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VISUAL OUTCOME, TREATMENT RESULTS AND PROGNOSTIC FACTORS IN PATIENTS WITH SCLERITIS

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ABSTRACT

Purpose: To analyze the visual outcome, systemic associations, effectiveness of treatment and predicting features of 104 scleritis patients.
Design: Retrospective case series.
Participants: 104 patients treated for scleritis at the University Medical Centers of Groningen and Utrecht.
Methods: The clinical records of 104 patients diagnosed with scleritis between 1992 and 2011 at the University Medical Centers of Groningen, (n= 64) and Utrecht (n=40) were retrospectively analyzed.
Main outcome measures: Loss of visual acuity, ocular complications, related systemic disease, type of treatment, time to treatment success and predictive features.
Results: Mean age was 51.5 (standard deviation[SD], ±13.6) years, 63 (60.6 %) patients were female. Mean follow up was 38.2 (SD± 33.8) months. A loss of more than two lines of Snellen acuity was observed in 23 patients, 3 of whom had a final visual acuity of no light perception (NLP). In general, patients with necrotizing scleritis (n=15) had a poorer outcome.
Ocular complications were observed in 88 (84.6%) patients. Underlying systemic disease was identified in 34 (32.7 %) patients. Steroid-sparing immunosuppressive medication was used in 47 patients, 36 of these were treated with methotrexate (MTX). This led was successful in 17 (47.2%) patients over the course of a mean ± SD 103.7 ± 83.7 weeks. Mycophenolate mofetil (MMF) was the treatment in 10 patients, and in 5 patients treatment success was achieved in a mean ± SD 65.3 ± 37.4 weeks. Treatment with tumor necrosis factor-alpha (TNF-α) antagonists led to treatment success in a mean ± SD 32.6 ± 21.8 weeks in 5 of the 11 treated patients. Patients with loss of visual acuity or those treated with oral steroid-sparing immunosuppressive drugs had more often an underlying associated disease, a bilateral scleritis and a longer period of symptoms at presentation.
Conclusions: Scleritis is a severe ocular inflammation often associated with ocular complications. In this population roughly half of the patients were treated with systemic immunosuppressive medication. MMF and TNF-α antagonists can be used in case of MTX-failure. TNF-α antagonists seemed to be more effective than MTX. Within this group, an underlying associated disease, a bilateral scleritis and a longer period of symptoms at presentation were predictive features for a more severe disease course.

INTRODUCTION

Scleritis is a rare, usually painful inflammation of the sclera that can threaten vision.[1] Scleritis is still classified according to the classification proposed by Watson and Hayreh[2] in 1976 based on anatomic location and appearance (Table 1). Few patients convert from episcleritis to scleritis,[2,3] and only a small group of scleritis patients change from one variant of scleritis to another.[3] Complications such as corneal and scleral thinning, corneal ulcers, serous retinal detachment, papilledema, glaucoma, cataract, and uveitis frequently are seen.[4,5] In 40% to 50% of patients, scleritis is an expression of an underlying systemic disease.[5] Rheumatoid arthritis, Wegener's disease, relapsing polychondritis, systemic lupus erythematosus, inflammatory bowel disease, polyarteritis nodosa, and seronegative spondylarthropathies[5,6] are the most common autoimmune causes. In 4% to 18% of patients, an infectious cause is found, of which herpes zoster is the most frequent cause, followed by tuberculosis, syphilis, leprosy, and Lyme borreliosis.[3,5–7] Other causes of scleritis, such as malignancies, medication, surgery, and trauma, are reported to be rare in all studies. 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. 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 increasingly are be-ing used,[8 –14] sometimes in combination with other steroid- sparing immunosuppressive drugs. Because of the low incidence and prevalence of scleritis,[1] the numbers of studies with large numbers of patients are limited,[15] and well-documented clinical experience in predicting the course of the disease and guidelines for its treatment are not widely available. This retrospective study examined patient characteristics, visual outcomes, ocular complications, and efficacy of treatment for 104 scleritis patients. Furthermore, prognostic factors that correlated with a worse visual prognosis, steroid-sparing immunosuppressive treatment, or prolonged disease duration were investigated.

METHODS AND PATIENTS

One hundred four patients diagnosed with scleritis between 1992 and 2011 at the University Medical Centers of Groningen, The Netherlands (n = 64), and of Utrecht, The Netherlands (n = 40), were analyzed. The Medical Ethical Committee of the University Medical Center of Groningen ruled that approval was not required for this study. Patients were identified by searching on the diagnosis code 'scleritis' in the digital uveitis databases of both centers. If in doubt about the diagnosis of scleritis, the opinion of an academic uveitis specialist based on the patient's file was decisive. Only patients with a follow-up of more than 3 months were included. The Watson and Hayreh classification was used for the type of scleritis, with the diagnosis of posterior scleritis or panscleritis confirmed by ultrasound. Necrotizing scleritis was classified as necrotizing (with inflammation) or scleromalacia perforans (without inflammation).

