








Multidisciplinary management of auto-immune ocular diseases in adult patients by ophthalmologists and rheumatologists

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ABSTRACT.

Purpose: Management of chronic vision threatening auto-immune ocular diseases (AIOD, e.g. uveitis, scleritis) can be challenging. Guidelines recommend a multidisciplinary approach (MDA) with ophthalmologists and rheumatologists, to enhance the recognition of systemic diseases and guide the use of immunosuppressives. However, the indications and results of such an approach have not yet been studied.

Methods: A monocentre, retrospective chart review of all patients treated in a MDA between ophthalmologists and rheumatologists, in a Dutch tertiary center. The collaboration was twofold: a combined multidisciplinary team meeting every 2 weeks, and an ophthalmology-dedicated rheumatology outpatient clinic. Primary endpoints of this descriptive study were as follows: indications for MDA, new diagnoses of systemic auto-immune diseases and changes in systemic immunosuppression and prednisone dosages.

Results: In total, 157 adults (mean age 46 years, 57% female, median disease duration 19 months) were included, mainly with uveitis (74%) and scleritis (12%). Multidisciplinary approach (MDA)-indications included diagnostic workup (32%), treatment support (44%), diagnostic-and-treatment support (10%) and side effects (8%). A systemic disease was newly diagnosed in eight and already present in 34 patients. At baseline, 54 patients used oral prednisone at >7.5 mg/day. Non-corticoid immunosuppressives, mostly methotrexate, were started in 41% of the patients. During follow-up, systemic prednisone was lowered to ≤7.5 mg/day in 68% of the patients.

Conclusion: This evaluation of an MDA-programme in the management of AIOD demonstrated its added value. Mainly, it addressed the high demand for support in managing systemic immunosuppression, resulting in significant corticosteroid tapering. In addition, it resulted in the recognition of underlying systemic diseases.

Key words: Uveitis – scleritis – multidisciplinary – treatment – systemic diseases – immunosuppression – corticosteroids

*Both authors contributed equally to this work.

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Introduction

The management of auto-immune ocular diseases (AIOD), such as uveitis and scleritis, can be a challenge. These diseases are frequently associated with an underlying systemic disease and might require long-term systemic immunosuppressive treatment. This requires extensive experience and, according to guidelines, can benefit from a multidisciplinary approach (Nederlands-Oogheekundig-Genootschap 2015; Wakefield et al. 2017; Dick et al. 2018). However, such an approach has not yet been specified nor evaluated in previous studies or guidelines.

Auto-immune ocular diseases (AIOD), in particular uveitis, are among the major causes of ocular morbidity, resulting in vision loss in up to 35% of patients and accounting for 5–10% of blindness worldwide (de Smet et al. 2011; Miserocchi et al. 2013). These diseases can be associated with infections, systemic immune-mediated diseases and eye syndromes. Importantly, underlying systemic diseases, such as spondyloarthritis, sarcoidosis, Behçet's disease, vasculitis and juvenile idiopathic arthritis, can be present in up to 40–50% of patients with AIOD, although prevalences may differ for different countries (Schwartzman 2016; Lopalco et al. 2018; Bro & Tallstedt 2019). In some diseases, such as in spondyloarthritis, eye involvement can be the first symptom of the disease (Braakenburg et al. 2008; Haroon et al. 2015; Pasadhika & Rosenbaum

2015). Timely diagnosis can limit the (non-ocular) complications, but might also influence choices for therapeutic management.

The treatment of AIOD depends on different variables, such as anatomic site and associated auto-immune diseases, but generally starts with a corticosteroid. If local treatment is insufficient, systemic corticosteroids are indicated, initially in high doses to rapidly control the inflammation and prevent visual loss (Nederlands-Oogheelkundig-Genootschap 2015). However, systemic corticosteroids alone might not control the inflammation sufficiently in all patients. Furthermore, prolonged treatment with >7.5 mg prednisone during >3 months is undesirable, as it is associated not only with systemic complications such as hypertension, obesity, diabetes mellitus and osteoporosis, but also with ocular complications such as cataract and glaucoma (Wei et al. 2004; Huscher et al. 2009). In these cases, treatment guidelines recommend initiation of corticoid-sparing therapy with conventional disease-modifying antirheumatic drugs (cDMARDs, e.g. methotrexate or mycophenolate mofetil) or biological DMARDs (bDMARDs, e.g. TNF inhibitors, such as adalimumab or infliximab) (Nederlands-Oogheelkundig-Genootschap 2015).

In 2011, Nguyen and colleagues studied the treatment patterns of ophthalmologists specialized in uveitis. One of their conclusions was that patients were treated with higher corticosteroids doses (>7.5–10 mg per day), much longer (>3 months) than recommended by guidelines (Nguyen et al. 2011). As this can be harmful, Nguyen emphasized the importance of multidisciplinary collaboration in the management of these diseases. Accordingly, ophthalmological guidelines recommend the consultation of a rheumatologist in case of persistent or recurrent ocular inflammation, as rheumatologists are specialized in the recognition of systemic diseases and are familiar with the use of corticoid-sparing immunosuppressives (Nederlands-Oogheelkundig-Genootschap 2015; Dick et al. 2018). Unfortunately, current guidelines neither provide recommendations on the form, nor report on the effect of this collaboration. In addition, literature on the subject is lacking, a need that was specifically mentioned by the FOCUS (Fundamentals Of Care for Uveitis) initiative recently (Dick et al. 2018).

