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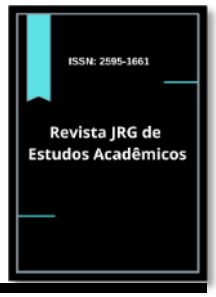

Ocular Inflammation and Uveitis: Insights into Immunology and Therapeutics

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Gabriela Cecilio Ventura Bariani Belem [1]
https://orcid.org/0000-0002-9882-1493
http://lattes.cnpq.br/8513679024282263
Médica pela Universidade Federal do Rio de Janeiro, RJ, Brasil
E-mail: gabivbariani@gmail.com

George Harrison Ferreira de Carvalho[2]
https://orcid.org/0000-0002-7377-9284
http://lattes.cnpq.br/4133790678180764
Faculdade de Brasília FBr, DF, Brasil
E-mail: georgeharrisonfc@gmail.com

Resumo

A inflamação ocular, particularmente a uveíte, representa uma causa global significativa de deficiência visual e cegueira, afetando indivíduos em diferentes faixas etárias e regiões geográficas. Este trabalho fornece uma visão abrangente da base imunológica da inflamação ocular, com ênfase em citocinas, quimiocinas e processos de infiltração celular que contribuem para a fisiopatologia da uveíte. O estudo analisa a epidemiologia, classificação e manifestações clínicas da uveíte, destacando o impacto das etiologias infecciosas e não-infecciosas. Uma atenção especial é dada às vias moleculares envolvidas na imunidade ocular, assim como aos avanços nas terapias imunomoduladoras e biológicas, tais como os anticorpos monoclonais e as estratégias emergentes baseadas em nanomedicina. A discussão também aborda os desafios da adesão ao tratamento, os efeitos adversos das terapias convencionais e a necessidade de medicina personalizada. Perspectivas futuras apontam para a integração da terapia gênica e inteligência artificial como ferramentas promissoras para otimizar o diagnóstico, o manejo e o prognóstico de doenças inflamatórias oculares. Estes *insights* contribuem para uma compreensão mais profunda da imunopatologia ocular e abrem o caminho para estratégias terapêuticas mais seguras e eficazes.

Palavras-chave: Inflamação ocular. Uveíte. Imunologia. Terapias biológicas.

[1] Médica pela Universidade Federal do Rio de Janeiro – UFRJ, 2017; Fellow clínico e cirúrgico em córnea e doenças externas pela Universidade Federal de Goiás - UFG – CEROF, 2022.
[2] Doutor em Ciências Médicas pela Universidade de Brasília (UnB) 2018. Mestre em Medicina Tropical pelo Instituto de Patologia Tropical e Saúde Pública da Universidade Federal de Goiás IPTSP/ UFG (2011). Especialização em Epidemiologia Multidisciplinar e Especialização em Estética Clínica ambas pela CGESP (2023). Graduações superiores (Biologia e Enfermagem) sendo, licenciatura em Biologia e bacharelado em Enfermagem.

Abstract
Ocular inflammation, particularly uveitis, represents a significant global cause of visual impairment and blindness, affecting individuals across different age groups and geographical regions. This work provides a comprehensive overview of the immunological basis of ocular inflammation, with emphasis on cytokines, chemokines, and cellular infiltration processes that contribute to the pathophysiology of uveitis. The study reviews the epidemiology, classification, and clinical manifestations of uveitis, highlighting the impact of infectious and non-infectious etiologies. Special attention is given to the molecular pathways involved in ocular immunity, as well as to the advances in immunomodulatory and biological therapies, such as monoclonal antibodies and emerging nanomedicine-based strategies. The discussion also addresses the challenges of treatment adherence, adverse effects of conventional therapies, and the need for personalized medicine. Future perspectives point to the integration of gene therapy and artificial intelligence as promising tools to optimize diagnosis, management, and prognosis of ocular inflammatory diseases. These insights contribute to a deeper understanding of ocular immunopathology and pave the way for safer and more effective therapeutic strategies.

Keywords: *Ocular inflammation. Uveitis. Immunology. Biological therapies.*

1. Introduction

1.1. Introduction to Ocular Inflammation

Ocular inflammation denotes the intricate process by which the eye reacts to pathogenic challenge. Providing an instructive framework through which to understand ocular inflammatory disease, the following chapter focuses on immune and molecular features of inflammatory eye disease, with particular reference to uveitis (XU; RAO, 2022; ZHANG et al., 2024).

Uveitis constitutes a significant cause of ocular inflammatory disease worldwide (J BARRY et al., 2014). Epidemiologic studies have evaluated the frequency, associated systemic diseases, and incidence of visual loss among patients with uveitis. Ocular immune privilege is maintained by endogenous cortisol and immunomodulators such as transforming growth factor-beta and neuropeptides, including alpha-melanocyte stimulating hormone, which regulate dendritic cell function and alter T-cell-programmed death, expansion, and cytokine production. Autoreactive T-cells have been identified in Vogt-Koyanagi-Harada disease. Patients with uveitis invariably present with heterogeneous clinical patterns. Studies of referral patterns from a uveitis referral centre describe the frequency of various systemic diseases and clinical entities; instances of hypopyon signify the diversity of different inflammatory processes that underlie the clinical expression of uveitis (JOLTIKOV; LOBO-CHAN, 2021).

