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REVIEW ARTICLE

Artur Bachta[1], Anna Byszewska[2], Robert Kruszewski[1], Marek Rękas[2], Mateusz Tłustochowicz[2], Witold Tłustochowicz[1]

[1]Klinika Chorób Wewnętrznych i Reumatologii Wojskowego Instytutu Medycznego w Warszawie
[2]Klinika Okulistyki Wojskowego Instytutu Medycznego w Warszawie

Uveitis in rheumatic diseases — therapeutic management

ABSTRACT

Treatment of uveitis requires a special approach because of the risk of significant complications, including loss of vision. The causes of the disease cannot always be determined, but a significant proportion of cases have a strong association with systemic connective tissue disorders, particularly spondyloarthropathies. This indicates the need for cooperation between an ophthalmologist and a rheumatologist in order to provide the patient with proper care. Several stages can be distinguished in the course of treatment, depending on the duration of therapy and the persistence of symptoms. Current research data justify the use of topical and systemic corticosteroids, as well as immunosuppressive drugs in subsequent lines of therapy. The article summarizes current recommendations and clinical observations, and presents a therapeutic regimen based on them.

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KEY WORDS: iritis; rheumatic disorders; glucocorticoids; disease-modifying antirheumatic drugs; uveitis

All structures of the eye can be involved in the course of rheumatic disorders, as part of extra-articular manifestations.

The most common is the dry eye syndrome, keratoconjunctivitis sicca, also known as Sjögren's syndrome. It is present in approximately 30% of patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Less commonly, isolated corneal inflammation (keratitis) occurs in the rare Cogan syndrome, but also in RA, SLE, or ANCA-associated (anti-neutrophil cytoplasmic antibody) vasculitis.

The second most common manifestation is uveitis, which occurs in a wide variety of disorders, including rheumatic ones. It should be noted that uveitis is not synonymous with a diagnosis of rheumatic disorder, although certain features in the clinical presentation of uveitis can suggest a rheumatic origin.

Episcleritis is rarely associated with rheumatic disorders, while scleritis is a manifestation in 40% of cases. It is most common in RA (up to 1% of patients) and ANCA-associated vasculitis (up to 15% of patients), but also in SLE, inflammatory bowel disease, and recurrent cartilage inflammation. The mainstay of therapy is aggressive treatment of the underlying condition with additional ophthalmic treatment. Retinal vasculitis is a fairly typical manifestation of Behçet's disease, and rarely occurs in systemic vasculitis or systemic lupus erythematosus. Retinal vein occlusion, which may accompany antiphospholipid syndrome, should also be kept in mind. Involvement of periorbital structures in the form of granulomas occurs in ANCA-associated vasculitis and optic nerve ischemia occurs in giant cell arteritis [1, 2].

Anatomically, uveitis can involve the anterior segment of the eye (anterior uveitis, which includes iritis, iridocyclitis, anterior cyclitis), the intermediate segment (intermediate uveitis, the vitreous — pars planitis, posterior cyclitis, and hyalitis), the posterior segment (posterior uveitis, the retina, choroid, or optic nerve — choroiditis, retinitis, chorioretinitis, neuroretinitis), and all of the above (panuve-

Address for correspondence:
Robert Kruszewski
Klinika Chorób Wewnętrznych
i Reumatologii, Wojskowy Instytut
Medyczny w Warszawie
Szaserów 128
04–141 Warszawa, Poland
e-mail: rkruszewski@wim.mil.pl

itis). In 75–90% of patients it affects the anterior segment of the uvea [1, 2].

