8 FUTURE PERSPECTIVES
CAN VISUAL OUTCOME AND TREATMENT IN SCLERITIS BE IMPROVED?

Recent papers on the outcome of patients with scleritis \(^1, 2\) do not report better visual outcomes than the results presented in our study. Improvement of visual outcome depends on early recognition, adequate assessment of the severity and tailored treatment of the scleritis and its complications. Early recognition can sometimes be difficult in posterior scleritis causing delay in diagnosis and treatment \(^3, 4\). For diagnosing posterior scleritis, ultrasound is necessary. Performing and interpreting ultrasound is not a standard competence of every ophthalmologist. Recent developments in easy and accessible imaging such as enhanced depth OCT may improve diagnostics in posterior scleritis \(^5, 6\). Studies on the immunopathology of necrotizing scleritis provide insight in the disease mechanism and perhaps a chance of more effective treatment \(^7, 8\). Studies on histopathological specimens, usually with chronic and severe end stage disease have revealed four types of scleritis, each with different disease associations, involved cell types, immune complexes and cytokines \(^7 - 10\). New treatments should be based upon the improved understanding of the immuno-pathogenesis and should ideally be targeted at specific mediators and cells of the immune system and be as local as possible. Still, almost all cases of scleritis need systemic treatment, although the temporally positive effect of subconjunctival injections with local steroids has been described \(^11, 12\). The deliberate use of financial resources in health care should also be considered in treating patients with scleritis. The optimal use of older proven medications such as methotrexate is of benefit for patients because effect and side-effects are well-known \(^13, 14\) and in many cases these medications are cheaper than newly developed drugs. A number of attempts have been made to develop and validate a clinically applicable grading system for the severity of scleritis \(^15, 16\). In our study, these grading systems could not be validated. Recent, another simplified grading system was proposed but not validated \(^17\). In the busy clinical ophthalmology practice, a clinical assessment should be practical and quick. The clinical picture, the severity of the patients complaints, the presence or absence of an underlying systemic disease and the necessary additional investigations should ideally guide diagnosis, treatment and thus prognosis. Questions such as how long treatment should be continued before dosage is tapered or treatment can be stopped still remain unanswered.
THE GREAT MASQUERADER STRIKES AGAIN. REMAINING QUESTIONS REGARDING OCULAR SYPHILIS.

Does HIV positivity have an impact on presentation, outcome and prognosis of ocular syphilis?

In earlier publications on ocular syphilis, HIV positivity has been associated with a more posteriorly located uveitis, neurosyphilis and a worse visual outcome 18-21. These findings could not be confirmed by us and other recent studies 22-25. This is probably due to the improved treatment and immune status of HIV-positive patients in which they react and respond similar to infection and treatment as HIV negative patients. This is in line with current IUSTI guidelines which state that HIV co-infected syphilitic patients should be treated as immunocompetent patients, except for those who have CD4+ cell counts of ≤ 350/µL 26.

What is the relationship between ocular syphilis and neurosyphilis?

There is an ongoing debate as to whether ocular syphilis should be classified as neurosyphilis. In particular in isolated anterior uveitis, with involvement of structures that are embryonically not derived from the neuroepithelium 27. Some suggest that structures derived from the neuroepithelium should be regarded as part of the brain and therefore retinitis and optic neuritis should be classified as neurosyphilis 24,28. Others suggest that involvement of any eye structure, irrespective of its embryogenesis, should be managed identically to neurosyphilis 24, 28. This advice is adopted by the current guidelines on the treatment of ocular syphilis 26 wherein- regardless of the anatomical location of the uveitis - a treatment regimen identical to that of neurosyphilis is advised. The diagnosis of neurosyphilis depends on a combination of positive serologic test results, neurologic signs and symptoms and cerebrospinal fluid (CSF) abnormalities 26, 27. Up to 60% of patients with ocular syphilis will have cerebrospinal fluid (CSF) abnormalities 27 and there is no definite evidence that anterior uveitis is associated with a decreased risk of having abnormal CSF compared with posterior uveitis 24. CSF examination can be helpful in the differential diagnosis by excluding other pathologies and if found to be abnormal and consistent with neurosyphilis, appropriate follow-up to ensure all markers return to acceptable levels is required 26.

Can syphilis screening and confirmatory tests be improved?

