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Review Article

Interleukins and cytokine biomarkers in uveitis

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Interleukins and cytokines are involved in the pathogenesis of uveitis of heterogeneous origin. Understanding the basics of the ocular immune privilege is a fulcrum to discern their specific role in diverse uveitis to potentially translate as therapeutic targets. This review attempts to cover these elements in uveitis of infectious, noninfectious and masquerade origin. Insights of the molecular targets in novel therapy along with the vision of future research are intriguing.

Key words: Biologicals, chemokines, interleukins, masquerades

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Uveitis is an important cause of blindness in both developing and developed world.[1] Its estimated prevalence in children and elderly is around 5%–16% and 6%–21%, respectively.[2] Despite uveitis being multifactorial, testing for particular markers like human leukocyte antigens (HLA) can help provide supportive evidence for the diagnoses of a particular disease process.[3] In addition, the varied uveitogenic proteins that can incite intraocular inflammation proposed are rhodopsin, retinal arrestin, recoverin, phosducin, retinal pigment epithelium-derived protein, and interphotoreceptor retinoid-binding protein [Table 1]. These target retinal proteins are identified in rats, mice, and subhuman primates by varied experimental autoimmune uveitis (EAU) [Table 2] models. This helps to understand the varied complex immune mechanisms and its translation into novel therapeutic targets.[4] This review article attempts to present the basics of ocular immunology and current concepts of interleukins (IL) and cytokines in varied uveitis. The practical application of the assessment of cytokines in serum and ocular fluid shall guide an astute clinician to fathom the diverse role played by varied biomarkers in uveitis of infectious, noninfectious, masquerade origin. A systematic detailed literature search was carried out using PubMed, Epub, Google Scholar, and Embase databases using the MeSH terms cytokines or chemokines or biologics or biomarkers or ILs in varied uveitis disorders. Novel therapeutic targets that are in vogue are covered along with the recent advances of tear film biomarkers, personalized proteomics to point to future advances in the anvil.

Anterior chamber associated immune deviation (ACAID)

Anterior chamber associated immune deviation (ACAID) is the induction of a systemic form of tolerance to a foreign antigen introduced into the ocular microenvironment. Immune privileged sites in the eye are cornea, anterior chamber, vitreous cavity, and subretinal space.[5] The "immune privilege" is based on the expression of immunosuppressive factors on ocular tissue and in ocular fluids, that inhibits immune defense mechanisms responsible for damage to sensitive ocular tissues. The induction of ACAID is dependent on infiltration of these circulating monocytes that then emigrate to the thymus and spleen where they induce regulatory T cells that inhibit the inductive or effector phases of a cell-mediated immune response [Fig. 1]. Other suppressive factors are tumor growth factor-beta (TGF-β) and neuropeptides, including melanocyte-stimulating hormone and vasointestinal peptide.

More recently, experimental data have shown that the eye can induce apoptosis of infiltrating inflammatory cells by

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Table 1: Various uveitogenic retinal proteins

Protein	Location	Biological function
Retinal soluble antigen (arrestin, recoverin)	Intracellular	Photo transduction cascade
Interphotoreceptor retinoid-binding protein (IRBP)	Extracellular	Transport of vitamin A derivatives between the photoreceptor and the retinal pigment epithelium
Phoducin	Intracellular	Phosphoprotein
Recoverin	Intracellular	Calcium-binding protein
Rhodopsin (and its illuminated form, opsin)	Intracellular	Rod visual pigment
RPE 65	Intracellular	Conversion of all-trans-retinyl esters to 11-cis-retinol during phototransduction

Table 2: Comparative analysis of various EAU models[4]

Study	Background	Methodology	Results	Conclusion
Aneta *et al.*	Induction of experimental autoimmune uveitis.	Subcutaneous injection of IRBP protein in complete Freund's adjuvant and pertussis toxin in C57BL/6 mice.	Critical steps in EAU protocol were described.	The mouse model of EAU has practical value for preclinical studies and is robust and well established. Induction of inflammation of the eye can be quite challenging when important details of the protocol are not recognized and adhered to.
Caspi *et al.*	Discussed the salient features of the experimental autoimmune uveitis model and its mechanisms.	In first model, HLA class II transgenic mice were immunized with 200 g of S-Ag in CFA and were given pertussis toxin as an additional adjuvant. In other model, B10. RIII mice were immunized with IRBP.	Effector Mechanisms and Cells in EAU Development were decoded	EAU models help to shed light on the mechanisms driving human disease, from genetic, through cellular, to molecular.
Meng *et al.*	Preventive effect of chrysin on experimental autoimmune uveitis triggered by injection of human IRBP peptide 1-20 in mice.	C57BL/6J mice were immunized with human interphotoreceptor retinoid-binding protein peptide 1-20 to induce EAU. Chrysin was administered intragastrically at 25 mg/kg daily to the chrysin-treated mice from 3 days before immunization to 21 days after immunization.	Chrysin significantly decreased the proportions of Th1, Th17, and CD4 + CD3 + CD62L + Th0 cells, and increased the proportion of Treg cells. NF-κBp65 was downregulated after chrysin treatment.	Chrysin exerts a preventive effect on EAU by modulating the balance among helper T-cell subsets and suppressing ocular inflammation, thereby maintaining the integrity of the BRB.
Pennesi *et al.*	A humanized model of experimental autoimmune uveitis in HLA class II transgenic mice.	Experimental autoimmune uveitis (EAU) was induced in neural retina induced by immunization with retinal antigens, such as interphotoreceptor retinoid-binding protein (IRBP) and arrestin (retinal soluble antigen, S-Ag).	HLA-DR3 TG mice developed severe EAU with S-Ag, to which wild-type mice are highly resistant.	EAU in HLA TG mice offers a new model of uveitis that should represent human disease more faithfully than currently existing models.
Fang *et al.*	Amelioration of experimental autoimmune uveitis by leflunomide in Lewis rats.	Lewis rats were immunized with interphotoreceptor retinoid-binding peptide (IRBP) in order to generate EAU.	Histopathological and clinical data revealed severe intraocular inflammation in the immunized rat.	Oral administration of leflunomide effectively suppressed IRBP-induced uveitis in rats. These results suggest that leflunomide may be a potential clinical application in uveitis.

virtue of FasL expression.[6] FasL is a type II integral membrane protein homologous with tumor necrosis factor (TNF). In addition, as a result of selective Fas-FasL deletion, immune privilege within the eye is in part a result of selective activation of a Th2 population.[7] Recent clinical data showed FasL-mediated suppression of intraocular inflammation in both idiopathic acute anterior uveitis[8] and posterior uveitis.[9] ACAID, therefore, protects the eye from collateral damage of an immune response to infection by inducing immune unresponsiveness and systemic antigen-specific immune suppression.[10]

Cytokines and types of T lymphocytes

The CD4+ T cells play a critical role in achieving a regulated effective immune response to pathogens. Once the naive CD4+ T cells interact with antigen-Major histocompatibility complex (MHC), they are activated and multiply into specific subtypes depending mainly on the cytokine milieu of the microenvironment. The classical T cells are T-helper 1 which

