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# Clinical Relevance of Autoantibodies and Inflammatory Parameters in Non-infectious Scleritis

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**ABSTRACT**

**Purpose:** Scleritis is a potentially blinding disorder, with highly unpredictable course and outcome. We analyzed the prevalence and clinical relevance of autoantibodies and inflammatory parameters in non-infectious scleritis.

**Methods:** Retrospective analysis of laboratory findings in all consecutive patients at the department of Ophthalmology of the Erasmus MC with non-infectious scleritis.

**Results:** We included 81 patients with non-infectious scleritis. A systemic autoimmune disease was present in 46%. Positive anti-nuclear antibodies were found in 30%, anti-neutrophil cytoplasmic antibodies were positive in 19%, and the presence of rheumatoid factor was shown in 17%. The aforementioned autoantibodies, as well as inflammatory parameters, failed to show prognostic clinical value. In contrast, anti-citrullinated peptide antibodies (ACPA), found in 9% of scleritis patients, were significantly associated with the development of scleral necrosis ($P = .01$).

**Conclusions:** The presence of ACPA in patients with non-infectious scleritis was associated with the development of scleral necrosis.

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Scleritis; serum autoantibodies; anti-nuclear antibodies; anti-cytoplasmic neutrophil antibodies; anti-citrullinated peptide antibodies; inflammatory parameters; prognostic value

Scleritis is a potentially blinding eye disorder, characterized by inflammation of the sclera and pain. It is regularly associated with multiple severe complications, and frequently requires an aggressive treatment approach.[1–3]

The pathogenesis of non-infectious scleritis is since long attributed to autoimmune processes, however, exact mechanisms are yet unresolved.[4] Systemic autoimmune diseases, including rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA), and relapsing polychondritis (RPC) are frequently present in patients suffering from scleritis, as well as their associated autoantibody markers, such as anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA, including specific proteinase 3 (PR3)-cANCA and myeloperoxidase (MPO)-pANCA antibodies), anti-citrullinated peptide antibodies (ACPA, mostly anti-cyclic citrullinated antibodies (anti-CCP)), and rheumatoid factor (RF).[4–8] The presence of these autoantibodies is often used to support the diagnosis of an associated systemic autoimmune disease.

The development and prognosis of scleritis are highly unpredictable, and a clear association between clinical parameters and autoimmune markers is lacking. Similarly, the clinical value of classical biomarkers of inflammation, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), as well as soluble IL-2 receptor (sIL2R), has not been identified in scleritis.

We performed an evaluation of laboratory findings to determine the prevalence and clinical relevance of autoantibodies and commonly examined inflammatory parameters in non-infectious scleritis.

## Materials and methods

### *Study population*

We conducted a retrospective study, in which we reviewed medical data of all consecutive scleritis patients evaluated at the department of Ophthalmology of the Erasmus MC (Rotterdam, The Netherlands), between 2008 and 2020. We included 81 patients with non-infectious scleritis, who had undergone laboratory assessment at the moment of diagnosis, and/or at an arbitrary moment during the disease course. Included patients underwent full ophthalmic evaluation and work–up examination for scleritis according to national uveitis guidelines, which included analysis of ESR, CRP, HLA-B27, ANA (including anti-ENA and –dsDNA), ANCA (including specific PR3-cANCA and MPO-pANCA), RF, ACPA (anti-CCP), syphilis serology and interferon gamma release assay (IGRA, QuantiFERON–TB Gold In-Tube). Radiologic chest imaging was also performed.[9] According to the clinical manifestations, additional examinations and referral to appropriate subspecialists were performed (tailored approach). The diagnosis of non-infectious scleritis was made by an experienced ophthalmologist after full evaluation, including ultrasound B-scan when appropriate. According to the national guidelines, patients were treated using a step-up-approach with 1$^{st}$ line (non-steroidal anti-inflammatory drugs or short course, <3 months, of corticosteroids), 2$^{nd}$ line (disease modifying anti-rheumatic drugs or long course, >3 months, of corticosteroids), or 3$^{rd}$ line treatment (biological or cytostatics). The change to a more aggressive treatment step included either

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addition of a new agent to previous treatment, or its substitution, depending on the individual situation (severity of disease, drug tolerance, or others). Included patients had regular ophthalmic re-examinations.

