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General discussion and future perspectives
GENERAL DISCUSSION

In this chapter we will discuss the most important findings and compare them with the current literature. We will also discuss some future perspectives for the purpose of further research. This thesis focuses on two types of anterior uveitis (AU), herpetic and HLA-B27 associated AU. The most common infectious and non-infectious forms of AU. All types of uveitis differ in ocular and patient characteristics. Therefore we studied homogeneous uveitis groups on ocular characteristics, complications, visual acuity (VA) and quality of life (QOL). This will result in a better understanding of the individual prognosis and impact of the disease with the ultimate aim to contribute to a more personalized care of uveitis patients.

Ocular characteristics, complications and the visual prognosis in herpetic and HLA-B27 associated anterior uveitis

The knowledge of different ocular and patient characteristics of the various types of uveitis in different populations is important in making the diagnosis, inform the patient and to customize treatment strategies. There are a lot of differences in reported rates of ocular complications. Factors contributing to the differences include non-uniform definitions and variable follow-up times, which is a well-recognized problem in the field of uveitis. 1 That is why we conducted a study that gives information on the rate of complications, ocular characteristics and the visual prognosis in herpetic compared to HLA-B27 associated AU, which are relatively large and homogeneous AU patient groups at our center (chapter 2).

We performed a retrospective, observational study of 62 herpetic and 113 HLA-B27 associated AU patients, seen at the ophthalmology department of the University Medical Center of Groningen. We used the guidelines for uniform reporting in uveitis studies as developed by the standardization of uveitis nomenclature (SUN) working group. 1

The results show similarities and differences between herpetic and HLA-B27 associated AU. In herpetic AU, the most common complications are keratitis, elevated intraocular pressure (IOP), cataract, posterior synechiae and glaucoma and in HLA-B27 AU posterior synechiae, elevated IOP, cataract, cystoid macular oedema and glaucoma. The incidence rate of ocular complications overall is higher in herpetic compared to HLA-B27 associated AU, which is mainly due to higher incidence rates of glaucoma, cataract and keratitis in herpetic AU.

Rates of ocular complications given in the literature vary for both groups. For glaucoma they range from 1.8 to 30% in herpetic AU and in HLA-B27 associated AU this varies between 0 and 20%. 2-8 Also the development of cataract varies in the literature, and is reported to develop in 13 to 32% in herpetic and in 5 to 28% in HLA-B27 associated AU. 3,4,7-10 This difference in reported ocular complications seems to be caused by nonhomogeneous patient groups, non-uniform definitions, and different ways to report data.
Previous studies have often focused on large groups of heterogeneous uveitis patients. The benefit of this type of research is that this results in large numbers of patients. The disadvantage is that it says less about the different uveitis entities and the subgroups in these studies are often small, resulting in less reliable outcomes. An exception is HLA-B27 associated anterior uveitis, wherein a reasonable amount of research, with homogeneous patient groups, has been conducted. Unfortunately, these HLA-B27 positive patients were often compared with HLA-B27 negative patients, which represents a very heterogeneous group of patients of various uveitis entities. Additionally, these HLA-B27 negative patient groups consists for a substantial part of patients with idiopathic uveitis. During follow-up many of these idiopathic patients will be diagnosed with a specific uveitis entity. This means that it is unsure which comparison is made. To understand the individual prognosis and impact of the disease per uveitis entity, it is important to investigate larger homogeneous patient groups. In recent years more and more research is conducted in this way, for example research on herpetic anterior uveitis. Eventually this will lead to the development of more individualized entity-related counseling strategies.

A second problem in the field of uveitis are non-uniform definitions. In 1987, the International Uveitis Study Group developed criteria based on the anatomical localisation of the inflammation. In 2005 this was updated by the SUN working group, which developed guidelines for reporting clinical data in the field of uveitis, including the use of definitions for ocular complications. Because of the lack of given definitions in the earlier guidelines (before 2005), many researchers came up with their own definitions, or did not specify the definitions used. In addition, a lot of studies are still conducted without using guidelines for reporting clinical data, even after the SUN working group published their guidelines. This use of non-uniform definitions has led to a wide variety in reported incidences of ocular complications and makes it difficult to compare studies (see chapters 2 and 3). In addition, it is unsure what exactly has been investigated without specifying the used methods. Fortunately, in recent years more research is conducted with the use of the guidelines mentioned by the SUN working group. Most studies only use this guidelines for the classification of uveitis, others also use the guidelines for determining the definitions of ocular complications. The use of these guidelines enables comparisons of studies in the field of uveitis. Hopefully, in the future, it will become more accepted to use these guidelines and as a consequence the variety in reported incidences of ocular complications will decline.

