Aging. 2012;29(12):963-70.
42. Sihota R, Konkal VL, Dada T, Agarwal HC, Singh R. Prospective, long-term evaluation of steroid-induced glaucoma. Eye 2006;22(1):26-30.
43. Clark AF, Wilson K, Kater AW, Allingham RR, McCartney MD. Dexamethasone- induced ocular hypertension in perfusion-cultured human eyes. Invest Ophthalmol Vis Sci. 1995;36:478-89.
44. Clark AF, Wordinger RJ. The role of steroids in outflow resistance. Exp Eye Res. 2009;88:752-9.
45. Wilson K, McCartney MD, Miggans ST, Clark AF. Dexamethasone induced ultrastructural changes in cultured human trabecular meshwork cells. Curr Eye Res. 1993;12(9):783-93.
46. Johnson DH, Bradley JM. The effect of dexamethasone on glycosaminoglycans of human trabecular meshwork in perfusion organ culture. Invest Ophthalmol Vis Sci. 1990;31(12):2568-71.
47. Patel PD, Kodati B, Clark AF. Role of Glucocorticoids and Glucocorticoid Receptors in Glaucoma Pathogenesis. Cells 2023;12(2452).
48. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics. Arch Ophthalmol. 1963;70:482-91.
49. Biedner BZ, David R, Grudsky A, Sachs U. Intraocular pressure response to corticosteroids in children. Br J Ophthalmol. 1980;64:430-1.
50. Hutcheson KA. Steroid-induced glaucoma in an infant. J AAPOS. 2007;11:522-3.
51. Becker B, Bresnick G, Chevrette L, Kolker AE, Oaks MC, Cibis A. Intraocular pressure and its response to topical corticosteroids in diabetes. Arch Ophthalmol. 1966;76(4):477-83.
52. Podos SM, Becker B, Morton WR. High myopia and primary open-angle glaucoma. Am J Ophthalmol. 1966;62(6):1038-43.
53. Spaeth GL. Traumatic hyphema, angle recession, dexamethasone hypertension, and glaucoma. Arch Ophthalmol. 1967;78(6):714-21.
54. Gaston H, Absolon MJ, Thurtle OA, Sattar MA. Steroid responsiveness in connective tissue diseases. Br J Ophthalmol. 1983;67(7):487-90.
55. Stone EM, Fingert JH, Alward WLM, Nguyen TD, Polansky JR, Sunden SL, et al. Identification of a gene that causes primary open angle glaucoma. Science. 1997;275:668-70.
56. Phulke S, Kaushik S, Kaur S, Pandav SS. Steroid-induced glaucoma: an avoidable irreversible blindness. J Curr Glaucoma Pract. 2017;11(2):67-72.
57. Li P, Zheng Y, Chen X. Drugs for Autoimmune Inflammatory Diseases: From Small Molecule Compounds to Anti-TNF Biologics. Front Pharmacol. 2017;8(460).
58. Palimeris G, Koliopoulos J, Velissaropoulos P. Ocular side effects of indomethacin. Ophthalmologica 1972;164:339–53.
59. Burns CA. Indomethacin, reduced retinal sensitivity, and corneal deposits. Am J Ophthalmol. 1968;66(5):825–35.

60. Graham CM, Blach RK. Indomethacin retinopathy: case report and review. Br J Ophthalmol 1988;72:434–8.
61. Palimeris G, Koliopoulos J, Velissaropoulos P. Electrophysiological findings in patients treated with indomethacin. Adv Exp Med Biol 1972;24:323–9.
62. Henkes HE, van Lith GH, Canta LR. Indomethacin retinopathy. Am J Ophthalmol. 1972;73(6):846–56
63. Groomer AE, Terry JE, Westblom TU. Subconjunctival and external hemorrhage secondary to oral anticoagulation. J Am Optom Assoc. 1990;61:770–5.
64. Mortada A, Abboud I. Retinal haemorrhages after prolonged use of salicylates. Br J Ophthalmol 1973;57:199-200.
65. Black RA, Bensinger RE. Bilateral subconjunctival hemorrhage after acetylsalicylic acid overdose. Ann Ophthalmol 1982;14(11):1024–5
66. Wallace DJ. The history of antimalarials. Lupus. 1996;5.
67. Lee S-J, Silverman E, Bargman JM. The role of antimalarial agents in the treatment of SLE and lupus nephritis. Nature Reviews Nephrology. 2011;7(12):718-29.