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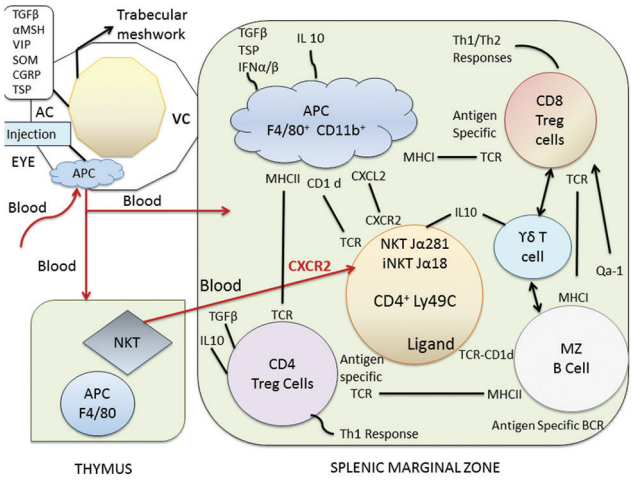


Figure 1: Chemical and molecular mechanisms of anterior chamber associated immune deviation (ACAID)

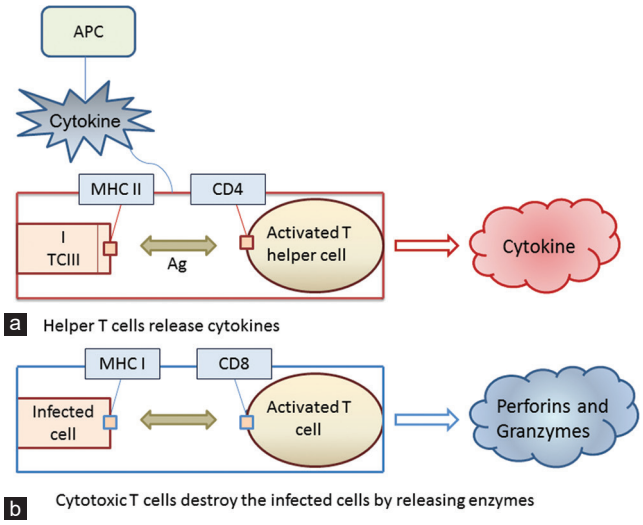


Figure 2: (a) MCH 2 and helper T cells interaction mechanism (b) MHC 1 and cytotoxic cells interaction mechanism

secrete interferon-γ and interleukin-2 and T-helper 2[11] which secrete IL-4 required for bloodborne parasitic responses and other subsets include induced T-regulatory cells (iTreg), and the regulatory type 1 cells (Tr1), follicular helper T cell, T-helper 9, and T-helper 17 each with a characteristic cytokine profile [Fig. 2].[11] The CD4+ Th1 cells and interferon gamma (IFN-γ) are considered as the major effectors in the pathogenesis of EAU. A variety of cytokine signaling pathways coupled with activation of lineage-specific transcription factors and epigenetic modifications at appropriate genes are required for a specific phenotype to manifest.

The cluster of differentiation 4 (CD4) is a glycoprotein reside on the surface of major immune cells like T helper cells, monocytes, macrophages, and dendritic cells. The vast majority of T-lymphocytes are a complex of CD4+ T cells along with CD8+ T cells [Fig. 3]. The CD4+ T cells perform multitude of functions, starting from activation of the cells of the innate immune system, B-lymphocytes, cytotoxic T cells, as well as nonimmune cells, and also mediate a critical role in the suppression of immune reaction.[12]

While the specificity of T cell recognition is determined by the interaction of T cell receptors with MHC/peptide complexes, the development of T cells in the thymus and their sensitivity to antigen are also dependent on coreceptor molecules CD8 (for MHCI) and CD4 (for MHCII).

Chemokines

Chemokines are polypeptides that are produced during inflammation and can be produced by endothelial cells in response to cytokines, such as TNF-α and IL-1. They majorly functions in the control of leucocyte adhesion, chemotaxis, and activation. These chemotactic cytokines can be classified as inflammatory chemokines (CC and CXC) and immune chemokines (C and CXC3).[13] They are thought to play a major role in inducing/regulating inflammation and various immune responses. Normal T cell mRNA (RANTES), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1), CCL2 (MCP-1), CCL5 (RANTES), CCL11 (Eotaxin), TGF-β2 and CXCL12 (SDF-1) and interferon-γ-inducible protein-10 have also been studied in experimental autoimmune anterior uveitis.[14] Recently, the dual-adhesion molecule-chemokine, fractalkine (CX3C), was also described in a variety of ocular tissues.[15]

The hallmark of both acute and chronic inflammation is the accumulation of specific leucocyte subpopulations.[16] Chemokines also appear to have an important role in the pathogenesis of certain viral infections that are relevant to inflammatory eye disease. It has been observed that CC chemokines such as MIP-1a, MIP-1b, and RANTES inhibit HIV replication.[17] The role of chemokines in the regulation of T cell recruitment to lymph nodes in HIV infection has also been studied. Thus, chemokines are thought to play a major role in inducing/regulating inflammation and various immune responses.

Measurement of cytokines

Measurements of cytokines can also play a critical role in predicting recurrences and in monitoring the disease activity. The bead-based multidetection assays have been used to detect multiple cytokine levels from a miniscule volume of aqueous fluid or serum.[18] Bio-Plex Pro™ magnetic color-bead-based multiplex assay (Bio-Rad Laboratories, Inc., Hercules, CA) was used to measure aqueous cytokine concentrations by Ang *et al.*[19] in tuberculosis (TB). In a study by Lane *et al.*, aqueous humor (AH) fractions were obtained and analyzed for the concentration of 41 different cytokines, chemokines, and growth factors associated with cytomegalovirus-induced inflammation, with the FlexMAP 3D (Luminex) platform using the Milliplex Human Cytokine kit.[20]

Cytokines levels can also be estimated in a biological sample by employing multiplex immunoassays. This will help clinicians or researchers in characterizing an inflammatory disease. For idiopathic uveitis, shotgun mass spectrometry (MS) is used. Another powerful analytical tool is liquid chromatography-tandem mass spectrometry (LC-MS/MS) that ionizes molecular species and sorts ions based on their mass-to-charge ratio (m/z). Cytokines sampling can be done by using strong-cation exchange chromatography or isoelectric focusing and ultra-high-pressure liquid

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chromatography.[21,22]After separation of ions and before entering the mass spectrometer, aqueous phase analytes are ionized to form gas-phase ions. Soft ionization techniques like electrospray ionization and matrix-assisted laser desorption ionization are used because they leave large molecules intact.[22] Once identified, peptides are quantified using unlabeled and labeled methods. The unlabeled methods employ spectral counting or data-independent acquisition and labeled methods include isotope-coded affinity tags, isobaric tags for relative and absolute quantification, and multiple reaction monitoring (MRM).[22] MRM has advantages over multiplex ELISAs, since it does not rely on antibody quality, and can pick up post translational modifications (PTMs) and short nucleotide modifications (SNPs) that would otherwise be missed by ELISA. MS will also facilitate vitreous and aqueous serum sampling which contain abundant levels of albumin and immunoglobulins.[23-25]