The decimal equivalent of the Snellen visual acuity of both eyes at presentation and at last follow-up and the maximum visual acuity were recorded. This visual acuity was converted to logarithm of the minimum angle of resolution units and, after computation of mean and standard deviation, was calculated back to Snellen decimal acuity. Loss of visual acuity was defined as a decrease of more than 2 lines on the Snellen chart. No light perception in the affected eye was defined as blindness. Patients whose loss of visual acuity was not a result of the scleritis were excluded from this analysis. Corneal complications were characterized as ulcerative or peripheral thinning. Uveitis was diagnosed when cells could be observed in the anterior chamber or in the vitreous and was classified as anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis. The lens was graded as clear, having cataract, pseudophakic, or having posterior capsule opacification. The presence of cystoid macular edema was noted only if confirmed by fluorescein angiography or optical coherence tomography. Serous retinal detachments were diagnosed by funduscopy or ultrasound. Ocular hypertension was defined as an intraocular pressure of more than 21 mmHg, and the given treatment was recorded.

All 104 patients underwent screening for underlying systemic disease, and 88 patients underwent screening in accordance to the guidelines of the Dutch Ophthalmologic Society: (http://www.oogheelkunde.org/uploads/fl/ve/flvem3mKxt8ThFFYVhn8GQ/Richtlijn- voor-diagnostiek-en-behandeling-van-uveitis-15-mei-2007-1.pdf; accessed January 23, 2012). The other 16 patients were screened by a tailored approach or screening was not performed when scleritis was considered a manifestation of a known systemic disease. Laboratory testing included blood and urine tests, chest radiography, and tuberculin skin testing. Serologic and general laboratory tests included complete blood count, white cell differential, inflammatory parameters (C-reactive protein

and erythrocyte sedimentation rate), liver and kidney function tests, antinuclear antibody analysis, antineutrophil cytoplasmic antibody (ANCA) analysis, and rheumatoid factor analysis. Other tests, such as Treponema pallidum antibody titers, Lyme antibody titers, angiotensin-converting enzyme, and human leukocyte antigen (HLA)-B27, were not obtained routinely, but were based on history and physical examination. In case of an underlying systemic disease, the patient was diagnosed by a specialist in that area. Associated systemic diseases were classified as infectious or autoimmune. The most common autoimmune and infectious causes were recorded. The rare causes were listed per patient. When known, the smoking status was included in the analysis.

In these patients, treatment was administered mainly according to a stepladder approach: In infectious causes, the cause of the infection was treated. In autoimmune nonnecrotizing scleritis, NSAIDs were given as a first choice, and in case of NSAID failure, high-dose corticosteroids were given. In case corticosteroids could not be reduced to a dosage of less than 10 mg daily, a corticosteroid-sparing immunosuppressive drug was considered, which was usually MTX. Methotrexate was started orally in a dosage between 7.5 and 15 mg weekly and was increased according to clinical response to a maximum of 25 mg weekly via subcutaneous injection or 30 mg weekly orally. In most patients, this was carried out in at least 3 steps each with an interval of at least 2 months. In case of MTX failure, MMF was started, and in case this failed as well, a TNF-α antagonist was introduced. In case of necrotizing scleritis, corticosteroids and corticosteroid-sparing medication were started immediately.

Treatment success was defined as a subjective and an observable inactive disease for longer than 3 months using less than 10 mg daily oral prednisone alone or in combination with corticosteroidsparing drugs. A relapse was defined as a recurrence of the scleritis after a quiet episode described in the patient file. The total followup time (disease duration including treatment of secondary complications) and time to treatment success were documented. In case of a multiple medication regimen, a stepwise approach was used and the time to control of the inflammation was related to the last added systemic immunosuppressive drug. In patients who were already receiving systemic medication for a systemic disease at presentation, the change in medication or dosage responsible for treatment success was recorded.

How clinical characteristics, visual outcome, ocular complications, and differences in treatment affected outcome was analyzed using SPSS software version 18 (SPSS, Inc, Chicago, IL) based on 3 end points: loss of visual acuity, treatment with steroid-sparing immunosuppressive drugs, or longer disease duration. A P value of 0.05 or less was considered to be statistically significant. To assess the value and weight of the prognostic factors, the chi-square test

for categorical variables, the Student *t* test for comparing independent groups with a continuous variable, and the Spearman bivariate correlation coefficient for analysis of a correlation between 2 continuous variables were used. These findings were verified and confirmed by logistic and linear regression models. Two patients were identified by SPSS analysis (boxplot) as extreme outliers (more than 3.0 times the interquartile range above the third quartile) and therefore were excluded from the analysis. Kaplan-Meier curves were used to display graphically the type of treatment related to time to disease remission.

