Literature Review

Biological therapy in treatment of uveitis. Contemporary trends

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Uveitis is a cause of blindness in about 10% of cases. According to many studies, TNF-α plays an important role in the development of uveitis. Anti-TNF-α are widely used in rheumatology and recently in ophthalmology. We carried out the analysis of literature on the use of anti-TNF-α. Large studies have been carried out and good results of anti-TNF-α usage in uveitis associated with JIA, Behcet's disease, ankylosing spondylarthropathies, sarcoidosis have been obtained. The profile of side effects and safety anti-TNF-α is quite acceptable for use in clinical practice. It is highly important that anti-TNF-α has a corticosteroid preserving effect which reduces side-effects associated with treatment, at this time has high efficacy of therapy.

Key-words:
uveitis, anti TNF, adalimumab

It is known that at least 150 diseases are associated with intraocular inflammation. Uveitis is a complicated intraocular inflammatory disease caused by several etiological factors and resulting in blindness in about 10 % of cases [1, 2, 3]. Some uveitides are caused by infectious agents, others can be associated with systemic autoimmune diseases, of which the most frequently observed ones are spondylarthropathy, sarcoidosis, and Behcet's disease [4].

In 1987 International Uveitis Study Group (IUSG) developed criteria based on the anatomic location of inflammation; and, in 2004, Standardization of Uveitis Nomenclature working group (SUN) analyzed the criteria, found them very useful, and added them with criteria of detection, duration, and the course of uveitis. Also, the SUN working group proposed a useful gradation for cell element amount and opalescence of the anterior chamber in uveitis [1, 5, 6]. Although the SUN classification has certain disadvantages (the method's subjectivism), this particular classification is used in most investigations [7].

Uveitis is an anomalous T-cell-mediated immune response to antigens in the eye that leads to acute or chronic deregulation of eye's normal immune response [8, 9]. Over the last years the role of anti-Tumour Necrosis Factor-α (TNF-α) and other interleukins in ocular inflammation pathogenesis has been reported [10]. TNF-α is an anti-inflammatory cytokine that plays a key role in inflammation response. In addition, apart from a normal inflammation response, TNF-α also induces pathologic immune response including excess inflammation and alteration. This cytokine is secreted by macrophages and lymphocytes and some non-immune cells [11]. The most important cascade effect of TNF receptor binding is a fast induction of cytokines (such as interleukin (IL)-1 and IL-6) followed by pro-inflammatory cascade which can result in the tissue damage and destruction [12]. High TNF levels are detected in intestinal tract of patients with inflammatory bowel disease and in synovial fluid of patients with rheumatoid arthritis (RA). In patients with uveitis, a high level of TNF-α has been detected in the blood serum and aqueous humor [13, 14, 15]. The activation of the T-cells increases production of interleukin-2 (IL2), gamma interferon and TNF-α. Herewith, autoimmune uveitis is mediated mostly by T-cells [16].

These observations have become the basis for using TNF-α inhibiting agents in uveitis treatment. Suppression of the TNF-α activity has appeared to be successful in the treatment of such systemic inflammatory diseases as rheumatoid arthritis and Crohn's disease [17]. Experimental studies have shown that TNF-α, being a pro-inflammatory cytokine, has induced uveitis in experimental animals

while injection of antibodies to TNF-α has suppressed the development of experimental autoimmune uveoretinitis in mice [18, 19]. In a lipopolyssacharide uveitis model, TNF-α and IL-1 have been determined as key mediators. And injection of TNF-α antagonist has reduced the number of infiltrating neutrophils by 50%, mononuclear cells by 58%, and protein leakage by 42% [20].

A multi discipline approach to diagnostics and treatment of patients with inflammatory eye diseases is crucially important, which can be explained by a number of reasons. Uveitis-related ophthalmologic examinations can help in revealing a basic systemic disease. In turn, general practitioners can participate in control of ophthalmology-prescribed treatment and reveal potential adverse effects of corticosteroids, immunosuppressive drugs, and new biological agents. A standardized protocol for treatment of non-infectious uveitis has not been developed yet. A therapy usually starts with corticosteroids and is followed by addition or change to other immunosuppressive agents [21]. However, using corticosteroids and immunosuppressants is associated with development of many complications, both local and systemic ones [22, 23]. Biologic agents such as adalimumab are increasingly being used because of their efficacy and corticosteroid-preserving effect, which can reduce adverse events related to treatment [24].