Interleukin and Cytokine Biomarkers in Infectious Uveitis

Toxoplasmosis

Toxoplasma can be mediated by autoimmune mechanisms that reflect the presence of immune-dominant membrane antigens in the retina.[26] The organism *T. gondii* has the ability to penetrate the host cells and avoid the cellular response.[27-29] The tachyzoites secrete the necessary factors that interact with cell's phospholipid bilayer and invade the human cells rapidly in an alkaline pH.[27,28] In the process, the antibodies for IgM, IgG, IgA, and IgE get positive in the serum according to the stages of infection.[29] Cell-mediated immunity is the chief mechanism involved in the resolution. The immune response is due to the activation of macrophages, natural killer (NK) cells, and T-cells with release of cytokines such as IL-4, IL-5, IL-10, IL-12, IL-27, and TNF-α.[29] Some of these cytokines stimulate CD8+ T lymphocytes and NK cells to produce IFN-γ.[29] This IFN plays a key role in the immune response of *T. gondii*.[29] The CD4+ Th 2 cell can produce IL-4, IL-5 and IL-10 which can prevent excessive inflammatory response.[26] Eye being immune-privileged site, CD8+ T cells and CD4+ Th 2 cells' affection is mediated by Fas, Fas ligand, and TGF-β.[29] IL-10 gene polymorphism is associated with toxoplasma retinochoroiditis.[29]

Tuberculosis (TB)

Pathogenesis of TB depends on the targeted cell-mediated immunity (type IV reaction-delayed).[30,31] In post primary TB, it could be reactionary tissue hypersensitivity response to mycobacterial antigen.[19,32-35] Pathological features in pulmonary TB are the caseation necrosis and granuloma formation.[33,34] Bacteria enter macrophage endosomes in the presence of mannose receptors in the macrophages. There is formation of phago-lysosome and bacilli continue to proliferate.[33,34] During the phase in lung, mycobacteria proliferate in pulmonary macrophages. However, by 3–4 weeks, cell-mediated immunity develops. Mycobacteria reach the regional lymph nodes and are presented to CD4+ cells.[33,34] Secretion of IFN-γ by these cells can activate the macrophages once more.[33,34] Macrophages, thereafter, get converted into epithelioid cells and these cells accumulate forming a granuloma.[33,34] Sometimes these can turn into disseminated involvement having miliary TB.[30,34] The lesion can resolve or due to fresh bacterial invasion, there may be reactivation of primary TB and can lead to secondary TB (Post Primary TB).[33,34] Here, the extrapulmonary TB is seen in various organs including eyes. Thus, immunopathogenecity process of infection can be due to the bacteria and their virulence factors or host immune response.[19,30-32] TB bugs can be latent in different sites and reactivated by secondary infections.[31,32] The study of cytokines and chemokines analysis in TB-related uveitis had shown autoimmune mechanisms involvement rather than active TB after anti-TB medications course.[19] Anti-TNF therapy for other rheumatologic diseases had also shown reactivation of TB.[33] Peripheral blood mononuclear cells (PBMCs) in children with active TB lower IFN-γ production rather than did PBMCs of children with Mantoux positivity but without systemic involvement.[34-36] Basu *et al*. had proposed an alternative hypothesis in which mycobacterial recognition by macrophages and dendritic cells led to the activation of immune pathway of Th1 and Th 17 cells.[37-39]

Viral diseases

Cell-mediated immunity in viral infection is critical.[40] There may be delayed hypersensitivity reaction following vaccination at this stage.[40,41] Skin activity can be seen as in herpes zoster infection (DNA virus) or mumps (RNA virus).[41] Normal resistance can also be seen in agammaglobulinemia due to cell-mediated immunity.[41] Individuals with deficient cellular immunity such as diabetics and human immunodeficiency virus (HIV) can have heightened susceptibility to herpes group of virus (DNA) or measles virus (RNA).[41] The hallmark of the herpes virus family is its ability to cause latent infections.[41] Recent findings on herpes group of viruses suggest that some viral lytic genes might be expressed during latency without virions formation.[41] The full reactivation can be prevented by constant vigilance of host immune system tailored by nonspecific modifications.[41] Dendritic cells are antigen-presenting cells for initial activation of naive T-cells.[41] Cell-mediated immunity can play a major role in viral diseases in which infected cells in the uveal and corneal tissue have viral-specific antigens on their surface.[41] Cell-mediated immunity can cause specific tissue damage like in acute retinal necrosis (ARN) and cytomegalovirus retinitis.[41] Various immune-regulatory cytokines (IL-6, IL-10, and IFN-γ) were detected in ocular fluids samples from patients with viral uveitis. The interleukins 2, 4, 6, 10 and IFN-γ were found to be associated with samples obtained from herpes group of virus in ARN.[41] Some specific viral infection like HIV can strike at the center of immune system by infecting CD4+ helper T cells.[41] Intrinsic inflammatory mediators in viral uveitis are poorly understood. IL-6, IL-8, MCP-1 and MCP-2 regulates on activation to normal T cells expressed for those inflammatory markers along with I-309 and sTNFR1 which support viral infections particularly the herpes groups of viruses. That evidence was mostly from in-vitro studies.

Fungal uveitis

In keratouveitis, there are expressions of IL-1 β, IL-6, IL-8, and IFN-γ.[42] Trafficking of CD4+ cells and their regulation through effectors cytokines (IL-12, IL-6, IL-4, and IL-1β) during invasive aspergillosis will be future for targeted immune therapy.[43] Candida seems to settle in the vitreous but Aspergillus has propensity for deeper retinal tissue including retinal pigment epithelium.[44] The assembly and localization of

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various phospholipases in growing fungal buds is detected in phospholipid rich tissues of eye such as retina.[44] Detection of galactomannan in invasive pulmonary Aspergillosis is found to be marker in bronchoalveolar lavage.[44] Systemic Aspergillosis can induce type I and type III hypersensitivity reaction.[44]

Capacity of fungus particularly *Candida* may promote stimulation of interphotoreceptor retinoid-binding protein-mediated Card 9,[44] as card 9 is essential signaling molecule of subgroup C-type lectin receptor (CLR1) which is important to defense host.[39] Dectin 1 and 2 activation can have signaling axis of IL (IL-17).[44]

Interleukin and Cytokine Profiles in Noninfectious Uveitis

Noninfectious uveitis (NIU) refers to a subgroup of uveitis that arises without a known cause of an infectious trigger and that has an autoimmune component that can be associated with systemic diseases[45,46] NIU is a significant cause of blindness and morbidity due to its chronicity and severe complications. The complexity of the disease's etiopathogenesis, the difficulty of diagnosis and subjectivity in clinical assessment may delay treatment and increase the rate of disease-related and treatment-related complications. NIU patients are in dire need of more individualized immune modulatory treatments in order to avoid drug-related side effects due to over or under treatment.[45] A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[47] It is well established that ILs and cytokines play a major role in the pathogenesis and persistence of intraocular inflammation.[15,46,48-54] They are also known to resemble the systemic/intraocular inflammatory activity.[45,46,48,54,55]

Successful therapeutic strategies in NIU might require characterization of the immune response. Interleukins and cytokines may represent indicators for a certain inflammatory pathway or may correlate with disease activity, or susceptibility of the disease to a certain treatment modality. Novel therapies with biologics have opened a door to a precise targeted therapy via blockage of specific cytokines and/or their receptors. This provides the basis for developing biomarkers for future diagnostic testing in ocular inflammatory conditions.[45,46,55] In that respect, cytokine biomarkers may potentially aid in the diagnosis as well as the management of uveitis patients in a more tailored fashion with various biologic agents.