68. Raines MF, Bhargava SK, Rosen ES. The blood retinal barrier in chloroquine retinopathy. Invest Ophthalmol Vis Sci 1989;30:1726-31.
69. Sundelin SP, Terman A. Different elements of chloroquine and hydroxychloroquine on lysosomal function in cultured retinal pigment epithelial cells. . APMIS. 2002;100:481-9.
70. Yam JC, Kwok AK. Ocular toxicity of hydroxychloroquine. Hong Kong Med J 2006;12:294-304.
71. Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. Am J Med. 1983;75:25-34.
72. Kellner S, Weinitz S, Farmand G, Kellner U. Cystoid macular oedema and epiretinal membrane formation during progression of chloroquine retinopathy after drug cessation. Br J Ophthalmol 2014;98:200-6.
73. Vu BL, Easterbrook M, Hovis JK. Detection of color vision defects in chloroquine retinopathy. Ophthalmology. 1999;106:1799-803.
74. Rodriguez-Padilla JA, Hedges III TR, Monson B, Srinivasan V, Wojtkowski M, Reichel E, et al. High-Speed Ultra-High-Resolution Optical Coherence Tomography Findings in Hydroxychloroquine Retinopathy. Arch Ophthalmol. 2007;125(6):775-80.
75. Stepien KE, Han DP, Schell J, Godara P, Rha J, Carroll J. SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY AND ADAPTIVE OPTICS MAY DETECT HYDROXYCHLOROQUINE RETINAL TOXICITY BEFORE SYMPTOMATIC VISION LOSS. Trans Am Ophthalmol Soc 2009;107:28-33.
76. Tobin DR, Krohel G, Rynes RI. Hydroxychloroquine. Seven-year experience. . Arch Ophthalmol. 1982;100:81-3.
77. Maturi RK, Yu M, Weleber RG. Multifocal electroretinographic evaluation of long-term hydroxychloroquine users. Arch Ophthalmol. 2004;122:973-81.
78. Mititelu M, Wong BJ, Brenner M, Bryar PJ, Jampol LM, Fawzi AA. Progression of hydroxychloroquine toxic effects after drug therapy cessation: new evidence from multimodal imaging. JAMA Ophthalmol. 2013;131:1187- 97.

79. Michaelides M, Stover NB, Francis PJ, Weleber RG. Retinal toxicity associated with hydroxychloroquine and chloroquine: risk factors, screening, and progression despite cessation of therapy. Arch Ophthalmol. 2011;129:30-9.
80. Salu P, Uvijls A, van den Brande P, Leroy BP. Normalization of generalized retinal function and progression of maculopathy after cessation of therapy in a case of severe hydroxychloroquine retinopathy with 19 years follow-up. Doc Ophthalmol 2010;120:251-64.
81. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. . JAMA Ophthalmol 2014;132:1453–60.
82. Shroyer NF, Lewis RA, Lupski JR. Analysis of the ABCR (ABCA4) Gene in 4-Aminoquinoline Retinopathy: Is Retinal Toxicity by Chloroquine and Hydroxychloroquine Related to Stargardt Disease? Am J Ophthalmol. 2001;131:761-6.
83. Farrell DF. Retinal toxicity to antimalarial drugs: chloroquine and hydroxychloroquine: a neurophysiologic study. Clin Ophthalmol 2012;6:377-83.
84. Marmor MF. Comparison of Screening Procedures in Hydroxychloroquine Toxicity. Arch Ophthalmol. 2012;130:461-9.
85. Ugwuegbu O, Uchida A, Singh RP, Beven L, Hu M, Kaiser S, et al. Quantitative assessment of outer retinal layers and
ellipsoid zone mapping in hydroxychloroquine retinopathy. British Journal of Ophthalmology. 2019;103(1):3.
86. Kalra G, Talcott KE, Kaiser S, Ugwuegbu O, Hu M, Srivastava SK, Ehlers JP. Machine Learning-Based Automated Detection of Hydroxychloroquine Toxicity and Prediction of Future Toxicity Using Higher-Order OCT Biomarkers. Ophthalmol Retina. 2022;6(12):1241-52.
87. Avendaño C, Menéndez JC. Medicinal Chemistry of Anticancer Drugs,. Elsevier. 2008:9-52.
88. Mohammadi O, Kassim TA. Azathioprine Treasure Island (FL): StatPearls Publishing; [updated Updated 2023 May 1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542190/.