In Polish studies, a definitive diagnosis was established in 76.3% of patients, of which specific ocular disorders accounted for 31.8% of cases, infections for 27.9%, and systemic disorders for only 16.8% (5.7% of patients had the HLA B27 antigen, all of whom had anterior uveitis). In 23.6% of the cases, a diagnosis could not be determined. It follows, therefore, that the primary obligation is to refer the patient to an ophthalmologist to rule out a specific or infectious cause [3]. Only after these have been excluded, an autoimmune disorder can be considered. The HLA B27 antigen is found in over 50% of patients in this group. Among systemic disorders, it is most commonly associated with ankylosing spondylitis (AS) and other spondyloarthropathies (SpA) (9.6% of cases), autoimmune thyroiditis (4.8%), inflammatory bowel disease (4.8%), sarcoidosis, juvenile idiopathic arthritis, and less commonly rheumatoid arthritis, multiple sclerosis, tubulointerstitial nephritis, vasculitis, Still's disease (no more than 1% of cases each) [4]. These diseases account for 17–30% of all cases of uveitis; the remaining inflammations are treated as idiopathic if no diagnosis is made despite targeted diagnostics. However, after years of observation, approximately 40% of patients in the last group are diagnosed with spondyloarthritis [5, 6].

Observations of large groups of patients with spondyloarthropathies showed that in 26.4% of cases, uveitis preceded the symptoms of SpA, in 58% it occurred during the first 10 years of the disease, and in 15% it appeared after 10 years. 24% of patients had more than 10 episodes, 25.4% had more than 2 exacerbations per year, and 13% had chronic uveitis that lasted over 3 months. Isolated iridocyclitis was found in 84% of patients, panuveitis in 8%, and isolated posterior uveitis only in 0.01%. 87% of patients had unilateral uveitis, 13% had bilateral uveitis, 45% had alternating uveitis. After many years in the course of the disease, complications that negatively affected the quality of vision occurred in 29% of cases, and these included: synechiae (18%), vitreous floaters (14%), cataracts (23%), glaucoma (9%), maculopathy (4%), band keratopathy (4%), optic nerve atrophy (2%), blindness (6%, and up to 10–20% in children). The presence of the HLA B27 antigen, psoriasis, and inflammatory bowel disease have been identified as independent predisposing factors for uveitis. Thus, it can be summarized that uveitis associated with SpA occurs mainly during the first 10 years of the disease, is predominantly unilateral, is recurrent, and impairs vision in about 1/3 of patients [7, 8].

Clinically, uveitis poses the greatest problem in children with juvenile idiopathic arthritis, as it occurs in 10–20% of cases, and in 70–75% of patients, it presents with scant symptoms and is chronic. Predisposing factors for this form of uveitis are early onset of arthritis, oligoarthritis, and an aggressive disease course. Only 25–30% have acute inflammation associated with the HLA B27 antigen, and arthritis takes the form of juvenile spondyloarthritis. As mentioned previously, it can lead to blindness in 10–20% of patients, which is why it is of special concern and has separate diagnostic and therapeutic recommendations from both EULAR (European League Against Rheumatism) and ACR (American College of Rheumatology). The EULAR recommendations, supplemented by later ACR recommendations, are presented in Tables 1, 2, and 3. The authors emphasize that the cessation of immunosuppressive treatment is a critical moment, which can provoke new uveitis as well as exacerbations of previously treated uveitis within 2 years [9, 10].

According to the recommendations, close cooperation between ophthalmologists and rheumatologists experienced in uveitis treatment is essential, especially in the absence of strictly developed criteria for assessing disease

Table 1. Recommendations for diagnosis of anterior uveitis in juvenile idiopathic arthritis (JIA) [9, 10]

1. All patients with suspected JIA should be screened for uveitis according to the current and audited protocol. The protocol should be used in all centers where children with suspected JIA are screened
2. The frequency of ophthalmologist visits must be based on disease activity and is up to the ophthalmologist's decision
3. Patients who have discontinued all immunosuppressive treatment have a high risk of new or recurrent uveitis, despite the prolonged remission. After discontinuing systemic immunosuppressive therapy, it is recommended that all JIA patients be examined by an ophthalmologist at least every 3 months for at least one year. The ACR recommends that during the treatment of uveitis, visits should be at least every 3 months in stable disease, within a month of every change in glucocorticoid treatment, and at least every 2 months after any change in immunosuppressive drug dosage

Table 2. Recommendations for the assessment of uveitis activity in patients with juvenile idiopathic arthritis (JIA) [9, 10]