Idiopathic uveitis

Intraocular levels of various proinflammatory cytokines such as IL-1, IL-2, IL-6, TNF-alpha (TNF-α), IFN-γ, IL-8, and monocyte chemotactic protein (MCP)-1 were found to be elevated in idiopathic uveitis.[15,56] Curnow *et al*. were able to classify idiopathic uveitis among other uveitic entities by applying cluster and random forest analysis to certain cytokine and chemokine AH data. This classification required the measurement of IL-6, IL-8, MCP-1, IL-13, IL-2, and TNF-α levels in AH.[15]

HLA-B27-associated uveitis

HLA-B27-associated anterior uveitis (HLA-B27-AU) constitutes almost 50% of all the cases of acute anterior uveitis. Anterior uveitis is mostly unilateral, alternating, and nongranulomatous in nature. T-helper (Th) cell-mediated immune response is thought to play a major role in the pathogenesis of the disease. High AH levels of TNF-α, IFN-γ, IL-2, IL-6, IL-12, IL-15, and IL-17 have been demonstrated in NIU by different investigators.[56] Kumar *et al*.[57] found higher IL-6 levels and IL-6/IL-10 ratios in the tear samples of HLA-B27-AU patients as compared to healthy controls. In the study, IL-6 levels were found to be associated with active disease as well. Carreno *et al*.[58] performed cytokine analysis in tear samples from uveitis patients with various etiologies and compared those to healthy controls. There were significant differences in the detection of IL-1, IL-23, IL-15, and MCP-1 between two groups. The concentrations of IL-1 and IL-8 in uveitis tear samples were elevated as compared to controls.

Pediatric uveitis

Sijssens *et al*.[59] found significantly higher levels of IL-2, IL-6, IL-13, IL-18, IFN-γ, and TNF-α in AH of children with Juvenile Idiopathic Arthritis-associated Uveitis (JIAU) than in controls. AH cytokine levels were similar in children having other uveitic entities compared to those with JIAU.

In tubulointerstitial nephritis and uveitis (TINU) syndrome, both cellular and humoral immunity have been held responsible in the disease development.[60] In children with TINU, the density of T regulatory cells in kidney biopsies were shown to be lower suggesting an autoimmune mechanism to persistent inflammation.[61] Besides that, autoantibodies against modified C-reactive protein (anti-mCRP) were found in renal and ocular tissues. The prevalence of anti-mCRP was significantly higher when compared to other renal autoimmune disease and normal controls, simply suggesting a TINU specific relevance for anti-mCRP.[62] β2-microglobulin is a sensitive marker for renal tubular damage. For this reason, elevated urinary β2-microglobulin in combination with high serum creatinine levels is considered as important biomarkers in patients being investigated for TINU syndrome.[63] In another study, cytokine patterns in the AH of children, adolescents, and adults with uveitis were compared and found significant lower levels of IL-2, IL12, IL-18, IFN-γ, TNF-α, IL-4, IL-13, and IL-10 in adults as compared to children and adolescents.[64] Only IL-6 was higher in adults than in children and adolescents.

Fuch's uveitis syndrome

Muhaya *et al*.[52] compared cytokine profiles in AH of FUS uveitis with Idiopathic Anterior Uveitis (IAU) where IFN-γ was found to be higher and IL-12 levels to be lower in FUS compared to IAU. On the other hand, Curnow *et al*.[15] found that IL-6 levels in AH of FUS patients did not differ from noninflammatory controls and IL-8, and MIP-1β levels did not reach statistical significance in contrast to Behcet's disease (BD) and herpes-viral uveitis patients. Furthermore, Pohlmann *et al*.[53] found lower levels of IL-8 and IL-10 when compared to Posner–Schlossman Syndrome attributing this finding to the low-grade chronic inflammation in FUS eyes. A recent study conducted in Chinese patients showed significantly higher levels of IFN-γ, MCP-1, macrophage inflammatory protein (MIP)-1β, and TNF-α in AH samples of FUS patients when compared to other uveitic entities including BD and Vogt-Koyanagi-Harada (VKH) disease. Multivariate analysis showed a significant association of MIP-1β with FUS.[65]

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Behcet's disease

Behcet's disease (BD) is a chronic systemic inflammatory disease associated with HLA-B51 phenotype. Furthermore, genome-wide association studies identified IL23R-IL12RB2 and IL-10 as BD susceptibility loci.[66] BD patients frequently experience nongranulomatous relapsing intraocular inflammation in the form of posterior or panuveitis including occlusive retinal vasculitis. Previous literature suggests that BD pathogenesis is predominated by a Th1 and Th17 immune response.[67]

Mesquida *et al*.[68] demonstrated significantly higher levels of serum IFN-γ and TNF-α in sera of active BD uveitis patients compared to inactive BD and healthy subjects. AH levels of IFN-γ, TNF-α, IL-2, IL-12, IL-6, IL-17A, and IL-8 were found to be higher in patients with BD uveitis in few reports.[49,65] Interestingly, AH IL-15 levels were significantly higher in BD uveitis patients than in normal controls and other causes of endogenous uveitis. IL-15 promotes the development, activation, homing, and survival of immune effector cells, particularly NK and CD8+ T cells.[49]

Sarcoid uveitis

Sarcoidosis is a multisystem, chronic inflammatory disorder characterized by noncaseating granulomas with uveitis being the most common ocular manifestation.[69] Many cytokines including IL-1, IL-6, IL-8, IFN-γ, and TNF-α and chemokines such as MIP-1α, MIP-1β have been reported to be present in higher concentrations in the vitreous humor of eyes with sarcoidosis than in controls.[69,70] In addition, vitreous and bronchoalveolar lavage samples with high CD4/CD8 ratios of vitreous-infiltrating lymphocytes in flow cytometric analysis were shown to be highly suggestive of ocular sarcoidosis.[58]

Vogt-Koyanagi-Harada disease

Vogt-Koyanagi-Harada (VKH) disease is a chronic autoimmune disorder characterized by bilateral granulomatous panuveitis. It is associated with HLA-DR1 and HLA-DR4 phenotype.[72] Works of literature strongly suggest a Th1/Th17-weighted immune response in the pathogenesis of VKH disease.[72] TNF-α, IFN-γ, IL6, IL-17, and IL-15 were found to be significantly higher in the AH of VKH patients than in controls. IL-8 and MIP-1β levels were found to be higher than in controls in AH.[65]

Birdshot retinochoroidopathy

Birdshot retinochoroidopathy (BSRC) is characterized by multiple hypopigmented chorioretinal lesions that often leads to atrophy of retina and optic disc resulting in serious vision and visual field loss. BSRC is strongly associated with HLA-A29.[73,74] T-cell-mediated disease pathogenesis has been suggested with recent attention on Th17 system. Kuiper *et. al.* found elevated AH levels of IL-1β, IL-2, IL-6, IL-17, and TNF-α in BSRC patients compared to controls.[74] In a study by Yang and Foster,[75] serum levels of interleukin IL-21, IL-23, and TGF-β1 were elevated in BSRC patients with active disease suggesting Th17 cell-mediated inflammation.