A third issue is the way to report data, since this can be done in different ways. The ocular complications in our study were expressed as percentages at the end of follow-up and as rate/eye-years (see chapter 2, 'data'). In this way, data is corrected for variable follow-up times. However, this method will not show when the specific complication took place in the course of the disease. If we assume that most of the complications occur in the beginning of the follow-up, a short follow-up time will lead to a higher rate/eye-years (number of events divided by the sum of less follow-up
time) and a longer follow-up time will lead to lower rate/eye-years (number of events divided by the sum of longer follow-up time). Another way of presenting data would be to give information on complications at certain time points (e.g. at 1 year follow-up, 2 year follow-up, 10 year follow-up). This would make the distribution of the complications over time more transparent.

In chapter 2 we further found that HLA-B27 associated AU patients score better on VA at onset and during follow-up, compared to herpetic AU. In the latter, VA was lower in patients with keratitis as compared to those without. Tugal-Tutkun et al. also reported that their patients with only iridocyclitis had no permanent visual loss. In addition, at ten years of follow-up, VA of herpetic AU patients without keratitis seemed to be comparable with that of HLA-B27 associated AU patients. In our study, most patients end up with a reasonably good VA at ten years follow-up. In contrast, previous studies described visual impairment in a substantial proportion of HLA-B27 associated AU patients. Except for shorter follow-up times, there is no obvious explanation for this dissimilarity. In recent years, there is a development in more advanced systemic therapies (e.g. adalimumab, certolizumab and golimumab) for the prevention of uveitis flares in HLA-B27 uveitis. The assumption is that with less uveitis flares, the VA will remain better. The efficacy and visual prognosis of these treatment options should be further investigated.

**Elevated intraocular pressure and glaucoma in herpetic anterior uveitis**

Because we found a high prevalence of elevated IOP and eventually secondary glaucoma in patients with herpetic AU (chapter 2), we performed a study on risk factors for the development of glaucoma (chapter 3). Identifying these risk factors can help to determine how therapeutic modalities can prevent glaucoma in this patient group.

We found that elevated IOP and secondary glaucoma are frequent complications of herpetic AU. In addition, we found a wide variety between studies regarding the definitions of elevated IOP and secondary glaucoma, and as a result a wide variation in reported incidences of these complications (chapter 3). This finding underlines the need for using standardized guidelines as mentioned in the discussion above.

Previous studies showed that elevated IOP is a risk factor for the development of secondary glaucoma and that specific the level of IOP and the reduced diurnal-to-nocturnal change of habitual IOP are of importance. In our study, herpetic AU patients who developed secondary glaucoma had more often elevated IOP during follow-up and endured significantly more IOP peaks than patients without glaucoma. These IOP peaks may be prevented by early and prolonged use of antiviral and anti-glaucoma medication. In a recent review by Zandi et al. the authors also concluded that prophylactic treatment may need to be continued indefinitely, frequently in conjunction with the administration of topical corticosteroids at low doses and of anti-glaucoma agents. Future studies are needed to evaluate whether this eventually prevents the development of secondary glaucoma.
Comparison of unilateral and bilateral HLA-B27 associated anterior uveitis

In HLA-B27 associated AU, the uveitis can be unilateral (always the same eye) or bilateral (simultaneous or alternating), it would be interesting to know if these different manifestations represent the same or different disease entities. That is why we evaluated the ocular and patient characteristics of these two patient groups (chapter 4).

We found that unilateral and bilateral HLA-B27 associated AU are generally comparable. They differ in age at the onset of uveitis and the presence of an associated systemic disease. In addition, HLA-B27 AU is more frequently seen in men, it is mainly bilaterally alternating, and more than half of the patients have signs of a severe inflammation, such as anterior chamber fibrin and posterior synechiae.

