1 GENERAL INTRODUCTION
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Scleritis and uveitis are inflammatory eye-diseases which can threaten vision. In general, inflammatory eye-diseases can be triggered by auto-immune disease, infections, masquerade syndromes presenting as inflammatory eye-disease, medication, trauma and repeated ocular surgery. Scleritis and uveitis can occur at any age so the burden of visual loss, the uncertain prognosis of the eye-disease and its complications and the side-effects of treatment on daily life are profound.

Epidemiology of scleritis

Published epidemiologic data about the incidence and prevalence of scleritis in adults is scarce. The estimated reported annual incidence of scleritis is between 4 to 6 per 100,000 person-years. This scarcity of epidemiologic data confirms that scleritis is a rare condition. Studies on scleritis are hampered by disease severity, its rarity and the intense pain reported by most patients suffering from scleritis. Scleritis as an expression of underlying auto-immune disease such as rheumatoid arthritis or granulomatosis with polyangiitis is the most common. Loss of vision is more common in eyes with posterior or necrotizing scleritis and a loss of 2 or more lines Snellen visual acuity despite optimal treatment has been noted in 30% of patients. Patients with severe disease often have multiple causes for loss of visual function, such as corneal involvement, cataract, glaucoma, maculopathy, papilledema or retinal detachment. Information about the incidence of scleritis in children is even less available. One study reported that 1.2% of all scleritis cases are found in children and others reported a female preponderance. Among subtypes, posterior scleritis is relatively common in children. Although there is no literature supporting this, outcome and disease development in pediatric scleritis are probably worse than outcome and disease development in adults. It seems likely that children with scleritis have a greater risk of visual loss due to the higher reported incidence of posterior scleritis and a greater risk of ocular complications related to longer life expectancy and disease duration in this chronic disease. Pharmacological developments in the treatment of auto-immune diseases such as rheumatoid arthritis are promising. Hopefully, patients with scleritis can benefit from this.

Epidemiology of uveitis

The overall reported annual incidence of uveitis is between 17 and 52 per 100,000 person-years and the prevalence is 38 to 714 cases per 100,000 persons. The variation in reported incidences and prevalences between publications is due to variations worldwide in several predisposing factors such as genetic, geographic, social and environmental factors. It has been estimated that uveitis accounts for about 10% of the visual handicap in the Western world, and up to 35% of all uveitis patients have been reported to suffer significant visual impairment or...
legal blindness. More recent publications on long-term clinical outcome in adults show more favorable visual outcomes due to improved treatment options. Uveitis in children is relatively uncommon and accounts for 5 to 10% of the total uveitis population. The reported annual incidence is 4 per 100,000 population and the prevalence 28 per 100,000 population. It is estimated that in the western world 17-28% of the children with uveitis become legally blind in one eye. Uveitis in childhood offers specific challenges when compared to uveitis in adults. The risk of poorer visual outcome is possibly greater in children when compared to adults. In most cases of uveitis in childhood the uveitis is related to juvenile idiopathic arthritis (JIA). The onset is insidious in most cases of JIA-uveitis and diagnosis is often delayed resulting in deterioration of the visual prognosis. Ocular complications such as cataract, glaucoma, band keratopathy and amblyopia may silently develop and are reported in up to 50% of children with uveitis.

### Diagnosis of inflammatory eye disease.

Early diagnosis of inflammatory eye disease and start of adequate therapy are the most important factors improving visual outcome. Diagnosis of scleritis is usually suspected from the clinical history with severe pain as a hallmark, and is confirmed by its characteristic clinical signs. Scleritis is classified by its anatomic location and clinical appearance (table 1). In case of posterior scleritis clinical signs may be less obvious and evaluation by ultrasonography or other imaging techniques are necessary. The main differential diagnosis of scleritis is episcleritis. Episcleritis is usually a mild non-vision threatening form of inflammation of the superficial episcleral tissue, for which no treatment is required in most cases. The diagnosis in uveitis is more difficult. There are various etiologies and the systemic associations of uveitis differ between adults and children. In general, the differential diagnosis of uveitis is based upon the anatomical location of the inflammation (Table 2), the recognition of specific ophthalmic clinical signs and the outcome of the different serological tests and – when necessary – outcome of analysis of intraocular fluid.

