Immune Mechanisms, Clinical Features and Course of Non-infectious Uveitis

M.V. Sydorova,¹ Cand. Sc. (Med)
V.Ie. Kondratiuk,² Dr. Sc. (Med), Prof.
N.G. Bychkova,² Dr. Sc. (Med), Prof.

¹ LLC Medical Center Dobrobut-Poliklinik
² Bogomolets National Medical University
Kyiv (Ukraine)
E-mail: mariasydorova@gmail.com

Key words: uveitis, rheumatic diseases, the immune system, clinic, treatment

In most countries, the uveitides are responsible for 5-13% of all cases of blindness. Non-infectious uveitides are divided into those with and without known systemic association (both in children and adults). The Standardization of Uveitis Nomenclature (SUN) Working Group used anatomic location of the inflammation as an ontologic dimension, defined the criteria for the activity of inflammatory process, divided uveitis into groups and subgroups based on its course, and defined the tactical treatment algorithm. The uveitis development is based mainly on the alterations in the mechanisms of immunotolerance toward self ocular antigens, and on the emergence of autoagression toward these antigens. An alteration in immune tolerance to ocular antigens occurs if (1) regulatory CD25+ T cell subset is insufficient, and (2) B cells are activated with production of specific antibodies to the uveal tract structures. Systemic therapeutical agents for uveitis include corticosteroids, nonsteroidal anti-inflammatory drugs, cytostatics and immunobiologic agents. There are, however, no clinical guidelines involving the uveitis treatment approaches listed. The analysis of correlations between the degree of the alterations in the immune system and the course of uveitis will allow the development of the algorithm for the treatment of uveal inflammation entities.

Introduction

Since the uveitides are highly prevalent, tend to make restoration of visual functions difficult to evolve, and, in 76% of cases, follow a recurrent course, studying them is an issue that must be urgently addressed [1, 2, 3]. Uveitis ranks as the fourth most common blinding disease in most countries, behind macular degeneration, diabetic retinopathy and glaucoma, and is responsible for 5-13% of all cases of blindness [4, 5, 6]. It has an annual incidence of 12 to 15 per 100,000 in Ukraine [7], with a worldwide prevalence ranging from 36 to 40 per 100,000 adults [8; 9; 10]. The disease is acute, recurrent, or chronic in one third, 55-59%, and 4-6%, respectively, of uveitic patients. These forms, although different in clinical signs and course, are common in the basic pathogenesis involving alterations in immune tolerance to ocular antigens [7, 11, 12].

Uveitis results in temporary or permanent incapacitation and reduced visual acuity, thereby significantly influencing the quality of life. The main age group affected is 25-55 years. Although men and women are approximately equally affected, idiopathic uveitis is more common in women, whereas systemic disease associated uveitis is found mostly in men.

Classification of Uveitis

In 2005, the Standardization of Uveitis Nomenclature (SUN) Working Group (WG) presented the classification which divides uveitis into anterior uveitis (iritis, iridocyclitis and anterior cyclitis), intermediate uveitis (pars planitis, posterior cyclitis and hyalitis), posterior uveitis (chorioretinitis and neuroretinitis), and panuveitis [13]. Table 1 shows the anatomic uveitis classification as per the SUN WG. In 2008, the International Uveitis Study Group (IUSG) designed an etiology-based classification of uveitis (infectious, non-infectious and that presenting as masquerade syndrome) [14]. Non-infectious uveitides are divided into those with and without known systemic association (both in children and adults). The former include idiopathic uveitis, Fuchs’ syndrome, glaucomatocyclitic crisis, phacolytic uveitis, toxic uveitis, allergic uveitis, posttraumatic uveitis, and postoperative uveitis [3, 14], whereas the latter include rheumatic-associated (human leukocyte antigen (HLA) B-27-associated) uveitis, Behçet’s disease-associated (HLA B-5 and B51-associated) uveitis, and juvenile rheumatoid arthritis (JRA)-associated (HLA DR5-associated) uveitis [3, 14, 15].