RESULTS

Patients' characteristics are summarized in Table 1. Of the 104 scleritis patients, 63 (60.6%) were female. Mean follow-up was 38.2 months (range, 3–154 months). Mean age was 51.5 years (range, 18–91 years). The 6 patients with necrotizing disease were the oldest; the 4 patients with posterior disease were the youngest. The latter were all female. Most patients (n = 64) had unilateral disease. Diffuse anterior scleritis was the most common type of scleritis, followed by panscleritis.

Table 2 summarizes ocular complications. Complications were observed in 88 (84.6%) patients. The largest percentage of complications were seen in necrotizing scleritis patients. Uveitis was the most common complication (n = 47). Cataract formation was documented in 30 patients, whereas 6 patients were pseudophakic at presentation. Posterior scleral swelling as shown by ultrasound was found in 31 patients, and 2 patients had posterior scleral thickening related to severe anterior scleritis.

Table 3 shows the loss of visual acuity related to type of scleritis and severity. A loss of more than 2 lines of Snellen acuity occurred in 23 patients (Table 3), 3 of whom became blind (no light perception visual acuity) because of scleritis. All 3 of the latter patients had necrotizing scleritis. In 2 of these patients, there was an association with Wegener's disease, and the third patient had a scleromalacia perforans without known underlying systemic disease.

The 23 patients with a decrease in visual acuity had an average Snellen visual acuity standard deviation (SD) at presentation of 0.9 ± 0.34, and their final average Snellen visual acuity ±SD was 0.66±0.38. The remaining 81 patients showed, on average, an increase in visual acuity of 0.17 (range, 0.007–1.0).

Of the 43 patients (Table 2) with an intraocular pressure to more than 21 mmHg, 26 patients were diagnosed as steroid responders because of the use of local or systemic corticosteroids. Because of the elevation in intraocular pressure, 20 patients were administered antiglaucoma medication, and glaucoma surgery was undertaken in 6 patients.

Table 1. Patient characteristics

Diagnosis/type	N	Mean age (range)	Male N (%)	Female N (%)	Bilateral N (%)
Scleritis total	104	51.5 (18.6 - 91.8)	41 (39.8%)	63 (60.6 %)	40 (38.5%)
Anterior scleritis	71	51.9 (25.4 – 91.8)	29 (40.8%)	42 (59.2%)	29 (40.8%)
Diffuse	36	51.4 (25.4 – 79.5)	13 (36.1%)	23 (63.9%)	18 (50%)
Nodular	20	50.1 (30.5 – 67)	7 (35%)	13 (65%)	5 (25%)
Necrotizing	6	62.5 (41.3 – 91.8)	3 (50%)	3 (50%)	3 (50%)
Scleromalacia	9	50.9 (38.6 – 71.6)	6 (66.7%)	3 (33.3%)	3 (33.3%)
Posterior scleritis (incl SINS)	7	47.9 (18.6 – 73.1)	2 (28.6%)	5 (71.4%)	1 (14.3%)
Posterior	4	39.4 (18.6 – 56.5)	0	4	1 (25%)
Surgery induced (SINS)	3	59.2 (39.8 – 73.1)	2 (66.7%)	1 (33.3%)	0
Panscleritis (anterior + posterior)	26	51.4 (25.6 – 69.2)	10 (38.5%)	16 (61.5%)	10 (38.5%)

Table 2. Ocular complications

Feature	Anterior Diffuse	Anterior nodular	Anterior necrotizing	Sclero-malacia	Posterior	Surgery Induced	Pan-scleritis	N (%)
N total	36	20	6	9	4	3	26	104
Bilateral	18	5	3	3	1	0	10	40 (38.5%)
Ocular complications	31	11	6	7	4	3	26	88 (84.6%)
Corneal Thinning	2	2	2	2	0	0	1	9 (8.7%)
Corneal ulcerative	8	2	4	2	1	0	2	19 (18.3%)
Uveitis	20	1	4	4	2	1	15	47 (45.6%)
Anterior uveitis	18	1	2	3	2	1	10	37 (35.9%)
Intermediate uveitis	2	0	0	1	0	0	1	4 (3.9%)
Panuveitis	0	0	2	0	0	0	4	6 (5.8%)
Cataract	10	2	4	5	1	0	8	30 (28.8%)
CME	5	1	3	1	1	0	11	22 (21.4%)
Exudative retinal detachment	0	0	2	1	0	0	6	9 (8.7%)
T-Sign (US)	0	1	1	0	4	0	25	31 (30.1%)
VA-loss*	10	3	2	4	0	0	4	23 (22.1%)
Ocular hypertension§	13	8	3	3	0	2	14	43 (41.7%)
Steroidresponder	9	4	2	2	0	2	7	26 (25.2%)

CME = cystoid macular edema; US = ultrasound; VA = visual acuity. *Decrease in visual acuity of 2 Snellen lines or more (worse of the 2 eyes) at the end of the follow up. § Intra-ocular pressure higher than 21 mmHg