### Data collection & statistical analysis

We collected data on serum autoantibodies, including ANA, anti-ENA, anti-dsDNA antibodies, (c/p)ANCA, anti-MPO, anti-PR3, ACPA (anti-CCP), and RF, during an arbitrary moment in the disease course. ANA were determined using gold standard indirect immunofluorescence on HEp2 cells according to manufacturer's instructions (Inova, San Diego, CA), and were visually evaluated by fluorescence microscopy according to the International Classification on ANA Patterns (ICAP) nomenclature.[10] ANCA were determined using indirect immunofluorescence on human granulocytes (Inova) and were visually evaluated by fluorescence microscopy based on presence of cytoplasmic (cANCA) or perinuclear (pANCA) patterns.[11] Anti-ENA (including SSA, SSB, UIRNP, Sm, CenpB, Scl70 and Jo-1), anti-dsDNA, RF (IgM), ACPA (anti-CCP), anti-PR3, and anti-MPO were determined using FEIA on the Phadia 250 system according to manufacturer's instructions (Thermo Fisher Scientific, Freiburg, Germany), and were registered as negative or positive. In addition, we gathered data regarding levels of common inflammatory parameters CRP (mg/l) and ESR (mm/h), determined by standard clinical chemistry, during the first laboratory evaluation of patients with active scleritis (within 90 days of onset of scleritis; only data of patients without systemic immunosuppressive treatment were used, N = 21). Further, we gathered data on sIL-2 R levels (pg/ml), determined by human sCD25/IL-2 R ELISA Kit according to manufacturer's instructions (Diaclone, Besancon Cedex, France), which were recorded during active scleritis. Missing laboratory data were supplemented whenever possible from frozen stored sera of included patients.

Clinical data of included patients were collected from medical charts and included demographics, associated systemic autoimmune disease (if present), use of systemic immunosuppressive treatment, including the use of third line treatment options, and the time interval from onset of scleritis to third line treatment in months. In addition, clinical ocular data was gathered, including activity of scleritis, latest known visual acuity (VA), scleritis subtype (categorical variable), presence of scleral necrosis (dichotomous variable), and other ocular complications, which are specified in the subscript of Table 3.

Continuous data were reported as mean ± range or standard deviation (SD), and categorical data were reported as number with percentage. Mann-Whitney-U test, Kruskal–Wallis test, Chi-square or Fischer's exact test, and logistic regression was performed to analyze results using SPSS version 25.0. In the logistic regression the dichotomous variable scleral necrosis was used instead of scleritis subtype for the presence of scleral necrosis. Statistical significance was defined as $P < .05$. The local Medical Ethics Committee (Erasmus MC, MEC-2012-016) has reviewed and approved this study, and waived requirement for informed consent. The research was performed according to the Tenets of the Declaration of Helsinki.

**Table 1.** Demographics of patients with non-infectious scleritis ($N = 81$).

| | No. (%) or mean ± SD (range) |
|---|---|
| Age onset | 51.2 ± 16.3 (13–83) |
| Male | 31 (38) |
| Caucasian | 69 (85) |
| Bilateral disease | 51 (63) |
| Location scleritis | |
| • Anterior | 42 (53) |
| • Posterior | 11 (14) |
| • Panscleritis | 15 (19) |
| • Sclerouveitis | 12 (15) |
| Subtype scleritis | |
| • Diffuse | 38 (49) |
| • Nodular | 13 (17) |
| • Necrotizing | 15 (20) |
| Etiology | |
| • Idiopathic | 43 (53) |
| • Surgically induced | 1 (1) |
| • Systemic disease | 37 (46) |
| • *Granulomatosis with polyangiitis* | 12 (32) |
| • *Rheumatoid arthritis* | 6 (16) |
| • *Relapsing polychondritis* | 7 (19) |
| • *Giant cell arteritis* | 3 (8) |
| • *Systemic lupus erythematodes* | 2 (5) |
| • *Others*[a] | 7 (19) |