In 1973, HLA-27 antigen was found to have the most significant HLA haplotype association with systemic rheumatic diseases. The protein encoded by HLA-27 is used in presentation of various antigens (including their self cell determinants) to effector T lymphocytes [12, 16]. As a result, there emerges a subset of active T cells which then migrate to the target tissue to start the inflammatory process; it can involve several organs or systems simultaneously and lead to arthritis, dermatitis and...
Uveitis. Elimination of autoaggressive T cells ensures immune tolerance to self-tissues [17, 18, 19].

Uveitides can be classified according to the course as acute, recurrent and chronic. Acute anterior uveitis is idiopathic (in 50% of cases), or may be associated with seronegative spondyloarthritis, Behçet's disease or Reiter's syndrome.

The term “recurrent uveitis” means that between attacks there is a period of inactivity without treatment of at least three months. The mean duration of an attack of acute uveitis or of a repeated episode is about two weeks, with the maximum up to four weeks. In about a half of uveitis patients, repeated episodes occur 2 to 3 times a year; however, such episodes have been reported to occur as late as 5 to 10 years after the initial episode [4, 20]. Recurrent uveitis is mostly HLA B-27-associated; the number of repeated episodes and disease activity in such cases correlate with the systemic inflammatory activity of [21, 22]. A torpid course of recurrent HLA-B27-positive uveitis eventually changing to the chronic form, although rare, has been reported, and mostly related to patients with enteropathy [3, 15, 20]. Recurrent uveitis without systemic and HLA association should be meticulously assayed for viral infection.

Recurrent uveitis and HLA-B27 antigen are important signs to raise clinical suspicion of association with a systemic disease. In uveitis associated with a systemic disease, repeated episodes occur 2 to 3 times a year, whereas the frequency and activity of uveitis correlate with joint syndrome scores, C-reactive protein level, erythrocyte sedimentation rate, and serum rheumatoid factor.

The most common systemic uveitis syndromes are seronegative spondylarthitis (Behçet's disease), reactive arthritis, rheumatoid arthritis, enteropathic arthritis and juvenile rheumatoid arthritis (JRA) [1, 5, 23]. Anterior uveitis occurs in 25-30% of patients with Behçet's disease, whereas conjunctivitis and recurrent uveitis occur in almost all (96%) and 11%, respectively, of those with Reiter's syndrome [5, 15, 24]. Anterior uveitis is found in 7-9% of patients with psoriatic arthritis [18, 25], whereas bilateral chronic uveitis (sometimes with asymmetric choroiditis) is found in 5-7% of patients with nonspecific ulcerative colitis [3, 4, 5]. JRA is the most common systemic disease associated with pediatric uveitis, accounting for 30% of all diagnoses, with as much as 3-4 recurrent episodes a year. In JRA children, the mean age at uveitis onset is 5.9 years, and that at arthritis onset is 4.8 years [5, 15, 23].

Chronic uveitis is found in 4-6% of uveitis patients; it is caused by persistent inflammation with relapse within three months after discontinuation of the treatment, and requires antiinflammatory management of acute attacks [2, 22]. Fuchs' syndrome, glaucomatocyclitic crisis, and JRA-associated uveitis are the most common chronic uveitis diseases.