1.2. Understanding Uveitis

The term uveitis is derived from the Latin “uvea”, describing the middle layer of the eye containing its blood vessels. The International Uveitis Study Group, convened in 1973, defined uveitis as inflammation of the uvea, a tactic still used despite the inclusion of conditions such as retinal vasculitis and retinitis under the umbrella term. To reflect clinical practice and research, the 2005 Standardization of Uveitis Nomenclature project defined uveitis as an inflammatory process affecting the eye. Based on an international survey, uveitis was classified anatomically using the categories anterior, intermediate, posterior, or panuveitis; the character of inflammation as granulomatous or nongranulomatous, an item of limited clinical or

prognostic value; and a plethora of specific, poorly standardized criteria of activity and duration. Symptomatology often suggests but seldom ascertains the aetiology, with much information instead contained in clinical, immunological, and laboratory findings (TEO et al., 2023).

Large systematic studies are rare and hard to extrapolate to other populations since the incidence and prevalence of specific forms of uveitis vary widely within and across countries, reflecting environmental and genetic factors, as well as the populace's age and ethnic composition. In the First Liverpool Uveitis Clinic series 500 patients recruited from a multidisciplinary eye rheumatology clinic at a tertiary centre during 1999 - 2004 the commonest disorders were idiopathic anterior uveitis (22%), sarcoidosis (17%) and ankylosing spondylitis (15%); intermediate uveitis (pars planitis) is typically idiopathic (HYSA et al., 2021).

Infectious uveitis results from local infection of the eye (or, rarely, systemic infection), which provokes an immune response. Noninfectious uveitis is often associated with a systemic autoimmune or autoinflammatory condition (e.g., ankylosing spondylitis, sarcoidosis, or Behçet's Disease). Even after thorough investigation, more than 30% of cases remain idiopathic. Uveitis of undetermined cause should be diagnosed only after exclusion of the infectious and autoimmune/autoinflammatory disorders mentioned earlier. Misguided treatment of infectious uveitis can rapidly have disastrous consequences: appropriate antimicrobial agents must be administered promptly, often by eye injection, and substantial disease remission is usually necessary prior to commencing immunosuppressive agents (J BARRY et al., 2014).

1.3. Definition and Classification of Uveitis

Uveitis encompasses a large and heterogeneous group of inflammatory diseases affecting the middle layer of the eye. It is typically classified anatomically according to the Standardization of Uveitis Nomenclature (SUN) criteria, dividing the condition into anterior, intermediate, posterior, and panuveitis subgroups. This classification not only facilitates a systematic approach to diagnosis and treatment but also provides insight into the underlying pathophysiological mechanisms. Both the anatomical site and the nature of the inflammatory response generate a spectrum of adverse clinical consequences that ultimately threaten visual function and prognosis (J BARRY et al., 2014). These discriminatory features permit a robust framework for both clinical and biological research, since clinical data form the groundwork for laboratory experiments, while laboratory findings provide insight into novel pathways and potential therapeutic targets. A detailed understanding of immunological mechanisms is therefore essential to understand the molecular basis of uveitis and its clinical manifestations.

Uveitis is a substantial global health problem responsible for approximately 5–20% of legal blindness in Western countries; such estimates rise to 25–30% in the developing world. The incidence in Europe has been reported at around 17–52 per 100 000 population per year, with a prevalence of about 38–284 per 100 000 (A. M. VAN LAAR et al., 2015). Males are affected more commonly than females, and the condition primarily manifests in the third and fourth decades. Risk factors include age (15–55 years), sex, race, and genetics, with the latter two varying according to the clinical entity encountered. Although a wide spectrum of uveitides exists, most cases are divided between HLA-B27 autoimmune disease and the idiopathic group, with the balance distributed amongst rarer entities. Management commences with a clinical history and examination focused on detecting any known local or systemic disease

correlations. The entire eye must be examined with attention not only to the site of inflammation but also to signs of cellular activity within the anterior chamber, vitreous, and retina. Uveitis can result in irreversible visual impairment and is a contributing factor in 5–20% of blindness cases globally. Visual loss can arise from the inflammatory process, macular oedema, chorioretinal scarring, or severe complications such as glaucoma or cataract (LI et al., 2024).

Infectious uveitis arises when local infection triggers immune activation that clears the organism but causes tissue damage in the process. It is most commonly caused by viruses such as cytomegalovirus, toxoplasma gondii, and mycobacterium tuberculosis. Conversely, non-infectious uveitis results from inappropriate immune activation generating a local inflammatory response that damages ocular tissues directly. It is often associated with systemic autoimmune diseases such as ankylosing spondylitis, sarcoidosis, and Behçet's disease, but many cases are idiopathic, constituting the largest cohort encountered in Western clinical practice. Treatment of infectious uveitis focuses on pathogen eradication using systemic or local antimicrobial therapy; immunosuppressive agents may be employed once the infection is controlled to limit tissue damage. Non-infectious uveitis requires immunosuppression to control potentially acute or chronic activity and prevent irreversible damage caused by ongoing inflammation (WILDNER et al., 2023).

2. Methodology

This study is structured as a narrative literature review. Articles were selected from PubMed, Scopus, and Web of Science between 2013 and 2024, focusing on keywords such as 'ocular inflammation', 'uveitis', 'immunology', and 'biological therapy'. Studies addressing pathophysiology, epidemiology, and treatment were prioritized. Comparative insights from international data were considered to highlight the impact of underreporting, as exemplified during the COVID-19 pandemic (DE CARVALHO; DE MEDEIROS; MAGALHÃES, 2024). The methodology emphasizes critical analysis of experimental, clinical, and epidemiological findings.

3. Results and Discussion

3.1. Epidemiology and Risk Factors

Uveitis denotes inflammation in or adjacent to the uvea and includes ocular immune conditions such as iritis, choroiditis, and retinitis. It is responsible for approximately 10% of all cases of blindness in the Western world as well as 15%–20% of blindness in the economically productive age group of 20–60 years. Although the exact mechanisms underlying uveitis development remain elusive, infectious and autoimmune processes are postulated as significant factors in its pathogenesis (J BARRY et al., 2014).

