Uveitis is a general term for inflammatory disorders of the uveal tract, the vascular membrane of the eye, and encompasses a wide range of underlying etiologies. In fact, untreated uvea inflammation leads to 5–10% of visual impairment worldwide and it is one of the main causes of blindness [1-4]. The prevalence and phenotypic expression of various uveitis types depend on age, sex, race, geographic distribution, environmental influence, genetic factors, and social habits [5, 6]. Since uveitis typically affects the working age group (20–60 years of age), not only may quality of life be severely impacted but there may also be profound socioeconomic consequences for affected patients. [7-10].

Uveitis may be idiopathic, associated with systemic diseases or result from a variety of infectious agents. Until recently, although uveitis was proposed to be frequently an autoimmune disease, repeated attempts to induce experimental uveitis with uveal antigens met with failure [11]. In the latter form, a uveal component, whether tissue damage or a microbial trigger, stimulates the generation of antigen-specific T cells and/or auto-antibodies that are believed to play a pathogenetic role, hence the term autoimmune uveitis (AU) [12]. AU can present as an isolated entity or associated with a systemic autoimmune disorders. Diseases such as rheumatoid arthritis (RA) [13, 14], systemic lupus erythematosus (SLE) [13], Vogt Koyanagi Harada Syndrome (VKHS) [15] are commonly associated with posterior type of uveitis. On the other hand, anterior uveitis typically appears as the initial manifestation in autoinflammatory diseases such as psoriatic arthritis (PA) [16, 17], Behcet’s disease (BD) [18, 19, 20], Juvenile idiopathic arthritis (JIA) [13, 21, 22], Crohn’s disease (CD) [23], ankylosing spondilitis (AS) [23, 24] There is a clear association described with the HLA-B27 positivity and a higher risk of presenting recurrent anterior uveitis in AS [25].

There are no standardized treatment protocols for AU. Topical corticosteroids are the typical first-line agent, although systemic corticosteroids are used in intermediate, posterior intraocular inflammation, and panuveitis. Corticosteroids are not considered to be long-term therapy due to potential ocular and systemic side effects [26-28]. This impact has stimulated the development of more effective treatment strategies for uveitis.

Etiological treatments for autoimmune diseases affecting millions of patients worldwide are still lacking and current available therapies do not control satisfactorily the disease evolution [29]. Current therapeutic strategies for all autoimmune diseases rely on immunosuppressive and/or symptomatic therapies that preserve only partially the patients’ quality of life. Thus, new technological approaches to these disorders should be developed [30].

**THE AIM**

The aim of this review was to make the evaluation of the interleukins influence on intraocular inflammation in available literature and summarize the expediency of using anti-interleukins agent in case of AU.
available literature and summarize the expediency of using anti-interleukins agent in case of autoimmune uveitis.

MATERIALS AND METHODS
This article is a review and summary of the up-to-date results of pivotal experimental and clinical trials targeting the Interleukins (IL), including IL-6, IL-10, IL-17, IL-22, IL-23, and tumor necrosis factor alpha (TNF-α). Also, reviews focus on the potential use of anti-interleukin therapy for the treatment of autoimmune diseases (AD). An extensive literature research was performed in the Medline database (PubMed) for articles, also some additional references were taken from books written on the subject. Additionally, attention was given to articles referenced in the selected articles.

REVIEW AND DISCUSSION
Immune-mediated inflammation can be tolerated in many organs, however in the eye it has devastating consequences, as many of the tissues in the visual axis have limited or no capacity for regeneration. Multiple mechanisms and anatomical adaptations limit the expression of immune-mediated inflammation in the eye. Among these is the generation of regulatory T cells (Tregs), which act to prevent the induction and expression of T cell inflammation [31]. Tregs formerly known as suppressor T cells, are a subpopulation of T cells that modulate the immune system, maintain tolerance to self-antigens, and prevent autoimmune disease. Tregs are immunosuppressive and generally suppress or downregulate induction and proliferation of effector T cells. [32]. T cells expressing the surface marker cluster of differentiation 4 (CD4) are known as T helper (Th) cells play important roles in the pathogenesis of autoimmune diseases including uveitis. Th cells can be classified into different functional categories: defined by the transcription factor T-bet and secretion of interferon gamma, were the dominant cell type 'helping' cellular immunity, and Th2 cells, defined by the transcription factor GATA binding protein 3 and secretion of IL-4 and IL-5, were responsible for helping humoral immunity [33].