For syphilis screening, serologic tests are used. If a screening test is found to be positive, a confirmatory test, in most cases an enzyme immunoassay (EIA), chemiluminescence immunoassay (CIA) or immunoblot is used 24. Different tests are available for the diagnosis and staging of syphilis. Untreated syphilis is divided into four stages, ocular syphilis may occur in all stages, except in the primary stage. Serologic screening tests are divided into nontreponemal and treponemal tests. Nontreponemal are not specific for treponemal infection and are generally used to monitor responses to treatment or to indicate new infections in patients...
with possible syphilis re-infection. False-positive nontreponemal tests have been associated with multiple conditions 29 and nontreponemal test results might be falsely negative in longstanding latent infection 30. Treponemal tests, which are based on antigens derived from T. pallidum, have higher sensitivity and specificity than nontreponemal tests. However, because treponemal antibodies may survive a lifetime after infection, they cannot distinguish between current infection and past infection and they cannot be used for evaluation of therapeutic effect 29. Analysis of ocular fluid for treponemal DNA has been reported to be helpful for diagnosis in some case reports 31-34. However it is not well-validated for aqueous and vitreous humor and neither sensitivity nor specificity are clear 31. Ongoing research is aimed at developing new generations of immunotests with advanced diagnostic capabilities which will hopefully be able to detect immunoreactivity in different syphilis stages and a decreasing immune response after the infection regresses 25.

DEVELOPMENTS IN UNDERSTANDING OF THE PATHOGENESIS AND POSSIBLE THERAPEUTIC APPROACHES IN RETINAL DYSTROPHIES

Retinal dystrophies are a rare group of retinal diseases and a major cause of incurable blindness in the western world. Retinal dystrophies have remained largely untreatable due to the challenges posed by their genetic heterogeneity and due to lacunae in the understanding of the mechanisms of these diseases 36. Recent developments in research have improved knowledge of the pathogenesis and mutations in over 200 genes are now known to be involved in the pathogenesis of this group of diseases 36. Several pathways of disease are likely to be involved in retinal dystrophies depending on the genes involved, and may require different therapeutic approaches for genetically different groups of patients 37. Therapeutic approaches that are being explored in clinical trials include dietary supplements of carotenoids and related compounds to promote retinal function 38, 39 administration of neurotrophic factors 40-42 gene replacement therapy 43-47, and the use of prosthetic devices 48, 49. Some of these trials have so far indicated safety and efficacy in humans of the treatments tested 36, 38-49. These results are promising and future challenges in research and treatment are focused on further unraveling of the heterogenic disease mechanisms and safety and efficacy of its possible treatments.

THE ROLE OF MTX IN THE ERA OF EXPANDING TREATMENT OPTIONS IN PEDIATRIC NON-INFECTIONOUS UVEITIS

For decades, MTX monotherapy has been the cornerstone of systemic treatment for auto-immune ocular inflammatory disease (OID) 13, 14, 50. This is mainly based upon its well-known safety profile and its effectiveness in about 70 % of patients with OID 14, 50. Treatment options for patients suffering from auto-immune OID
disease have expanded profoundly over the last decades and have been proven safe and effective\textsuperscript{51-53}. In the treatment of adult rheumatoid arthritis (RA) patients there are concerns that since the introduction and advent of TNF inhibitors MTX is less aggressively dosed, duration of use is shorter and a more rapid escalation to biologicals is made\textsuperscript{54, 55}. This was confirmed by a large study performed in adult RA patients\textsuperscript{56}. In this study, a large part of the patients switched to other, more expensive treatments with less well known efficacy and long term safety. In children with non-infectious uveitis, ineffectiveness or side effects are common reasons for switching to other forms or treatment. If side effects such as nausea, needle phobia or elevated liver enzymes can be managed, MTX treatment can be continued. The frequency and consequences of MTX-induced nausea has probably the greatest impact in clinical practice and frequently leads to non-adherence or discontinuation of MTX\textsuperscript{57-59}. Gastrointestinal (GI) related symptoms in children with JIA and treated with MTX can be evaluated with the Methotrexate Intolerance Severity Score (MISIS)\textsuperscript{58} or the Gastrointestinal Symptom Score for Kids (GISSK)\textsuperscript{60}. In some cases, switching to oral or subcutaneous administration solves the GI symptoms. In others patients, co-medication with anti-emetics or behavioral interventions for MTX-induced anticipatory nausea can be tried. In case of ineffectiveness, a switch to another medication is inevitable, although this can sometimes be combined with a lower dose of MTX in combination with another route of administration. This concomitant use of MTX during treatment with certain TNF-α inhibitors has been demonstrated to decrease the formation of antidrug antibodies (immunogenicity)\textsuperscript{61}. These anti-drug antibodies can be functionally neutralizing and thereby directly affect treatment efficacy. Prevention or reduction of immunogenicity, results in higher systemic exposure and enhanced clinical efficacy\textsuperscript{62-64}. Next to that, combination therapy may enable dose reductions of individual agents, thereby decreasing toxicity and improving tolerability and compliance\textsuperscript{61}. MTX remains the anchor DMARD (disease modifying anti rheumatic drug) for OID, it is effective, well-tolerated, economical and universally recommended by all treatment guidelines and it can optimize treatment with TNF-α inhibitors\textsuperscript{50-52, 56, 61, 65, 66}.