Other noninfectious uveitis entities

In Systemic Lupus Erythematosus (SLE), antibodies and immune complexes are so central that both diagnosis and classification focus on these features but not on other biomarkers of inflammation.[75] On the other hand, cytokines which are directly induced by those immune complexes such as IFN-α, IL-6, IL-10, IL-15, IL-18, and TNF-α were found to be elevated in serum during active disease.[75] In antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, ANCAs play a major role in the pathogenesis and induce excessive neutrophils activation. Therefore, ANCAs are considered as valuable laboratory markers for the diagnosis. Again, TNF-α and IL-6 serum levels were found to be much higher in AAV patients than healthy individuals [Table 3]. Serum levels of IL-6 are also considerably increased in patients with active disease.[75] Despite the heterogeneity and complexity of NIU entities, evidence-based research on cytokines as biological markers will hopefully allow us to characterize specific biological imprints of these pathologic conditions. This in turn may pave the way to more customized and optimal ocular therapies for NIU.

Interleukins and Cytokines Biomarkers in Masquerade Uveitis

Primary vitreoretinal lymphoma (PVRL)

PVRL often masquerades as intermediate and posterior uveitis. Early diagnosis and treatment are very crucial in the management of this aggressive ocular tumor. Often intraocular lymphoma patients, prior to vitreous biopsy receive systemic corticosteroids due to initial misdiagnosis of uveitis. Corticosteroids have lytic effect on lymphoma cells.[76] As lymphoma cells degenerate and necrotize easily, previous corticosteroid treatment, trauma from vitrectomy cutter, and delay in transport of vitreous samples itself can damage these fragile tumor cells and lead to false-negative results. Therefore, corticosteroid therapy must be stopped few weeks prior to vitreous biopsy. Prompt transfer and processing of specimen is recommended to avoid false negatives. Although cytological analysis of vitreous sample gives a definitive diagnosis, often it can be difficult to establish and, therefore, cytokine assay is very helpful in establishing early diagnosis. An elevated interleukin (IL)-10 to interleukin (IL)-6 (IL-10/IL-6) ratio of more than 1.0 in vitreous sample is most sensitive test for B-cell VRL.[77] IL-10 is a cytokine derived from T-cells and promotes growth and differentiation of activated B lymphocytes.[78] Cytokine analysis of vitreous and aqueous demonstrated predominantly higher levels of IL-10 in active B-cell lymphomas and elevated IL-6 levels in uveitis.[79] Higher levels of IL-10 or IL-10/IL-6 ratio of more than 1.0 in vitreous or aqueous is also useful to monitor response to treatment and relapse.[80,81] In PVRL, mean levels of IL-10 in pure vitreous samples were reported to be 5636 pg/mL and >190 pg/mL in undiluted aqueous samples, which was consistent with various other studies.[82,83] However, multiple reports also demonstrated exceptions where elevated levels of IL-10 were noted in infectious uveitis and lower IL-10 levels noted in early or low-grade vitreoretinal lymphoma (VRL).[80-84] Another study reported elevated levels of IL-10 in all cases of VRL except in one case of T cell lymphoma.[83] Interleukin score for intraocular lymphoma diagnosis (ISOLD) is formula which determines probability score for diagnosing PVRL using levels of IL-10 and Il-6 in aqueous and vitreous samples.[85] Reduction and spikes noted in IL-10 and IL-6 levels in serial samples of aqueous following chemotherapy correlate with improvement and recurrence, respectively, and are useful biomarkers to monitor treatment response.[86]

Carbello *et al*. compared multiple other cytokines in aqueous of active VRL, inactive VRL, and uveitic eyes [Table 4].[81] Higher levels of soluble cytokines receptors and soluble

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Table 3: Cytokines as biomarkers in noninfectious uveitis[15,45-75]

	Elevated serum levels	Elevated aqueous humor levels	Elevated vitreous levels
IL-1	HLA-B27-AU	HLA-B27-AU BSRC	Sarcoid uveitis
IL-2	IPU BD FUS	HLA-B27-AU IAU, FUS JIAU BSRC, BD	IPU
IL-6	HLA-B27-AU, FUS IAU, BD	HLA-B27-AU IAU BSRC, BD, VKH	HLA-B27-AU, FUS, JIAU, Sarcoidosis, PP, MS IPU BD
IL-15		HLA-B27-AU BD, VKH	
IFN-γ	BD, Sarcoid uveitis	HLA-B27-AU IAU FUS, JIAU, BD, VKH	Sarcoid uveitis[52,53]
TNF-α	BD	HLA-B27-AU, FUS, JIAU BSRC, VKH BD	Sarcoid uveitis
IL-17	Sarcoid uveitis, IAU, IPU, BSRC, VKH, BD	HLA-B27, IAU, BSRC, BD VKH	
IL-23	BSRC, BD VKH		
IL-8		IAU BD, VKH	Sarcoid uveitis
MCP-1		FUS,	
MIP-1β		FUS, VKH	Sarcoid uveitis
IL-10	Elevated intraocular levels are attributed to regulatory mechanisms activated along with inflammation. IL-10/IL-6 <1; suggestive of uveitis IL-10/IL-6 >1; suggestive of intraocular lymphoma		
TGF-β	Elevated intraocular levels are attributed to regulatory mechanisms implicated in the maintenance of immune privilege through the inhibition of antigen-driven T cell activation and proliferation. Inhibits T cell proliferation and suppresses cytotoxic T cells.		

IL-1=Interleukin-1, IL-2=Interleukin-2, IL-6=Interleukin-6, IL-8=Interleukin-8, IL-10=Interleukin-10, IL-15=Interleukin-15, IL-17=Interleukin-17, IL-23=Interleukin-23, IFN-γ=Interferon-gamma, TNF-α=Tumor necrosis factor-alpha, MCP-1=monocyte chemoattractant protein-1, MIP-1β=Macrophage inflammatory protein-1beta, TGF-β=Transforming growth factor-beta. FUS=Fuch's uveitis syndrome, HLA-B27-AU=Human leucocyte antigen-B27 associated uveitis, BSRC=Birdshot retinochoroidopathy, BD=Behcet's disease, VKH=Vogt-Koyanagi-Harada disease, JIAU=Juvenile idiopathic arthritis associated anterior uveitis, MS=Multiple sclerosis, PP=Pars planitis, IAU=Idiopathic anterior uveitis, IPU=Idiopathic posterior uveitis

receptors of VEGF 1 and 2 (vascular endothelial growth factor) were demonstrated in vitreous of VRL eyes as compared to uveitic eyes. Soluble receptors of VEGF 1 and 2 (sVEGFR1 and sVEGFR2) levels were identified as important biomarkers to differentiate systemic metastatic retinal lymphoma (SMRL) from PVRL and PCNSL, as the levels are higher in SMRL. Higher levels of sIL-2Rα (soluble receptor of IL-2α) were also found to be associated with increased risk of retinal and or subretinal tumor infiltration in VRL [Table 3].[87] Using multicolor flow cytometric immunophenotyping technique another group compared vitreous samples of PVRL and non-PVRL cases and demonstrated higher level of IL-10, IL-1 receptor α, MCP-1, macrophage infiltrating protein-1β, and IL10/IL-6 ratio more than 1.0 in vitreous of PVRL group.[88]