89. Ahmed AR, Moy R. Azathioprine. Int J Dermatol 1981;20:461–7.
90. Puga M, Carpio D, Sampil M, Zamora MJ, Fernandez-Salgado E. Ocular toxoplasmosis reactivation in a patient with inflammatory bowel disease under treatment with azathioprine. 2016;50:610.
91. Zhao Z, Hua Z, Luo X, Li Y, Yu L, Li M, et al. Application and pharmacological mechanism of methotrexate in rheumatoid arthritis. Biomedicine & Pharmacotherapy. 2022;150.
92. Bedoui Y, Guillot X, Sélambarom J, Guiraud P, Giry C, Jaffar-Bandjee MC, et al. Methotrexate an Old Drug with New Tricks. Int J Mol Sci. 2019;20(20):5023.
93. Doroshow JH, Locker GY, Gaasterland DE, Hubbard SP, Young RC, Myers CE. Ocular Irritation from High-Dose Methotrexate Therapy: Pharmacokinetics of Drug in the Tear Film. Cancer. 1981;48:2158–62.
94. Maestá I, Nitecki R, Horowitz NS, Goldstein, D. P., de Freitas Segalla Moreira M, Elias KM, Berkowitz RS. Effectiveness and toxicity of first-line methotrexate chemotherapy in low-risk postmolar gestational trophoblastic neoplasia: The New England Trophoblastic Disease Center experience. Gynecologic Oncology. 2018;148(1):161-7.
95. Lepore FE, Nissenblatt MJ. Bilateral Internuclear Ophthalmoplegia After Intrathecal Chemotherapy and Cranial Irradiation. American Journal of Ophthalmology. 1981;92(6):851-3.
96. Balachandran C, McCluskey PJ, Champion GDH, G.M. Methotrexate-Induced optic neuropathy. Clin Exp Ophthalmol 2002;30:440-1.

97. Clare G, Colley S, Kennett RE, J.S. Reversible Optic Neuropathy Associated With Low-Dose Methotrexate Therapy. J Neuroophthalmol 2005;25:109-12.
98. Johansson BA, 91–94. Visual field defects during low-dose methotrexate therapy. Documenta Ophthalmologica. 1992;79(1):91-4.
99. Sbeity ZH, Baydoun L, Schmidt S, Loeffler KU. Visual field changes in methotrexate therapy. Case report and review of the literature. J Med Liban 2006;54:164-7.
100. Kempen JH, Gangaputra S, Daniel E, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, et al. Long-term Risk of Malignancy Among Patients Treated With Immunosuppressive Agents for Ocular Inflammation: A Critical Assessment of the Evidence. American Journal of Ophthalmology. 2008;146(6):802-12.
101. Gorovoy I, Prechanond T, Abia M, Afshar AR, Stewart JM. Toxic Corneal Epitheliopathy After Intravitreal Methotrexate and Its Treatment With Oral Folic Acid. Cornea. 2013;32:1171-3.
102. Klemencic S. Cotton wool spots as an indicator of methotrexate- induced blood dyscrasia. Optometry. 2010;81:177-80.
103. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology. 2000;47:85-118.
104. Sievers TM, Rossi SJ, Ghobrial RM, Arriola E, Nishimura P, Kawano M, Holt CD. Mycophenolate mofetil. Pharmacotherapy. 1997;17(6):1178-97.
105. Zacharias LC, Damico FM, Kenney MC, Gasparin F, Acquesta FB, Ventura DF, et al. In vitro evidence for mycophenolic acid dose-related cytotoxicity in human retinal cells. Retina 2013;33:2155–61.
106. Padda IS, Goyal A. Leflunomide Treasure Island (FL): StatPearls Publishing; [updated Updated 2023 Jun 3. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557799/.
107. Breedveld FC, Dayer JM. Leflunomide: mode of action in the treatment of rheumatoid arthritis. Ann Rheum Dis. 2000;59(11):841-9.
108. Barak A, Morse LS. Leflunomide (Arava)-induced cystoid macular oedema. Rheumatology 2004;43:246–8.
109. Tapia C, Nessel TA, Zito PM. Cyclosporine Internet Treasure Island (FL): StatPearls Publishing; 2023 [updated Updated 2023 Aug 28. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482450/.
110. Kahan BD. Cyclosporine. N Engl J Med. 1989;321:1725-38.
111. Siak J, Chee S-P. Cytomegalovirus Anterior Uveitis Following Topical Cyclosporine A. Ocul Immunol Inflamm 2018;26:90-3.
112. Apaydin C, Gur B, Yakupoglu G, Saka O. Ocular and visual side effects of systemic cyclosporine. Ann Ophthalmol 1992;24:465-9.