### Mechanisms of immunotolerance toward ocular antigens

Uveitis pathogenesis is intimately associated with the immune reactions which occur when the mechanisms of immunotolerance toward self ocular antigens break down and autoaggression toward these antigens emerges [12, 26, 27]. The current opinion is that, in inflammatory diseases, the character of immune response depends on prevailing activation of specific T cell subsets which can migrate to uveal tract, synthesize various cytokines and trigger a local inflammatory response, with T and B cells playing a primary role [17, 28, 19]. Notwithstanding the presence of immunocompetent cells in all ocular tissues, normally, the immune response does

### Table 1. The SUN Working Group anatomic classification of uveitis

<table>
<thead>
<tr>
<th>Type</th>
<th>Primary Site of Inflammation</th>
<th>Includes (clinical forms of uveal inflammation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior uveitis</td>
<td>Anterior chamber</td>
<td>Iris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iridocyclitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anterior cyclitis</td>
</tr>
<tr>
<td>Intermediate uveitis</td>
<td>Vitreous</td>
<td>Pars planitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior cyclitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyalitis</td>
</tr>
<tr>
<td>Posterior uveitis</td>
<td>Retina or choroid</td>
<td>Focal, multifocal or diffuse choroiditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chorioretinitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retinochoroiditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retinitis</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>Anterior chamber, vitreous, and retina or choroid</td>
<td>All intraocular structures</td>
</tr>
</tbody>
</table>
not develop due to numerous immunotolerance mechanisms provided by nature both intraocularly and in immune supervisors.

The specificity of intraocular immune processes is associated with the absence of lymphatic vessels in the eye, a specific structure of the capillaries in the iridociliary zone and choroid, and the choroid acting as a repository of lymphoid elements [3, 29]. Macrophages, dendritic cells and T cells of the iris and choroid have been identified as self antigen or foreign antigen presenting cells (APC) [18, 26]. The ocular APCs, in contrast to those from other organs and systems, do not migrate to the regional lymph node, but travel with the blood to the thymus and spleen [18, 26] where there is a system to control and suppress the macrophages and lymphocytes which are autoreactive towards self ocular antigens [19; 30]. According to numerous investigators, immunotolerance toward ocular antigens is ensured, above all, by blood retinal barrier and blood-ocular barrier protection of ocular antigens from the immune system: in the early ontogenesis, T memory cells are formed in immune supervisors to destroy autoreactive cell subsets. Additionally, the ocular APCs have no major histocompatibility complex (MHC) class II molecules (only class I proteins are phylogenetically present) required for activation of T and B cells in the thymus and spleen [21; 28].

If however this protection fails and autoreactive T cells are formed and migrate to the interstitial space of the uveal tract, regulatory CD25+FOXP3+ T cells found in the intercellular spaces of the uveal tract can suppress a local delayed type hypersensitivity response [31, 32]. An additional local factor for suppressing the autoreactivity toward ocular antigens is the expression of major histocompatibility complex (MHC) class I molecules only, which inhibits APC presentation of eye-derived antigens to T cells.

The capacity for ocular and lymph node immune tolerance is however not always adequate to inhibit autoreactive T cell proliferation. The inherited susceptibility to autoimmune processes, when combined with antigenic mimicry between bacterial/viral endotoxins and synovium/uveal tract proteins, results in impairment of immune tolerance and production of antibodies against self-antigens [3, 8, 26].

Experimental uveitis studies

In 1910, Elschnig [34] was the first to develop a concept of an uveitogenic antigen in the retina. Later Wacker [35] used animal models to show that uveitis can be induced after intraocular injection of retinal emulsion. The following studies of initiation of uveitis were based on the use of purified retinal S-antigen (55 kDa). In different animals, this antigen was introduced parenterally into different body sites distant from the eye. As a result, an acute uveal inflammatory processes differing in level of activity emerged in all the animals [36]. Hankey et al. described and used another retinal antigen, interphotoreceptor retinoid binding protein (IRBP) (140 kDa), to induce uveitis experimentally. They found that that the inflammatory response induced by this protein had less apparent exudative manifestations and was more chronic than that induced by retinal S-antigen [37].
The more recent history of uveitis animal studies involves different models of parenteral immunization with the following ocular antigens with Freund's adjuvant: soluble retinal antigen (S-Ag), IRBP and melanin-associated antigen. Although the forms of uveitis differed in clinical features, in 96% of cases, the immunization-induced uveitis was acute, with no repeated episodes [32, 36, 37].

