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 [1 - 3]. 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 [4 - 7].

Epidemiology of scleritis

Published epidemiologic data about the incidence and prevalence of scleritis in adults is scarce [8]. The estimated reported annual incidence of scleritis is between 4 to 6 per 100,000 person-years [8, 9]. 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 [2, 8]. Scleritis as an expression of underlying auto-immune disease such as rheumatoid artritis or granulomatosis with polyangiitis is the most common [2, 8]. 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 [2]. Patients with severe disease often have multiple causes for loss of visual function, such as corneal involvement, cataract, glaucoma, maculopathy, papilledema or retinal detachment [2, 8, 10]. 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 [11] and others reported a female preponderance [12, 13]. Among subtypes, posterior scleritis is relatively common in children [11]. 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 [14]. 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 [14, 15]. 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 [16]. More recent publications on long-term clinical outcome in adults show more favorable visual outcomes due to improved treatment options [17]. Uveitis in children is relatively uncommon and accounts for 5 to 10% of the total uveitis population [14, 18]. The reported annual incidence is 4 per 100,000 population and the prevalence 28 per 100,000 population [18]. It is estimated that in the western world 17-28% of the children with uveitis become legally blind in one eye [19, 20]. Uveitis in childhood offers specific challenges when compared to uveitis in adults [21]. The risk of poorer visual outcome is possibly greater in children when compared to adults [21]. In most cases of uveitis in childhood the uveitis is related to juvenile idiopathic arthritis (JIA) [20]. The onset is insidious in most cases of JIA-uveitis and diagnosis is often delayed resulting in deterioration of the visual prognosis [22]. Ocular complications such as cataract, glaucoma, band keratopathy and amblyopia may silently develop and are reported in up to 50% of children with uveitis [20, 21].

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 [2, 8]. Scleritis is classified by its anatomic location and clinical appearance (table 1) [23].In case of posterior scleritis clinical signs may be less obvious and evaluation by ultrasonography or other imaging techniques are necessary [2].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 [2, 8]. The diagnosis in uveitis is more difficult. There are various etiologies and the systemic associations of uveitis differ between adults and children [14, 18, 24]. In general, the differential diagnosis of uveitis is based upon the anatomical location of the inflammation (Table 2) [25], the recognition of specific ophthalmic clinical signs and the outcome of the different serological tests and – when necessary – outcome of analysis of intra-ocular fluid.

Table 1. Classification of scleritis [23]

Anterior scleritis
Diffuse
Nodular
Necrotizing
Scleromalacia
Posterior scleritis (incl SINS[a])
Posterior
Surgery induced (SINS)
Panscleritis (anterior + posterior)

[a]SINS = surgically-induced necrotizing scleritis

Table 2. Classification of uveitis [25]

Anatomic location uveitis
Anterior uveitis
Intermediate uveitis
Posterior uveitis
Pan uveitis

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- α) antagonists such as infliximab and adalimumab or chimeric monoclonal antibodys 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-α) 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 [36, 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 [4, 38 - 41]. It has been suggested that the effects of uveitis on HR QoL in children are similar to those of children with other chronic conditions [42] and the disease burden of uveitis can affect quality of life even when there is no loss of vision [42].