Uveal melanoma

In uveal melanoma, aqueous demonstrated cytokine's profile is similar to that of aqueous of uveitic eyes. None of the cytokines had any prognosticating value. These proinflammatory cytokines IL-6 and GM-CSF (Granulocyte Macrophage Colony Stimulating Factor) were found to be produced both by tumor cells and normal surrounding tissue, thereby promoting tumor growth. Elevated levels of cytokines were proposed to determine T-cell infiltration in tumor cells and not macrophage infiltration. Higher levels of VEGF noted in aqueous were attributed to ischemia caused by large growing tumors.[84] GM-CSF is proinflammatory cytokines which increases MHC class II expression by myeloid cells like macrophages. This promotes apoptosis of hostile cells by increasing TRAIL (TNF-related apoptosis-inducing ligand) secretion and by stimulation of antigen presentation to CD4+ T helper cells.[89,90]

Retinoblastoma

In children, retinoblastoma is the most common primary intraocular malignancy and is not accessible for direct biopsy because of the risk of tumor dissemination. However, analysis of aqueous humour gives insight to various biomarkers. Elevated levels of survivin, an antiapoptotic protein, and transforming growth factor β1 have reported to have positive correlation with optic nerve infiltration and poor tumor differentiation, respectively. Significant reduction in the serum levels of these biomarkers was noted post treatment. High sensitivity and specificity make these two biomarkers very promising for early diagnosis, assessing prognosis, and monitoring response to treatment.[91] In aqueous samples of 35 patients, diagnosed with retinoblastoma, significant higher levels of VEGF-A and PIGF (Placental Growth Factor) were noted. VEGF and PIGF help in angiogenesis and vascularization which promotes tumor growth.[92,93] RAS-MAPK/P13K-Akt/STAT signaling pathways are involved in tumor growth, spread, and upregulation of VEGF. Significant higher levels of IL-6, IL-7, and IL-8 were also demonstrated. The study proposed that therapy directed to inhibition of VEGF, PIGF, and these signaling pathways and blocking of IL-6, IL-7, and IL-8 can open doors to new options for adjunctive therapy for retinoblastoma. Other cytokines like FGF2 (fibroblast growth factor), HGF (hepatocyte growth factor), and βNGF (nerve growth factor) were significantly elevated and IP-10 (interferon $_{\gamma}$-induced protein 10kDa) levels were low as compared to controls.[93]

Retinal detachment (RD)

Kiang *et al*. studied vitreous samples of 24 patients with retinal detachment and demonstrated elevated levels of IL-6, IL-8, MCP-1, IP-10, and various other cytokines like fractalkine, GRO, and MDC, and also suggested that microglial cells play an important part in inflammatory response in eyes with retinal detachment.[94] CCL-19 (Chemokine (C-C motif) ligand 19) has been identified as a promising biomarker for early progression to PVR changes in eyes with rhegmatogenous RD.[95]

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Table 4: Cytokines to differentiate PVRL and uveitis

Study	PVRL	Uveitis
Carbello *et al.*[81]	Compared IL-1b, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, IFN-γ, TNF-α, IL-1rα, MCP-1, G-CSF, GM-CSF and VEGF-A in aqueous of active PVRL, inactive PVRL and uveitic eyes-no statistical difference in three group	Higher levels of IL 8, growth factor G CSF, and VEGF A in aqueous
Takeda *et al.*[87]	Higher levels of sIL-2Rα, sIL-6R, sTNFR1, sTNFR2 and soluble receptors of VEGF 1 and 2 sVEGFR1 and sVEGFR2 in vitreous	Higher levels of soluble interleukin-1 receptor 1 and 2 and soluble IL-4 receptors in vitreous

PVRL=Primary vitreoretinal lymphoma; IL=Interleukin; IFN-γinterferon-γ; TNF=Tumor necrosis factor, MCP-1-monocyte chemotactic protein-1; VEGF vascular endothelial growth factor; GCSF=Granulocyte colony stimulating factor; GM CSF=Granulocyte macrophage colony stimulating factor; IL=1rα interleukin-1 receptor α; sIL-2Rα-soluble IL-2 receptor-α; sIL-6R-soluble receptors of IL-6; sTNFR1 and sTNFR2=Soluble receptors of TNF1 and 2; sVEGFR1 and sVEGFR2=Soluble receptors of VEGF 1 and 2.

Table 5: TNF Inhibitors[97-103]

Medicine	Brand	Target	Route	Dose	Side effects
Infliximab	Remicade	TNF-α	I.V	Loading dose of 3-5 mg/kg IV on weeks 0, 2, 6 then maintenance therapy with 3-10 mg/kg IV every 8 weeks	Injection site reaction, reactivation of infections, such as tuberculosis, demyelination, lupus-like syndrome, psoriatic skin lesions, paradoxical ocular inflammation, sarcoidosis-like disease onset, neutralizing antibodies, congestive heart failure, malignancy
Adalimumab	Humira	TNF-α	S.C	80 mg s.c. on day 0, then 40 mg s.c. every 14 days starting on day 7	
Etanercept	Enbrel	TNF-α,β	S.C	50 mg s.c. weekly	
Golimumab	Symponi	TNF-α	S.C	50 mg s.c. monthly; in UC 200 mg s.c. then 100 mg s.c. 2 weeks later then 100 mg s.c. every 4 weeks	
Certolizumab Pegol	Cimzia	TNF-α	S.C	Loading dose of 400 mg s.c. on weeks 0, 2, 4 then 200 mg s.c. every 2 weeks or 400 mg s.c. every 4 weeks	

I.V=Intravenous; S.C=Subcutaneous; TNF=Tumor necrosis factor; UC=Ulcerative colitis

Table 6: Interleukin Inhibitors[104-107]

Medicine	Trade name	Target	Route	Dose	Side effects
Anakinra	Kineret	IL-1 receptor	S.C	100 mg s.c. daily	Injection-site reaction, headache, fever, GI distress, infection
Canakinumab	Ilaris	IL-1b	S.C	150 mg s.c. every 8 weeks	Headache, GI distress, infection
Gevokizumab		IL-1b	I.V/S.C	30 or 60 mg IV or s.c. every 4 weeks	Infection
Tocilizumab	Actemra	IL-6 receptor	I.V/S.C	4-8 mg/kg IV every 4 weeks or 162 mg s.c. every 1-2 weeks	GI distress, hypersensitivity reaction, infection
Secukinumab	Cosentyx	IL-17A	I.V/S.C	300 mg SC every 2-4 weeks or 10 mg/kg IV every 2 weeks or 30 mg/kg IV every 4 weeks	GI distress, hypersensitivity reaction, infection
Guselkumab	Tremfya	IL-23	I.V/S.C	100 mg s.c. on weeks 0, 4 then every 8 weeks	Injection-site reaction, headache, arthralgia, infection
Ustekinumab	Stelara	IL-12, IL-23		Under investigation	Injection-site reaction, headache, GI distress, arthralgia, dizziness, infection

GI=Gastrointestinal; IL=Interleukin; i.v.=Intravenous; s.c.=Subcutaneous

Table 7: Lymphocyte Inhibitors[98,108,109]