113. Nakamura T, Sasaki H, Nagai K, Fujisawa K, Sasaki K, Suzuki K, Tsugawa R. Influence of cyclosporin on steroid-induced cataracts after renal transplantation. Jpn J Ophthalmol 2003;47:254-9.
114. Kötter I, Günaydin I, Batra M, Vonthein R, Stübiger N, Fierlbeck G, Melms A. CNS involvement occurs more frequently in patients with Behçet's disease under cyclosporin A (CsA) than under other medications—results of a retrospective analysis of 117 cases'. . Clin Rheumatol 2006;25:482-6.
115. Openshaw H. Eye movement abnormality associated with cyclosporin. J Neurol Neurosurg Psychiatry
. 2001;70:809.

116. de Jonge ME, Huitema ADR, Rodenhuis S, Beijnen JH. Clinical pharmacokinetics of cyclophosphamide. Clin Pharmacokinet 2005;44:1135–64
117. Kende G, Sirkin SR, Thomas PRM, Freeman AI. Blurring of vision. A previously undescribed complication of cyclophosphamide therapy. . Cancer. 1979;44:69-71.
118. Loprinzi CL, Love RR, Garrity JA, Ames MM. Cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)-induced ocular toxicity. . Cancer Invest 1990;8:459-65.
119. Stevens A, Spooner D. Lacrimal duct stenosis and other ocular toxicity associated with adjuvant cyclophosphamide, methotrexate and 5-fluorouracil combination chemotherapy for early stage breast cancer. Clin Oncol 2001;13:438-40.
120. Karamitsos A, Kokkas V, Goulas A, Paraskevopoulos P, Gougoulias K, Karampatakis V, Boboridis K. Ocular surface and tear film abnormalities in women under adjuvant chemotherapy for breast cancer with the 5-Fluorouracil, Epirubicin and Cyclophosphamide (FEC) regimen. . Hippokratia. 2013;17(2):120-5.
121. Vitiello L, Lixi F, Coco G, Giannaccare G. Ocular Surface Side Effects of Novel Anticancer Drugs. Cancers 2024;16.
122. Choi J, Fenando A. Sulfasalazine Treasure Island (FL): StatPearls Publishing; 2022 [updated Updated 2022 Nov 11. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557809/.
123. Lee C-K, Lee EY, Chung SM, Mun SH, Yoo B, Moon H-B. Effects of disease-modifying antirheumatic drugs and antiinflammatory cytokines on human osteoclastogenesis through interaction with receptor activator of nuclear factor kappaB, osteoprotegerin, and receptor activator of nuclear factor kappaB ligand. Arthritis Rheum 2004;50:3831–43.
124. Rodenburg RJ, Ganga A, van Lent PL, van de Putte LB, van Venrooij WJ. The antiinflammatory drug sulfasalazine inhibits tumor necrosis factor alpha expression in macrophages by inducing apoptosis. Arthritis Rheum. 2000;43(9):1941-50.
125. Santodomingo-Rubido J, Gilmartin B, Wolffsohn JS. Drug-induced bilateral transient myopia with the sulphonamide sulphasalazine. Oph Phys Optics 2003;23:567-70.
126. Padda IS, Bhatt R, Parmar M. Tofacitinib Treasure Island (FL): StatPearls Publishing; 2023 [updated Updated 2023 Jul 3. Available from: https://www.ncbi.nlm.nih.gov/books/NBK572148/.
127. Mease P, Charles-Schoeman C, Cohen S, Fallon L, Woolcott J, Yun H, et al. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. Ann Rheum Dis. 2020;79(11):1400-13.
128. Winthrop KL, Yamanaka H, Valdez H, Mortensen E, Chew R, Krishnaswami S, et al. Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014;66(10):2675-84.
129. Yamaoka K. Benefit and Risk of Tofacitinib in the Treatment of Rheumatoid Arthritis: A Focus on Herpes Zoster. Drug Safety. 2016;39(9):823–40.
130. Benjamin O, Goyal A, Lappin SL. Disease-Modifying Antirheumatic Drugs (DMARD) Treasure Island (FL): StatPearls Publishing; 2023 [updated Updated 2023 Jul 3. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507863/.
131. Cordero-Coma M, Sobrin L. Anti–tumor necrosis factor-α therapy in uveitis. Surv Ophthalmol 2015;60:575–89.
132. Éric Toussirot FA. Paradoxical reactions under TNF-α blocking agents and other biological agents given for chronic immune- mediated diseases: an analytical and comprehensive overview. RMD Open. 2016;2.