Shao et al. were the first to develop a successful animal model of recurrent uveitis [38]. Uveitogenic T cells were prepared from the draining lymph nodes after active immunization with R16 peptide R16, and introduced into the vitreous of naive rats. Over the following 80 days the recipient rats developed acute uveitis with several recurrences. The clinical score and duration of recurrent episodes depended on the number and activation status of T cells transferred, with these numbers and status regulated by the duration of T cell blast culturing in IL-2-containing medium prior to the injection. Thus, injection of a low (3 x 10^6) number of active T cells caused the early (3-4 days post injection) onset of active uveitis with frequent recurrences. Injection of a lower (0.5 x 10^6) number of active T cells caused the delayed (6-7 days post injection) onset of acute and monophasic uveitis with a low clinical score. The authors explain this as follows: active T cells find their way to the uveal tract and initiate inflammation; however, because the number of T cells is low, they are successfully eliminated and blocked by local defense mechanisms and cause no recurrent inflammation. There was no principal difference in histology between the acute monophasic uveitis and relapsing process: monocytic and lymphocytic infiltration was found in the presence of interstitial edema [38].

Immune homeostasis studies have been performed also with other activated T cell subsets, regulatory CD4+CD25+FoxP3-T cells in particular: their numbers were found to be reduced significantly in blood, lymphatic nodes, ocular tissue and joints of patients with systemic diseases and animal models [28, 31, 39]. These cells, when taken from the animals with the acute monophasic uveitis and introduced parenterally to those with recurrent uveitis, resulted in elimination of recurrences, i.e., the resolution of uveitis [31, 32]. The authors believe that such an effect of CD4+CD25+FoxP3-T cells is associated with their suppression of other activated T cells and produces IL10 and TGF-β2, both of which are capable of inhibiting the local inflammatory process in the uveal tract. Therefore, although some arms of the immunologic disorder and autoantibody production impairment in uveitis have been revealed, numerous issues related to the autoimmune processes common to the eye, joints, skin and mucosae are still unsolved, and there is some uncertainty related to the site of primary damage to immune tolerance. Additionally, the question is still open regarding the influence of the ocular-antigen autoreactive T cells on synovium, joint ligament, skin and mucosal structures. Answering this question requires analysis of both proinflammatory and inhibiting substances and the presence of specific T cell subsets in patients with acute and recurrent uveitis and different levels of inflammatory activity in the eye and joints. Correlation analysis of clinical and immunological data will allow identification of clinical and immunological risk factors for relapse of uveitis and the transition from acute to chronic uveal inflammation.

Clinical characteristics of uveitis

Anterior uveitis is usually unilateral; however, it is alternatively bilateral, albeit asymmetric, in 13-19% of cases, and simultaneously bilateral in up to 5% of cases [15, 20]. The clinical symptoms of uveitis correspond to the location of inflammation in the eye [3, 4, 22]. Thus, in anterior uveitis, patients usually complain of pain, photophobia, redness, blurred vision, and there is biomicroscopic evidence of cell detritus in the anterior chamber, iridal edema or spasm of the iridal sphincter muscle. Precipitates and fibrin deposit on the lens can result in alterations in aqueous humor dynamics with the development of complicated uveal glaucoma. Pain syndrome and injection of the globe are characteristic for all anterior uveitis entities because of (1) the blood supply type and (2) innervation of the iris and ciliary body by trigeminal fibers. The only exception to this principle is JRA-associated anterior uveitis: the inflammation is asymptomatic and painless, which makes it difficult to identify the disease correctly and provide effective treatment [3, 10, 16].