Uveitis affects all ages and races, exhibiting no particular sex predilection. Increasing incidence rates among older age groups may be linked to rising autoimmune conditions within the same demographic. Nonetheless, precise estimations of uveitis incidence and prevalence are challenging due to variability in case definitions, study populations, and geographic locations (TSIROUKI et al., 2018).

Geographical and environmental factors substantially influence the pattern of entities causing uveitis globally; notably, tuberculosis prevails as a common underlying etiology in areas where it remains endemic. Age and ethnicity also affect the distribution of uveitic entities; anterior uveitis commonly presents in individuals aged 20–50 years, whereas posterior uveitis generally occurs between 50 and 70 years.

Noninfectious uveitis has been associated with white Caucasian and female populations (TSIROUKI et al., 2018).

3.2. Clinical Manifestations

Uveitis may also be classified anatomically according to the primary site of inflammation into anterior, intermediate, posterior or panuveitis (LOPES TRONCOSO et al., 2017). Although the mechanisms underlying the disease remain unclear, it may be caused by pathogens (bacteria, viruses or parasites), trauma, environmental factors or metabolic conditions. It can be idiopathic, have a drug-induced origin or be associated with a systemic disease, with approximately 45 % of cases having an identifiable underlying aetiology, of which 15 to 20 % are associated with ankylosing spondylitis, sarcoidosis, Behçet's disease, reactive arthritis or other inflammatory disorders such as inflammatory bowel disease or tuberculosis (J BARRY et al., 2014).

Uveitis may present as an acute, recurrent or chronic disorder characterised by vascular dilation and congestion (red eye), peri-limbal conjunctival injection, aqueous flare, hypopyon and the presence of free-floating or deposited inflammatory cells within the aqueous and vitreous. Vitreous opacities are generally responsible for reduced visual acuity. Anterior uveitis is the most prevalent fraction of uveitis and is reported in up to 90 % of uveitis cases. Posterior uveitis accounts for 5 to 15 % of cases and is the leading cause of severe visual loss, followed by intermediate and panuveitis. Anterior uveitis may be further classified as granulomatous or non-granulomatous, based on the type of inflammatory infiltrate and the macroscopic features of the keratic precipitates. Anterior uveitis has an insidious, longstanding and bilateral course in inflammatory bowel disease (IBD) patients and is not related to intestinal disease activity (J BARRY et al., 2014).

3.3. Pathophysiology of Ocular Inflammation

The pathophysiological mechanisms of ocular inflammation link the risk factors associated with uveitis to the inflammatory response. The presence of cytokines, chemokines, and cellular infiltration in aqueous humor, vitreous, and retina defines the characteristics of the immune response. These molecules of communication and interaction between immune cells organize an orchestrated immune response to facilitate the resolution and restoration of tissue function. The signaling cascades in uveitis confirm the role of genes that regulate the expression of chemokines, cytokines, and interleukins and, by extension, the immune response in the pathogenesis of ocular inflammation (OZGA et al., 2021).

The continuous evolution in the field of molecular biology has recently introduced new immunomodulatory drugs, both molecules and biological therapy. Development of monoclonal antibodies, such as anti-IL6, anti-TNFα, or anti-IL1β, for the treatment of non-infectious uveitis offers the possibility of using directed, more effective therapies with fewer side effects than conventional treatments. An overview of the biologics used in uveitis is indispensable. Treatment of uveitis remains a challenging field with many aspects still to be overcome. Although uveitis comprises a group of ocular diseases with different pathologies and diverse etiologies, the global prevalence of this heterogeneous group of disorders is still very high, affecting young people with consequent significant visual impairment and even blindness. The important adverse effects of corticosteroids and immunosuppressors lead to poor adherence to medication, inadequate control of the inflammatory process, and consequently worsening of ocular prognosis. To address these concerns, the search for specific therapies that focus on local immune mediators and their receptors in the

eye remains necessary and continues to challenge researchers (ZAKI; SUHLER, 2021).

3.4. Immune Response Mechanisms

Excessive ocular inflammation leads to tissue destruction and subsequent visual impairment. A thorough understanding of the inflammatory processes involved is indispensable for effectively managing the condition. The eye, despite being immunologically privileged, can exhibit severe intraocular inflammation involving both the innate and adaptive immune systems. Cytokines and chemokines secreted by endogenous ocular cells and infiltrating leukocytes contribute to intraocular inflammation and facilitate chronic cell infiltration, creating a feed-forward loop (MASSILAMANY et al., 2015). This complex interaction between the immune system and the eye is discussed in detail in the following paragraphs.

3.5. Role of Cytokines and Chemokines

The immune response in ocular inflammation is mediated by the infiltration of diverse inflammatory cells. Cytokines, key signaling proteins involved in cell communication, and chemokines, potent chemoattractant proteins directing leukocyte recruitment in damaged tissue, are pivotal to this process (MÉRIDA et al., 2015). Alongside cytokines such as interferon-γ (IFN-γ) and interleukins (IL-2, IL-4, IL-6, IL-10, IL-12), chemokines like chemokine (C-C motif) ligand 2 (CCL2) and (C-X-C motif) ligand 8 (CXCL8) contribute to the pathophysiology of uveitis.