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<thead>
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<th>Table 1. Classification of scleritis</th>
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<td><strong>Anterior scleritis</strong></td>
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<td>Diffuse</td>
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<td>Necrotizing</td>
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<td>Scleromalacia</td>
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<td><strong>Posterior scleritis (incl SINS)</strong></td>
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<td>Surgery induced (SINS)</td>
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<td><strong>Panscleritis (anterior + posterior)</strong></td>
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*SINS = surgically-induced necrotizing scleritis*
Treatment in general
The treatment of inflammatory eye diseases depends on the etiology and possible underlying disease. In many cases, the uveitis or scleritis are part of an autoimmune process. The treatment is aimed at suppressing the inflammatory response and limiting the resulting damage. For scleritis, local therapy is insufficient and systemic therapy is required, although in some cases of non-infectious anterior scleritis a subconjunctival injection with corticosteroids can be given 26. In general, nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed as the first step in the treatment of scleritis. In case of unsatisfactory therapeutic response, the next step is administration of oral corticosteroids at high doses for a short period of time. If prolonged treatment is necessary or in case of contraindications for corticosteroids, steroidsparing immunosuppressive drugs such as methotrexate (MTX), mycophenolate mofetil (MMF), azathioprine, cyclosporine, and sometimes cyclophosphamide are used, often in combination with low-dose corticosteroids. In refractory or therapy resistant ocular inflammatory eye disease, tumor necrosis factor (TNF-\(\alpha\)) antagonists such as infliximab and adalimumab or chimeric monoclonal antibodies targeted on B lymphocytes like rituximab, are increasingly being used, 27 - 31 sometimes in combination with other steroid- sparing immunosuppressive drugs.

For the treatment of uveitis, the first step in treatment are topical corticosteroids. If these are insufficient, local corticosteroid injections can be considered. Systemic corticosteroids are started in the case of severe uveitis or in case of failure of topical therapy. In case of chronic uveitis or underlying systemic disease, steroid-sparing immunosuppressive medication is required to maintain disease remission and to avoid the side effects of prolonged oral corticosteroids. Methotrexate (MTX) is the steroid sparing immunosuppressive agent of first choice in almost all cases of non-infectious uveitis 32 - 34. If MTX is ineffective or side effects occur, a switch towards another steroid sparing immunosuppressive agent such as mycophenolate mofetil (MMF), azathioprine or cyclosporine can be made. In persistent active uveitis despite treatment, tumor necrosis factor (TNF-\(\alpha\)) antagonists such as infliximab and adalimumab and others are increasingly being used 20, 35. When the scleritis or uveitis has developed as a result of an infectious process, the primary treatment is aimed at the infectious pathogens. When the treatment against the infectious process starts, systemic immune suppression may additionally be necessary to reduce the inflammatory response - and thus reduce the resulting damage.

Outcome
Inflammatory eye diseases are still a leading cause of visual impairment 26, 37. The main goal of the treatment of inflammatory eye diseases is to maintain visual function by reducing the inflammation and by the timely treatment of complications such as glaucoma, macular edema, and cataract 14, 35. Visual
outcome is measured as visual acuity. In case of posterior and panuveitis or secondary glaucoma, visual outcome can be impaired by visual field loss through loss of function in the affected tissues by the inflammation itself or by damage to the optic nerve as a result of high intra-ocular pressure. Loss of vision and side effects of systemic treatment are related to loss of health-related quality of life (HR QoL) in children and adults with uveitis. It has been suggested that the effects of uveitis on HR QoL in children are similar to those of children with other chronic conditions and the disease burden of uveitis can affect quality of life even when there is no loss of vision.

Aims and outline of this thesis
The aim of this thesis is to improve the care for patients with inflammatory eye disease on a number of aspects. This thesis consists of 2 parts and describes studies on both the diagnostic and therapeutic challenges in the treatment and counseling of patients with inflammatory eye disease. In the first part the focus is on scleritis and uveitis in the adult population, the second part concerns uveitis in childhood. The first 3 chapters are about improving the diagnostic and therapeutic process in adult patients with rare inflammatory eye diseases such as scleritis, syphilitic uveitis and retinal dystrophies masquerading as intermediate uveitis. In the 3 chapters of the second part, efficacy and outcomes of different dosages of methotrexate (MTX) in non-infectious pediatric uveitis are evaluated, physical and psychosocial outcomes in pediatric uveitis are analyzed and risk factors for the development of secondary glaucoma in childhood uveitis are addressed.

Scleritis
As mentioned before, scleritis is a rare disease. Because of this and the prompt need for treatment, there is a paucity in the literature regarding studies predicting disease-course and visual outcome, and offering guidelines for treatment. Therefore, chapter 2 describes patient characteristics, visual outcome, ocular complications and treatment results in a cohort of 104 patients with scleritis from 2 tertiary uveitis centers in the Netherlands. Also, predictors for a worse visual outcome, the need for steroid-sparing immunosuppressive treatment and a longer period of active disease were analyzed.