A structured multidisciplinary collaboration between ophthalmologists, who are specialized in AIOD, and rheumatologists was initiated, at a Dutch University Medical Centre, in 2017. The collaboration was mainly aimed at supporting the ophthalmologist in recognizing underlying systemic diseases and managing immunosuppressive treatment for adult patients with AIOD. This descriptive study aimed to illustrate the use and benefits of this multidisciplinary approach (MDA), in terms of (1) the indications for a MDA and (2) the results of this MDA, subdivided into the type of provided recommendations, newly diagnosed systemic auto-immune diseases, management of systemic immunosuppression and corticosteroid-sparing effect.

Materials and Methods

Framework multidisciplinary collaboration

The multidisciplinary collaboration (MDA) consisted of regular multidisciplinary team meetings (MTMs) and an easily accessible, specialized ocular rheumatology outpatient clinic ('clinic') for more intensive support. The MTMs were carried out once every two weeks and could be used to discuss any type of questions or problems arising during the management of the AIOD. The 'clinic' was an outpatient clinic at the Department of Rheumatology, to which ophthalmologists could refer patients for any indication related to their AIOD, in case a diagnostic workup or changes in immunosuppressive treatment were needed.

Study design and population

A retrospective chart review was conducted, including all adult patients with AIOD who were treated within the multidisciplinary collaboration, either the MTM, clinic or both, between the Ophthalmology (uveitis clinic) and Rheumatology department of the Amsterdam University Medical Centre location VUmc, a tertiary center, between January 2017 and July 2019. There were no exclusion criteria. The study protocol was approved by the medical ethics committee of the Amsterdam UMC, location VUmc (number: 2020.039). The study was carried out according to the declaration of Helsinki.

Study parameters

Clinical data and MTM-data were abstracted from the medical records, recorded by ophthalmologists and rheumatologists in the electronic health records (EHR) of each patient.

Baseline parameters

Baseline was set at the first MTM referral meeting or the first patient visit to the Department of Rheumatology. Baseline data were collected on: age, sex, pre-existing rheumatic/systemic disease, treatment with systemic immunosuppressives (corticosteroids, cDMARDs, bDMARDs) and details regarding the eye disease.

Eye disease details were determined based on the most recent information in the EHR, as classified by the ophthalmologist: disease duration (months), localization (anterior, intermediate, posterior, or panuveitis; scleritis, conjunctivitis or other), and diagnosis (systemic disease, eye syndrome, infection, masquerade syndrome, or idiopathic). A 'systemic disease' implied systemic auto-immune disease such as axial spondyloarthritis, Behçet's disease, sarcoidosis, juvenile idiopathic arthritis or multiple sclerosis. An eye syndrome entailed different posterior uveitis disorders that confine to the eye (e.g. white dot syndromes such as: birdshot chorioretinopathy, acute zonal occult outer retinopathy (AZOOR), or multifocal choroiditis).

Outcome parameters

The following main outcome parameters were collected for the multidisciplinary approach (MDA) in general, and subdivided for the multidisciplinary team meetings (MTM) and clinic.

(1) *Indications for multidisciplinary approach*: Indications for collaboration were abstracted from the official referral question defined in the clinic-referral-form or MTM-record. Multidisciplinary team meetings (MTM) indications were reported for every MTM, and not per patient, as some patients were discussed multiple times. Indications were classified as: 'diagnostic workup', 'treatment support' (including the indication, preferred medication, and initiation of a new therapy), 'treatment side effects', 'both diagnostics and therapy', or 'other' (e.g. logistical questions). The indications were abstracted by two reviewers and discussed when different options

were chosen; agreement was reached in all cases.

(2) *Type of actions following multidisciplinary approach.* Actions were defined as either recommendations provided at the MTM, or management executed at the clinic. Actions were classified as: continue current treatment, start (new) therapy, change current therapy, referral to rheumatologist, referral to other specialist (not ophthalmologist or rheumatologist), diagnostic testing, or logistical advice (e.g. how to deal with therapy refusal by patient, or frequency of follow-up visits to monitor therapy).

In addition, the number of days between the date of recommendation and the date the recommendation was effectuated, e.g. ordering laboratory examination, starting medication, or referral to another specialist, was collected.

(3) *Results from the approach. New diagnoses systemic disease*—Any new diagnosis of a systemic auto-immune disease made after referral to the clinic. *Systemic treatment*—All details concerning immunosuppressive medication were recorded: pre-existing medication, new medication, duration of treatment and changes in dosing. Recorded medication included: cDMARDs (methotrexate, azathioprine, mycophenolate mofetil, sulfasalazine), bDMARDs (adalimumab, infliximab, rituximab), corticosteroids or other systemic immunosuppressives.