3.6. Cellular Infiltration in Ocular Tissues

Following tissue injury or autoimmune processes, monocyte-derived macrophages (MDMs) and tissue-resident macrophages (TRMs) infiltrate damaged ocular tissue. Primary experimental uveitis models induce extensive leukocyte trafficking, with various subsets populating the inflamed microenvironment according to disease characteristics. Macrophages remain a component of the uveitic infiltrate. The anterior uvea contains melanocyte-rich stroma wherein melanin can mask infiltrating macrophages, but the vitreous and retina are accommodating sites for these leukocytes and thus better suited for studying the consequences of inflammation. Macrophage accumulation in the retina increases throughout disease progression and is defined by the expression of adhesion molecules and influx pathways. In the steady state, immunosurveillance is mediated by a dynamic network of myeloid cells that traffic through the retina rather than through the extracellular matrix towards vascular sites of egress. Immune-privileged tissue maintain a randomly migrating population of myeloid cells that reseed the resident niche, and the cellular dwell time within this system is defined as the “immunosurveillance cycle” (J. EPPS et al., 2018).

During persistent non-infectious socioeconomically dominant posterior uveitis, such as intermediate and panuveitis, both cohorts previously characterised as macrophage-driven inflammatory events, the infiltration of MDMs through the immunosurveillance system is disrupted. Also, in steady state, juvenile proliferative retinopathy (JRP) and cystoid macular oedema (CME) are driven by a distinct population of MDMs that enter the tissue and differentiate into their macrophage lineage, homing in on the inflamed locus. At peak histological disease, a population of F4/80hi mononuclear cells inject into the extracellular environment and adopt tissue-like characteristics (MÉRIDA et al., 2015). These conclusions account for the unique behaviours of the macrophage populations associated with intermediate and panuveitis—cohorts that together are responsible for approximately 30% of all the

clinical cases reported in Western populations. The well-established CX 3 CR1hi maturation pathway is a strong candidate for mononuclear retention.

3.7. Molecular Pathways in Ocular Immunology

Ocular inflammation constitutes a complex set of responses triggered by injury or antigenic stimuli. It involves migration of leukocytes into the inflamed region in and around the eye, resulting in vascular changes and exudation typical of inflammatory processes. In uveitis, an immune process intensifies, with inflammatory cells infiltrating different eye segments, principal damage sites being the uveal tract and the retina. A substantial rise of cytokines and chemokines in the aqueous humor, vitreous humor, and retina has been documented. Each condition affecting the eye had a unique set of cytokines and chemokines that directly influence its pathogenesis. The underlying reasons for each uveitis type may differ; however, disease progression consistently follows the same molecular pathway (MRUGACZ et al., 2021).

Knowledge advances have revealed new pathways influencing disease progression and possible targets for novel therapies. Monoclonal antibodies that specifically recognize inflammatory mediators like TNF-α have improved quality of life for patients. Several other biological response modifier agents are under evaluation for ocular inflammation management. These agents not only reduce adverse effects but also enhance patient compliance. Steroids continue to be the most potent inhibitors of ocular inflammation; nevertheless, non-steroidal anti-inflammatory drugs and newer immunomodulatory agents are also employed to prevent end-organ damage and maintain remission (SÁNCHEZ-ROBLES et al., 2021).

3.8. Key Signaling Pathways

Key signaling pathways mediating inflammatory activity in experimental models have been defined and outlined in human aqueous and vitreous samples. In one naïve model, host components of the endotoxin response pathway—including Toll-like receptor (TLR) 4, myeloid differentiation factor 88 (MyD88), Interleukin (IL)-1 receptor-associated kinase-4 (IRAK-4), IL-1, IL-18 and the IL-1 receptor type I—have also been implicated in endotoxin-induced uveitis. These pathways lead to the activation of nuclear factor κB (NF-κB) and subsequent expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), generating prostaglandin E2 (PGE2) and nitric oxide (NO), respectively. A specific and selective peptidomimetic antagonist of the MyD88 homodimerization step can prevent pro-inflammatory cytokine expression in human monocytes and macrophages and also block endotoxin-induced uveitis in vivo, further confirming MyD88's critical role in mediating the sequelae of TLR4 engagement (REEKIE et al., 2021).

Signal transduction pathways mediated by mitogen-activated protein (MAP) kinases have similarly been described in ocular inflammation. Activation of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK), but not the p38 MAP, pathway occurs in endotoxin-stimulated RAW 264.7 cells, leading to enhanced expression of NF-κB component p65 and subsequent induction of cytokines, e.g., tumor necrosis factor (TNF) α and IL-6. These inflammatory activities are inhibited by the anti-inflammatory agent berberine. In atomic force microscopy (AFM) assessments, berberine reverses endotoxin-induced elevations in expression of the LPS receptor cluster of differentiation (CD) 14, down-regulates ERK and JNK phosphorylation, inhibits phosphorylation and degradation of the inhibitor of NF-κB (IκB) 1, and reduces pro-inflammatory cytokine release. Similarly, mitogen-activated protein kinase phosphatase (MKP)-1 and early growth response (Egr-) 1 and -2 act as

potential negative regulators of endotoxin signaling. Biological and gene expression profiling studies have described a large number of additional cell receptors—including nucleotide-binding oligomerization domain (Nod) 1, microthrombomodulin-1 (MTM-1), anti-Müllerian hormone (AMH), and aquaporin-1 (AQP-1)—thought to regulate endogenous ocular inflammation as well as those implicated in EAU (MOUSTARDAS et al., 2023).