[a]Other systemic diseases included Psoriatric Arthritis, Behcet's disease, Cogan's syndrome, Colitis ulcerosa, Crohn's disease, Sjogren's disease, and Sarcoidosis)

## Results

Baseline characteristics of 81 included scleritis patients are presented in Table 1. Average age at onset of scleritis was 51 years, and the majority of patients was female (50/81; 62%). Systemic autoimmune disease was present in 46%, and included GPA (12/37; 32%), RPC (7/37; 19%), RA (6/37; 16%), or other systemic disease as indicated (12/37, 32%).

### Presence of autoantibodies in scleritis

Results of autoantibody detection are presented in Table 2. ANA were found in 30% (24/80), while ANCA were found in 19% (15/80), both in varying titers. cANCA was seen in the majority (12 /15; 80%), mainly caused by specific PR3 antibodies, which were positive in 15% (11/72) of the entire cohort. pANCA was seen in 33% (5/15), while the clinically most relevant pANCA specificity MPO was not detected in the complete cohort. RF was positive in 17% (13/75), and ACPA (anti-CCP) was positive in 9% (7/75).

### Association between autoantibodies and clinical features of scleritis

The associations between the most prevalent autoantibodies and clinical features of scleritis are shown in Table 3. No associations were found between the autoimmune parameters examined and demographic features, such as age at onset, race, gender and laterality, and neither were any associations found with ANA positivity. ANCA positive scleritis patients required 3$^{rd}$ line treatment for their scleritis more often than ANCA negative patients ($P = .01$). In patients with PR3 antibodies (largely overlapping with ANCA positive patients), anterior type of scleritis was seen more frequently than in patients lacking these antibodies ($P = .03$). In addition, these patients

**Table 2.** Autoantibodies in patients with non-infectious scleritis ($N = 81$)[a].

| | No. (%) or mean ± SD (range) |
|---|---|
| ANA (total $N = 80$) | |
| • ANA titer (range) | 24 (30) |
| • ANA pattern | 1/80 – 1/ 1280 |
| • Homogeneous (AC-1) | 6 (25) |
| • Speckled (AC-2,4,5,29) | 11 (46) |
| • Nucleolar (AC-8,9,10) | 3 (13) |
| • Nuclear dots (AC-6,7) | 1 (4) |
| • Cytoplasmic reticular/ AMA pattern (AC-21)[b] | 1 (4) |
| • Unknown | 3 (13) |
| Anti-ENA[c] (total $N = 68$) | 4 (6) |
| Anti-dsDNA (total $N = 72$) | 0 (0) |
| ANCA (total N = 80) | |
| • ANCA titer (range) | 15 (19) |
| • ANCA subtype | 1/20 – 1/5120 |
| • cANCA[d] | 12 (80) |
| • pANCA[d] | 5 (33) |
| Anti-MPO (total $N = 72$) | 0 (0) |
| Anti-PR3 (total $N = 72$) | 11 (15) |
| • Mean level (IU/ml) | 312.6 ± 602.9 (3.4–2044.0) |
| RF (total $N = 75$) | 13 (17) |
| • Mean level (IU/ml) ($N = 7$)[e] | 54.3 ± 72.1 (5.3–200) |
| ACPA (anti-CCP, total $N = 75$) | 7 (9) |
| • Mean level (U/ml) | 205.3 ± 152.7 (39–350) |

AC: ANA-pattern classification by the international consensus on ANA patterns; ANA: anti-nuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibodies; MPO: myeloperoxidase; PR3: proteinase 3; ACPA: anti-citrullinated protein antibodies; Anti-CCP: anti-cyclic citrullinated peptide; RF: IgM rheumatoid factor; ENA: extractable nuclear antigens; anti-dsDNA: antibodies against double stranded DNA

[a]Please note that the number of tested patients for specific antibodies slightly varied (68–80).