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 [43, 44] and is a rare sexually transmitted infection (STI) nowadays accounting for 1% to 2% of all uveitis patients [45 -47]. In the pre-antibiotic era, syphilis was more common [46]. 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 [47]. 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 [47]. Ocular syphilis is a treatable disease and because of the changes in epidemiology and unpredictability of the anatomical presentation of the uveitis [43, 44, 46, 47] 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 [48, 49]. 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 [48, 49]. 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 [48]. 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 [50, 51]. 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 [52]. Worldwide, the prevalence of RD is approximately 1 in 3,000 individuals [53, 54]. 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 [55]. A retinal dystrophy can present itself with intraocular inflammation and cystoid macular edema masquerading as intermediate uveitis [56]. 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 [56 - 58]. 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 [59] and good safety profile, is the steroid-sparing agent of first choice in almost all cases of non-infectious inflammatory eye diseases [32-34]. MTX is effective in about 70% of patients [32-34] 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 [60 - 62]. Several studies in rheumatoid arthritis (RA) indicate that MTX exerts its effect by influencing multiple inflammatory pathways [63 - 65]. 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 [66]. But, due to its known [32-34] efficacy in ocular inflammation it is likely that the extraocular effects of MTX on the immune system provide the primary therapeutic mechanism by which systemically administered MTX affects ocular inflammation [34]. Systemic administration of MTX leads to detectable intraocular MTX levels [67, 68] and the efficacy of intraocular MTX on uveitis and cystoid macular edema has been described in the literature [69, 70]. However, the current evidence about dosage, duration of treatment and best route of administration for MTX in ocular inflammation is limited [32 - 34]. 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 [62, 71, 72]. 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 [73]. 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) [74--77]. In the developed countries the majority (41.5%) of the pediatric uveitis cases are related to juvenile idiopathic arthritis (JIA) [18, 78]. 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 [79] which does not restore after remission has been reached [80, 81]. 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 [82 - 84]. Hypoactive children are often at greater risk of preventable health problems, such as obesity and cardio-metabolic diseases [82, 85].This higher risk of cardiovascular diseases is increased by the inflammation itself, circulating cytokines and the use of systemic immunosuppressive medication [83, 84, 86, 87]. Cardiovascular health in children can be improved by sufficient physical activity (PA) and physical fitness [88], whereas PA also has a beneficial effect on HR-QoL[73]. 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 [4, 6]. 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 [39, 40]. 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 [89]. 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 [7, 41, 90, 91]. 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% [92]. 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 [93]. 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 [94]. 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 [92, 95]. 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 [96]. 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 [97]. 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

1. Tuft SJ, Watson PG. Progression of scleral disease. Ophthalmology 1991;98:467-71.
2. Okhravi N, Odufuwa B, McCluskey P, Lightman S. Scleritis. Surv Ophthalmol 2005;50:351-63.
3. Cobo M. Inflammation of the sclera. Int Ophthalmol Clin 1983;23:159-71.
4. Schiffman RM, Jacobsen G, Whitcup SM. Visual functioning and general health status in patients with uveitis. Arch Ophthalmol. 2001 Jun;119(6):841-9
5. Hoeksema L, Los LI. Vision-related quality of life in herpetic anterior uveitis patients. PLoS One. 2014 Jan 2;9(1). eCollection 2014.
6. Haasnoot AJW, Sint Jago NFM, Tekstra J, de Boer JH. Impact of Uveitis on Quality of Life in Adult Patients With Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2017 dec;69(12):1895-1902
7. Angeles-Han ST. Quality-of-life metrics in pediatric uveitis. Int Ophthalmol Clin. 2015;55(2):93-101
8. Lagina A, Ramphul K. Scleritis. Source; StatPearls [Internet]. [cited 15-07-2018] Treasure Island (FL): StatPearls Publishing; 2018-.2018 Apr 23.
9. Gelareh Homayounfar, Natalie Nardone, Durga S. Borkar, Vivien M. Tham, Travis C. Porco, Wayne T.A. Enanoria, John V. Parker, Aleli C. Vinoya, Aileen Uchida, Nisha R. Acharya.Incidence of Scleritis and Episcleritis: Results From the Pacific Ocular Inflammation Study. American Journal of Ophthalmology, Volume 156, Issue 4, 2013, pp. 752-758.e3
10. McCluskey P, Wakefield D. Prediction of response to treatment in patients with scleritis using a standardised scoring system. Aust N Z J Ophthalmol 1991;19:211-5.
11. Majumder PD, Ali S, George A, Ganesh S, Biswas J. Clinical Profile of Scleritis in Children. Ocul Immunol Inflamm. 2018 Jan 25:1-5.
12. Sainz De La Maza M, Molina N, Gonzalez-Gonzalez LA,Doctor PP, Tauber J, Foster CS Clinical characteristics of a large cohort of patients with scleritis and episcleritis. Ophthalmology. 2012;119(1):43–50.
13. Akpek EK, Thorne JE, Qazi FA, Do DV, Jabs DA Evaluation of patients with scleritis for systemic disease. Ophthalmology.2004;111(3):501–506.
14. Wakefield D, Chang HC. Epidemiology of uveitis. International Ophthalmology clinics. 45(2):1-13, apr 2005.
15. Chan NS, Choi J, Cheung CMG. Pediatric Uveitis. Asia Pac J Ophthalmol (Phila). 2018 May-Jun;7(3):192-199
16. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P, Murray PI. Degree, duration, and causes of visual loss in uveitis. Br J Ophthalmol. 2004 Sep;88(9):1159-62.
17. Tomkins-Netzer O, Talat L, Bar A, Lula A, Taylor SR, Joshi L, Lightman S. Long-term clinical outcome and causes of vision loss in patients with uveitis. Ophthalmology. 2014. Dec; 121(12): 2387-92.
18. Päivönsalo-Hietanen T, Tuominen J, Saari KM. Uveitis in children: population-based study in Finland. Acta Ophthalmol Scand. 2000 Feb;78(1):84-8.
19. Zierhut M, Michels H, Stübiger N, Besch D, Deuter C, Heiligenhaus A. Uveitis in children. Int Ophthalmol Clin. 2005 Spring;45(2):135-56.
20. Angeles-Han ST, Rabinovich CE. Uveitis in children. Curr Opin Rheumatol. 2016 Sep;28(5): 544-9.
21. Wentworth BA, Freitas-Neto CA, Foster CS. Management of pediatric uveitis. F1000Prime Rep. 2014;6:41-41. eCollection 2014.
22. BenEzra D, Cohen E, Maftzir G. Uveitis in children and adolescents. Br J Ophthalmol. 2005 Apr;89(4):444-8.
23. Watson PG, Hayreh SS. Scleritis and episcleritis. Br J Ophthalmol 1976;60:163-91
24. Smith JA, Mackensen F, Sen HN, et al. Epidemiology and course of disease in childhood uveitis. Ophthalmology. 2009;116(8):1544-51, 1551.e1.

25. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. results of the first international workshop. Am J Ophthalmol. 2005;140(3):509-516.

26. Sohn EH, Wang R, Read R, Roufas A, Teo L, Moorthy R, Albini T, Vasconcelos-Santos DV, Dustin LD, Zamir E, Chee SP, McCluskey P, Smith R, Rao N. Long-term, multicenter evaluation of subconjunctival injection of triamcinolone for non-necrotizing, noninfectious anterior scleritis. Ophthalmology. 2011 Oct;118(10):1932-7.

27. Chauhan S, Kamal A, Thompson RN, et al. Rituximab for treatment of scleritis associated with rheumatoid arthritis. Br J Ophthalmol 2009;93:984 –5.

28. Iaccheri B, Androudi S, Bocci EB, et al. Rituximab treatment for persistent scleritis associated with rheumatoid arthritis. Ocul Immunol Inflamm 2010;18:223–5.

29. Kurz PA, Suhler EB, Choi D, Rosenbaum JT. Rituximab for treatment of ocular inflammatory disease: a series of four cases. Br J Ophthalmol 2009;93:546–8.

30. Restrepo JP, Molina MP. Successful treatment of severe nodular scleritis with adalimumab. Clin Rheumatol 2010;29:559 – 61

31. Sen HN, Sangave A, Hammel K, et al. Infliximab for the treatment of active scleritis. Can J Ophthalmol 2009;44:e9–e12.

32. Simonini G, Paudyal P, Jones GT, Cimaz R, Macfarlane GJ. Current evidence of methotrexate efficacy in childhood chronic uveitis: A systematic review and meta-analysis approach. Rheumatology (Oxford). 2013;52(5):825-831.

33. Ali A, Rosenbaum JT. Use of methotrexate in patients with uveitis. Clin exp rheumatol 2010 sep-oct;28(5 Suppl 61):S145-50

34. Gangaputra Sapna et al. Methotrexate for Ocular Inflammatory Diseases. Ophthalmology. 2009; 116:2188-2198

35. Dick AD, Rosenbaum JT, Al-Dhibi HA, Belfort R Jr, Brézin AP, Chee SP, Davis JL, Ramanan AV, Sonoda KH, Carreño E, Nascimento H, Salah S, Salek S, Siak J, Steeples L; Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative. Ophthalmology. 2018 May;125(5):757-773.

36. de Smet MD, Taylor SR, Bodaghi B, et al. Understanding uveitis: the impact of research on visual outcomes. Prog Retin Eye Res. 2011;30:452–470.

37. Miserocchi E, Fogliato G, Modorati G, et al. Review on the worldwide epidemiology of uveitis. Eur J Ophthalmol. 2013;23:705–717.

38. Miserocchi E, Modorati G, Mosconi P, Colucci A, Bandello F. Quality of Life in Patients with Uveitis on Chronic Systemic Immunosuppressive Treatment. Ocul Immunol Inflamm. 2010;18(4):297-304.