	Medicine	Trade Name	Target	Route	Side Effects
B-Lymphocyte Inhibitors					
Rituximab	Rituxan	CD20	I.V	1000 mg IV on days 0, 14 then 500-1000 mg every 6 months as needed	Infusion reactions, muscle spasms, headache, GI distress, infection, cardiac events
T-Lymphocyte Inhibitors					
Abatacept	Orencia	CTLA-4	I.V/S.C	Loading dose of 500-1000 mg IV then 125 mg s.c. weekly	Injection site reaction, headache, GI distress, infection
Daclizumab Zenapax, Zinbryta	Zenapax, Zinbryta	IL-2a receptor		1-2 mg/kg IV or s.c. every 2-4 weeks	Immune-mediated encephalitis, headache, GI distress, hypersensitivity

CTLA-4=Cytotoxic T-lymphocyte-associated antigen-4; GI=Gastrointestinal; IL=Interleukin; i.v.=Intravenous; s.c.=Subcutaneous

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Table 8: Janus Kinase Inhibitors[98,111]

Medicine	Trade name	Target	Route	Dose	Side effects
Tofacitinib	Xeljanz	JAK-1, 2,3	P.O	5 mg p.o. twice daily	Hyperlipidemia, nephrotoxicity, hepatotoxicity, headache, cytopenias, HTN, GI distress, infection
Filgotinib GLPG0634/ GS-6034	GLPG0634/GS-6034	JAK-1		Under investigation	Under investigation

GI=Gastrointestinal; JAK=Janus kinase; p.o., by mouth

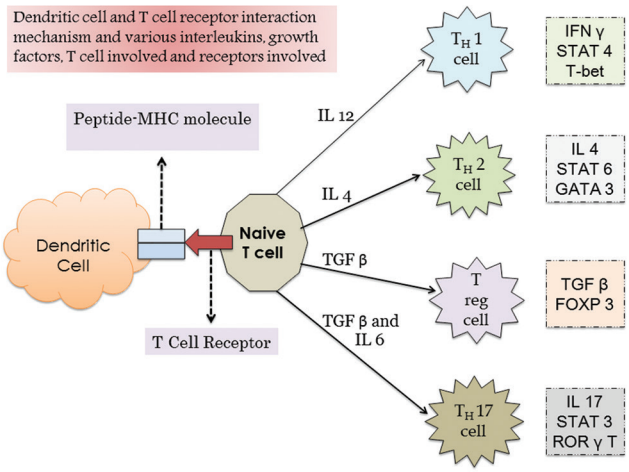


Figure 3: Dendritic cell and T cell interaction mechanism

4.5 Retinitis pigmentosa (RP)

Aqueous samples of 20 eyes with RP demonstrated disturbances in extracellular matrix due to significant increase in levels of MMP-2, MMP-3, MMP-7, MMP-8 (matrix metalloproteinases), PDGF-AA (platelet-derived growth factor), PAI-1(plasminogen activator inhibitor), and TSP-2 (thrombospondin) and lower levels of BMP-4 (Bone morphogenetic protein). They also concluded that this was responsible for postoperative complication, capsule contraction syndrome. Various other cytokines like MCP-1, IL-8, IP-10, HGF, and IL-6 were found to be elevated in aqueous of RP eyes. Higher levels of proinflammatory cytokines were responsible for pathogenesis of posterior subcapsular cataracts and masquerade uveitis in eyes with RP.[96]

Application in Therapeutics of Uveitis

TNF-α inhibitors

TNF-α inhibitors are currently the most commonly used biologics in the treatment of NIU. Infliximab (IFX) is a human murine chimeric monoclonal antibody against TNF-α, while adalimumab (ADA) is a fully human monoclonal antibody against TNF-α. ADA is the only biologic agent, which is FDA approved for the treatment of NIU for the treatment of intermediate, posterior, and panuveitis.

Several studies have established the efficacy of Infliximab and Adalimumab in controlling inflammation, improving visual acuity, reducing macular edema, and decreasing flare-up in uveitis related to Behcet's, juvenile idiopathic arthritis (JIA), ankylosing spondylitis, and other NIU.[97,98] Comparison of infliximab and adalimumab shows that the ADA is as effective or better than IFX in terms of clinical efficacy and safety.[99,100]

Etanercept is a humanized recombinant fusion protein, which prevents TNF from binding to its receptor. It is less effective in controlling ocular inflammation and, hence, it is recommended that ADA or IFX be used in preference to Etanercept in the treatment of uveitis.[97,98]

Golimumab (GOL) is a fully humanized monoclonal antibody against TNF-α. Certolizumab pegol (CZP) has a unique structure composed of the antibody-binding fragment (Fab) of humanized monoclonal antibody against TNF conjugated to polyethylene glycol (PEG); unlike other agents, it does not contain the constant fragment of immunoglobulin (Fc). This lack of the Fc portion is thought to make certolizumab less immunogenic and less likely to cross the placenta. Both GOL and CZP may be effective in uveitis related to JIA, spondyloarthropathy, and Behcet's when other TNF inhibitors have failed[101,102] but may cause a paradoxical inflammatory response mimicking sarcoidosis [Table 5].[103]

Interleukin inhibitors

IL-1 inhibitors

Anakinra is an IL-1 receptor antagonist. There is a single report of anakinra inducing remission of bilateral panuveitis in a child with chronic infantile neurological cutaneous articular (CINCA) syndrome.[104]

Canakinumab is a human monoclonal antibody targeting IL-1b. Canakinumab and anakinra have been shown to reduce the number of uveitis flares in patients with BD-related uveitis.[105] Canakinumab has also been reported to successfully treat uveitis associated with JIA, CINCA syndrome, and Blau syndrome.

Gevokizumab is a monoclonal antibody that binds IL-1b. In phase III trials of patients with Behcet's uveitis and NIU, it has failed to show significant results.[98]

IL-6 inhibitors

Tocilizumab (TCZ) is a monoclonal antibody directed against both soluble and bound the IL-6 receptor. TCZ is effective in the treatment of JIA associated uveitis, Behcet's uveitis, Blau syndrome, birdshot chorioretinopathy, and scleritis. Promising results have also been found in the treatment of uveitic macular edema not responding to conventional immunosuppressive and biologics.[106]

IL-17 inhibitors

Secukinumab is a monoclonal antibody, which binds IL-17A. Results from randomized controlled a study suggest that it can be given intravenously than via subcutaneous route and may be more effective in the treatment of uveitis.[98] There are case reports of exacerbation of BD in patients treated with secukinumab.[107]

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IL-23 inhibitors

Guselkumab is a monoclonal antibody, which binds to the p19 subunit of IL-23. Isolated case report found that a patient with inactive sarcoidosis-related panuveitis, who was being treated for cutaneous sarcoidosis with guselkumab, had worsening of his uveitis while on this medication.[108]

Ustekinumab is a monoclonal antibody targeting the IL-12p40 subunit of both IL-12 and IL-23 [Table 6].The uveitis associated with PsA and Crohn's can be successfully treated by use of this monoclonal antibody.