Corticoid-sparing effect—For patients with a baseline prednisone dose of >7.5 mg per day, adjustments in oral prednisone use were evaluated, as Ophthalmological guidelines recommend to start corticoid-sparing therapy (e.g. DMARDs) in case long-term (>3 months) treatment with prednisone dosages of >7.5 mg is expected to be required (Nederlands-Oogheelkundig-Genootschap 2015; Dick et al. 2018). Therefore, details were collected on whether the prednisone dose could be decreased to ≤7.5 mg, and the time until that threshold was reached in months. The last noted contact in the EHR was used as last follow-up.

Data analysis

Data analysis was performed with IBM SPSS Statistics for Windows, version 24.0 (Armonk, New York, 2016). Patient characteristics were presented as mean with standard deviation (SD) or median with interquartile range (IQR).

The indications for collaboration, the type of actions (recommendations/management), the new therapies and new diagnoses were described as numbers and percentages of the total. Median prednisone dosages at baseline and follow-up were compared using Wilcoxon signed-rank test, two-sided and a level of significance of $p < 0.05$. For patients with a baseline prednisone of >7.5 mg, in whom a DMARD was initiated or increased in dose, a Kaplan–Meier plot was generated to visualize the decrease of prednisone over time.

Results

During the multidisciplinary collaboration, 157 patients with a mean age of 46 years (SD 16) and 57% female were treated between January 2017 and July 2019 (Table 1). At referral, the median duration of the AIOD was 19 months (IQR; 3–100) from diagnosis. At referral, 41% ($n = 65$) of the patients were using systemic

corticosteroids, 83% ($n = 54$) with a daily dose of >7.5 mg.

Of the 157 patients, 129 (82%) were referred to the clinic and 92 (59%) were discussed at the MTM and 41% were included in both, MTM and clinic (Fig. 1). The number of newly evaluated patients was the highest in the first year (2017: MTM $n = 40$, clinic $n = 62$), and decreased in the subsequent years (2018: MTM $n = 40$, clinic $n = 44$; 2019 until August: MTM $n = 12$, clinic $n = 23$) as many patients were discussed repeatedly.

Type of Eye disease

Uveitis was diagnosed in 74% ($n = 116$) of the patients, 12% had scleritis ($n = 19$), 3% conjunctivitis ($n = 4$), and 11% another diagnosis ($n = 18$; e.g. keratitis, optic papillitis, occlusive retinal vasculitis). The associated disease was already known in 39% of the patients, being most frequently a previously diagnosed systemic disease ($n = 37$, 24%; Table 1) or an eye syndrome ($n = 24$, 15%; Table 1).

Table 1. Patient characteristics at baseline.

| | Total ($n = 157$) | MTM ($n = 92$) | Clinic ($n = 129$) |
|---|-------------------------|---------------------|-------------------------|
| Age in years, mean ± SD | 46 ± 16 | 45 ± 16 | 47 ± 16 |
| Sex, female (%) | 89 (57) | 51 (55) | 75 (58) |
| Eye disease duration in months, median (IQR) | 19 (3–100) | 20 (3–90) | 18 (3–99) |
| Location of the eye disease | | | |
| Anterior uveitis, n (%) | 40 (25) | 17 (18) | 31 (24) |
| Intermediate uveitis, n (%) | 24 (15) | 17 (18) | 20 (16) |
| Posterior uveitis, n (%) | 28 (18) | 19 (21) | 25 (19) |
| Panuveitis, n (%) | 24 (15) | 18 (20) | 20 (16) |
| Scleritis, n (%) | 19 (12) | 8 (9) | 18 (14) |
| Other, n (%) | 22 (14) | 13 (14) | 15 (10) |
| Aetiology of eye disease | | | |
| Systemic inflammatory disease ^I , n (%) | 37 (24) | 32 (35) | 19 (15) |
| Eye syndrome, n (%) ^{II} | 26 (17) | 17 (18) | 23 (18) |
| Idiopathic, n (%) | 83 (53) | 40 (44) | 77 (60) |
| Infection, n (%) ^{III} | 1 (1) | 1 (1) | 1 (1) |
| Masquerade syndrome, n (%) ^{IV} | 1 (1) | 1 (1) | 1 (1) |
| Treatment at baseline | | | |
| Systemic corticosteroids, n (%) | 65 (41) | 49 (53) | 53 (41) |
| Daily dose, mg, median (IQR), Dosage > 7.5 mg, n (%) | 15 (10–22.5) 54 (83) | 40 (82) | 46 (87) |
| Conventional DMARD, n (%) | 33 (21) | 25 (26) | 22 (17) |
| Biological DMARD, n (%) | 9 (6) | 9 (10) | 1 (1) |

Values are depicted as mean (standard deviation, SD), median (interquartile range, IQR) or number (%). I: axial spondyloarthritis ($n = 10$), sarcoidosis ($n = 9$), systemic lupus erythematosus ($n = 4$), multiple sclerosis ($n = 3$), rheumatoid arthritis ($n = 3$), granulomatosis with polyangiitis ($n = 2$), juvenile idiopathic arthritis ($n = 2$), Behçet disease ($n = 1$), psoriatic arthritis ($n = 1$), hyper eosinophilic syndrome ($n = 1$). II: birdshot chorioretinopathy ($n = 10$), multifocal choroiditis ($n = 4$), Vogt-Koyanagi-Harada syndrome (restricted to the eye; $n = 3$), AZOOR ($n = 2$), chronic relapsing inflammatory optic neuropathy ($n = 1$), Fuch’s heterochromie iridocyclitis ($n = 1$), Tolosa Hunt syndrome ($n = 1$), serpiginous choroiditis ($n = 1$), granulomatous inflammation restricted to the eye ($n = 3$). III: Lues infection. IV: B-cell lymphoma. Clinic = Rheumatology outpatient clinic, DMARD = disease-modifying antirheumatic drug (Conventional: methotrexate, azathioprine, mycophenolate mofetil; biological: TNF inhibitors, rituximab).