133. Wendling D, Paccou J, Berthelot J-M, Flipo R-M, Guillaume-Czitrom S, Prati C, et al. New Onset of Uveitis During Anti-Tumor Necrosis Factor Treatment for Rheumatic Diseases. Semin Arthritis Rheum 2011;41:503-10.
134. Gaujoux-Viala C, Giampietro C, Gaujoux T, Ea HK, Prati C, Orcel P, et al. Scleritis: A Paradoxical Effect of Etanercept? Etanercept-associated Inflammatory Eye Disease. J Rheumatol 2012;39:233-9.
135. Hashkes PJ, Shajrawi I. Sarcoid-related uveitis occurring during etanercept therapy. Clin Exp Rheumatol 2003;21:645–6.
136. Robicheaux Clementine R, Lyman J, Zakem J, Mallepalli J, Lindsey S, Quinet R. Tumor necrosis factor-alpha antagonist-induced sarcoidosis. JCR: Journal of Clinical Rheumatology. 2010;16(6):274–9.
137. Seve P, Varron L, Broussolle C, Denis P, Kodjikian L. Sarcoid-related Uveitis Occurring During Adalimumab Therapy. Ocul Immunol Inflamm 2012;20:59-60.
138. Suzuki J, Goto H. Uveitis Associated with Sarcoidosis Exacerbated by Etanercept Therapy. Jpn J Ophthalmol 2009;53:439-40.
139. Wladis EJ, Tarasen AJ, Roth ZJ, Farber MG, Ross J, Michaels VM. Orbital Sarcoid-Like Granulomatosis After Inhibition of Tumor Necrosis
Factor-α. Ophthal Plast Reconstr Surg 2016;32.
140. Shin I-SJ, Baer AN, Kwon HJ, Papadopoulos EJ, Siegel JN. Guillain-Barré and Miller Fisher syndromes occurring with tumor necrosis factor α antagonist therapy. . Arthritis Rheum 2006;54:1429-34.
141. Ratnarajan G, Thompson A, Dodridge C, Parry A, Elston J. Novel variant of Miller Fisher syndrome occurring with tumor necrosis factor α antagonist therapy. JAMA Neurol 2015;72:1377-8.
142. Simsek I, Erdem H, Pay S, Sobaci G, Dinc A. Optic neuritis occurring with anti-tumour necrosis factor therapy. Ann Rheum Dis. 2007;66:1255-8.
143. Winthrop KL, Chen L, Fraunfelder FW, Ku JH, Varley CD, Suhler E, et al. Initiation of anti-TNF therapy and the risk of optic neuritis: from the safety assessment of biologic thERapy (SABER) study. Am J Ophthalmol 2013;155:183-9.
144. Clifford LJ, Rossiter JD. Peripheral visual field loss following treatment with etanercept. Br J Ophthalmol 2004;88:842.
145. Do HH, Mohamed A, Klistorner A, Grigg J. Ophthalmic manifestations of demyelination secondary to etanercept. Clin Exp Ophthalmol 2008;36:392-4.
146. Drury J, Hickman SJ. Internuclear Ophthalmoplegia Associated with Anti-TNFa Medication. Strabismus 2015;23:30-2.
147. Rossman MD, Newman LS, Baughman RP, Teirstein A, Weinberger SE, Miller WJ, Sands BE. A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2006;23(3):201-8.
148. Damento G, Kavoussi SC, Materin MA, Salomão DR, Quiram PA, Balasubramaniam S, Pulido JS. Clinical and histologic findings in patients with uveal melanomas after taking tumor necrosis factor-a inhibitors. Mayo Clin Proc 2014;89(11):1481–6
149. Raaschou P, Simard JF, Holmqvist M, Askling J. ARTIS Study Group: rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. BMJ 2013;346.

150. Marticorena-Álvarez P, Chaparro M, Pérez-Casas A, Muriel-Herrero A, Gisbert JP. Probable diffuse retinopathy caused by adalimumab in a patient with Crohn's disease. J Crohns Colitis. 2012;6:950-3.
151. Matet A, Daruich A, Beydoun T, Cosnes J, Bourges J-L. Systemic adalimumab induces peripheral corneal infiltrates: a case report. BMC Ophthalmol 2015;15:57.
152. Hsu C-K, Cheng C-Y, Hung J-H, Li ML, Huang F-C, Yang W-L, Lee JY-Y. Central retinal vein occlusion and subsequent neovascular glaucoma after adalimumab treatment for psoriasis. Clin Exp Dermatol 2014;39:72-3.