4. Close communication between the ophthalmologist and pediatric rheumatologist is crucial in terms of changes in disease activity and responsibility for monitoring treatment
5. There is a need to develop common endpoints to facilitate decision-making during systemic treatment
6. There are currently no validated biomarkers useful for monitoring uveitis activity
7. There are currently no universally accepted definitions of inactive uveitis in JIA. The goal of treatment should be the absence of any cells in the anterior chamber. The presence of macular and/or disc edema, ocular hypotony, and rubeosis iridis may require anti-inflammatory treatment, even in the absence of cells in the anterior chamber
8. Experts recommend 2 years of inactive uveitis without topical steroids before tapering systemic immunosuppressants (both DMARDs and biologic therapy)

Table 3. Recommendations for the treatment of uveitis in the course of juvenile idiopathic arthritis (JIA) [9, 10]

9. Active uveitis in the course of JIA requires immediate treatment
10. The first line of treatment is topical steroids (prednisolone acetate or dexamethasone are preferred)
11. Topical and systemic NSAIDs have no significant effect on uveitis as a monotherapy but can be used as an adjunct treatment
12. Systemic immunosuppression in active uveitis is recommended if poor prognosis factors are identified during the first visit. The appearance of poor prognosis factors and lack of remission later in the course of the disease require systemic immunosuppression
13. Systemic immunosuppression is recommended if uveitis remission has not been achieved within 3 months or if there has been an exacerbation during steroid tapering
14. Methotrexate is a first-line drug as a systemic immunosuppressant; according to the ACR, subcutaneous administration is preferred
15. In the event of ineffectiveness or intolerance of methotrexate, addition or replacement with biologic drugs is recommended
16. In patients with persistent uveitis or resistant to DMARD treatment, mainly methotrexate, the introduction of biologic drugs is recommended (adalimumab > infliximab > golimumab)
17. Based on current data, etanercept should not be considered for treatment
18. If uveitis is resistant to first-line anti-TNF treatment, switching to another anti-TNF drug may be beneficial, even though the data comes from a small case series or preliminary studies
19. In case of ineffectiveness, consider testing for the presence of anti-drug antibodies and drug concentration. If the patient does not have anti-drug antibodies or the drug concentration is low, consider increasing the dose or shortening the intervals between doses
20. Tocilizumab, rituximab, and abatacept may be potential therapies in cases of resistance to prior anti-TNF treatments

activity or a definition of an inactive disease. It is important that the treatment is continued for an appropriate length of time, as tapering of systemic immunosuppression should not occur earlier than 2 years after discontinuation of topical steroids.

In uveitis in adults, the recommendations developed by the FOCUS Initiative should be followed regardless of etiology and after an infectious cause has been excluded. They omit the first line of treatment, which is oral and potentially systemic glucocorticoids (GCs), and focus on the issue of systemic immunosuppression in case GCs are ineffective [11]. The recommendations are presented in Table 4.

The indications for the introduction of systemic immunosuppressive treatment are similar to those in the recommendations for juvenile idiopathic arthritis. Unlike the latter, failure of at least one periocular administration of glucocorticosteroids and oral GCs treatment, their intolerance, or the need to discontinue them were taken into account in addition to topical treatment. The authors of the recommendations do not specify GC doses, referring to daily clinical practice. Recommendations in this regard were developed in 2000 and are still valid today (Tab. 5 and 6) [12].

The FOCUS Initiative does not specify which immunosuppressant drug should be selected. Effective choices include mycophenolate mofetil, tacrolimus, cyclosporine, azathioprine, methotrexate (MTX), and cyclophosphamide, although mycophenolate mofetil (not reimbursed by the National Health Service) and methotrexate seem to

Table 4. Indications for initiating systemic immunosuppressive therapy according to the FOCUS Initiative [11]