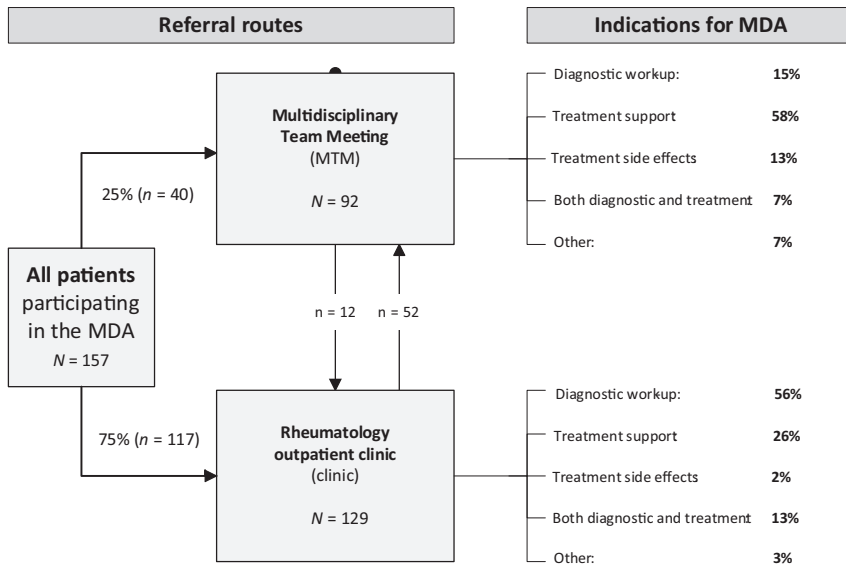


Fig. 1. Flow chart of patients ($n = 157$) and indications for the multidisciplinary collaboration (MDA). Indications for multidisciplinary collaboration were reported in percentage per type of collaboration. Clinic, ocular rheumatology outpatient clinic ($n = 129$); MTM, multidisciplinary team meeting (92 patients were discussed in 173; meetings, as some patients were discussed several times. The indications were described for the total number of MTMs). Diagnostic workup: examination of a possible underlying systemic disease. Other indications were ‘procedural questions’ (MTM $n = 12$, 7%) and ‘restart follow-up Rheumatology’ (Clinic: $n = 4$, 3%).

However, in 53% of the patients, the eye disease was idiopathic (not related to systemic disease, nor a specific ocular diagnosis).

Indications for multidisciplinary collaboration (MTM or referral to the clinic)

In total, 129 patients were evaluated at the clinic, and 173 MTM discussions were performed concerning 92 patients (40 patients were discussed at multiple meetings; 20 more than twice).

Figure 1 depicts the indications for multidisciplinary collaboration, being most commonly: treatment support ($n = 133$, 44%), diagnostic workup ($n = 98$, 32%), combination of diagnosis and therapeutic indication ($n = 29$, 10%) and treatment side effects ($n = 26$, 8%). At the MTM, the most important reason for consultation was treatment advice (65%), whereas at the clinic, the most prevalent reason for referral was diagnostic workup for an associated systemic disease (69%).

Type of actions following multidisciplinary approach

At the MTMs (173 MTM contacts on 92 patients), recommendations mostly concerned therapeutic advice: e.g. to start (21%) or change (18%) therapy, (Fig. 2 and 3). MTM recommendations were provided in 99% of the contacts, and implemented in 94% (162/172), with a median time to implementation of 0 days (IQR 0–12).

At the clinic (129 referred patients), actions mostly encompassed a diagnostic workup ($n = 110$) and the initiation of new immunosuppressive ($n = 54$; Fig. 2). The median duration of follow-up at the Rheumatology outpatient clinic was 3 months (IQR 1–9).

New diagnoses at the clinic

In 110 of the 129 patients referred to the clinic, the rheumatologist examined the patient for any undiagnosed underlying systemic disease, resulting in eight new diagnoses (7.3%): axial spondyloarthritis ($n = 5$), sarcoidosis ($n = 1$), eosinophilic granulomatosis with polyangiitis ($n = 1$), and remitting seronegative symmetrical synovitis with pitting Oedema ($n = 1$).