B-lymphocyte inhibitors

Rituximab is a B-cell depleting-chimeric anti-CD20 monoclonal antibody. It is indicated in ANCA-associated ocular disease as a first or second-line agent.[108] It is also indicated in treating ANCA-negative orbital diseases, such as nonspecific orbital inflammation, thyroid eye disease, IgG4-related orbital disease, severe ocular cicatricial pemphigoid, refractive scleritis, refractory Behcet's-related panuveitis, VKH, diffuse subretinal fibrosis uveitis syndrome, nonparaneoplastic autoimmune retinopathy, and Susac syndrome.[109]

T-Lymphocyte inhibitors

Abatacept is a fusion protein made of a fragment of human immunoglobulin 1 (IgG1) and the ligand-binding domain of cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). Abatacept binds and blocks the CD80/86 molecule of antigen-presenting cells, which is normally needed for T-cell activation. In JIA-associated uveitis, abatacept showed comparable efficacy as a first-line or second-line biologic.[98]

Daclizumab is a humanized monoclonal antibody, which binds the interleukin (IL)-2a receptor found on most lymphocytes. Although promising, it has been withdrawn from the market after multiple cases of immune-mediated encephalitis were reported [Table 7].[98]

Interferons

Interferons (IFN) are naturally occurring proteins that augment the body's immune response. A variety of interferons—IFN-a2a, IFN-a2b, and IFN-b—have been reported to be useful in treating uveitis. Most of these studies have been on uveitis related to BD, multiple sclerosis, and refractory uveitic macular edema though its efficacy in other forms of NIU has also been documented.[110]

Janus kinase inhibitors

The Janus kinase (JAK)-signal transducers and activator of transcription (STAT) pathway are critical for the biological activity of cytokines. After soluble cytokines bind their receptors, the JAKs, a type of nonreceptor tyrosine kinases, transduce their signals. Thus, JAK inhibitors have become a new therapeutic target for the treatment of autoimmune diseases. A recent case series reported that on treatment with JAK inhibitors, namely, baricitinib (three cases) and tofacitinib (One case), all patients showed improvement in JIA associated uveitis.[111] Filgotinib is a selective JAK1 inhibitor which is currently undergoing a phase II, randomized, placebo-controlled trial for the treatment of NIU [Table 8].[98]

Intravitreal biologics in uveitis

Both IFX and ADA have been tried, as intravitreal injections in the treatment of NIU. Although some of the studies have reported improvement in anatomical and functional outcome, the results are not conclusive.[112]

Tear cytokine profiling

Evaluation of biomarkers in tears is another innovative and noninvasive technique which can aid in accurate diagnosis.

Significance of profiling tear biomarkers was described, and several proteins were identified in tears of patient with primary Sjogren's syndrome and rheumatoid arthritis [Table 9 and 10].[113,114] A recent study in pediatric age group described tear cytokine profile in NIU and its usefulness in assessing the risk of developing ocular inflammation in children with JIA, especially when they have no evidence of uveitis and are not due for any ocular surgery. They compared the tear biomarkers in JIA and idiopathic chronic anterior uveitis (I-CAU) children [Table 11]. Protein associated with arthritis showed higher expression in tears of JIA children also. Ease of sample of collection in tear profiling makes it a promising tool for additional diagnosis and serial monitoring of disease.[99]

Future Trends

A constant desire for improvising diagnostics and treatment of uveitis has constantly led various researchers to set new milestones in the field of uveitis. Approval of adalimumab for treatment of a range of NIU globally was a very significant advancement in improvising systemic therapy. Recent advances in molecular diagnostic and personalized proteomics analysis of ocular samples were able to identify different biomarkers in various ocular inflammation [Table 12].[116-121] Identification of these biomarkers has opened new gates for additional accuracy of diagnosis, targeted treatment, and avoiding unnecessary drugs, thereby reducing the

Table 9: Upregulated proteins in tears of patient with primary Sjogren's syndrome[113]

Number	Gene	Related protein	Classification and function
1	APEX1	DNA-(apurinic or apyrimidinic site) lyase	Enzyme; oxidative stress, DNA repair, regulation of transcriptional factors
2	PRDX3	Thioredoxin-dependent peroxidase reductase	Enzyme; redox regulation, regulates NF-kappa-B activation (B cell survival)
3	CPNE1	Copine 1	Phospholipid-binding protein (calcium-dependent), TNF-α receptor signaling
4	ACO2	Aconitate hydratase	Enzyme; tricarboxylic acid cycle/Krebs cycle, carbohydrate metabolism
5	LMO7	LIM domain only protein 7	Cell signaling, cell adhesion, ubiquitination

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Table 10: Upregulated/downregulated proteins in tears of patient with rheumatoid arthritis[114]

Tear protein	
Upregulated	Downregulated
Ecto-ADP ribosyltransferase 5 precursor (in 80% cases)	Lactotransferrin isoform 1 precursor (in 100% cases)
Rho-related GTP-binding protein (in 80% cases) RhoJ precursor (in 80% cases)	SHC transforming 1 isoform (in 60% cases) Ribonuclease P protein subunit 20, protocadherin, and heterogeneous nuclear ribonucleoprotein Q isoform 6 (in 80% cases)

Table 11: Higher/lower expression of proteins in tears of children with JIA as compared to I-CAU[115]

Tear proteins	
Higher expression[124]	Lower expression
SEMA3G, TIMP1, HEXB, ERN1, and SAA1, sCD14, S100A8	S100A9, LAP3, TTR, and MIF

SAA1, HEXB, TIMP1, and ERN1 are elevated in tears of RA and JIA patients, TIMP: Tissue Inhibitor of Metalloproteinases, MIF: Migration Inhibitory Factor

Table 12 : Personalized proteomics analysis unveiling few biomarkers in uveitis[100,117]

Study	Uveitis condition	Sample	Biomarkers
Velez *et al.*[122,123]	Posterior uveitis	Vitreous	IL-23, PDGFRb, SCF, TIMP-1, TIMP-2, BMP-4, NGF, IGFBP-2, IL-17R, IL-1RI
Kalinina *et al.*[118]	Anterior uveitis	Aqueous	TTR
Sen *et al.*[125]	JIA	Vitreous	TNF-a
Ooi *et al.*[126]	Behcet's disease, sarcoidosis, Fuch's heterochromatic cyclitis	Vitreous	IL-6
Sauer *et al.*[127]	Viral uveitis	Vitreous	IL 17-A, IL-10

IGFBP: Insulin like Growth Factor Binding Proteins, TIMP: Tissue Inhibitor of Metalloproteinases, SCF: Stem Cell Factor, TTR: Transthyretin

systemic side effects and improving the quality of life.[116,117] Future trends of treatment include IL-6, IL-23, and mTOR inhibitor and complement directed therapies (clinicaltrials.gov NCT01526889). Signal transduction inhibitors have been successfully used for treating rheumatoid arthritis.[128] Recent biologicals, the therapeutic molecules, target selective signaling pathways, for example, the intracellular JAK/STAT pathway (Janus kinase/signal transducer activating pathway) which alters the effects of cytokines within the immune cells (www.clinicalTrials.gov NCT02914561).[129] Tear profiling and AH sampling are promising fields for further research and to improve diagnostic accuracy.[115] Enormous research and larger studies are required to identify these biomarkers and unveil the pathogenesis of inflammtion in order to further improve diagnostic accuracy and treatment.

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Conflicts of interest

There are no conflicts of interest.

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