An example of success of the SUN WG was the development of inflammation grading schemas for anterior chamber cells (Table 2) and anterior chamber flare (Table 3). Each recurrence causes cell re-migration to the anterior chamber, and exudation of cytokines, growth factors, and fibrinogen to the anterior aqueous humor and tissues. All these things together result in alterations in aqueous humor dynamics, opacification of the optical media, and interstitial retinal edema, which significantly decreases the chances for complete visual recovery [8, 16, 23]. Nevertheless, under some circumstances, ophthalmologists miss some of the signs of inflammation during the routine examination of the anterior chamber. Fundus and peripheral retina examination should be performed with wide-angle contact lenses, and standard fundus photos should be used for grading vitreous cells [3, 15]. Acute anterior uveitis can be the only early clinical manifestation of a systemic disease, even with no pain in the lumbosacral spine and peripheral joints: in about one-fourth of patients with acute HLA-B27-associated uveitis, the initial examination reveals a systemic disease of connective tissue [12, 16, 17]. A typical unilateral
sudden onset uveitis with pain and photophobia is a manifestation of a systemic connective tissue disease with high clinical and laboratory activity scores.

A feature of the course of rheumatic disease-associated uveitis is the involvement of inflammation of the uveal tract and other ocular structures (the conjunctiva, retina, sclera etc.), which significantly worsens the prognosis [4, 10, 22]. Additionally, according to Drozdova [4], in 37% and 22% of rheumatoid and psoriatic arthritis patients, the involvement of both scleral inflammation and uveitis has resulted in the development of necrotizing scleritis and peripheral corneal ulcers, respectively. In patients with a systemic disease, generalized uveitis is diagnosed less often (3-5%) than other forms [3, 5, 20]. Among the posterior uveitis entities which have been described are diffuse chorioretinitis and focal chorioretinitis with macular edema and edema of the healthy optic nerve [3, 4, 7]. Evidence has been reported of the development of isolated posterior uveitis in Reiter’s disease presenting as focal central or peripheral chorioretinitis with the development of multiple small or solitary large foci and exudation under the retina, resulting in retinal detachment [10]. In enteropathic patients, ocular manifestations can present as serous retinal detachment resulting from diffuse choriocapillaris vasculitis [3].

JRA-associated uveitis has the following features: asymptomatic onset, chronic painless iris and ciliary body inflammation, with early clinical manifestation of limbal widening, retinal opacification at the lower limbus, and vitreous destruction and liquefaction [23]. In the later course, retinal crescent shaped opacities will appear at the palpebral fissure, at the 2-4 and 8-10 o’clock positions. The disease is characterized by the classic triad of ocular abnormalities (uveitis, band keratopathy, and complicated cataract) [15, 20]. JRA-associated uveitis may be accompanied by the inflammation of the healthy optic nerve which follows the pattern of papillitis and retrobulbar neuritis [10, 17].

There is, however, a category of patients with systemic connective tissue diseases who do not develop uveitis, despite high activity of the disease. This paradox might be explained by the genetic features of the HLA complex and high activity of immunosuppressive substances and immunoregulatory T cell subsets in the eye, lymph nodes and thymus.

Uveal tract inflammation certainly influences intraocular structures, and one of the first complications of anterior uveitis is uveitic cataract that is associated with alterations in the content of the aqueous and inflammatory detritus and fibrin deposit on the lens surface. The most increased lens opacification rate is found in chronic recurrent uveitis, and the increase in cataractogenesis might depend on whether glucocorticoids are administered as intravitreal implants and systemic therapy [3, 40, 41]. Alterations in choriocapillaris and retinal vascular circulation occur in uveitis entities having different locations. In anterior uveitis, there are dystrophic iris and sclerotic trabecular meshwork changes. Cystoid macular edema (CME) is found in 8-19% and every third of anterior uveitis and choroiditis patients, respectively. According to Uy et al. [16], CME occurs in 13.4% of HLA-B27-positive uveitis patients, and the prognosis for the development of retinal edema can be made based on the number of vitreous inflammatory cells. CME