39. Maca SM, Amirian A, Prause C, Gruber K, Mejdoubi L, Barisani-Asenbauer T. Understanding the Impact of Uveitis on Health-related Quality of Life in Adolescents. Acta Ophthalmol. 2013;91(3):219-224.

40. Petrina Tan, Yan Tong Koh, Poh Ying Wong & Stephen C. Teoh. Evaluation of the Impact of Uveitis on Visual-related Quality of Life. Ocular Immunology and Inflammation. 2012;20(6):453-459

41. Angeles-Han ST, Griffin KW, Lehman TJ, et al. The importance of visual function in the quality of life of children with uveitis. J AAPOS. 2010; 14(2):163–168. [PubMed: 20236847]

42. Parker DM, Angeles-Han ST, Stanton AL, Holland GN. Chronic Anterior Uveitis in Children: Psychosocial Challenges for Patients and Their Families. Am J Ophthalmol. 2018 Jul;191:xvi-xxiv.

43. Davis JL. Ocular syphilis. Curr Opin Ophthalmol. 2014 Nov;25(6):513-8.

44. Amaratunge BC, Camuglia JE, Hall AJ. Syphilitic uveitis: A review of clinical manifestations and treatment outcomes of syphilitic uveitis in human immunodeficiency virus-positive and negative patients. Clin Experiment Ophthalmol. 2010;38(1):68-74.

45. Schlaegel TF,Jr, O'Connor GR. Metastatic nonsuppurative uveitis. Int Ophthalmol Clin. 1977;17(3):87-108.

46. Fenton KA, Breban R, Vardavas R, et al. Infectious syphilis in high-income settings in the 21st century. Lancet Infect Dis.2008;8:244-253.

47. Hughes G, Field N. The epidemiology of sexually transmitted infections in the UK: impact of behavior, services and interventions. Future Microbiol. 2015;10:35-51.

48. Janier M, Hegyi V, Dupin N, et al. 2014 European guideline on the management of syphilis. J Eur Acad Dermatol Venereol. 2014.

49. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines,2015. MMWR Recomm Rep. 2015;64:1-137.

50. Balaskas K, Sergentanis TN, Giulieri S, et al. Analysis of significant factors influencing visual acuity in ocular syphilis. Br J Ophthalmol. 2011;95:1568–1572.

51. Moradi A, Salek S, Daniel E, et al. Clinical features and incidence rates of ocular complications in patients with ocular syphilis. Am J Ophthalmol. 2015;159:334–343.e1.

52. Francesco Parmeggiani. Clinics, Epidemiology and Genetics of Retinitis Pigmentosa. Curr Genomics. 2011 Jun; 12(4): 236–237.

53. Bessant DA, Ali RR, Bhattacharya SS. Molecular genetics and prospects for therapy of the inherited retinal dystrophies. Curr Opin Genet Dev. 2001 Jun;11(3):307-16.

54. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet. 2006;368:1795–809

55. Sevgi DD, Davoudi S, Comander J, Sobrin L. Retinal pigmentary changes in chronic uveitis mimicking retinitis pigmentosa. Graefes Arch Clin Exp Ophthalmol. 2017 Sep;255(9):1801-1810

56. Yoshida N, Ikeda Y, Notomi S, et al. Clinical evidence of sustained chronic inflammatory reaction in retinitis pigmentosa. Ophthalmology. 2013;120(1):100–105

57. Tamm S, Whitcup SM, Gery I, et al. Immune response to retinal antigens in patients with gyrate atrophy and other hereditaryretinal dystrophies. Ocul Immunol Inflamm. 2001;9(2):75–84.

58. Stunkel M, Bhattarai S, Kemerley A, et al. Vitritis in pediatric genetic retinal disorders. Ophthalmology. 2015;122(1):192–199.

59. Wong VG. Methotrexate treatment of uveal disease. Am J Med Sci. 1966;251(2):239-241.

60. Herman RA, Veng-Pedersen P, Hoffman J, Koehnke R, Furst DE. Pharmacokinetics of low-dose methotrexate in rheumatoid arthritis patients. J Pharm Sci. 1989;78(2):165–171

61. van Roon EN, van de Laar MA. Methotrexate bioavailability. Clin Exp Rheumatol 2010;28(Suppl):27-32.