New therapies

New systemic therapy was started in 59 (41%) of all 157 patients, mostly a cDMARD (76%; e.g. methotrexate, Fig. 3,4), or a bDMARD ($n = 13$, 12%). Medication was generally started very soon, at a median of 0 months after baseline (IQR 0–3), by

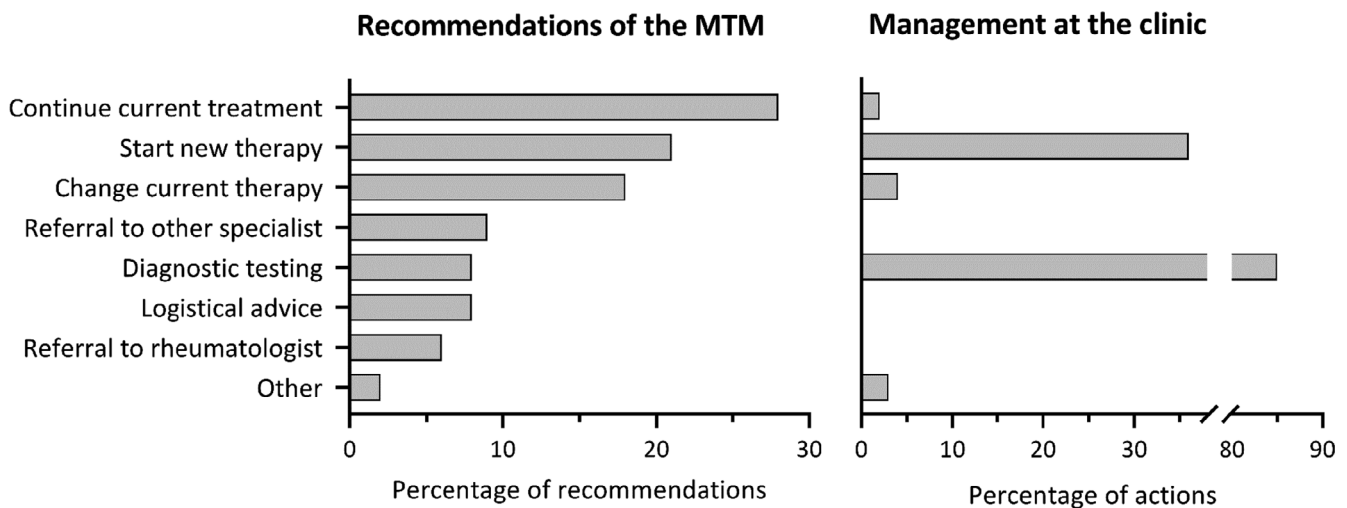


Fig. 2. Actions following multidisciplinary approach. Either recommendations provided by the multidisciplinary team meeting (MTM; 173 MTMs; 172 recommendations) or management performed at the clinic (129 patients; 69 actions).

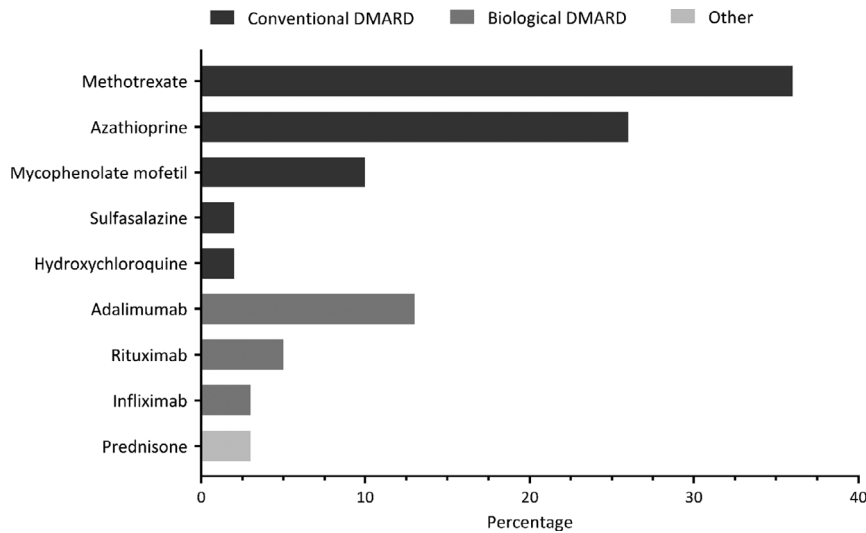


Fig. 3. Type of medication started, anytime during follow-up (62 new treatments in 59 patients). This implies newly prescribed systemic medicaments, as a result of the collaboration, either at the multidisciplinary team meeting or at the ocular rheumatology outpatient clinic.

Patients with initiation or increase of DMARD (n = 38)

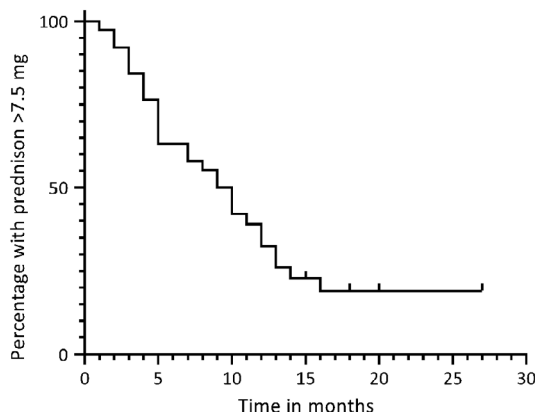


Fig. 4. Percentage of patients with a prednisone dose of >7.5 mg/day (n = 38), in whom a DMARD was initiated or increased, in months after the first evaluation in multidisciplinary context (either multidisciplinary team meeting or clinical evaluation). Decrease to ≤7.5 mg was achieved in 29 patients within median 10, IQR 5–13, months. DMARD = disease-modifying antirheumatic drug.

the rheumatologist (71%) or the ophthalmologist (29%). The indications for new systemic medication were posterior uveitis (30%), intermediate uveitis (25%), panuveitis (19%), scleritis (11%), anterior uveitis (8%) and other diagnoses (7%).