**A HOLISTIC APPROACH IN THE TREATMENT OF PEDIATRIC UVEITIS**

Patients with chronic diseases are suffering from the direct and indirect consequences of their disease\textsuperscript{67}. Physical and psychosocial consequences not directly related to the disease are of importance for assessment and comparison of the level at which a patient is functioning despite their illness. Treatment goals in chronic disease should therefore include patient reported outcomes with regard to physical and psychosocial functioning next to satisfactory medical outcome. Questionnaires used for testing quality of life (QoL) should incorporate questions addressing visual function for testing vision related QoL and these questionnaires
should be suitable and validated for use in children with uveitis 68, 69. In roughly 40% of the children, the uveitis is related to JIA. From the literature, we know that patients with JIA and other chronic diseases are physically less active and have reduced physical fitness levels 70, 71. Also, lower health-related quality of life (HR QoL) and more fatigue is reported for adult and pediatric patients with uveitis and other auto-immune diseases 68, 69, 72-82. Further, it is known that in auto-immune disease physical activity performed in the appropriate way is safe, improves QoL, decreases fatigue and has a number of positive effects on the immune system 82. Further research focused on the pathophysiology of non-infectious uveitis is needed to assess whether the inflammation in uveitis is really limited to the eye or may extend itself systemically and on what aspects JIA-patients with uveitis are different from JIA-patients without uveitis 79, 84. Finally, children with uveitis are treated in a multidisciplinary approach. Patients and their parents benefit from optimal communication between all involved physicians 65. Next to that, creating awareness for a healthy lifestyle, encouraging hobbies or sports activities and being a role model are recommended for every involved physician.

DEVELOPMENTS IN PEDIATRIC UVEITIC GLAUCOMA

In uveitic glaucoma, IOP’s are generally unacceptable high on maximal medication and the only solution to prevent irreversible visual loss or blindness is glaucoma surgery. Anatomical and biochemical changes in the anterior part of the eye related to the inflammation and its treatment are responsible for the rise in IOP. An important factor is the ocular-hypertensive response to topical steroids. This response is well documented in children and is known to occur more frequently, severely and rapidly than reported in adults 85, 86. Unfortunately, avoidance of topical steroids is in most cases no option because alternative eye drops with equal effectiveness are currently not available 87. Other, more experimental, local treatment alternatives such as MTX, infliximab and sirolimus should be administered by frequent intravitreal injection. 88 - 92. This route of administration is much more invasive and too little is known about efficacy and safety. This in contrast to systemic immune suppression wherein safety and efficacy have been shown extensively 93, 94. In one study, a delay in time to necessary cataract extraction with 3.5 years is reported in patients treated early with systemic MTX 95. But, evidence supporting starting or increasing systemic immune suppression in an attempt to reduce topical steroids and thus reducing or preventing the ocular-hypertensive response to topical steroids is lacking in the current literature. As shown in our study and by others, children with JIA-uveitis 96, 97 are more prone to develop secondary glaucoma. Recent studies suggest that neuro-inflammation is a contributing factor for glaucomatous neurodegeneration 98, 99. It is suggested that IOP elevation can activate inflammatory responses and production of cytokines and chemokines especially by microglia 98, 99.
Microglial activation is reported to be one of the first events in glaucomatous neural damage occurring prior to retinal ganglion cell loss. This neuro-inflammatory reaction shows overlap and similarities with reported neuro-inflammation in autoimmune conditions. These findings support the theory that neuro-inflammation increases the occurrence of glaucoma in patients with JIA-uveitis. Further research is necessary to unravel these disease pathways and possible treatment options. A number of different surgical techniques are used in the surgical management of medically uncontrollable high IOP. The traditional procedure of first choice is a trabeculectomy. If trabeculectomy fails or is not possible, aqueous shunts such as Ahmed, Baerveldt or Molteno implants can be used. In the literature, slightly lower IOP and lower complication rates are reported for the Baerveldt implant when compared to trabeculectomy and Molteno and Ahmed implants. Recent publications in small groups of uveitis patients report positive results from angle surgery procedures like goniotomy and trabeculotomy. The latter have the advantage that in case of ineffectiveness or complications they can be followed by implant surgery. Next to that, in angle surgery systemic immune suppressives can be continued. In contrast, in our clinic, patients who are planned for glaucoma implant surgery are advised to stop MTX two months prior to surgery, because MTX gives a higher chance of hypotonia due to less marked encapsulation of the implant. This procedure is based upon our own clinical experience of postoperative hypotonia and on the results of in vitro studies showing that MTX inhibits the proliferation of fibroblasts and induces their apoptosis.

Developments and insights in disease mechanisms, pharmacological and surgical treatments in pediatric uveitis glaucoma are promising. But, the disease course and its treatment remain complex and challenging for the clinician, patients and their parents.

In conclusion, the results of the research presented in this thesis emphasize the need for a tailored and multidisciplinary treatment approach in inflammatory eye diseases. Ideally, treatment should be based upon disease mechanisms, location of the inflammation, necessary treatment of ocular complications, presence of underlying systemic disease, effectiveness and side-effects of medication, effects on general well-being and functioning, judicious use of available financial resources and individual patient characteristics.
REFERENCES