62. Bello AE, Perkins EL, Jay R, Efthimiou P. Recommendations for optimizing methotrexate treatment for patients with rheumatoid arthritis. Open Access Rheumatol. 2017 Mar 31;9:67-79.

63. Chan ES, Cronstein BN. Molecular action of methotrexate in inflammatory diseases. Arthritis Res. 2002;4(4):266–273.

64. Milne GR, Palmer TM. Anti-inflammatory and immunosuppressive effects of the A2A adenosine receptor. ScientificWorldJournal.2011;11:320–339.

65. Tian H, Cronstein BN. Understanding the mechanisms of action of methotrexate: implications for the treatment of rheumatoid arthritis. Bull NYU Hosp Jt Dis. 2007;65(3):168–173.

66. Hashkes PJ, Becker ML, Cabral DA, Laxer RM, Paller AS, Rabinovich CE, Turner D, Zulian F. Methotrexate: new uses for an old drug. J Pediatr. 2014 Feb;164(2):231-6

67. Puchta J, Hattenbach LO, Baatz H. Intraocular levels of methotrexate after oral low-dose treatment in chronic uveitis. Ophthalmologica. 2005; 219:54–5.

68. de Smet MD, Stark-Vancs V, Kohler DR, et al. Intraocular levels of methotrexate after intravenous administration. Am J Ophthalmol. 1996; 121:442–4.

69. Taylor SR, Banker A, Schlaen A, Couto C, Matthe E, Joshi L, Menezo V, Nguyen E, Tomkins-Netzer O, Bar A, Morarji J, McCluskey P, Lightman S. Intraocular methotrexate can induce extended remission in some patients in noninfectious uveitis. Retina. 2013 Nov-Dec;33(10):2149-54.

70. Taylor SR, Habot-Wilner Z, Pacheco P, Lightman SL. Intraocular methotrexate in the treatment of uveitis and uveitic cystoid macular edema. Ophthalmology. 2009 Apr;116(4):797-801. doi: 10.1016/j.ophtha.2008.10.033.

71. Pincus T, Gibson KA, Castrejón I. Update on methotrexate as the anchor drug for rheumatoid arthritis. Bull Hosp Jt Dis. 2013;71(Suppl 1):S9–S19.

72. Rohr MK, Mikuls TR, Cohen SB, Thorne CJ, O'Dell JR. The underuse of methotrexate in the treatment of RA: a national analysis of prescribing practices in the U.S. Arthritis Care Res (Hoboken). Epub 2016 Nov 18.

73. 4. Sharif K,Watad A, Bragazzi N.L, Lichtbroun M, Amital H, Shoenfeld Y. Physical activity and autoimmune diseases: Get moving and manage the disease. Autoimmun Rev. 2018; 17(1), 53-72.

74. Takken T, Bongers BC, van Brussel M, Haapala EA, Hulzebos EHJ. Cardiopulmonary Exercise Testing in Pediatrics. Ann Am Thorac Soc. 2017; Supplement 1, S123-S128.

75. van Brussel M, van der Net J, Hulzebos E, Helders PJ, Takken T. The Utrecht approach to exercise in chronic childhood conditions: the decade in review. Pediatr Phys Ther. 2011; 23, (1): 2-14

76. Gualano B, Bonfa E, Pereira RMR, Silva CA. Physical activity for paediatric rheumatic diseases: standing up against old paradigms. Nat Rev Rheumatol. 2017;13, (6): 368-379.

77. Barthel D, Ravens-Sieberer U, Nolte S, Thyen U, Klein M, Walter O, Meyrose AK, Rose M, Otto C. Predictors of health-related quality of life in chronically ill children and adolescents over time. J Psychosom Res. 2018 Jun;109:63-70.

78. Mehta PJ, Alexander JL, Sen HN. Pediatric uveitis: New and future treatments. Curr Opin Ophthalmol. 2013;24(5):453-462.

79. Lelieveld OT, Armbrust W, van Leeuwen M a, et al. Physical Activity in Adolescents with Juvenile Idiopathic Arthritis. Arthritis Rheum. 2008;59(10):1379-1384

80. van Brussel M, Lelieveld OTHM, van der Net J, Engelbert RHH, Helders PJM, Takken T. Aerobic and Anaerobic Exercise Capacity in Children with Juvenile Idiopathic Arthritis. Arthritis Rheum. 2007;57(6):891-897.