Corticosteroid use

At referral, 65 patients used oral prednisone, for a median period of 4 months (IQR 1–12, Table 1). A daily prednisone dose of >7.5 mg (median 20 mg, IQR 15–25) was used by 54 patients for a median of 4 months (IQR 1–12, range 1–240).

Among the 54 patients with prednisone >7.5 mg, in 70% (n = 38) a DMARD was either newly initiated (n = 33) or increased in dose (n = 5). In the remaining 30% (16), of whom 5 already used a DMARD, no changes in immunosuppressive treatment were carried out, because the duration of the uveitis flare was expected to be short, and corticosteroids could be tapered within three months.

Of the 38 patients with >7.5 mg prednisone at baseline for whom changes in cDMARDs or bDMARDs were carried out, 63% had used this high prednisone dose already for ≥4 months (median duration 20 months, IQR 15–

25, min–max 1–240). Of these 38 patients, 29 (76%) achieved a decrease to ≤7.5 mg (Fig. 4), of whom 15 patients were even able to discontinue systemic prednisone. Of the 9/38 patients who did not reach a prednisone dose of ≤7.5 mg, eight patients had a very complex disease course (several flares, comorbidity, therapy unresponsiveness or incompliance), but with ongoing intensive involvement of both ophthalmologist and rheumatologist. For these 38 patients, the mean follow-up duration after the first MDA consultation was 19 (SD7) months.

Of the 16 patients with a baseline prednisone of >7.5 mg, in whom DMARD therapy was neither initiated nor increased, 13 (81%) achieved a decrease to ≤7.5 mg, within a median of 3 months, (IQR 0–10). Nine (56%) patients were able to discontinue oral prednisone, of whom one discontinued because no further improvement in vision was expected. Two patients did not reach a low prednisone dose (≤7.5 mg) during their <3 months follow-up. For these 16 patients, the mean follow-up duration was 11 (SD 8) months.

Discussion

The present study evaluated a multidisciplinary collaboration (MDA) between ophthalmologists and rheumatologists in the management of a variety of autoimmune ocular diseases (AIOD). Although the importance of such a collaboration has been stressed in various guidelines and by the FOCUS initiative, to our knowledge, this is the first study that looked into its practical implementation (Dick et al. 2018).

The collaboration proved to be useful for several reasons. The two most important reasons for ophthalmologists to refer patients to the ophthalmology-dedicated Rheumatology clinic were the need for therapeutic advice regarding systemic immunosuppressive drugs (54%) and a diagnostic workup for underlying systemic disease (42%). In the regular Multidisciplinary Team Meetings (MTM), a larger variety of questions was discussed, questions that would not always require a full rheumatology workup, such as whether to change/initiate DMARD, interpretation of side effects and use of additional diagnostics. The management of treatment-related adverse events was subject of MDA in 2% (clinic) and

13% (MTM). Recently, an expert committee also reported this to be an important reason to collaborate on these patients (Wakefield et al. 2017). Importantly, 41% of the patients were both discussed at the MTM and seen in the clinic, with different indications for the clinic and MTM, emphasizing the complexity of these type of patients. The recommendations were effectuated in the majority of the situations (94%). This indicates not only the need for multidisciplinary support, but also that this support resulted in useful and applicable recommendations.

New systemic immunosuppressives were initiated in 41%, resulting in a substantial decrease in the use of high corticosteroid doses, which emphasizes the beneficial effects of this collaboration. A recent report demonstrated that the lack of experience with corticoid-sparing immunosuppressants (DMARDs) among ophthalmologists could delay the tapering of corticosteroids (Nguyen et al. 2011). In accordance with Nguyen, also in the current study, the majority of patients with a high baseline prednisone already used high doses for far more than the recommended three months, before a DMARD was considered. Easily accessible multidisciplinary support, with experts experienced in the prescription of DMARDs, could enhance a corticoid-sparing approach. Consequently, the MDA resulted in corticoid-sparing treatment in 70% of the patients with high baseline corticosteroid doses (>7.5 mg/day). Importantly, this resulted in a more acceptable, low (≤ 7.5 mg) daily prednisone dose in the majority (76%) and was not achieved mostly in patients with a more complex disease course and despite intensive involvement by both specialists. In 30% of patients with high baseline prednisone, a DMARD was considered but regarded not to be indicated, which appeared to be justified, as in 83% of these patients the prednisone could be tapered within four months without additional non-corticoid immunosuppression. Overall, these results demonstrate that corticoid-sparing treatment can effectively reduce prednisone doses in most patients and should therefore not be delayed. However, it is important to acknowledge that control of

inflammation is still an important challenge in a small group with a more complex disease.