153. Schechet SA, Garff K, Klima K, Campbell W, Schocket LS. Acute retinal necrosis after administration of adalimumab, a systemic antitumor necrosis factor antibody. Retin Cases Brief Rep 2018;12:307-9.
154. Roos JCP, René C, Ostor AJK. Necrotizing group A streptococcal periorbital infection following adalimumab therapy for rheumatoid arthritis. Cutan Ocul Toxicol 2011;30:160-2.
155. Kato T, Noguchi K, Uehara M, Nobuhara M, Takahashi S, Kisamori Y, et al. Angioedema of the Periorbital Region that Developed during Treatment with Etanercept in a Case
of Refractory Adult-Onset Still's Disease. Intern Med 2012;51:2801-4.
156. Caramaschi P, Biasi D, Carletto A, Bambara LM. Orbital myositis in a rheumatoid arthritis patient during etanercept treatment. Clin Exp Rheumatol 2003;21:136-7.
157. Couderc M, Mathieu S, Tournadre A, Dubost J-J, Soubrier M. Acute ocular myositis occurring under etanercept for rheumatoid arthritis. Joint Bone Spine 2014;81:445-6.
158. Song WK, Cho AR, Yoon YH. Highly suspected primary intraocular lymphoma in a patient with rheumatoid arthritis treated with etanercept: a case report. BMC Ophthalmol 2018;18:156.
159. Arriola-Villalobos P, Díaz-Valle D, Alejandre-Alba N, López-Abad C, Méndez-Fernández R, Benítez-del-Castillo JM. Bilateral Candida chorioretinitis following etanercept treatment for hidradenitis suppurativa. Eye. 2008;22:599-600.
160. Fonollosa A, Segura A, Giralt J, Garcia-Arumi J. Tuberculous uveitis after treatment with etanercept Graefe's Arch Clin Exp Ophthalmol. 2007;245(9):1397–9.
161. Lassoued S, Zabraniecki L, Marin F, Billey T. Toxoplasmic Chorioretinitis and Antitumor Necrosis Factor Treatment in Rheumatoid Arthritis. Semin Arthritis Rheum 2007;36:262-3.
162. Puli SR, Benage DD. Retinal Vein Thrombosis After Infliximab (Remicade) Treatment for Crohn's Disease. Am J Gastroenterol 2003;98:939-40.
163. Veerappan SG, Kennedy M, O'Morain CA, Ryan BM. Retinal vein thrombosis following infliximab treatment for severe left-sided ulcerative colitis. Eur J Gastroenterol Hepatol 2008;20:588-9.
164. Vergou T, Moustou AE, Maniateas A, Stratigos AJ, Katsambas A, Antoniou C. Central retinal vein occlusion following infliximab treatment for plaque-type psoriasis. Int J Dermatol 2010;49:1215-7.
165. Fasci-Spurio F, Thompson A, Madill S, Koay P, Mansfield D, Satsangi J. Sight-threatening keratopathy complicating anti-TNF therapy in Crohn's disease: a case report. Inflamm Bowel Dis. 2014;20(1).
166. Agarwal PK, Gallaghar M, Murphy E, Virdi M. Endogenous endophthalmitis in a rheumatoid patient on tumor necrosis factor alpha blocker. Indian J Ophthalmol 2007;55:230-2.
167. Haerter G, Manfras BJ, de Jong-Hesse Y, Wilts H, Mertens T, Kern P, Schmitt M. Cytomegalovirus Retinitis in a Patient Treated with Anti–Tumor Necrosis Factor Alpha Antibody Therapy for Rheumatoid Arthritis. Clin Infect Dis. 2004;39.

168. Roos JCP, Ostor AJK. Orbital Cellulitis in a Patient Receiving Infliximab for Ankylosing Spondylitis. Am J Ophthalmol. 2006;141:767-9.
169. Yoshida M, Yokokura S, Kunikata H, Takada N, Maruyama K, Toyokawa M, et al. Endophthalmitis associated with Purpureocillium lilacinum during infliximab treatment for surgically induced necrotizing scleritis, successfully treated with 27-gauge vitrectomy. Int Ophthalmol 2018;38:841-7.
170. Jin X, Namba K, Saito W, Iwata D, Ishida S. Bacterial endophthalmitis caused by an intraocular cilium in a patient under treatment with infliximab. J Ophthalmic Inflamm Infect. 2013;3(1):50.