Bilateral patients were younger than unilateral patients (31 versus 37 years). Unfortunately, a direct comparison with other studies is not possible, because we could not find any information on differences in age at onset between unilateral and bilateral patients in the literature. Patients with bilateral AU more often had an associated systemic disease as compared to patients with unilateral AU (62% versus 37%). In the literature there is no significant difference found between unilateral and bilateral patients, however these studies are not primarily designed to examine the difference of unilateral and bilateral patients. Knowing that bilateral patients are more at risk for developing an associated systemic disease, can be useful in the clinical setting. It may be worth considering to refer these patients sooner to a rheumatologist for a systemic evaluation, especially if they have systemic complaints.

In most patients the AU begins unilaterally and becomes bilateral during follow-up. In our study, the median interval between uveitis in the first and second eye was 4.2 years. The total follow up of the unilateral patients was 2.7 years. This indicates that it could well be that the second eye of seemingly unilateral patients will get involved in the future. In the literature the prevalence of bilateral disease varies from 27 to 52%, the follow up in these studies varied between 1.2 and 5.2 years. The relatively short follow-up in the performed studies indicate that probably the percentage of bilateral patients will eventually be even higher if the follow-up is longer.

Our study shows that unilateral and bilateral patients both have a good prognosis with regard to VA and the development of ocular complications. Also the VA at the end of follow-up did not differ between the first and second affected eye in bilateral patients. Altogether, because unilateral and bilateral HLA-B27 associated AU are generally comparable with regard to ocular complications, course of the disease, VA, and treatment, they represent probably the same disease entity.
Vision related quality of life in anterior uveitis

Awareness of the ocular and patient characteristics of the different uveitis entities is important in making the right diagnosis and to start the appropriate treatment, trying to prevent ocular complications and support a better VA outcome. A better VA in the long run and less ocular complications should eventually result in a better QOL. In recent years there is more and more interest in the QOL of patients, not only by clinicians, but also by the patient and patient associations. QOL is defined as a state of complete physical, mental and social well-being. Outcomes of QOL questionnaires give information on the impact of the disease on the patient’s daily life. This is why we evaluated the vision related quality of life (VR-QOL) in herpetic and HLA-B27 associated AU patients (chapters 5 and 6).

Schiffman et al. found already in 2001 that uveitis patients have a poorer visual functioning and a lower general health status compared to healthy subjects. A recent study by Shamdas et al. showed that poor vision in the better seeing eye, bilateral disease and concurrent glaucomatous optic neuropathy were predictors of poor QOL in uveitis patients. In addition, Verhagen et al. found in patients with non-infectious uveitis that ocular pain also has an impact on QOL. In recent years there is more research conducted into specific uveitis entities. These studies found that VR-QOL is impaired in patients with birdshot chorioretinopathy, Behçet’s disease and adult patients with juvenile idiopathic arthritis and a history of uveitis.

Vision related quality of life in herpetic anterior uveitis

Previous research focuses mainly on non-infectious uveitis or nonhomogeneous uveitis groups. Research on QOL in infectious uveitis is scarce. As far as we know, there is no information available in the literature on QOL in a homogeneous herpetic AU group. For this reason we examined the VR-QOL and the prevalence and severity of depression in herpetic AU (chapter 5).

We found that VR-QOL is reasonably high in herpetic AU patients. Generally herpetic AU patients score almost the same as those in the working population and in acute posterior vitreous detachment patients. A possible explanation for a better QOL in our patient group, despite the relatively high percentage of patients with glaucoma and keratitis (chapter 2 and 3), is that all our patients had a unilateral disease. These patients generally have no complaints and a good VA in the unaffected eye.

We also looked at the prevalence and severity of depression. A worse depression score (BDI-II) was correlated with a worse VR-QOL (NEI-VFQ-25). However depression itself was scarce in our study group, with only one patient having a moderate depression. Onal et al. showed that a positive screening test for depression and anxiety is common in patients with uveitis. In this study low vision and panuveitis are associated with depression and depression is associated with impairment of VR-QOL. Our study shows that depression is less common in AU with a relatively
good visual prognosis. The relatively good VR-QOL and low number of patients with depression, indicate that these patients do not need specific screening and intervention measures on QOL and depression.