A number of studies have demonstrated successful outcomes of using TNF –α inhibitors for uveitis treatment [25, 26]. However, a retrospective character of most series of clinical trials, a small sample size, different terms of observation, the absence of standardized criteria for assessment of disease activity and disease outcome indices as well as reports on patients with different general diseases influence on the significance level in these studies [17].

Food and Drug Administration (FDA) Guidance for Industry (2004) specifies that "… a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effect to a defined exposure is known." Pharmacokinetics and pharmodynamics of TNF antagonists have been studied well enough. The main therapeutic purpose of TNF antagonist injections is elimination of TNF redundancy from blood circulation and inflammation sites. Pharmacokinetic features of TNF antagonists should be interpreted in the concept of the "therapeutic window" paradigm. When achieving the therapeutic purpose, TNF levels should not be reduced below physiologic values since that can compromise the individual's immunocompetency and increase opportunistic infection development [27, 28]. Adalimumab (Humira®; AbbVie Inc., North Chicago, IL, USA) is a recombinant human IgG1 monoclonal antibody, which contains only peptide sequences, specific for human TNF-α. It is produced using recombinant DNA technologies. The half-life of a single 40 mg dose is approximately 14 days. At the appropriate administration frequencies, adalimumab has a smooth and uniform time–concentration profile due to a slow absorption rate from the subcutaneous (SC) tissue and a slow elimination rate. Once adalimumab is administered SC, absorption from the SC tissue to the circulation begins, at which point the drug then is distributed to other tissues, binding both soluble and cell-bound TNF-α [24]. The dose of adalimumab depends on indications and patient's age and varies from 10 mg to 40 mg a week/two weeks [29].

In June 2016, adalimumab was approved by the US Food and Drug Administration (FDA) as the first noncorticosteroid medication for the treatment of noninfectious intermediate, posterior, and panuveitis in adults [24]. And in spring 2017, adalimumab was approved in Ukraine for the same indications for ophthalmological use [29]. Other indications for adalimumab use include RA; psoriatic arthritis; axial spondyloarthritis; ankylosing spondylitis; axial spondyloarthritis without radiographic confirmation of AR; Crohn's disease; ulcerative colitis; plaque psoriasis; hidradenitis suppurativa; juvenile idiopathic arthritis; polyarticular juvenile idiopathic arthritis; enthesitis-related arthritis; Crohn's disease in children; plaque psoriasis in children [29].

In children, uveitis usually develops in juvenile idiopathic arthritis (JIA). The incidence of JIA varies from 15 to 67% among all causes of pediatric uveitis. Besides, uveitis can precede the development of other symptoms and JIA diagnosing [25, 30].

In 2012, there was published a review with meta-analysis of results of TNF inhibitor application for JIA within the period between 2000 and 2012. The main criterion for efficacy assessment was reduced intraocular inflammation according to SUN classification. It was shown that summed response to treatment was 87% for adalimumab, 72% for infliximab, and 33% for etanercept. It was possible to discontinue corticosteroids or to reduce a dosage in 22 of 31 children receiving adalimumab. Besides, remission was achieved in 20 of 25 children. Infliximab and adalimumab were shown to have a similar positive effect on uveitis in JIA although randomized controlled investigations were required [31]. In 2015, results of the biggest first randomised controlled trial of adalimumab for juvenile idiopathic arthritis-associated uveitis. In this trial, children with active for juvenile idiopathic arthritis-associated uveitis, who had unsuccessfully been treated with methotrexate, were divided into groups receiving either placebo or adalimumab in addition to methotrexate. The follow-up period was two years. The trial was terminated due to obvious efficacy since intermediate analysis corresponded to prescribed trial termination regulations [32, 33]. Another open-label prospective trial compared adalimumab versus infliximab regarding the ability to maintain remission in children with refractory noninfectious uveitis. The trial enrolled 33 children, including 22 children with JIA. Adalimumab compared to infliximab was shown to be more efficacious in maintaining remission for three years. Herewith, there was no statistically significant difference between two