1. Ocular and anatomic Onset and course: — Acute disease that is sight threatening — Chronic persistent inflammation Exudative retinal detachment Posterior and macular involvement Binocular sight-threatening diseases
2. Therapeutic Regional failure to respond to: — Periocular steroid administration — Topical steroid administration in JIA Systemic therapy failure: — Active uveitis while taking doses of 30 mg or 0.5 mg/kg prednisone per day or more — Recurrence of uveitis after reduction of oral corticosteroid dose to less than 7–10 mg/day prednisone Steroid intolerance Need for steroid dose reduction
3. Severity (in adults) Visual acuity worse than 20/100 Increase in vitreous haze of grade > 2 Recurrence of cystoid macular edema Disease that impacts the quality of life
4. Severity in JIA, including prognostic factors for vision loss, such as: Poorer presenting visual acuity Posterior uveitis Uveitic complications of glaucoma Advanced cataract Macular edema Synechiae Severe band keratopathy Ocular hypotony Rubeosis iridis

Table 5. Topical treatment for the entire period of inflammation [12]

Prednisolone acetate 1% or dexamethasone 0.1%	1 drop every 1h for 1–3 days, then 1 drop every 2h; gradual dose tapering over 6 weeks to ≤ 3 drops per day
Methylprednisolone acetate	Periocular injections
Dexamethasone phosphate 2–4 mg	Subconjunctival or intravitreal injections
Triamcinolone acetate 20–40 mg	Periocular or intravitreal injections
Fluocinolone acetonide	Intravitreal drug-releasing implant
Short-acting mydriatics	Prevention of synechiae

Table 6. Recommended GC doses in inflammatory diseases of the uvea

Initial dose	1 mg/kg/d prednisone (may be preceded by 3 × 1 g *i.v.* methylprednisolone) for < 1 month
Dose tapering schedule	> 40 mg/d — decrease by 10 mg/d every 1–2 weeks 40–20 mg/d — decrease by 5 mg/d every 1–2 weeks 20–10 mg/d — decrease by 2.5 mg/d every 1–2 weeks < 10 mg/d — decrease by 1–2.5 mg/d every 1–4 weeks
Maintenance dose	≤ 10 mg/d
Additional recommendations	Monitoring visit every 3 months, calcium and vitamin D supplementation

be preferred [11]. The efficacy of methotrexate was shown by Bachta et al. However, the study involved a small study group. Out of 19 patients with recurrent acute anterior uveitis treated with 25 mg methotrexate per week, despite discontinuation of glucocorticoids, 16 patients (84%) had no symptom exacerbations over a 3-year follow-up (19–59 months), 3 patients had the interval between exacerbations increase from 4.8 months to 18.3 months, and the number of exacerbations in the entire group decreased from 2.12 patient/year to 0.11 patient/year ($p < 0.001$) [13].

Recommended doses of immunosuppressive drugs are shown in Table 7.

Biologic therapy should be considered in patients for whom standard treatment (corticosteroids + immunomodulators) is ineffective. Monoclonal anti-TNF antibodies are recommended — adalimumab (first choice), infliximab (less data available for certolizumab or golimumab), and also interferons. Etanercept and secukinumab are not recommended, as they neither decrease nor increase the number of exacerbations [14–16].

Table 7. Doses of immunosuppressive drugs used in uveitis treatment

Drug	Recommended dose
Methotrexate	25 mg/week, preferably subcutaneously
Mycophenolate mofetil	2–3 g/day
Azathioprine	2–3 mg/kg/day
Cyclosporine A	3–5 mg/kg/day (max. 10 mg/kg/day with serum concentration monitoring)
Cyclophosphamide	1–3 mg/kg/day (oral)
Tacrolimus, chlorambucil	According to the SmPC

Janus kinase inhibitors may be the future treatment of uveitis resistant to the therapies described above. At present, there are no randomized trials, but a meta-analysis by Wen et al. showed that out of 11 patients with various forms of active ocular involvement (6 with uveitis), despite biologic therapy, 8 patients achieved good outcomes in terms of ocular symptoms, regardless of the effects on joint symptoms. Adverse effects were rare, only 1 patient had to discontinue baricitinib due to leukopenia [17].