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cells in the field (Field size is a 1x1mm slit beam)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>0.5+</td>
<td>1-5</td>
</tr>
<tr>
<td>1+</td>
<td>6-15</td>
</tr>
<tr>
<td>2+</td>
<td>16-25</td>
</tr>
<tr>
<td>3+</td>
<td>26-50</td>
</tr>
<tr>
<td>4+</td>
<td>&gt; 50</td>
</tr>
</tbody>
</table>

Table 3. Grading Scheme for Anterior Chamber Flare

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1+</td>
<td>Faint</td>
</tr>
<tr>
<td>2+</td>
<td>Moderate (iris and lens details clear)</td>
</tr>
<tr>
<td>3+</td>
<td>Marked (iris and lens details hazy)</td>
</tr>
<tr>
<td>4+</td>
<td>Intense (fibrin or plastic aqueous)</td>
</tr>
</tbody>
</table>
development is caused by alterations in blood-
ocular barrier and retinal vessels, and intraretinal
accumulation of exudates (in the retinal outer
plexiform layer and inner nuclear layer), which
results in significant loss of vision.

Nussenblatt affirms that CME is certainly
accompanied by the edema of a healthy optic
nerve, which may be subclinical and not diagnosed
during routine ocular examination: neuropathy will
be manifested only as enlargement of the blind spot
and reduced contrast sensitivity [3]. In the presence
of ocular hypotension and on the transition of
acute to chronic inflammation, CME is completed
with steady macular alterations, making the
vision loss irreversible. If inflammation involves
the choroid and retina, a rather large pathologic
zone appears, resulting in chorioretinal atrophy,
vitreous destruction and fibrosis, imminent retinal
detachment and phthisis bulbi [2,10].

**Treatment of non-infectious uveitis**

The goals of the therapy for uveitis are to
arrest ocular inflammation and save vision in the
patient. According to SUN WG guidelines, the
goals of chronic uveitis treatment are to reduce
the inflammatory activity and to stabilize visual
function, whereas the goal of acute and recurrent
uveitis treatment is to restore visual function [13].

Involvement of both local and systemic therapy
into any therapeutic approach to uveitis is a must.
Because autoreactive T cells, B cells, macrophages
and a complex of cytokines and immunoreactive
are essential for the pathogenesis of uveal
inflammation, pathogenetic treatment involves
glucocorticoids, nonsteroidal anti-inflammatory
drugs (NSAIDs), cytostatics and immunobiologic
agents.

In 1950, Gordon was the first to implement
and describe the use of glucocorticoids (GCs) for
treating ocular inflammation. Since that time, they
have been widely used for local therapy of patients
with uveitis where they can be administered via eye
drops, by periocular and intravitreal injections, and
as implants. In patients with inflammation refractory
to local therapy, and in those with recurrent and
chronic inflammation, GCs are administered
systemically. They suppress proliferation of T and
B cells, thus further inhibiting antibody production
and interleukine secretion. Clinically, it is presented
as reduced inflammatory infiltration and interstitial
edema in ocular tissues. The dosage and duration
of systemic therapy depends on the type and
resistance of inflammation. One should however
bear in mind that in complicated and refractory
uveitis cases, the most effective approach involves
using high-dose steroid therapy (60–80 mg/kg/day)
within a month, with the following decrease by 10
mg/day every 1–2 days for acute uveitis, or by 10
mg/day every 1–2 weeks for chronic inflammation
[4, 40, 42, 52].

For topical uveitis therapy, instillations of 0.1%
dexamethasone phosphate, 1% prednisolone
acetate, and 0.1% fluorometholone can be used.
Instillations of GC are most effective in anterior
uveitis patients, and have excellent penetration
even in aphakic and artiphakic eyes. Although the
frequency of instillation may vary from every hour
to every 24 hours, we must remember that potential
complications of GC instillation therapy, increased
intraocular pressure (IOP) and cataractogenesis,
are associated with the duration of GC treatment
and total daily doses [41,44].