81. Ploeger HE, Takken T, Wilk B, et al. Exercise Capacity in Pediatric Patients with Inflammatory Bowel Disease. J Pediatr. 2011;158(5):814-819.

82. Takken T, Bongers BC, van Brussel M, Haapala EA, Hulzebos EHJ. Cardiopulmonary Exercise Testing in Pediatrics. Ann Am Thorac Soc. 2017; Supplement 1, S123-S128.

83. Roubenoff R. Exercise and Inflammatory Disease. Arthritis Care Res (Hoboken). 2003;49(2): 263.

84. Gupta Y, Gupta A. Glucocorticoid-induced Myopathy: Pathophysiology, Diagnosis, and Treatment. Indian J Endocrinol Metab. 2013;17(5):913-916.

85. Zoico E, Roubenoff R. The Role of Cytokines in Regulating Protein Metabolism and Muscle Function. Nutr Rev. 2002;60(2):39-51.

86. Carnethon M, Gidding S, Nehgme R, Sidney S, Jacobs D, Liu K. Cardiorespiratory Fitness in Young Adulthood and the Development of Cardiovascular Diseases Risk Factors. JAMA. 2003;290(23):3092-3100

87. Steene-Johannessen J, Anderssen S a, Kolle E, Andersen LB. Low muscle fitness is associated with metabolic risk in youth. Med Sci Sports Exerc. 2009 Jul;41(7):1361–7.

88. Strong WB, Malina RM, Blimkie CJR, et al. Evidence Based Physical Activity for School-age Youth. J Pediatr. 2005;146(6):732-737.

89. Armbrust W, Lelieveld OH, Tuinstra J, Wulffraat NM, Bos GJ, Cappon J, van Rossum MA, Sauer PJ, Hagedoorn M. Fatigue in patients with Juvenile Idiopathic Arthritis: relationship to perceived health, physical health, self-efficacy, and participation. Pediatr Rheumatol Online J. 2016 Dec 6;14(1):65.

90. Angeles-Han ST, Griffin KW, Harrison MJ, Lehman TJ, Leong T, Robb RR, Shainberg M, Ponder L, Lenhart P, Hutchinson A, Srivastava SK, Prahalad S, Lambert SR, Drews-Botsch C. Development of a vision-related quality of life instrument for children ages 8-18 years for use in juvenile idiopathic arthritis-associated uveitis. Arthritis Care.Res.(Hoboken), 2011;63(9)1254-1261

91. Angeles-Han ST, Yeh S, McCracken C, Jenkins K, Stryker D, Myoung E, Vogler LB, Rouster-Stevens K, Lambert SR, Harrison MJ, Prahalad S, Drews-Botsch C. Using the Effects of Youngsters' Eyesight on Quality of Life Questionnaire to Measure Visual Outcomes in Children With Uveitis. Arthritis Care Res (Hoboken). 2015 Nov;67(11):1513-20.

92. Gautam Seth N, Yangzes S, Thattaruthody F, et al. Glaucoma Secondary to Uveitis in Children in a Tertiary Care Referral Center. Ocular Immunology and Inflammation. Published February 2, 2018.

93. Baneke AJ, Lim KS, Stanford M. The Pathogenesis of Raised Intraocular Pressure in Uveitis. Curr Eye Res. 2016;41(2):137-149.

94. Muñoz-Negrete FJ, Moreno-Montañés J, Hernández-Martínez P, Rebolleda G. Current Approach in the Diagnosis and Management of Uveitic Glaucoma. Biomed Res Int. 2015;2015:1-13.

95. Heinz C, Koch JM, Zurek-Imhoff B, Heiligenhaus A. Prevalence of uveitic secondary glaucoma and success of nonsurgical treatment in adults and children in a tertiary referral center. Ocul Immunol Inflamm. 2009;17(4):243-248.

96. Kalinina Ayuso V, Scheerlinck LM, de Boer JH. The effect of an Ahmed glaucoma valve implant on corneal endothelial cell density in children with glaucoma secondary to uveitis. Am J Ophthalmol. 2013 Mar;155(3):530-5.

97. Abu Samra K, Maghsoudlou A, Roohipoor R, Valdes-Navarro M, Lee S, Foster CS. Current Treatment Modalities of JIA-associated Uveitis and its Complications: Literature Review. Ocul Immunol Inflamm. 2016;24(4):431-439.