3.9. Inflammatory Mediators in Uveitis

Uveitis encompasses a collection of conditions characterized by intraocular inflammation, which may involve the uvea alone or extend to the vitreous body, retina, choroid, optic nerve, and retinal vessels. Current classification relies on anatomical principles that localize inflammation, directing pathophysiological and etiopathogenic considerations and guiding clinical management, prognosis, and epidemiology. Its annual incidence and prevalence approximate 17–52 and 9–730 cases per 100,000 people, respectively. Although uveitis can emerge from diverse origins, it often associates with certain uveal syndromes, systemic immune-mediated diseases, or infections. Risk profiles vary significantly with etiology. Clinical presentation typically includes blurred vision, floaters, and ocular redness and pain. The pathogenesis of ocular inflammation involves cellular infiltration within the vascularized layer of the eye, with a pivotal contribution from various cytokines (HYSA et al., 2021).

The immune response mediating ocular recurrent inflammation encompasses a complex network of molecular and cellular components. Molecules such as cytokines, interleukin-6 (IL-6), interleukin-10 (IL-10), chemokines, and their receptors display altered expression during uveitis. Research at the Instituto de Oftalmobiología Aplicada (IOBA) has underscored the significance of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway in animal models, noting that monoclonal antibodies targeting interferon (IFN)-γ (an activator of this signaling cascade) reduce inflammatory activity. Furthermore, biological therapies—including anti-tumor necrosis factor-alpha (anti-TNF-α) agents like infliximab and adalimumab, as well as anti-vascular endothelial growth factor (anti-VEGF) drugs—have demonstrated efficacy in controlling autoimmune ocular inflammation and mitigating neovascularization, respectively. Several investigations have thus identified novel molecules and molecular pathways involved in ocular inflammation, with implications for both understanding and treating uveitis (PUROHIT et al., 2023).

3.10. Genetic Factors Influencing Ocular Inflammation

Uveitis is a spectrum of inflammation affecting various ocular regions and includes a variety of etiologies (HUANG; A. BROWN, 2022). Genetic factors shape susceptibility to uveitis and influence its course. Uveitis may be inherited as a Mendelian condition or display a complex genetic profile. The Mendelian and complex disorders affecting ocular anterior segment usually arise when constitutive components of crucial innate and adaptive immune pathways become dysfunctional, causing excessive inflammation and/or immunodeficiency (Y. SERPEN et al., 2021).

3.11. Biological Therapies for Ocular Inflammation

Biological therapy encompasses all treatments that use or modify elements of the immune system, including monoclonal antibodies and soluble receptors produced with recombinant DNA technology. An improved understanding of the immune response has led to the development of molecules directed against key players in ocular inflammation—cytokines, chemokines, adhesion molecules, and effector cells—

thus, new molecular pathways have been identified as treatment targets (PAPIEŻ; KRZYŚCIAK, 2021).

Monoclonal antibodies represent an important milestone in uveitis management. Their use in ophthalmology has increased dramatically to control inflammatory reactions in several diseases, rapidly improving symptoms, visual prognosis, and patient quality of life. Current research is focused on limiting adverse events associated with these medications through new therapeutic schemes and the development of more selective agents. A better characterization of involved pathways may enable personalized treatment that targets not only symptoms but also the triggers of uveitis. New formulations, gene therapy, and artificial intelligence applied to diagnosis and prognosis prediction should provide better-tailored treatment with fewer adverse events (HYSA et al., 2024).

3.12. Monoclonal Antibodies

Therapeutic monoclonal antibodies represent a valuable class of drugs for treatment of noninfectious intermediate and posterior uveitis and other refractory ocular inflammatory conditions (M. HORNBEAK; E. THORNE, 2015). Of these, antibodies against tumour necrosis factor α (TNF-α) are the most widely used with considerable success. There is a range of agents, including infliximab, adalimumab and golimumab among others; a thorough discussion of these is beyond the scope of this chapter. Infliximab is a chimeric monoclonal antibody composed of the Fc region of human IgG1 combined with murine antigenbinding sequences. The dose used for ocular inflammation is usually in the range of 5–10 mg/kg every 4–6 weeks; more frequent administration has occasionally been necessary (PAPOTTO et al., 2017). Most of the experience with infliximab for patients with ocular inflammatory disease currently is based on its use in treatment of patients with Behçet's disease or refractory idiopathic uveitis. Uveitis associated with seronegative spondyloarthropathy usually responds well to higher doses, in the 5–10 mg/kg range. The drug appears to be effective regardless of whether uveitis or the underlying systemic disease is resistant to corticosteroids.

TNF-α is a pro-inflammatory cytokine whose levels are elevated both systemically and locally in many autoimmune inflammatory diseases. It is involved in several biological activities such as induction of the inflammatory cascade, leukocyte recruitment and initiation of endothelial activation with chemokine and adhesion molecule expression, apoptosis and tissue damage. TNF-α is also expressed on T lymphocytes, dendritic cells, fibroblasts and macrophages, and on the ocular surface (DENNISTON et al., 2021; GONZALEZ CALDITO, 2023).

3.13. Biologics in Uveitis Management

Biologics constitute targeted treatments that employ monoclonal antibodies directed against specific cytokines or cellular receptors to interrupt critical steps in the immune response of non-infectious uveitis (NIU). They complement standard immunomodulatory therapy by providing a more selective mechanism of action without the side effects associated with conventional therapies (M. SHARMA et al., 2018). Unlike antimetabolites and calcineurin inhibitors, which are unlicensed for uveitis and either fail to control intraocular inflammation or cause intolerable side effects in up to 40% of patients, biologics offer significant corticosteroid-sparing potential (M. HORNBEAK; E. THORNE, 2015). Arthritis and uveitis of juvenile idiopathic arthritis are the only forms of NIU for which randomized controlled trials (RCTs) of biologics have been published; guided by those data, these agents may be used, preferably in

conjunction with standard non-biologic immunomodulators, for patients who have an inadequate response or are intolerant of those conventional drugs. The cost of biologic therapies is a major obstacle to widespread use, although the introduction of biosimilars improves affordability.