Methotrexate (37%) and azathioprine (27%) were the most often prescribed corticosteroid-sparing therapies in this study. Existing guidelines recommend methotrexate and mycophenolate mofetil as the preferred corticosteroid-sparing therapy, and azathioprine and ciclosporin as alternatives. (Nederlands-Oogheekundig-Genootschap 2015; Schwartzman 2016; Rosenbaum et al. 2019) However, randomized controlled (and head-to-head) trials are limited, studies have been mostly performed in diverse inflammatory eye diseases, and guidelines do not specify which DMARD should be prescribed for the different inflammatory manifestations. (Nederlands-Oogheekundig-Genootschap 2015; Schwartzman 2016; You et al. 2017; Dick et al. 2018; Gangaputra et al. 2019; Rathinam et al. 2019) In daily practice, choices of medication are influenced by both the eye disease, the type of patient, the associated disease and experience of the clinician (Esterberg & Acharya 2012). In addition, previous studies have shown that ophthalmologists and rheumatologists may have different preferences, based on costs, sub-specialization and hospital authorization. All these factors emphasize the complexity of therapeutic decision-making in these patients and the importance of combining expertise (Ozzello et al. 2016; Palestine et al. 2016). The current study included many patients in reproductive age, whose possible desire to have children in the near future had to be taken into account. Azathioprine is known to be a safe medication during pregnancy and is also effective in treating inflammatory eye diseases, which is why it is chosen as the primary DMARD for some young patients (Wakefield et al. 2012; Nederlands-Oogheekundig-Genootschap 2015). This 'deviation' from the guidelines, emphasizes how a MDA can help in personalized medicine and still pursue effective treatment, as the treatment success rate in our study (70%, within 9 months) was still comparable to other studies that generally find the same response rate, with 6 months to reach a prednisone dose of <10 mg (Galor et al. 2008; Gangaputra et al. 2019; Rathinam et al. 2019).

The second main reason for this collaboration was to enable the earlier

recognition of associated systemic diseases, which are considered to cause 8–50% of AIOD (Schwartzman 2016; Lopalco et al. 2018; Bro & Tallstedt 2019). In this study, a new systemic disease was detected in 7% of the patients who underwent a diagnostic workup. Including the patients with a previously diagnosed systemic autoimmune disease, the prevalence in this study was 29%, most commonly spondyloarthritis and sarcoidosis. This is in accordance with epidemiologic studies, as uveitis in general is often associated with sarcoidosis and anterior uveitis is most frequently related to spondyloarthritis (Haroon et al. 2015).

This study has limitations. First, only patients with more complex disease, who had insufficient response to local treatment, or were suspected of having an associated systemic disease, were included. Second, as in all retrospective studies, the outcome measures depend on accurate recordkeeping. Therefore, main outcome measures were abstracted by two researchers and classified as accurately as possible. The main outcome parameters could be abstracted without difficulty, because they were explicitly defined in the records. Third, the effect of the MDA on successful treatment was based on the decrease in oral prednisone. Ideally, disease activity parameters could have been used, but this requires using detailed and standardized classification by the ophthalmologist (the SUN classification), which is generally not feasible in daily practice (Khairallah 2010). The prednisone dosage, as noted in the patient record, was considered a more measurable and reliable outcome summarizing the overall activity, as, in general, lower doses of prednisone implicate lower disease activity. Theoretically, end-stage vision loss, where systemic therapy is not expected to result in improvement, could also lead to corticosteroid tapering, but this was the case in only one patient. Also, the influence of changes in local immunosuppressive treatment of the AIOD was not incorporated in the results, as this was not part of the MDA. Fourth, the follow-up time was not equal in each patient (range 1–30 months), as data abstraction was performed within 1 month after inclusion of the last patient, potentially resulting in underreporting of treatment success in patients with a short follow-up. Nonetheless, the rapid and

significant decrease of prednisone is an interesting result. Fifth, there was no control group available; thus, we cannot say for how long corticosteroid treatment would have continued without the MDA. Finally, the current MDA focused mostly on the role of the rheumatologist in supporting the ophthalmologists, whereas the role of the ophthalmologist in supporting the rheumatologist in the treatment of rheumatic diseases with ocular manifestations, could be explored further. Following our experience, in future MDA, it could be considered to discuss patients first at the MTM, before referring them to the clinic, as in some cases, recommendations alone might already provide sufficient support. In addition, consulting a rheumatologists might be considered for all patients with high corticosteroid doses in order to enhance early corticosteroid-sparing therapy.

In summary, this study is the first to report on the implications and effects of a multidisciplinary collaboration between ophthalmologists and rheumatologists, on the management of AIOD in adults. This work offers valuable insights into the importance of collaboration for these potentially complex diseases and demonstrates it to be useful for a wide range of patients and indications. Importantly, there was a high demand for support in diagnostic workup and the management of immunosuppressives. Consequently, this multidisciplinary approach was beneficial both, in terms of the recognition of systemic diseases and lowering the threshold for starting systemic non-corticoid immunosuppressives, which resulted in a corticosteroid-sparing effect. This study supports the benefits of a multidisciplinary approach, in any center treating complex AIOD and emphasizes that it should, at least, provide easily accessible support in the use of systemic immunosuppressives.