The authors of the recommendations emphasize that in case of treatment failure, the possibility of a different diagnosis (masquerade syndromes, e.g. ocular neoplasm, retinal degeneration), lack of patient cooperation, or an infectious cause of the inflammation. If the diagnosis is confirmed, the first step should be to optimize drug dosage, change to a different immunosuppressant, add periocular or intravitreal treatments, and also consider surgical or non-medical treatments (vitrectomy, cryotherapy) [11].

The management algorithm shown in Figure 1 should be useful in daily practice.

Treatment of uveitis should be initiated by an ophthalmologist, and the process itself can be divided into several stages, depending on the patient's clinical condition and response to medication (the so-called stepladder approach).

The first step is topical treatment with steroids, non-steroidal anti-inflammatory drugs, and short- and long-acting mydriatics. These drugs act on the anterior segment of the eye and do not penetrate further. Another route of drug administration is periocular steroid injections in slow-release (depot) form — methylprednisolone or triamcinolone.

In case of intense inflammation with macular edema, vitreous exudate or posterior segment involvement, drugs can also be administered intravitreously as a bridge therapy until remission is achieved with the use of systemic drugs. Long-acting, intravitreal implants that release small doses of steroids for 6–24 months are also available.

In severe inflammation, after an infectious cause has been excluded, systemic glucocorticoid therapy is initiated and, depending on the clinical condition of the patient, is administered intravenously (in most severe cases) or orally. The dose should be later reduced, depending on the clinical situation.

Although topically administered steroid drops are the first line of therapy, it is important to remember that chronic use can cause cataracts (rarely when < 3 drops per day are administered, perhaps not at all when < 2 drops) and post-steroid glaucoma (regardless of the dose). Systemic steroids can only be used in children in cases of severe inflammation with macular edema. In case of remission, GCs should be discontinued first, regardless of administration route.

The next stage of therapy is immunosuppressants. However, their effects are only visible after 6 weeks of use. It is therefore necessary to wait at least 3 months to assess the final effect.

Risk factors for poor prognosis requiring early use of systemic immunosuppression are the onset of uveitis before arthritis, posterior synechiae, male gender, band keratopathy, glaucoma, cataracts, hypotony, macular edema, dense vitreous floaters, and lack of remission despite topical treatment (patient requires at least 1–2 drops/day after 3 months of treatment). Systemic immunosuppression reduces the risk of vision loss by about 60%.

Methotrexate plays a leading role in immunosuppression, according to the ACR it should be always administered subcutaneously as its bioavailability is much higher than in oral preparations. Methotrexate allows for control of inflammation and discontinuation of GCs, improves, and maintains visual acuity. In case it is ineffective, the maximum tolerated dose should be administered before switching to another immunosuppressive drug.

Other DMARDs (leflunomide, mycophenolate, cyclosporine) may be used if MTX is ineffective or poorly tolerated.

According to the ACR, starting a combined MTX and anti-TNF treatment is recommended in severe cases [14]. In case of ineffective first-line immunosuppressant therapy (methotrexate, preferably subcutaneously; failed if after 3 months of therapy patient needs 1–2 GC drops/day), the addition of a biologic drug is recommended (monotherapy only in case of contraindications or intolerance of methotrexate), although there is no data that, as is the case in rheumatoid arthritis, it increases the efficacy and survival of biologic drugs. Anti-TNF antibodies are preferred; the use of a false receptor like etanercept or anti-IL-17 is not recommended. If the first anti-TNF drug is ineffective, it should be