Table 3. Vision loss related to scleritis

Diagnosis/ type	Anterior Diffuse	Anterior nodular	Anterior necrotizing	Sclero-malacia	Posterior	Surgery Induced	Pan-scleritis	N (%)
N total	36	20	6	9	4	3	26	104
Loss of ≥ 2 Snellen lines*	7	1		1			1	10 (9.6%)
Severe loss > 3 Snellen lines§	3	2		2			3	10 (9.6%)
NLP			2	1				3 (2.9%)

NLP = No light perception. * Decrease in visual acuity of ≥ 2 Snellen lines at the end of the follow up period. § Decrease in visual acuity of > 3 Snellen lines at the end of the follow up period

Underlying systemic diseases are summarized in Table 4. In 34 (32.7%) patients, an underlying cause was found. Within the noninfectious group, rheumatoid arthritis (RA) was the most frequently identified underlying disease (n = 14), followed by Wegener's disease in 7 patients. In most of the patients (n = 26) with an underlying noninfectious cause, the disease was already diagnosed before the first episode of scleritis. In 2 patients, Wegener's disease was found by screening, and in 1 patient, RA was found by screening, and in another it manifested during follow-up. In 3patients, a likely infectious cause of the scleritis was found by screening (Table 4).

Table 4. Underlying systemic disease

Systemic disease	N (%)	Present before scleritis	Diagnosis through screening	Diagnosis during follow up
Total n (%)	34 (32.7%)	26 (25%)	6 (5.8%)	2 (1.9%)
Infectious	3 (2.9%)		3 (2.9%)	
Herpes zoster	2		2	
Lues/syfilis	1		1	
Non-infectious	31 (29.8%)	26 (25%)	3 (2.9%)	2 (1.9%)
Rheumatoid arthritis	14	12	1	1
Wegener's granulomatosis	7	5	2	
Inflammatory bowel disease	3	3		
Behçet's disease	2	2		
Myastenia Gravis	1	1		
Polyarteritis Nodosa	1	1		
Relapsing Polychondritis	2	1		1
Psoriatic Arthritis	1	1		

Screening according to the guidelines of the Dutch Ophthalmologic Society (http://www.oogheelkunde.org/uploads/fl/ve/flvem3mKxt8ThFFYVhn8GQ/Richtlijn-voor-diagnostiek-en-behandeling-van-uveitis-15-mei-2007-1.pdf; accessed January 23, 2012) was performed in 88 patients. The other 16 patients were screened by a tailored approach.

Inflammatory parameters (CRP and ESR) were raised in 52 of the 93 tested patients. In 4 of the 46 tested patients, HLA-B27 positivity was found. Lues serologic level was tested in 62 patients, and in 1 patient, Treponema pallidum antibodies were found. Elevated antinuclear antibody titers were found in 22 of the 79 patients tested. Seven of these patients had an autoimmune disease. Rheumatoid factors were demonstrated in 11 of 73tested patients; 5 of these patients had RA. P or c-ANCA autoantibodies were found in 12 of the 80 patients tested. In 5 of 7 patients with Wegener's disease, an increased c-ANCA titer was found. In 64 patients, the angiotensin converting enzyme (ACE) level was determined, 1 of which was out of normal range. In 82 patients, chest radiography was performed. In 7 of them, abnormalities were found, and in 3 cases, there was a probable association between the findings and scleritis.

To describe and analyze efficacy of treatment, medication at presentation and medication used for the treatment of scleritis are summarized in Tables 5 and 6. At presentation, 31 patients were treated with combinations of different drugs. In 23 patients, NSAIDs were combined with topical steroids, and MTX was combined with NSAIDs at presentation in 6 patients. Mycophenolate mofetil was combined with MTX in 1 patient, and another patient was treated with topical steroids, topical NSAIDs, and antibiotic eyedrops at presentation. None of the patients was taking oral corticosteroids at presentation, and 49 patients were not treated at presentation (Table 5).

Table 5. medication at presentation*

Medication	N (%)
None	49 (47.5%)
Local steroids	46 (44.2%)
NSAIDs	31 (29.8%)
MTX	6 (5.8%)
AZA	4 (3.8%)
MMF	1 (1%)
Cyclosporine	1 (%)
TNF-α antagonist	3 (2.9%)
Antiviral	2 (2.9%)
Antibiotics	5 (4.8%)

AZA = azathioprine; MMF = mycophenolate mofetil: MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs; TNF-α = tumor necrosis factor α. * 31 patients were treated with combinations (see text)

Most of the patients (n = 42) who were treated with NSAIDs had no underlying disease (n = 32). Of the 42 patients treated with NSAIDs, 33 patients also were treated with topical steroids (Table 5). Subconjunctival triamcinolone acetonide injections were used in 3 patients with diffuse anterior scleritis; of these, 1 patient achieved disease remission after 3 subconjunctival injections in 47.1 weeks. Oral corticosteroids were used in 64 patients (Table 6), usually in combination with local steroids (n = 52) and sometimes incombination with NSAIDs (n = 8). For patients who used oral corticosteroids for maintenance, the dosage varied between 5 and 20 mg. On average, patients used more than 7.5 mg daily oral corticosteroids for a mean ±SD of 65 ±72.4 weeks (median, 42 weeks).