3.14. Emerging Therapies in Clinical Trials

The increased understanding of ocular surface inflammation and the development of novel immunomodulatory therapies open new possibilities for more effective and safer uveitis treatment. However, further investigations involving pharmacological innovations such as targeted liposomal systems, cytokine therapy, experimental models, and preclinical studies are still necessary to corroborate these discoveries and optimize future clinical development (TEABAGY et al., 2023).

Nanomedicine is quickly evolving, with liposomes being one of the most promising nanocarriers. This drug delivery system can improve adherence and diminish adverse events by encapsulating corticosteroids within liposomes, thus preventing concomitant hypertension. Overcoming steroid side effects is a significant challenge in both uveitis and inflammatory bowel diseases, conditions associated with T-cell infiltration in the intestinal and ocular mucosa. Liposome enwrapping suppresses the drug's harmful effects while preserving its efficacy, which is especially beneficial when long-term corticosteroid use is required. Clinical trials are underway to evaluate liposome-encapsulated prednisolone phosphate administered intravitreally or as an eye drop for treating noninfectious intermediate uveitis (SU et al., 2024).

3.15. Immunomodulation Strategies

Corticosteroids and nonsteroidal anti-inflammatory drugs are the most commonly prescribed agents for ocular immunomodulation (M. SHARMA et al., 2018). Corticosteroids inhibit inflammatory cell recruitment and subsequent chemotaxis, phagocytosis, and release of lysosomal enzymes, as well as reduce the expression of adhesion molecules and other proinflammatory mediators that promote leukocyte migration. A number of toxicities, including cataracts, increased intraocular pressure, glaucoma, ocular infections, and delayed corneal epithelial healing, may manifest after extended corticosteroid administration (M. HORNBEAK; E. THORNE, 2015). Nonsteroidal anti-inflammatory drugs nonselectively inhibit the cyclooxygenase enzyme, thereby reducing prostaglandin production and arachidonic acid metabolism that mediate inflammation and pain. Cytokine-targeting antibodies such as interferon-alpha, interleukin-6, tumor necrosis factor alpha, and the B-cell inhibitor rituximab constitute additional immunomodulatory approaches.

3.16. Corticosteroids in Ocular Inflammation

Corticosteroids have played an important role in the management of ocular inflammatory diseases since the early 1950s, remaining the mainstay of therapy for most types of intraocular inflammation (BABU; MAHENDRADAS, 2013). Topical corticosteroids usually provide adequate control for anterior uveitis, whereas systemic corticosteroids are indicated for more severe inflammation at multiple sites, in the event of extension into the posterior segment, in bilateral involvement, in cases associated with systemic disease, or when adjunct immunosuppressive therapy is required. Administration routes include topical, periocular, intravitreal and systemic. Systemic corticosteroids continue to be the major treatment option for intraocular inflammatory diseases; their efficacy is correlated to dosage, with an initial range between 1 and 2 mg/kg/day of prednisone or equivalent. Restoring visual function in refractory uveitis

patients and those intolerant to standard treatment modes often relies on higher and long-term doses encompassing intravenous delivery (BAR et al., 2023).

Despite their rapid effectiveness in disease regression, corticosteroids can induce a wide variety of ocular and systemic adverse effects. Consequently, systemic corticosteroids are indicated only for severe ocular inflammations, with doses tapered to the minimum effective level once disease control is achieved (M. HORNBEAK; E. THORNE, 2015). Additional side effects such as ocular and systemic infections, increased blood pressure, glucose intolerance, reduced bone density, weight gain, adrenal insufficiency and erythrocytopenia limit the prolonged use of high corticosteroid doses. The challenge of delivering corticosteroids to specific intraocular targets without inducing these systemic and local adverse effects, together with a large fraction of patients failing to respond to initial corticosteroid treatment, underpin the development of novel targeted therapies. Nonetheless, corticosteroids remain the investigation reference standard for the evaluation of emerging treatments.

3.17. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

As an alternate approach, nonsteroidal anti-inflammatory drugs (NSAIDs) may also be employed for inflammation control. These pharmacologic agents act by causing reversible inhibition of the cyclo-oxygenase enzyme and thereby inhibiting prostaglandin production. Their role in anterior uveitis is considered less efficacious when compared to corticosteroids. Several pathways and inflammatory mediators converging on arachidonic acid have been described, which helps to identify various targets for NSAID action in ocular inflammation. Cytokines like interleukin-1 and tumor necrosis factor induce phospholipase-A2 that converts membrane phospholipid to arachidonic acid. Certain NSAIDs like flurbiprofen, indomethacin, and diclofenac inhibit phospholipase-A2, preventing generation of arachidonic acid. Corticosteroids act at a higher level by inducing arachidonic acid (BALASUBRAMANIAM et al., 2022).

3.18. Novel Immunomodulatory Agents

Corticosteroids and cyclophosphamide remain the cornerstones of immunomodulatory therapies but suffer from several well-known side effects that limit their use. Loteprednol, a C-20 ester corticosteroid and a soft drug, offers the advantage of being rapidly metabolized into inactive metabolites after exerting its anti-inflammatory effect. Researchers evaluated the efficacy of a novel cyclic non-steroidal anti-inflammatory prodrug of Δ2-esomeprazole for ocular inflammation and reported promising results. Immunomodulatory treatment of non-infectious anterior uveitis with infliximab has been reported; furthermore, biologic therapies represent promising treatment alternatives, especially for patients with inflammation refractory to corticosteroids and other conventional immunosuppressive therapies (SHARMA et al., 2024).