Cytokines are made by many cell populations, but the predominant producers are T cells, macrophages, dendritic cells, and NK. IL-22, which is pro-inflammatory and pro-regenerative, is part of the IL-17 family of cytokines. IL-17 is a cytokine that is produced by T cells called Tc17 cells in the lung and gut similar to IL-10. IL-22 promotes hepatic tissue survival in the liver and epithelial cells in the lung and gut similar to IL-10. In some contexts, the pro-inflammatory versus tissue-protective functions of IL-22 are regulated by the often co-expressed cytokine IL-17A [68, 69].

As a result of the analysis of many literary sources, it is known that the most important IL in the pathogenesis of uveitis are IL-6, IL-10, IL-17, IL-22, IL-23, and TNF-α. IL-6 stimulates the inflammatory and auto-immune processes in many diseases. There is evidence for the important role of IL-6 hyperproduction not only in RA, but also in other immune inflammatory BD, systemic lupus erythematosus, scleroderma systematica, idiopathic inflammatory myopathies, giant cell arteritis, etc., also in diabetes, atherosclerosis, Alzheimer’s disease, multiple myeloma and prostate cancer [35-43]. It is important mediator of AD including AU [44]. The binding of IL-6 to its receptor results in the activation of the mitogen-activated protein kinase pathways, ultimately leading to the expression of inflammatory cytokines, vascular endothelial growth factor and differentiation of naive CD4+ T cells into Th17 cells [45].

Some studies in mice with EAU found that inflammation is significantly attenuated in IL-6 deficient animals and intravitreal anti-IL-6 reduces inflammation [46, 47]. Also, in human’s studies, elevated levels of IL-6 have been detected in the aqueous humour of BD, VKHS, sarcoid, idiopathic uveitis, acute retinal necrosis and HLA-B27 mediated uveitis when compared with controls [48-50]. Furthermore, IL-6 also plays a role in uveitis complications such as neovascularization and macular oedema [51-53].

IL-10, also known as human cytokine synthesis inhibitory factor, and it continues to be one of the more important immunoregulatory cytokines, controlling and moderating inflammatory responses [54]. It is secreted by activated T cells, macrophages, dendritic cells, and NK cells and B-cells [55]. In patients and animals with uveitis, elevated intraocular IL-10 levels have been identified and it has protective roles [56-58]. Moreover, in animal model with endotoxin-induced uveitis protective role of local IL-10 was confirmed [59, 60]. Correlation between level of IL-10 to level of IL-6 allows to determine the diagnosis (uveitis or intraocular tumor) [61, 62].

One of the main subunit of IL-10 is IL-22, that is produced by T cells, Th1 and Th17 cells, NK cells and innate lymphoid cells. IL-22 initiates innate immune responses against bacterial pathogens especially in epithelial cells such as respiratory and gut epithelial cells. Generally, IL-22 may primarily have immune regulatory rather than inflammatory functions in the eye [63]. In experimental model IL-22 develops worse inflammation and led to a reduced severity of uveitis. In humans elevated levels of serum IL-22 have been identified in patients with uveitis in case of BD and scleritis [64-67]. Some authors review, that IL-22 can contribute to immune disease through the stimulation of inflammatory responses, S100s and defensins. IL-22 also stimulates the inflammatory and auto-immune processes in many diseases. There is evidence for the important role of IL-6 hyperproduction not only in RA, but also in other immune inflammatory BD, systemic lupus erythematosus, scleroderma systematica, idiopathic inflammatory myopathies, giant cell arteritis, etc., also in diabetes, atherosclerosis, Alzheimer’s disease, multiple myeloma and prostate cancer [35-43]. It is important mediator of AD including AU [44]. The binding of IL-6 to its receptor results in the activation of the mitogen-activated protein kinase pathways, ultimately leading to the expression of inflammatory cytokines, vascular endothelial growth factor and differentiation of naive CD4+ T cells into Th17 cells [45].
interphotoreceptor retinoid binding protein specific Th17 cells are sufficient to induce uveitis, and treatment with anti-IL-17 antibody is sufficient to block development of disease [71]. In humans, elevated levels of IL-17 were identified in the eyes of patients with immune-mediated uveitis, VKHS, birdshot chorioretinopathy, as well as in HLA-B27 and Behcet's uveitis [72-75].