Methotrexate was used as treatment in 36 patients (Table 6). The mean dose of MTX was 19 mg weekly (median, 20 mg; range, 10–30 mg), with 1 patient using 30 mg weekly. All patients received folic acid supplementation 24 to 48 hours after their weekly dose of MTX. Treatment success was achieved in 17 of 36 patients with a mean dose of 18 mg weekly (median, 17.5 mg weekly). Within this group, there was no relationship between MTX dosage and chance of treatment success. However, the patients who received a higher dose of MTX (mean, 26.3 mg weekly) showed a smaller range in time to treatment success (range, 80–215 weeks) than the patients who were treated with a lower dose (mean, 15.6 mg weekly) of MTX (range, 21–336 weeks).

Mycophenolate mofetil was used in 10 patients as a steroidsparing immunosuppressive treatment (Table 6); 5 of these patients were treated with MMF after MTX failure. Treatment success was achieved in 5 patients in a mean ±SD of 65.3 ±37.4 weeks (median, 73 weeks). Azathioprine was added to the immunosuppressive regimen in 13 patients; treatment success was achieved in only 1 patient in 192.8 weeks. In 3 patients, a combination of immunosuppressive drugs including azathioprine resulted in treatment success. In these cases, treatment success was attributed to the last added immunosuppressive drug.

In 5 of the 11 patients who received a TNF-α antagonist, treatment success was achieved in 32.6 weeks (SD, 21.8 weeks;median, 28.9 weeks; Table 6). The remaining 6 patients had no treatment success, which was ascribed to a short follow-up time or a change in treatment. Most patients were treated with 1 or 2 other immunosuppressives in addition to a TNF-α antagonist. Only 1patient achieved treatment success with adalimumab as monotherapy. The 4 other patients achieved treatment success with a combination of etanercept and MTX, adalimumab and MTX, or adalimumab combined with MTX and cyclosporine (n = 2). One patient was started on infliximab, but still had active disease at the end of the follow-up.

Of the 8 patients treated with cyclophosphamide (Table 6), 6 had Wegener's disease. Control of inflammation was reached in 4 of these patients with a combination of oral corticosteroids, cyclophosphamide, and azathioprine or MMF in a mean±SD of 68 ± 75.7 weeks. Of the other 4 patients, 1 patient became blind (no light perception visual acuity), 1 patient died during follow-up, 1 patient had active disease, and 1 patient had control of the inflammation with a high dose of oral corticosteroids.

There were 12 patients without described treatment success. Five of these 12 patients had no known systemic disease, and the other 7 patients had RA (n = 2), Wegener's disease (n = 3), or relapsing polychondritis (n = 2). Four patients died during followup; 2 of them had RA and 1 died of ovarian carcinoma. The time and chance of treatment success related to the type of treatment was displayed graphically using Kaplan-Meier curves (Fig 1). In 27 patients, medication was discontinued or changed because of side effects. Overall, 60 patients relapsed 1.65 times (range, 0–5; median, 1).

Table 6. Medication used for scleritis treatment

Medication	N	Remission N %	Mean time till remission (weeks)
NSAID	42	36 (85.7%)	48.8 (median 19.1, min-max 12 – 228.6)
Oral corticosteroids	64	19 (29.7%)	83.9 (median 56.7, min-max 12 – 301.1)
MTX	36	17 (47.2%)	103.7 (median 93.6, min-max 21.9 – 336.7)
AZA	13	1 (7.7%)	192.8
TNF-α antagonist	11	5 (45.5%)	32.6 (median 28.9, min-max 14 – 69.6)
MMF	10	5 (50%)	65.3 (median 73, min-max 26.3 – 115.6)
Cyclophosphamide	8	4 (50%)	68 (median 35.1, min-max 21.4 – 180.4)

AZA = azathioprine; MMF = mycophenolate mofetil: MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs; TNF- α = tumor necrosis factor α.

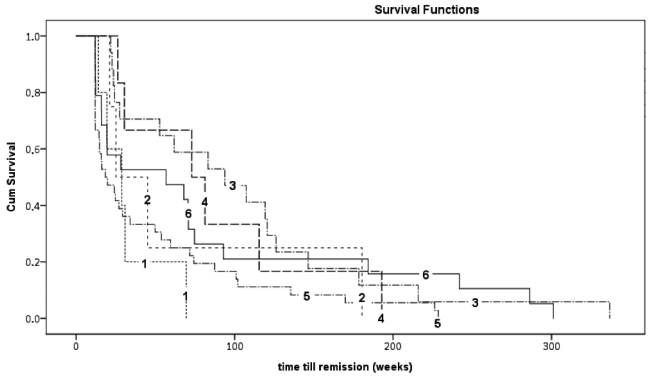

Figure 1. Kaplan-Meier curves showing the time and chance of treatment success related to the type of treatment. 1 = Tumor necrosis factor-alpha antagonists, 2 = Cyclophosphamide, 3 = Methotrexate, 4 = Mycophenolate mofetil, 5 = Nonsteroidal anti-inflammatory drugs, 6 = Oral corticosteroids.