Oral, intravenous, and intravitreal methotrexate, a folate analog that blocks DNA, RNA, and purine synthesis, has also been described as potentially effective for non-infectious uveitis. With the growing understanding of cytokine biology in uveal inflammation, there is a potential for targeted therapeutic interventions using these molecules or their inhibitors. A variety of agents targeting the TNF-α pathway have been described and are currently being tested. Agents such as etanercept, adalimumab, and infliximab have also demonstrated efficacy in non-infectious uveitis. These reports highlight the importance of ongoing exploration of newer biological agents to improve the management of ocular inflammation (WU et al., 2023).

3.19. Challenges in Treatment of Uveitis

Treatment of uveitis remains a considerable challenge. Adverse-effects problems caused by corticosteroids and other immunosuppressives, coupled with difficulties shared by all conditions necessitating long-term therapy, mean that adherence is often poor. Many patients are either unwilling or unable to be treated with corticosteroids or anti-TNF-α agents. A variety of other treatment options exist, so there are choices for almost all eventualities. Even with uveitis refractory to conventional therapies, the majority of patients will still respond well to alternative therapies (J BARRY et al., 2014). The beliefs, attitudes, and expectations of patients with chronic eye disease and their family members may also influence compliance.

Because of the multiple pathways involved in many forms of uveitis, therapy with a single agent can be ineffective, particularly in the more refractory cases; this may be associated with the long-term use of high-dose corticosteroids. In the future, therefore, a multidisciplinary approach may be necessary to evaluate the combined use of mono- or polypharmacological therapy, the outcome of which may provide safer and more effective regimens. Individualized treatment should become a possibility with further development of genetic and proteomic profiles of patients with uveitis. Because of the complex pathogenesis, discovery of new drugs will demand precise knowledge of molecules and pathways that mediate generation and production of the inflammatory mediators responsible for the chronicity and recurrence of the uveal inflammatory response (PRADO et al., 2024).

3.20. Adverse Effects of Current Therapies

The highly inflammatory nature of the uvea and the incorporation of a variety of pharmacological agents, ranging in administration from topical to systemic, combine to increase the risk of side effects and adverse events (J BARRY et al., 2014). Current therapies efficiently control ocular inflammation; however, their application is penalized by adverse effects that often severely hinder patient compliance (M. SHARMA et al., 2018). Deeper knowledge of underlying disease mechanisms enables targeting lessons for future molecular and cellular treatments. The widespread and redundant control exerted by immune response mediators on inflammatory progression, unfortunately, creates additional difficulties in devising an effective treatment strategy. Responses to specific drugs are frequently unpredictable, and no exhaustive consensus exists concerning efficacious approaches for various patient cohorts. The development and integration of personalized medicine may eventually offer penalization-free therapies and recommended approaches. Emerging molecular treatment options promise a gradual substitution of existing management strategies minimizing side effects.

3.21. Patient Adherence and Compliance

Adherence to therapy is a major concern for all chronic diseases and current evidence indicates that patients suffering from long-term ocular pathology present very high levels of non-adherence to treatment. It is now well understood that non-adherence rates to glaucoma treatment are high both for self-administered therapy (WELGE-LUSSEN et al., 2015). The rates of non-adherence with therapy in patients using topical steroids for inflammatory ocular conditions is also high, and, for some, more than 50% stop the steroids prematurely.

Where not transient, such ineffective therapy translates into progression of disease with all its consequences on visual function and quality of life. The constantly aging population in the coming years, as well as the significant number of new drugs

likely to arrive on the ophthalmological horizon, will further accentuate the issue of treatment adherence amongst eye-disease sufferers. Novel effectual options to improve the adherence to treatment, also avoiding the development of side effects associated with long-term steroid treatment, remain a target that awaits to be met in ophthalmology (M. HORNBEAK; E. THORNE, 2015).

3.22. Need for Personalized Medicine

The treatment of uveitis with immunomodulatory agents (IMT) presents several challenges. There are many different diseases with discrete clinical and immunological phenotypes, without precise boundaries, despite attempts to classify the anatomical location of inflammation or differentiate between infectious and immune-driven aetiologies (J BARRY et al., 2014). The adverse effects of corticosteroids and IMT are common and can be severe; the effectiveness of corticosteroids declines when administered over long periods. Even when effective, alleviating inflammation with agents such as corticosteroids can allow infectious entities such as atypical mycobacteria or herpetic keratouveitis to advance with more sheltered smoldering effects. Consequently, a need for personalized medicine has become ever more apparent in the chronic inflammatory eye diseases.

Uveitis is a generic term describing a heterogeneous group of clinical entities characterized by intraocular inflammation, commonly involving an autoimmune or autoinflammatory process that requires treatment with immunosuppressive, anti-inflammatory agents. New therapeutic agents that rapidly suppress disease activity, prevent accumulation of structural damage and preserve long-term visual function with fewer side-effects are much needed. Uveitis has an estimated incidence ranging from 14–50 per 100,000, but only a small proportion of such cases need systemic therapy and consequently it is difficult to perform large-scale clinical trials. In some countries the difficulty is partially ameliorated by cooperative groups, such as the SITE consortium that has created the largest chart review dataset of immunosuppression-outcomes, eg 910 person-years at a time; however, the heterogeneity amongst ocular inflammatory diseases also questions the gain of grouping such diseases in clinical trials (K DENNISTON; D DICK, 2013). Classification of ocular inflammatory entities remains an unsolved task; most clinicians group diseases according to the anatomical location of inflammation in anterior, intermediate, posterior and panuveitis. In addition, classification criteria take the presence/absence of infectious agents into the equation. Such heterogeneity of aetiologies, diagnostic approaches and treatments is an important challenge to the design of clinical trials.