References

- Braakenburg AM, de Valk HW & de Boer J et al. (2008): Human leukocyte antigen-B27-associated uveitis: long-term follow-up and gender differences. *Am J Ophthalmol* **145**: 472–479.
- Bro T & Tallstedt L (2019): Epidemiology of uveitis in a region of southern Sweden. *Acta Ophthalmol* **98**: 32–35.
- Dick AD, Rosenbaum JT, Al-Dhibi HA et al. (2018): Guidance on noncorticosteroid systemic immunomodulatory therapy in noninfectious uveitis: fundamentals of care for Uveitis (FOCUS) Initiative. *Ophthalmology* **125**: 757–773.
- Esterberg E & Acharya NR (2012): Corticosteroid-sparing therapy: practice patterns among uveitis specialists. *J Ophthalmic Inflamm Infect* **2**: 21–28.
- Galor A, Jabs DA, Leder HA 3rd & et al. (2008): Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. *Ophthalmology* **115**: 1826–1832.
- Gangaputra SS, Newcomb CW, Joffe MM et al. (2019): Comparison between methotrexate and mycophenolate mofetil monotherapy for the control of noninfectious ocular inflammatory diseases. *Am J Ophthalmol* **208**: 68–75.
- Haroon M, O'Rourke M et al. (2015): A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool). *Ann Rheum Dis* **74**: 1990–1995.
- Huscher D, Thiele K, Gromnica-Ihle E et al. (2009): Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis* **68**: 1119–1124.
- Khairallah M (2010): Are the Standardization of the Uveitis Nomenclature (SUN) Working Group criteria for codifying the site of inflammation appropriate for all uveitis problems? Limitations of the SUN Working Group classification. *Ocul Immunol Inflamm* **18**: 2–4.
- Lopalco G, Venerito V, Sota J et al. (2018): Epidemiological profile of non-infectious uveitis from the rheumatologist's perspective: a survey from two tertiary referral centres in Italy. *Clin Exp Rheumatol* **36**: 68–73.
- Miserocchi E, Fogliato G, Modorati G & Bandello F (2013): Review on the worldwide epidemiology of uveitis. *Eur J Ophthalmol* **23**: 705–717.
- Nederlands-Oogheelkundig-Genootschap (2015): Uveitis richtlijn [Uveitis guideline]. Nederlands Oogheelkundig Genootschap. Available from: <https://www.oogheelkunde.org/sites/www.oogheelkunde.org/files/richtlijnen/Richtlijn-Uveitis-def-geautoriseerde-versie.pdf>.
- Nguyen QD, Hatef E, Kayen B et al. (2011): A cross-sectional study of the current treatment patterns in noninfectious uveitis among specialists in the United States. *Ophthalmology* **118**: 184–190.
- Ozzello DJ, Kolfenbach JR & Palestine AG (2016): Uveitis specialists and rheumatologists select different therapies for idiopathic non-necrotizing anterior scleritis. *Ophthalmol Ther* **5**: 245–252.
- Palestine AG, Kolfenbach JR & Ozzello DJ (2016): Rheumatologists and ophthalmologists differ in treatment decisions for ocular behcet disease. *J Clin Rheumatol* **22**: 316–319.
- Pasadhika S & Rosenbaum JT (2015): Ocular sarcoidosis. *Clin Chest Med* **36**: 669–683.
- Rathinam SR, Gonzales JA, Thundikandy R et al. (2019): Effect of corticosteroid-sparing treatment with mycophenolate mofetil vs methotrexate on inflammation in patients with uveitis: a randomized clinical trial. *JAMA* **322**: 936–945.
- Rosenbaum JT, Bodaghi B, Couto C et al. (2019): New observations and emerging ideas in diagnosis and management of noninfectious uveitis: A review. *Semin Arthritis Rheum* **49**: 438–445.
- Schwartzman S (2016): Advancements in the management of uveitis. *Best Pract Res Clin Rheumatol* **30**: 304–315.
- de Smet MD, Taylor SR, Bodaghi B et al. (2011): Understanding uveitis: the impact of research on visual outcomes. *Prog Retin Eye Res* **30**: 452–470.
- Wakefield D, Abu El-Asrar A & McCluskey P (2012): Treatment of severe inflammatory eye disease in patients of reproductive age and during pregnancy. *Ocul Immunol Inflamm* **20**: 277–287.
- Wakefield D, McCluskey P, Wildner G et al. (2017): Inflammatory eye disease: Pre-treatment assessment of patients prior to commencing immunosuppressive and biologic therapy: Recommendations from an expert committee. *Autoimmun Rev* **16**: 213–222.
- Wei L, MacDonald TM & Walker BR (2004): Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med* **141**: 764–770.
- You C, Sahawneh HF, Ma L et al. (2017): A review and update on orphan drugs for the treatment of noninfectious uveitis. *Clin Ophthalmol* **11**: 257–265.

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