Table 7. Prognostic factors

Characteristic	(N) %	Visual- acuity loss, P value (N)	Steroid-sparing, P value (N)	Disease duration, P value (N) [§]
Gender (female/male)	61/43	NS[‡]	NS[‡]	NS[†]
Duration of symptoms (wks), no. (range) presentation	21.7 (1-286)	NS[†]	NS[†]	P=<0.000[*]
Smoking	41 (42.6%)	NS[‡] (10)	NS[‡] (21)	NS[†]
Underlying systemic disease	34 (32.7%)	P=0.024[‡] (12)	P=<0.000[‡] (25)	NS[†]
Bilateral scleritis	40 (38.5%)	P=<0.000[‡] (17)	P=0.002[‡] (26)	P=<0.000[†]
Uveitis	47 (45.6%)	NS[‡] (12)	NS[‡] (24)	NS[†]

NS = Not significant, [‡] Chi-square test. [†] Students t-test. [*] Bivariate correlation. [§] Two extreme outliers were excluded from this analysis. One patient had a scleritis related to Wegener's disease, the other patient was suffering from a scleritis related to rheumatoid arthritis.

In the analysis of the prognostic factors (Table 7), patients with a bilateral scleritis at any time had a worse prognosis for all 3 end points. Patients with underlying systemic disease more often demonstrated loss of visual acuity and were more likely to be treated with steroid-sparing immunosuppressive drugs. In the analysis for disease duration, 2 patients had an extremely long duration of disease and were identified by SPSS software (boxplot) as extreme outliers (more than 3.0 times the interquartile range above the third quartile), and therefore they were excluded from this analysis. This analysis showed that patients who had scleritis for a longer period at presentation also had a longer disease duration after presentation.

These different prognostic factors were confirmed by logistic and linear regression models for interrelationships and influence of the different factors. In addition to this, the multivariate linear model for disease duration found

that men—although fewer—had a longer disease duration. To investigate the effect of a longer disease duration on the risk of loss of visual acuity, a separate multivariate inear model was used. In this model, a longer disease duration was not predictive of loss of visual acuity.

This analysis suggests that the strongest predictor for a worse prognosis is bilateral disease at any time. Patients with bilateral disease lost significantly more visual acuity, were treated significantly more often with steroid-sparing immunosuppressive drugs, and had a significantly longer disease duration.

DISCUSSION

Within this cohort, 23 patients (22.1 %) lost more than two lines of visual acuity on the Snellen-chart. This in contrast to the 81 patients (77.9 %) who gained visual acuity or lost less than 2 lines on the Snellen-chart. Most patients with a loss of visual acuity in our group (n=10) had a diffuse anterior scleritis. Necrotizing scleritis was the most threatening variant of scleritis. Of the 15 patients with necrotizing scleritis, 3 had a final visual acuity of no light perception and 2 lost more than 3 Snellen lines of visual acuity. In contrast to some other studies, [5, 16] panscleritis had a good prognosis and no higher association with an underlying disease. Although these findings regarding visual acuities should be interpreted cautiously in a retrospective study [17, 18], they are in concordance with the literature where loss of visual acuity is found in 15.9 to 37 % of the patients with scleritis [1, 16,19, 20].

Screening of scleritis patients for an underlying systemic disease should be aimed at the high-impact diseases such as RA and Wegener's disease. The same holds true for infectious causes: They should be identified early on because they need a different therapeutic approach. In most of the current patients, systemic disease had already been diagnosed before scleritis onset. in few of them, this was newly identified by screening, and in even fewer patients systemic disease became manifest during follow-up. Screening for HLA-B27 positivity seems questionable, because an occurrence of HLA-B27 positivity equal to that in the normal population (8%) was found and because HLA-association with scleritis is rarely described in the literature [21 - 23]. Also, the use of screening for sarcoidosis is not evident, since this is considered a rare cause of scleritis [5, 24], and in this study only one patient had elevated ACE-levels, without systemic manifestations of sarcoidosis. These findings suggest that customizing the screening for each patient seems an approach by which more useful clinical information can be obtained at lower costs.

In the scleritis patients, MTX was the most frequently used primary steroid-sparing immunosuppressive drug. The dosage of MTX did not influence the treatment success rate, but it had an effect on the range in time span to reach treatment success, with a lower range in de maximally treated group. The time to treatment success of MTX in our study was long, but it is comparable to that in other reports on scleritis [25]. However, the time to success of MTX treatment in this study was considerably longer than the reported time to treatment success of MTX in uveitis eyes [26].