171. Hanafi H, Verdijk RM, Paridaens D. Eyelid Merkel cell carcinoma in a patient treated with golimumab. Orbit 2018;37:21-5.
172. Justiz Vaillant AA, Qurie A. Interleukin Treasure Island (FL): StatPearls Publishing; 2022 [updated Updated 2022 Aug 22. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499840/.
173. Sibley CH, Plass N, Snow J, Wiggs EA, Brewer CC, King KA, et al. Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra: a cohort study to determine three and five-year outcomes. . Arthritis & Rheumatism. 2012;64(7):2375-86.
174. Heissigerová J, Callanan D, de Smet MD, Srivastava SK, Karkanova M, Garcia-Garcia O, et al. Efficacy and Safety of Sarilumab for the Treatment of Posterior Segment Noninfectious Uveitis (SARIL-NIU):: The Phase 2 SATURN Study. . Ophthalmology. 2019;126(3):428-37.
175. Roux C, Breuil V, Albert C, Allam V, Grisot C, Chami H, et al. Ophthalmic Herpes Zoster Infection in Patients with Rheumatoid Arthritis Who Were Treated with Tocilizumab. J Rheumatol. 2011;38(2):399.
176. Terada Y, Kamoi K, Ohno-Matsui K, Miyata K, Yamano C, Coler-Reilly A, Yamano Y. Treatment of rheumatoid arthritis with biologics may exacerbate HTLV-1-associated conditions. Medicine. 2017;96.
177. Calvo-Río V, Santos-Gómez M, Calvo I, González-Fernández MI, López-Montesinos B, Mesquida M, et al. Anti-Interleukin-6 Receptor Tocilizumab for Severe Juvenile Idiopathic Arthritis-Associated Uveitis Refractory to Anti-Tumor Necrosis Factor Therapy: A Multicenter Study of Twenty-Five Patients. Arthritis Rheumatol. 2017;69(3):668-75.
178. Burstzyn L, Levin S, Rotenberg B, Van Hooren T, Leung A, Berard R, Ardelean DS. Fulminant bilateral papilloedema during low-dose steroid taper in a child with systemic idiopathic arthritis treated with tocilizumab. Clin Exp Rheumatol. 2017;35(1):149-51.
179. Stelara. Ustekinumab [package insert]. Bloomington; 2016.
180. Lønnberg AS, Zachariae C, Skov L. Targeting of interleukin-17 in the treatment of psoriasis. Clin Cosmet Investig Dermatol. 2014;7:251–9.
181. Martinez CE, Allen JB, Davidorf FH, Cebulla CM. Endogenous endophthalmitis and osteomyelitis associated with interleukin 17 inhibitor treatment for psoriasis in a patient with diabetes. BMJ Case Rep. 2017;56.
182. Weiner GJ. Rituximab: mechanism of action. Semin Hematol 2010;47:115–23.
183. Schuler S, Brunner M, Bernauer W. Rituximab and Acute Retinal Necrosis in a Patient with Scleromalacia and Rheumatoid Arthritis. Ocul Immunol Inflamm 2016;24:96-8.
184. Dogra M, Bajgai P, Kumar A, Sharma A. Progressive outer retinal necrosis after rituximab and cyclophosphamide therapy. Indian J Ophthalmol 2018;66(4):591-3.
185. Marinella MA. Bilateral conjunctivitis due to rituximab. Ann Pharmacother 2007;41:1318.

186. Bussone G, Kaswin G, de Menthon M, Delair E, Brézin AP, Guillevin L. Macular oedema following rituximab infusion in two patients with Wegener's granulomatosis. Clin Exp Rheumatol 2010;28(1):90-2.
187. Chan TSY, Cheung CYM, Yeung IYL, Hwang Y-Y, Gill H, Wong IY, Kwong Y-L. Cytomegalovirus retinitis complicating combination therapy with rituximab and fludarabine. Ann Hematol 2015;94:1043-7.
188. Hashida N, Ohguro N, Nishida K. Efficacy and Complications of Intravitreal Rituximab Injection for Treating Primary Vitreoretinal Lymphoma. Transl Vis Sci Technol 2012;1:1.
189. Ruderman EM, Pope RM. Drug insight: abatacept for the treatment of rheumatoid arthritis. Nat Clin Pract Rheumatol 2006;2:654-60.