**Vision related quality of life in HLA-B27 associated anterior uveitis**

Because we were interested if patients with HLA-B27 associated AU differ with regard to VR-QOL compared to herpetic AU patients in the same region, we evaluated this in chapter 6. Patients with HLA-B27 associated AU have a relatively high VR-QOL, scoring almost the same as those in the working population. In addition, they also score comparable to herpetic AU patients (chapter 5).

The difference that we found, is that HLA-B27 associated AU patients score lower on general health. In addition, patients with an associated systemic disease scored even lower on general health, compared to patients without an associated systemic disease. In the literature we found several studies on health related QOL in ankylosing spondylitis patients. These studies also found an evident influence of systemic disease on reported physical and mental health.

There were six patients with a mild depression in patients with HLA-B27 associated AU, compared to one in herpetic AU patients (10 versus 3%). Patients with a depression also scored lower on VR-QOL and more often had ankylosing spondylitis (5/6 (83%)). This suggests that a systemic disease increases the chance of developing a depression. Qian et al. also observed that non-infectious uveitis patients with a depression scored far lower on VR-QOL, than non-depressed patients, however this study also included severe posterior and panuveitis patients.

Overall, it seems that infectious and non-infectious AU patients have a relatively high VR-QOL. But awareness on lowered general health and depression, especially in patients with an associated systemic disease, is crucial.

**FUTURE PERSPECTIVES**

The research conducted in this thesis adds new information to the already existing literature. We used homogeneous patient groups and the guidelines for uniform reporting in uveitis studies as developed by the SUN working group. To be able to compare future studies, it is important to use a guideline for reporting data. This should for example prevent a wide variety of definitions of ocular complications between studies, hopefully leading to a less wide variety of reported incidences of these complications. In addition, the use of homogeneous patient groups is also important to compare future studies and to contribute to a more personalized care of uveitis patients.
Most studies performed in the literature are retrospective studies, just like the research that we conducted. To answer certain issues, prospective studies are needed. It would be interesting to try to tie the ocular complications to the disease process or the side effects of the uveitis treatment (e.g. steroid use). Since therapy and the disease process are entwined, this cannot reliably be done in a retrospective study. In addition, chapter 3 gives an indication that IOP peaks may be prevented by early and prolonged use of antiviral and anti-glaucoma medication. A prospective study is needed to determine the optimum starting point and duration of treatment and to evaluate whether this eventually prevents the development of secondary glaucoma.

Further, it would be interesting to know the chance for unilateral HLA-B27 associated AU patients to become bilateral. In our study (chapter 4) the median interval between uveitis in the first and second eye was 4.2 years and the total follow up of the unilateral patients was 2.7 years. This means that it could well be that the second eye of seemingly unilateral patients will get involved in the future. A longer (prospective) study is needed to provide clarity on this matter.

Patients often want to know the risk of recurrence of the uveitis and the factors that trigger a relapse. To answer these questions, factors that could lead to a uveitis should be investigated (e.g. stress, other diseases, season, compromised immune system) in a prospective way, at the time of the active uveitis. At this moment we cannot give an answer on this matter.

With regard to the QOL studies (chapter 5 and 6), both studies have a modest sample size. The sample size is considered adequate for overall analyses, but it may be too limited for all subgroup analyses. Further studies with larger patient groups are needed to investigate if there are additional associations. A possibility to obtain more patients is conducting a multicenter study.

Recent research emphasizes that the definitive diagnosis of herpetic AU can only be proven by aqueous humor analysis.60,61 Because the research we conducted is mainly retrospective, most of the herpetic patients we included were diagnosed by clinical characteristics for HSV or VZV, including unilateral AU, small or medium sized keratic precipitates, iris atrophy, elevated IOP at onset, keratitis and skin lesions. In recent years more aqueous humor analyses are performed, which allows for future (prospective) studies to include more patients who are proven herpetic.
REFERENCES