groups in regard to time to remission and time to steroid discontinuation [34]. Based on data of National Italian Registry, safety and efficacy of adalimumab and infliximab for the treatment of juvenile idiopathic arthritis-related anterior uveitis was evaluated. Adalimumab was shown to have a higher remission rate was observed (67.4% vs 42.8%). Also, the paper evidenced of adalimumab safety in JIA, based on three-year data of forty-three patients [35]. In 2014, a committee of the American Uveitis Society published recommendations that infliximab and adalimumab could be considered as second-line agents for the treatment of uveitis associated with juvenile arthritis [36].

Spondyloarthropathies is a diverse group of inflammatory arthritis similar in certain predisposing genetic (associated with the HLA-B2) and clinical features. The most widespread spondyloarthropathies include psoriatic arthritis, inflammatory bowel disease–associated spondyloarthropathy, reactive arthritis, and ankylosing spondylitis [37]. Since spondyloarthropathy is inhomogeneous, the prevalence of uveitis varied in this group and depended both on the type of spondyloarthropathy and disease duration. In spondyloarthropathy, uveitis had the highest incidence rates in ankylosing spondylitis (33%). Acute uveitis is noted in 90.5% and unilateral uveitis is noted in 87.3%. Recurrence occurs in 50.6% [38]. Adalimumab efficacy for active ankylosing spondylitis was evaluated in additional analysis of an earlier published multinational open-label clinical trial RHAPSODY ("Review of safety and effectiveness witH Adalimumab in Patients with active ankylosing SpOnDYlitis") in 1 250 patients. Trial results showed that adalimumab had a significant preventive effect on recurrence of anterior uveitis in patients with active ankylosing spondylitis including patients with anterior uveitis recurrence in a recent history [39]. Likewise for JIA and Behçet's disease, American Uveitis Society also provided recommendations for using infliximab and adalimumab in spondyloarthropathies. They could be considered as potential immunomodulatory agents for the treatment of severe ocular inflammatory conditions associated with seronegative spondyloarthropathy [36].

A large French multicenter study, published in 2015, reported the efficacy of anti-TNF agents in patients with severe and/or refractory manifestations of Behçet's disease. The study included 124 patients with impaired eyes being treated with adalimumab. Overall response (complete and partial) rate was 90.4%. Response rates were 96.3% in patients with severe and/or refractory ocular manifestations [40]. Another study on using adalimumab for uveitis with Behçet's disease showed that switching to adalimumab could achieve clinical remission in patients with infliximab-related allergic reactions or in patients having poor treatment response [41]. According to recommendations of American Association of Ophthalmology, TNF inhibitors, adalimumab and infliximab in particular, can be considered as a first-line therapy for ocular manifestations of Behçet's disease, contrary to JIA-associated uveitis where TNF inhibitors are considered as second-line agents [36].

A prospective study on efficacy of adalimumab in a series of cases (26 patients) of sarcoidosis patients with refractory posterior uveitis showed a decrease in intraocular inflammation in 85 % of patients and stabilization in the rest of patients (15%). Also, other sarcoidosis-related features including pulmonary function, serum parameters, and fatigability were improved [42].

Promising results were obtained in a recent open-label prospective pilot study of intravitreal adalimumab for noninfectious uveitis. There, adalimumab was injected in a dose of 1.5 mg at 0, 2, and then every 4 weeks. Total duration of the course was 26 weeks [43].