190. Tsuboi H, Matsumoto I, Hagiwara S, Hirota T, Takahashi H, Ebe H, et al. Efficacy and safety of abatacept for patients with Sjögren's syndrome associated with rheumatoid arthritis: rheumatoid arthritis with orencia trial toward Sjögren's syndrome Endocrinopathy (ROSE) trial-an open-label, one-year, prospective study-Interim analysis of 32 patients for 24 weeks. Mod Rheumatol. 2015;25(2):187-93.
191. Hatemi G, Christensen R, Bang D, Bodaghi B, Celik AF, Fortune F, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis. 2018;77(6):808-18.
192. Sullu Y. The results of interferon-alpha treatment in Behçet uveitis. Ocul Immunol Inflamm 2019;4:1-7.
193. Rentiya ZS, Wells M, Bae J, Chen KJ, Chao AN, Turgeon N, et al. Interferon-α-induced retinopathy in chronic hepatitis C treatment: summary, considerations, and recommendations. Graefes Arch Clin Exp Ophthalmol. 2019;257:447-52.
194. Yang L, Ji S, Wang L, Zhang Y. Episcleritis in a patient with mucosal melanoma treated with interferon alfa-2b and radiotherapy: a case report. J Med Case Rep 2018;12:388.
195. Ayaki M. Development of neovascular glaucoma in the course of interferon alfa therapy for hepatitis type C. Br J Ophthalmol 1994;78:238.
196. Fragoso YD, Paggiaro MS, Mastromauro R, Jacondino Gda S, Wilson HM. Literature systematic review on the ophthalmological side effects of interferons. Arq Bras Oftalmol. 2011;74(4):306-10.
197. Kang HY, Shin MC. Pegylated interferon-associated severe retinopathy in a patient with chronic hepatitis. Korean J Ophthalmol. 2012;26:147-50.
198. Knyazer B, Lifshitz T, Marcus M, Kratz A, Zlotnik A, Levy J. Anterior ischemic optic neuropathy in a patient with hepatitis C treated with interferon- alpha and ribavirin. Isr Med Assoc J 2011;13:251-3.
199. Kwon YS, Choe YH, Chin HS. Development of glaucoma in the course of interferon alpha therapy for chronic hepatitis B. Yonsei Med J 2001;42:134-6.
200. Lim JH, Lee YN, Kim YS, Kim SG, Jeong SW, Jang JY, et al. Vogt-Koyanagi-Harada disease occurring during PEGylated interferon-α2b and ribavirin combination therapy for chronic hepatitis C. Korean J Hepatol 2011;17:61-5.
201. Mangioni D, Soria A, Brighina L, Bandera A, Ferrarese C, Gori A. A case of classic neuromyelitis optica (Devic's syndrome) triggered by pegylated-interferon α. BMC Pharmacol Toxicol 2014;15:56.
202. Monzon JG, Hammad N, Stevens SD, Dancey J. Retinopathy associated with adjuvant high-dose interferon-2b in a patient with resected melanoma: a case report and review of the literature. Oncologist. 2012;17:384-7.
203. NAKAMURA A, TOJO K, TAKASU K, KANEKO K, KOMASTU H, IKEDA S. Unilateral oculomotor nerve palsy induced by combination therapy of interferon-α2b and ribavirin. Intern Med 2005;44:682-3.

204. Oishi A, Miyamoto K, Kashii S, Yoshimura N. Abducens palsy and Sjogren's syndrome induced by pegylated interferon therapy. Br J Ophthalmol 2007;91:843-4.
205. Rodney AJ, Gombos DS, Pagliaro LC, Tannir NM. Ischemic Optic Neuropathy Associated With Low-Dose Interferon Alfa: Report of Two Cases. Am J Clin Oncol 2009;32:86-7.
206. Sahidt Ortega-Ibarra F, Remes-Troche JM. Retinal thrombosis secondary to the combination therapy of pegylated interferon and ribavirin for chronic hepatitis C virus infection: a rare complication. Rev esp enferm dig. 2013;105:291-2.
207. Sene D, Touitou V, Bodaghi B, Saadoun D, Perlemuter G, Cassoux N, et al. Intraocular complications of IFN-α and ribavirin therapy in patients with chronic viral hepatitis C. WJG. 2007;13:3137-40.
208. Sheth H, Michaelides M, Siriwardena D. Cystoid macular edema and visual loss as sequelae to interferon alpha treatment of systemic hepatitis C. Indian J Ophthalmol. 2010;58:147-8.
209. Naithani N, Sinha S, Misra P, Vasudevan B, Sahu R. Precision medicine: Concept and tools. Med J Armed Forces India. 2021;77(3):249-57.