Reduction in time to treatment success of MTX could be attempted by introducing a quicker dose escalation scheme including a faster switch to subcutaneous administration. The latter will result in a better bioavailability of the drug, particularly in higher MTX doses [27 - 30].

In rheumatic disorders it is recommended to start with 10-15 mg weekly, with an escalation of 5 mg every 2-4 weeks up to 20-30 mg weekly, depending on clinical response and tolerance, whereas subcutaneous administration should be considered in case of an inadequate response or intolerance [29]. Such schemes are currently being used in the treatment of RA-patients and have resulted in a reduction of the time to treatment success and a better steroid-sparing effect [27 - 29]. It has been shown that subcutaneous administration of MTX is equally as well tolerated as oral administration [28].

Reducing time to reach the maximum MTX dose will probably lead to a reduction in time to treatment success in scleritis patients. Also, MTX failure will be sooner evident, so that therapy can be switched at an earlier point in time. A reduction in time to treatment success will probably also reduce ocular complications, which mainly are the result of active disease, steroid use, or a combination of both. Whether more patients can be successfully treated with monotherapy is an issue beyond the scope of this study and one that could be studied in a comparative study.

Mycophenolate mofetil seems a viable option after MTX-failure because it can induce treatment success in an additional 50 % of the patients. It is open to discussion whether MMF in selected patients is preferable as primary therapy based on underlying systemic disease or susceptibility to side effects. However, the availability of this option also depends on local healthcare policies.

In case both options fail, TNF-α antagonists can induce control of inflammation in a further half of the patients. In case of TNF-α antagonists, time to treatment success seems to be much shorter than that needed for MTX and MMF. This suggests a more effective mechanism of action compared to MTX and MMF. Whether TNF-α antagonists can be administered as monotherapy, cannot be concluded from this study because only 1 patient received monotherapy. With

regard to TNF-α antagonists, it is not known presently which drug is preferable in the treatment of scleritis, and long-term effectiveness needs to be established as well. Most reports are on infliximab, a humanized chimeric monoclonal antibody, which was the first TNF-α antagonist introduced [8, 10, 13, 14]. Several small case-reports describe that rituximab, a genetically engineered chimeric monoclonal antibody that recognizes CD20 on mature B lymphocytes can be successful in severe recalcitrant forms of scleritis [9, 11, 12]. This potential effectiveness is supported by 1 study [19] of a small number of eyes enucleated because of severe necrotizing auto-immune scleritis that showed CD20 positive cells along with plasma cells as major components of the inflammatory infiltrate. Finally, a case-report of a patient with nodular scleritis illustrates that adalimumab, a humanized monoclonal antibody against soluble and membrane-bound TNF-α, may be effective as well [13].

Within the present cohort, scleritis seems to be divided into 2 variants. A mild form which is responding well to NSAIDs and a more severe or recalcitrant variant that required other types of treatment. Low-dose corticosteroids as monotherapy seemed to be effective in only a minority of these patients. Because most patients in the severe group needed steroid-sparing immunosuppressive drugs, the threshold to start these should be low. Globally, for each steroid-sparing immunosuppressive drug, treatment success was achieved approximately half of the patients. Azathioprine seems to be an exception because this drug was much less effective in the present study.

Assessing the severity of scleritis at an early stage is important for an adequate choice of treatment regimen. Within this patient group necrotizing scleritis, male gender, a longer period of complaints at presentation, systemic disease, and bilateral disease at any time indicated a worse prognosis. By multivariate regression analysis, bilateral disease was the strongest predictor of worse prognosis. Patients with these characteristics at presentation had more loss of visual acuity, longer disease duration and were more often treated with steroid sparing immunosuppressive medication. Risk factors for visual loss or prolonged treatment in the literature include necrotizing or posterior scleritis [31], underlying systemic disease [15], corneal involvement [32], positive results for c-ANCA [20], a combination of anterior and posterior scleritis [16] and a posterior scleritis at an older age than 50 years [16]. With regard to necrotizing scleritis and systemic disease, the present results were in agreement with dose reported in the literature. Most of these factors are easy to observ at presentation or during the course of the disease and contribute to an early recognition of a more severe form of scleritis. In contrast, the scleritis scoring system proposed by McCluskey and Wakefield [4] did not contribute to estimating the severity of scleritis in the current patients.

However, the results of the current study are limited by the fact that the study was retrospective, the numbers of patients were small in some subgroups, there was a large variability in follow up and the inclusion period was relatively long [17, 18]. Also, the Snellen visual acuities were not obtained according to a standardized protocol and our study was conducted in 2 subspecialty clinics at university hospitals and therefore this population does not represent the total spectrum of scleritis. Regarding treatment; there is a bias towards personal experience and preferences of the ophthalmologists of the two university hospital centers and there is an unknown influence on treatment of the health insurance politics in the Netherlands. Despite this, the authors believe that they can make contributions and recommendations for the improvement of care for scleritis patients by sharing our treatment experiences, indicating prognostic factors and advising on steps to optimize treatment regimens.