Treatment of refractory uveitis is a task when it is necessary to weigh the risk of blindness and complications with toxity of immunosuppressive and cytotoxic therapy [8]. Various studies on heterogenic groups of patients with refractory uveitis showed success of adalimumab [24]. A pilot prospective nonrandomized study demonstrated the efficacy and safety of adalimumab in treatment of various etiology refractory uveitis in 10 patients [44]. Also, adalimumab for refractory uveitis treatment was studied in a prospective, multicenter clinical trial. The trial enrolled 31 patients. Clinical response was observed in 68% of patients with refractory uveitis at 10 weeks after trial enrollment; and maintained in 39% after 1 year [45]. The largest so far prospective multicenter study enrolling 131 patients with refractory uveitis was held in Spaine. The study involved both adults and children. Most patients included in the study had Behçet's disease, JIA, intermediate uveitis or idiopathic uveitis. Uveitis was considered as refractory if treatment in patients receiving anti-inflammatory or immunosuppressive agents in the highest doses was insufficient for disease control maintenance, which was evidenced by at least 1 disease recurrence during a year before study enrollment, and if this required increased doses of oral corticosteroid drugs or other immunosuppressants including infliximab, etanercept, or daclizumab. The study showed that adalimumab decreased inflammation in the anterior chamber and the vitreous, reduced a thickness of the macular area and made it possible to reduce steroid requirement. At 6 months after study initiation, 111 patients (84.7%) managed to reduce immunosuppression load at least by 50% as compared to baseline. During 6 months, severe relapses were recorded only in 9 patients (6.9%). All uveitis patients, who were not able to achieve sufficient inflammation control with many drugs including prednisolone, infliximab, etanercept, daclizumab, ciclosporin, mycophenolate, chlorambucil, azathioprine, and methotrexate, had good responses to adalimumab which appeared in an apparent decrease of intraocular inflammation six months after treatment [17].

In 2017, a new paper on evaluation of adalimumab effect on various noninfectious inflammatory eye diseases was published. The study enrolled 32 patients. Almost half of the patients comprised patients with anterior

uveitis. Treatment outcomes were assessed according to corticosteroid-sparing effect, visual acuity and control of inflammation. At 16 months of therapy, inflammation became inactive in 47%, and oral prednisolone was reduced to less than 10 mg/day in 2 of 4 patients. On average, visual acuity increased decreased by 0.13 lines. Adalimumab was discontinued because of lack of efficacy only in 4 patients [46].

Warnings of TFN inhibitor-associated development of severe complication, i.g. infections and malignancies, are rather controversial [47]. Initial concern of malignancy development was based, in general, on a review of the FDA's Adverse Event Reporting System in 2009. Then, there were reported of 48 cases of malignancy in children and adolescents, most of whom had inflammatory bowel disease. However, it is quite difficult to determine a causal relationship since all but six patients were simultaneously administering other immunosuppressive agents (most commonly azathioprine or 6-mercaptopurine) [24]. In 2011, a systematic review and meta-analyses of many data basis including MEDLINE, EMBASE, Cochrane database of Systematic Reviews and American College of Rheumatology was performed to assess the risks of malignancy in rheumatoid arthritis patients treated with TNF-inhibitors. As a result, TNF-inhibitors were not shown to increase the risk of malignancy, particularly lymphoma. However, the risk of skin cancer, including melanoma, was increased [48]. In 2012, there was another review evaluating the risk of malignancy when treating with TNF-inhibitors. The risk of malignancy was not supported except non-melanoma skin cancer [49]. A study in a year of 2014 evaluated the efficacy and safety of adalimumab for treatment of patients with JIA (289 patients, both children and adults) and reported of its safety and high efficacy. No death, malignancies, opportunistic infections, demyelinating diseases, or lupus-like reactions were recorded [50].

A biological therapy broke through the treatment of rheumatoid pathology and noninfectious uveitis, in particular. Despite the fact that this direction is very new there are fairly large number of data on the efficacy and safety of TNF-inhibitors for noninfectious uveitis treatment. There have been conducted large enough trials and obtained good results of using TNF-inhibitors for JIA-associated uveitis, Behçet's disease, spondyloarthropathies, sarcoidosis. In some studies, a special focus is made on refractory uveitis resistant to corticosteroid and immunosuppressant therapies. In such conditions, TNF-inhibitors also behave rather well. TNF-inhibitor safety profile is acceptable enough to be used in clinical practice. What is very important, TNF-inhibitors have steroid-sparing effect, which makes it possible to reduce treatment-related adverse events when therapy is highly successful.

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