Ocular syphilis
Ocular syphilis can mimic a wide range of ocular disorders and is a rare sexually transmitted infection (STI) nowadays accounting for 1% to 2% of all uveitis patients. In the pre-antibiotic era, syphilis was more common. Due to the improved screening and treatment programs it almost disappeared in the western world. Data on the epidemiology of STI needs to be interpreted carefully because they are influenced by multiple factors. The incidence and prevalence of the infection are affected by biological factors, such as transmission probability, infection duration and loss of protective immunity such as in HIV-positive
patients. Also, changes in sexual attitudes and behaviors and developments in service provision, treatment, interventions, diagnostic technologies and surveillance affect incidence and prevalence. Ocular syphilis is a treatable disease and because of the changes in epidemiology and unpredictability of the anatomical presentation of the uveitis ocular syphilis should always be considered in the differential diagnosis of uveitis. In the current guidelines, the recommended treatment for syphilitic uveitis is intravenous benzylpenicillin which is identical to the treatment for neurosyphilis. Next to adequate treatment for the syphilis infection, the use of oral corticosteroids as systemic immune suppression are recommended to prevent a Jarisch-Herxheimer reaction. Which is a reaction on the endotoxin-like products released by the death of harmful microorganisms within the body during antibiotic treatment and most commonly characterized by acute febrile illness with headache, myalgia, chills and rigors, resolving within 24 h. It is unclear if systemic immunosuppression next to anti-syphilitic treatment - improves visual outcome in syphilitic uveitis. Favorable visual outcome is related to early diagnosis and treatment. The clinical presentation of ocular syphilis has been described in many publications with relatively small numbers of patients. Due to the variability in clinical presentation, the sometimes confusing interpretation of serological tests and the debatable optimal treatment of a syphilis infection, the results from a large cohort of patients with serologically proven ocular syphilis are presented in chapter 3. More specifically, we report on the clinical manifestations and outcome of syphilitic uveitis in 85 patients with serologically proven syphilitic uveitis from 5 different tertiary uveitis centers in The Netherlands. The factors that correlate with a worse visual prognosis or a chronic disease course and the visual outcome of the different types of treatment are reported.

Masquerade uveitis
Retinital dystrophies (RD) are a rare group of progressive hereditary retinal degenerative diseases characterized by progressive degeneration of retinal photoreceptors leading to profound visual loss and blindness in middle or later life. Worldwide, the prevalence of RD is approximately 1 in 3,000 individuals. The diagnosis is made by recognition of the typical clinical picture, complaints of nyctalopia, a family history of retinal degenerative disease, visual field testing and a full-field electroretinogram (ERG). In most cases of advanced RD a progressively deteriorating ERG pattern is found, characterized by undetectable rod response and reduced cone response. In uveitis, the ERG response depends on the anatomical location of the uveitis. Most frequently, reduced amplitudes of a and b waves with long implicit times are found. In some cases, the ERG response normalizes with treatment, whereas in others it stays permanently abnormal. A retinal dystrophy can present itself with intraocular inflammation and cystoid macular edema masquerading as intermediate uveitis. Ongoing research suggests that in CRB1-linked retinal dystrophy masquerading as
intraocular inflammation, the disease is accompanied by molecular activation of inflammatory cytokine pathways and immune cells in the blood. These results on the role of inflammation in RD will hopefully provide insight in and possibilities for the treatment of RD and its complications in the future. At present, there are no treatment options besides corticosteroids and acetazolamide for macula edema and counseling of the patient. Nevertheless, patients can benefit from an early diagnosis which may result in more adequate counseling of the patient, and avoidance of prolonged treatment with high doses of immunosuppressive medication for a supposed uveitis. In chapter 4 the diagnostic process, clinical characteristics and outcome of 6 patients from 3 different tertiary uveitis centers in The Netherlands with retinal dystrophy presenting as intermediate uveitis are reported. This study intends to improve the diagnostic process and to provide insight into the specific characteristics and clinical signs in this patient group.