The periocular route is an effective
route of administration for GCs. Steroid
(40 mg triamcinolone acetonide, 40-80 mg
methylprednisolone acetate, and 5 mg
betamethasone dipropionate) injections into the
orbital fat are performed through the upper or
lower access, and are most effective in intermediate
uveitis, posterior uveitis, and retinal vasculitis [40,
41, 44]. Aside from anti-inflammatory effect in
anterior uveal tract, GCs cause improvement in
CME and reduced production of vasculotropic
agents in retinal fibroblasts and glialocytes [16, 44].

If the treatment of uveitis with instillations
and periocular injections of GCs proves to be ineffective, it is reasonable administer systemic oral
therapy with prednisolone or methylprednisolone,
with the latter having less systemic GC side
effects due to the presence of methyl group in the
molecule. The initial daily prednisolone dose is
1.0–2.0 mg/kg, with the subsequent step-by-step
dose reduction (one step a fortnight). Patients
with acute posterior uveitis should initially receive
intravenous (IV) pulse methylprednisolone therapy
at a dose of 1 g/day. Later they should be switched
to peroral methylprednisolone at a dose of 1.0–1.5
mg/kg/day and subsequent tapering, depending
on the clinical response [3,41,42]. GCs can
produce systemic side effects manifesting as arterial
hypertension, hyperglycemia, peptic ulcer disease
and gastroesophageal reflux.

Topical cycloplegics are mandatory for successful
treatment of anterior uveitis. They are effective not
only in dilating the pupil and preventing posterior
synechiae formation, but also in treating ciliary
muscle spasm which presents as photophobia and
ciliary pain. In the management of uveitis, the
choice of cycloplegic agent (either a short-acting,
1% solution of cyclopentolate HCl, or a long-
acting, 1% solution of atropine sulphate) depends
on the type and duration of inflammation, amount
of fibrin deposit, and iris adhesion to the anterior
lens capsule [3,15].

When topical uveitis therapy alone proves to
be ineffective, different authors advocate
supplementing topical uveitis therapy with systemic
GCs, or cytostatics, or NSAIDs [2,40,41]. Thus,
Foster finds an oral NSAID to be effective as an
adjunct to topical therapy in uveitis, since this
approach has resulted in the arrest of uveal tract
inflammation in 7-10 days in 70% of such patients
If the inflammation fails to resolve or become chronic, one more adjunct, a cytostatic, can be used with topical instillation of GCs and an oral NSAID [15]. Lee [41] believes that, it is a GC that should be used as the first systemic therapy for acute uveitis. If the inflammation does not resolve does not resolve within a proper period, intravitreal steroids should be administered as adjuncts [41]. The multi-center comparative study for clinical efficacy of combined methotrexate and prednisolone, the Systemic Immunosuppressive Therapy for Eye Diseases Cohort (2008), found that only 36.1% of acute uveitis patients achieved long-term remission with a maintenance dose of prednisolone (10 mg/day), whereas the rest had to increase the dose or be switched to other therapies for that purpose. 76% of acute uveitis patients achieved a remission of at least a year with initial combined methotrexate and prednisolone treatment [45].

The era of cytostatic treatment for recurrent and chronic uveitis began in the mid 1980s with the treatment of JRA-associated uveitis [46]. Antimetabolites (methotrexate and azathioprine) and alkylating agents (cyclophosphamide or chlorambucil) were the first cytostatics to be produced in bulk; however, they had numerous systemic side effects associated with their non-selective influence on human cells. T and B cell (tacrolimus, mycophenolate mofetil) and Janus kinase (tofacitinib) inhibitors represent the next generation of cytostatics. Several multi-center comparison studies have investigated the treatment of uveitis with different groups of cytostatic agents, sometimes injected even subconjunctivally and intravitreally [17, 47, 48]. One must, however, remember that cytostatics should be prescribed by an immunologist, rheumatologist or general physician, and patients’ blood biochemistry should be measured trimonthly to monitor for hepatotoxicity, nephrotoxicity, hematopoietic and immune depression. NSAIDs are cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors, and can be used for uveitis locally or systemically. Indomethacin and diclofenac sodium can be applied as eye drops, and selective COX-2 inhibitors are a reasonable choice for systemic treatment, since only this proinflammatory enzyme is secreted at inflammatory sites. Such COX-2 selective inhibitors as meloxicam, rofecoxib, celecoxib valdecoxib have minimal side effects and are involved in most treatment regimens used for a systemic disorder [1, 41, 49]. Combined parenteral administration of NSAIDs and antioxidants has been advocated for the management of uveitis in an attempt to potentiate the effects of each of these agents and to improve clinical efficiency [41, 49].