3.23. Future Directions in Ocular Immunology Research

Future research in ocular immunology continues to explore innovative therapeutic approaches for uveitis and related inflammatory disorders. Ongoing clinical trials evaluate the efficacy and safety of biological agents including anti-tumor necrosis factor inhibitors. Targeting specific cytokines, such as interleukin-6 with selective inhibitors, shows particular promise in the management of non-infectious uveitis. Studies of the underlying immunological mechanisms emphasize the significance of Th17 cells and regulatory T cell subsets. Characterization of cytokine profiles distinguishing active inflammation from remission further supports the development of personalized treatment strategies. The drive towards steroid-sparing immunosuppressive protocols seeks to minimize systemic and ocular side effects while maintaining disease control. Investigation of novel drug delivery systems, notably intravitreal implants, aims to optimize therapeutic efficacy and patient adherence (M.

SHARMA et al., 2018). The global incidence of uveitis ranges broadly with significant geographic variation, highlighting the necessity for continued refinements in understanding and intervention. The induction and regulation of intraocular inflammation represent a focus of intensive study. Recent discoveries concerning new molecular pathways and immunomodulatory mechanisms enhance comprehension of ocular surface immunity. Parallel introduction of biological therapies establishes additional treatment options (J BARRY et al., 2014).

3.24. Innovative Research Approaches

Recent developments in ocular surface immunology have revealed new molecular pathways and biological therapies for managing ocular inflammation and uveitis. The principal inflammatory pathways in uveitis involve cytokines, chemokines, and their receptors. Modulation of inflammatory mediators, particularly through biological agents, offers promising avenues for preventing and reversing tissue damage characteristic of ocular inflammatory diseases such as uveitis. At the same time, corticosteroids and nonsteroidal anti-inflammatory drugs maintain their established roles in systemic and topical treatments (MOUSTARDAS et al., 2023).

Progress in anti-inflammatory therapy for uveitis has been constrained by the adverse events associated with long-term corticosteroid use, patient adherence difficulties, and the increasing recognition of a personalized approach. A renewed interest in ocular inflammation has prompted the integration of biology, experimental models, clinical immunology, and artificial intelligence techniques to enhance diagnosis, classification, prognosis, and treatment of uveitis. The combined effects of these factors have reactivated investigation into biological therapies for ocular inflammatory diseases (THNG et al., 2023).

3.25. Potential for Gene Therapy

Gene therapy has revolutionized the treatment of inherited retinal diseases. It can be administered into the eye via intravitreal, subretinal, and suprachoroidal routes. The intravitreal route is most convenient and transduces the entire retina, but cannot reach the outer layers and provokes immune and inflammatory reactions. Antibody production can reduce treatment efficacy. Subretinal delivery causes more inflammation, whereas intravitreal evokes a stronger humoral response. At higher doses, increased antibody titers and inflammation were observed, manageable with steroids. Gene therapies mainly use viral vectors to deliver genes for monogenic diseases. Luxturna delivers the wild-type RPE65 gene to improve vision. Setbacks including adverse immune responses, vector neutralization and oncogene activation led to vector platform improvements. The eye's immune privilege favors gene therapy. Adeno-associated virus (AAV) vectors efficiently transduce specific retinal cell types with minimal systemic exposure. AAV vectors carry therapeutic genes, cross cell membranes, and deliver DNA to the nucleus, with tissue-specific targeting. Each development stage requires optimization, and host immune responses must be managed to prevent vector neutralization or inflammation. Current strategies often rely on steroids, but further understanding of ocular immunity and inflammation is essential. Advancing gene therapy to maximize its potential for treating inherited retinal diseases requires addressing immune activation and other barriers (KAI CHAN et al., 2021; GHORABA et al., 2022).

3.26. Role of Artificial Intelligence in Diagnosis and Treatment

Artificial intelligence (AI) enables remarkable accuracy in the evaluation of ocular images, such as OCT scans, fluorescein angiography, and microscopic frames, thereby assisting in decisions on treatment selection and monitoring disease progression. The application of AI to anterior segment diseases, including cornea and ocular surface pathology, facilitates timely intervention and management. Within anterior segment specialties, the adoption of AI holds promise for enhancing the analysis of slit lamp–acquired images, improving both the objective classification and quantification of disease severity. Analysis of vast datasets spanning basic and clinical sciences can reveal novel associations, risk factors, and biomarkers, as well as uncover new correlations that deepen understanding of disease and guide the development of targeted therapies. The integration of AI in ophthalmic practice ultimately streamlines clinical workflows, diminishes diagnostic delays, and leads to superior patient outcomes. Through the development of AI-assisted teleophthalmology platforms, patients affected by ocular disease gain access to off-site evaluations, enabling real-time tracking of disease status independently of frequent in-person consultations. Finally, AI contributes substantially to the understanding of inherited ocular disorders and supports the design of precise, personalized treatment strategies. Ongoing investigations aim to extend AI's applicability to an ever-widening array of conditions encountered within clinical practice (VENKATAPATHAPPA et al., 2024).

4. Conclusion

Recent advances in the immunological understanding of ocular inflammation have brought new and improved therapeutic frontiers for uveitis. These are evident from the dissection of inflammatory mechanisms, the delineation of novel immunoregulatory molecular pathways, and new biological and pharmacological therapies. A glimpse into the future of ocular inflammation and uveitis highlights the potential of next-generation ocular surface immunology research to provide new insights for the discovery of biomarkers and the development of safer, more effective immunomodulatory strategies. The strategies extend also to different ophthalmic pathology, including in dry eye syndromes.

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