In conclusion, these data shows that scleritis often is a severe, vision threatening, and chronic eye disease. Patients with a mild form of scleritis in most cases are treated adequately with oral NSAIDs. Patients with more severe or recalcitrant forms of scleritis can benefit from a more aggressive treatment strategy. Clinical features indicating a more severe form of scleritis make a fast recognition of the disease possible. Adequate treatment based on the severity of the scleritis and a timely switch to steroid-sparing immunosuppressive drugs can reduce total treatment time. Using an appropriate MTX dose-escalation scheme and an earlier switch to subcutaneous administration seems advisable in patients with non-infectious recalcitrant scleritis. Azathioprine should be avoided in patients with scleritis. After MTX failure, MMF is a good option as a secondary steroid-sparing immunosuppressive drug. Tumor necrosis factor-α antagonists may be a viable option for patients with noninfectious, recalcitrant scleritis who are not responding to MTX or MMF.

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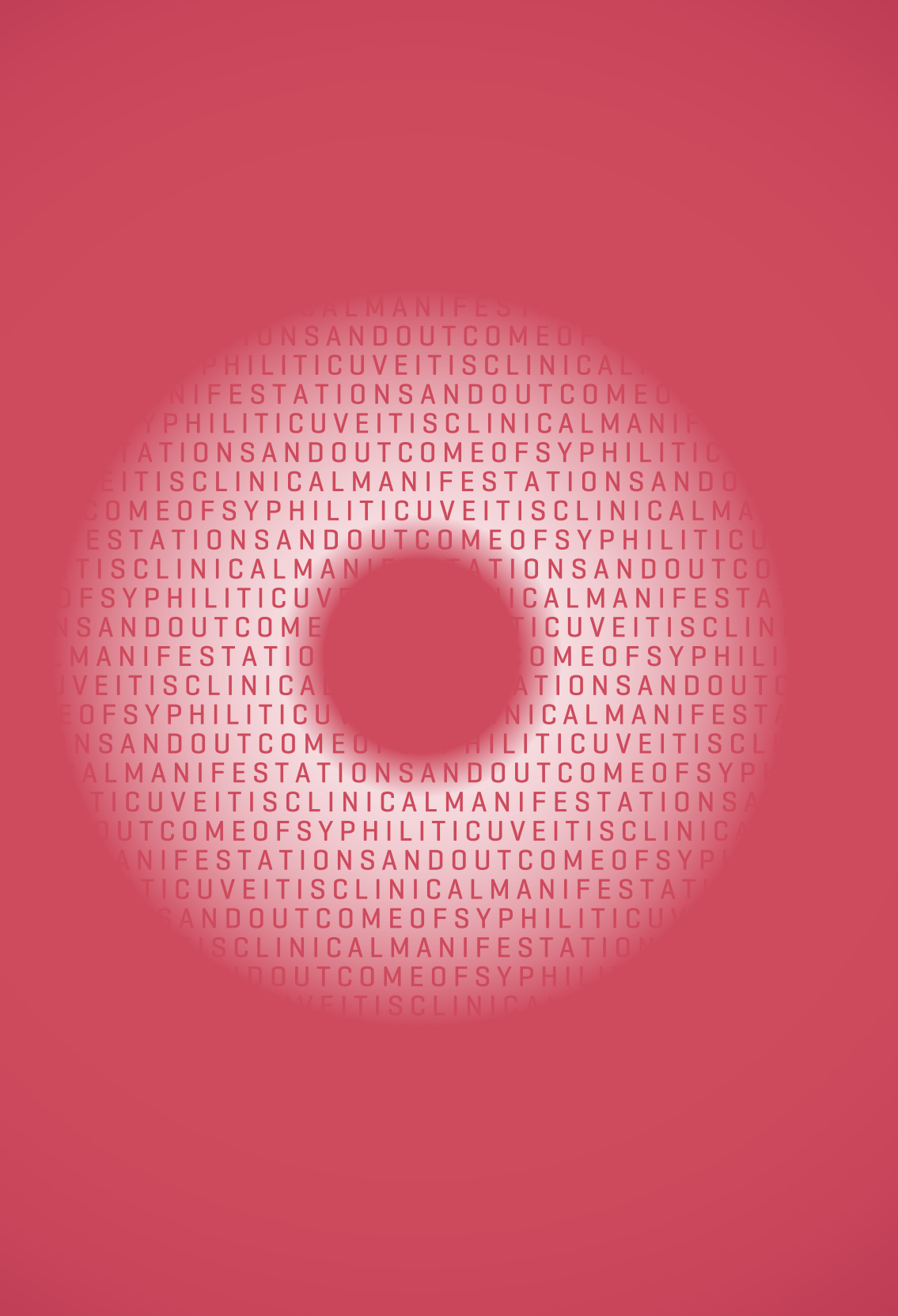
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