IL-23 is a heterodimeric cytokine composed of an IL12B and the IL23A. Prior to the discovery of IL-23, IL-12 had been proposed to represent a key mediator of inflammation in mouse models of inflammation. However, many studies aimed at assessing the role of IL-12 had blocked the activity of IL-12p40, and were therefore not as specific as thought. Studies which blocked the function of IL-12p35 did not produce the same results as those targeting IL-12p40 as would have been expected if both subunits formed part of IL-12 only [76, 77]. Inflammatory cells that express the IL-23R include CD4+ and CD8+ T cells, group 3 innate lymphoid cells and invariant NK cell [78]. The results from different studies are varied. One study identified increased IL-23 in vitreous samples from patients with posterior uveitis [79]. However, a results of analysing aqueous sample did not detect elevated IL-23 in patients with VKHS, Behcet's, idiopathic, HLA-B27 or sarcoid uveitis [80]. Single nucleotide polymorphisms in the IL-23R gene have also been associated with an increased risk of inflammatory disease, including ankylosing spondylitis associated uveitis, BD, VKHS, and sarcoid uveitis [81-83].

From literary sources it is known that TNFα is a cell signaling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute

<table>
<thead>
<tr>
<th>Generic Name/ Brand Name</th>
<th>Brand</th>
<th>Target</th>
<th>Disease area studied</th>
</tr>
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<tbody>
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<tr>
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<td>TNF</td>
<td>RA, AS, JIA, PA, chronic uveitis</td>
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phase reaction. It is produced chiefly by activated macrophages, although it can be produced by many other cell types such as CD4+ lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons. A local increase in concentration of TNFα will cause the cardinal signs of inflammation to occur: heat, swelling, redness, pain and loss of function. Whereas high concentrations of TNFα induce shock-like symptoms, the prolonged exposure to low concentrations of TNFα can result in cachexia, a wasting syndrome. This can be found, for example, in cancer patients. TNFα has both a membrane bound form and a soluble form. TNF Receptor 1 is the main receptor for either form and it is ubiquitously expressed on all cells. Receptor 2 is only expressed on immune cells and only responds to membrane bound TNFα [84-86]. It is interesting fact, that in the experimental autoimmune uveitis model, neutralization of TNFα suppresses disease and mice deficient in TNF Receptor 1 are resistant to the development of uveitis [87, 88]. Chen et al. showed that in patients with anterior uveitis (HLA-B27, idiopathic uveitis, VKHS and Behcet’s uveitis) in aqueous humor elevated TNFα levels has identified [89]. In contrast, in one patients with intermediate uveitis aqueous levels of TNFα were similar to controls; however, serum TNFα was elevated [90].

Over the last two decades, advances in the understanding of the pathogenesis of inflammatory diseases, as well as improved biotechnology, have enabled selective targeting of the chemical mediators of diseases. Recently, a new class of drugs called biologics, that target the various mediators of the inflammation cascade, may potentially provide more effective and less toxic treatment [91]. There are a wide variety of new and emerging biological agents currently being used in the treatment of uveitis which has expanded the therapeutic horizons far beyond previous limitations [92].

A large number of scientific research gives us the opportunity to make quality conclusions about the possibility of using anti-interleukin therapies in some diseases, as evidenced by experimental and clinical studies (table 1) The most studied agents among the anti-interleukins in case of autoimmune diseases are Tocilizumab, Sirukumab, Secukinumab, Ixekizumab, Brodalumumab, Ustekinumab, Risankizumab and Fazakinumab. Golimumab, Intliximab, Adalimumab, Ustekinumab, Secukinumab were studied in noninfection uveitis Just few agents (Golimumab, Intliximab, Adalimumab, Ustekinumab, Secukinumab) are showed positive therapeutic effect on uveitis. Future randomized controlled trials are urgently needed to be conduct to define both benefits and risks of these agents in the treatment of the autoimmune uveitis.

**CONCLUSIONS**

1. AU is an inflammatory process of the uveal components due to an autoimmune reaction to self-antigens. It can present as an isolated entity or associated with a systemic autoimmune disease. AU may lead to significant visual limitation or total blindness.

2. The most important interleukins in the pathogenesis of AU are IL-6, IL-10, IL-17, IL-22, IL-23 and TNF-α.

3. Anti-interleukin therapy is partially described. Golimumab, Intliximab, Adalimumab, Ustekinumab, Secukinumab were studied in noninfection uveitis Just few agents (Golimumab, Intliximab, Adalimumab, Ustekinumab, Secukinumab) are showed positive therapeutic effect on uveitis. Future randomized controlled trials are urgently needed to be conduct to define both benefits and risks of these agents in the treatment of the autoimmune uveitis.

**REFERENCES**


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According to the order of the Authorship.

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