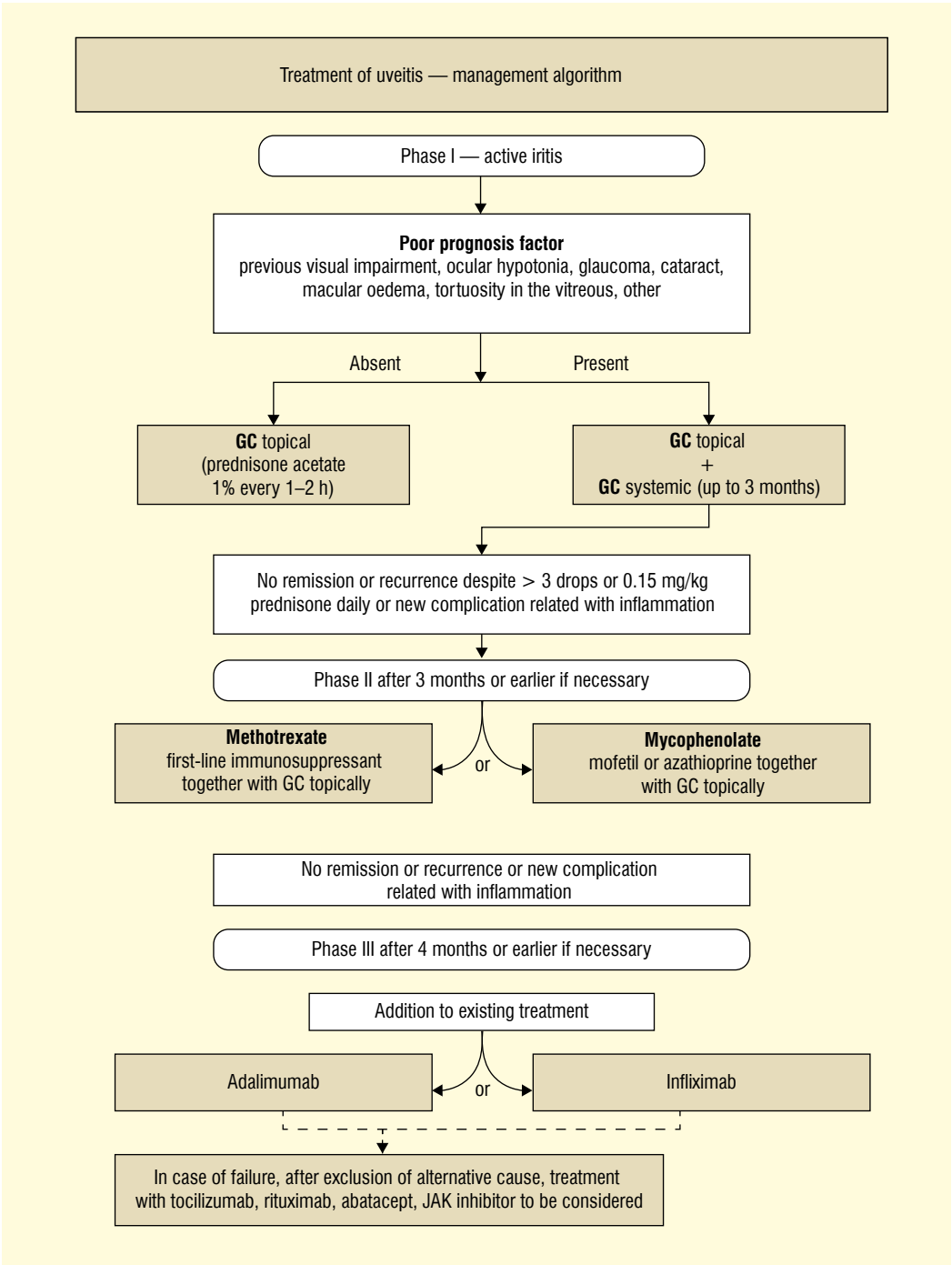

Figure 1. Management algorithm for uveitis treatment; GC — glucocorticoids

switched to another anti-TNF drug. The reason for its ineffectiveness should be considered. If the concentration of the drug is too low, the dose should be increased or intervals between doses shortened; if drug antibodies are present, switch it to a different one (combined treatment with methotrexate plays an important role in reducing the risk of their appearance). In case of anti-TNF antibody failure, tocilizumab, rituximab, and abatacept may be an option, but the ACR recommends they be used after at least 2 failed anti-TNF therapies.

In conclusion, uveitis can cause significant visual impairment, sometimes resulting in blindness, especially in children, and requires appropriate care. One of the more commonly identifiable causes may be juvenile idiopathic arthritis and spondyloarthropathies. Early diagnosis and appropriate treatment result in good outcomes in at least 60% of patients.

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