If no improvement is achieved after a month of treatment for uveitis, intravitreal triamcinolone acetonide (0.1 mL – 4 mg) or betamethasone dipropionate (0.1 mL – 0.5 mg) may be a reasonable step. One-time injection of these agents is usually enough to suppress inflammation for a period of 3 to 6 months. Additionally, cases of associated macular edema rapidly resolve after triamcinolone acetonide, which is supported by the increase in visual acuity [15, 40]. However, side effects of intraocular GCs (such as an increase in IOP or/and in lens opacity) have been also observed: 25% of patients required administration of hypotensive eye drops, and, in 1-2% of patients, a reduction in IOP could be achieved only with filtration surgery [3]. In 2005, a fluocinolone intravitreal sustained drug-delivery implant became the first GC implant approved for the treatment of uveitis. Yet, with application of fluocinolone implants, 75% of cases have developed ocular hypertension, and 37% of cases required filtration surgery. A new biodegradable implant which contains 0.7 mg dexamethasone has been used more recently, resulting in significant improvement in CMA and affecting IOP only in 17% of cases [50].

Immunobiologic therapy is a separate branch of medicine used in uveitis treatment and is related to monoclonal antibodies specifically binding to specific receptors and cytokines both at the surface of immunocompetent cells and in serum. Since such antibody preparations are highly specific, they have no side effects related to corticosteroids and cytostatics, and their therapeutic effect is predictable both in type and intensity [38, 51, 52]. Etanercept, involving monoclonal antibodies against TNF-α, has become the first immunobiologic agent developed for the treatment of systemic disease associated uveitis. Infliximab, the next agent of the same group, differs from etanercept in that it neutralizes the biological activity of both serum soluble and transmembrane TNF-α, and has higher clinical efficiency and no side effects such as recurrence of uveitis [53]. The following generation of immunobiologic agents is chimeric (human and animal) immunoglobulins capable of inhibiting not only TNF but also IL-2, antigen CD20 and IL-1 receptors on immunocompetent cells [2, 54, 55]. Immunobiologic therapy, although comparable to pulse therapy with GKs in terms of rapidity and markedness of therapeutic effect, is associated with reduced immunity and the potential for opportunistic infections. Additionally, the scarcity of clinical trials of biological response modifiers for the treatment of uveitis and the very heterogeneity of uveitis have not yet made it possible to develop the clinical guidelines and standards of treatment. Finally, the anticytokine preparation dose providing the best balance between therapeutic effect and side effects, and optimal duration of immunobiologic therapy for uveitis are yet to be determined.

**Conclusion**

Notwithstanding a sufficient amount of data on different presentations of inflammatory uveal disease, both as a standalone inflammation and rheumatic-associated pathological condition, the general picture of the uveitides appears fragmented...
Literature Reviews

and poorly systematized. Furthermore, there is no uniform algorithmic approach to examination and treatment of rheumatic disease-associated uveitis. The analysis of correlations between ocular inflammation score and joint inflammation score, and between immune system status and the course of uveitis, and the course of spondyloarthritis, will allow the development of the algorithmic approach to the treatment involving GKs, immune correctors and immunobiologic agents.
References