**Methotrexate in pediatric non-infectious uveitis**

Methotrexate (MTX), due to its effectiveness, long track record and good safety profile, is the steroid-sparing agent of first choice in almost all cases of non-infectious inflammatory eye diseases. MTX is effective in about 70% of patients and it is usually given orally or subcutaneously. The bioavailability of oral MTX varies per patient and appears to decrease at higher doses due to limits in absorption in the gastrointestinal tract. Several studies in rheumatoid arthritis (RA) indicate that MTX exerts its effect by influencing multiple inflammatory pathways. Firstly, MTX undergoes polyglutamation within the cells, after that MTX and its polyglutamates inhibit purine and pyrimidine synthesis, reduce antigen-dependent T-cell proliferation, and promote release of adenosine which in turn activates receptors on macrophages and neutrophils to decrease the release of proinflammatory cytokines and elevate the secretion of anti-inflammatory molecules. It is unclear if these mechanisms of action of MTX in RA are similar to uveitis. But, due to its known efficacy in ocular inflammation it is likely that the extracocular effects of MTX on the immune system provide the primary therapeutic mechanism by which systemically administered MTX affects ocular inflammation. Systemic administration of MTX leads to detectable intraocular MTX levels and the efficacy of intraocular MTX on uveitis and cystoid macular edema has been described in the literature. However, the current evidence about dosage, duration of treatment and best route of administration for MTX in ocular inflammation is limited. Also, there are concerns in the treatment of RA 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. In chapter 5 we present the results of our study on the efficacy of high dose in comparison to low dose MTX in 42 pediatric patients with non-infectious uveitis. Outcome measures are time to disease remission, steroid-sparing effect and side effects.
Physical and psychosocial health in pediatric uveitis patients

Patients with auto-immune diseases are more physically inactive compared to the general population. Also, aerobic fitness in children with different types of chronic conditions is reduced and they report more fatigue and lower health related quality of life (HR QoL). In the developed countries, the majority (41.5%) of the pediatric uveitis cases are related to juvenile idiopathic arthritis (JIA). Systemic immunosuppressive treatment in children with idiopathic uveitis who do not respond sufficiently to topical therapy is comparable to that used in the treatment of JIA. In JIA, children are found to be less physically active and have reduced physical fitness levels, which does not restore after remission has been reached. The causes of these persistent impairments of physical fitness and physical activity are not known, but it has been suggested that a combination of disease-related factors, treatment (e.g., medication), hypo-activity, and deconditioning could be involved. Hypoactive children are often at greater risk of preventable health problems, such as obesity and cardio-metabolic diseases. This higher risk of cardiovascular diseases is increased by the inflammation itself, circulating cytokines and the use of systemic immunosuppressive medication. Cardiovascular health in children can be improved by sufficient physical activity (PA) and physical fitness, whereas PA also has a beneficial effect on HR-QoL. The use of systemic immunomodulatory treatment or the presence of co-morbidity other than uveitis, did negatively influence general HR QoL scores in adult uveitis patients. Also, in adolescents with non-infectious uveitis despite quiescence of disease and good visual function, certain factors, such as a high number of recurrences, chronicity of the uveitis and fear of blindness were correlated with a decreased HR QoL. Fatigue is also highly present in patients with JIA and is related to many factors including PA, physical fitness and HR QoL of which cause and effect are not exactly known. In the literature, there are no publications about the physical fitness in children with uveitis and the information on the psychosocial health of children with uveitis is scarce. To add to a better understanding and treatment of the effects of a chronic disease - like uveitis - on a child's life, we present the results of our study on physical fitness, physical activity and psychosocial health in 23 children with uveitis in chapter 6.

Secondary glaucoma in pediatric uveitis

Childhood uveitis has an inherent predisposition to develop secondary glaucoma, with a prevalence of 5-13.5%. Secondary glaucoma occurs when uveitis is associated with raised intraocular pressure (IOP) and optic nerve damage, resulting in irreversible visual field loss and possible visual impairment. The damage to the trabecular system by the inflammation, but also the use of topical steroids as treatment of uveitis can increase the IOP. Secondary glaucoma in childhood uveitis has an unpredictable course, with large IOP fluctuations, varying responses to eye-pressure lowering medication and a frequent steroid-
response. Increased IOP is initially treated pharmacologically by using topical anti-glaucoma medication. If pharmacological treatment of IOP is insufficient, glaucoma surgery is required. Only small studies have investigated the risk factors of developing secondary glaucoma in childhood uveitis. Two studies reported a female preponderance, JIA as the most common etiology and anterior uveitis as the predictive anatomical site in the glaucoma group. Another small study compared the need of glaucoma surgery in children with uveitis who developed secondary glaucoma. Both mean age and the average number of previous intraocular surgeries in the surgery group were significantly higher than in the control group. To obtain the best long-term visual outcome, it is important to identify children with refractory glaucoma at an early stage and to treat them by glaucoma surgery before irreversible damage has occurred. In chapter 7 the results of our study on the possible risk factors for the development of secondary glaucoma needing glaucoma surgery are reported. The study was conducted in a large cohort of 196 children with uveitis from 2 tertiary uveitis centers in the Netherlands.
REFERENCES