[b]Cytoplasmic patterns on ANA IF are formally not registered as a positive ANA.

[c]Antibodies against SSA were present in 3 patients (2 patients both SSA 52kDa and 60kDa, in one patient only SSA 52kDa), antibodies against SSB, RNP and NXP2 were present in single patients.

[d]Two patients were both cANCA and pANCA positive.

[e]In 6 patients RF was measured using outdated units or dilution factor, range (1/25-1/400), and were not included in this analysis.

required 3rd line treatment more often ($P = .01$). Interestingly, necrotizing scleritis occurred more frequently in patients with positive ACPA (six with RA, one RPC), (71%; $P = .006$). Chi-square test of dichotomous variable presence of scleral necrosis resulted in the same outcome. (71% scleral necrosis; $P = .006$) In addition, ACPA positive patients had complications more often (86%; $P = .009$), and became visually impaired in one eye (VA <0.5) more frequently, compared to patients lacking these antibodies (57%; $P = .03$; Table 3). After correction for the use of third line treatment, the above-mentioned associations remained significant (respectively $P = .01$; $P = .05$; $P = .05$). No additional associations between the presence of examined antibodies or their levels and clinical characteristics (including posterior scleritis) were observed.

Patients with scleritis and systemic autoimmune diseases, most often GPA or RA, required 3rd line treatment more often than idiopathic cases ($P = .007$; Supplementary Table 1). Overall, 3rd line treatment was initiated after an interval of 26 months, however in GPA the onset of 3rd line treatment was much earlier compared to RA (4.0 ± 3.7 months in GPA, compared to 42 ± 78 months in RA; $P = .02$; Supplementary Table 1). After correction for the time interval from onset of scleritis to third line treatment, the association of scleral necrosis with ACPA remained significant ($P = .05$), however, the associations between ACPA and the development of complications ($P = .10$) or visual impairment ($P = .19$) disappeared. Patients with idiopathic scleritis less often had necrotizing scleritis compared to the patients with systemic autoimmune disease (5% versus 20%; $P = .02$), and were more often controlled with 1st or 2nd line treatment. (72% versus 52%; $P = .007$; Supplementary Table 1). ANA positivity (11/43, 26%) in idiopathic cases showed no association with clinical manifestations or development of complications.

### *Inflammatory parameters in scleritis*

During the active phase of the disease, average CRP was 6.2 mg/l (range 0–21), and ESR 25.4 mm/h (range 1–74). Elevated CRP >10 mg/l was observed in 19% (4/21), and elevated ESR >30 mm/h in 29% (6/21). No associations between CRP and/or ESR levels and clinical characteristics were identified. (Supplementary Table 2). SIL-2 R levels determined during active scleritis were not associated with development of necrosis ($P = .85$), ocular complications ($P = .64$), or visual impairment ($P = 1.00$) (Supplementary Table 2).

## Discussion

Autoantibodies including ANA, ANCA (mainly cANCA), RF, and ACPA are commonly found in patients with non-infectious scleritis. ACPA positivity was closely associated with having RA, as expected, and frequent development of scleral necrosis, various ocular complications and visual impairment. Remarkable was our observation, that the interval between the onset of scleritis and the start of 3rd line treatment for scleritis was shorter in patients with GPA, RPC and idiopathic scleritis compared to patients with RA.

The course of scleritis in patients with systemic autoimmune disease was previously found to be more severe than in idiopathic cases.[2,12] We generally confirm this finding, however, we observed that specifically GPA represented an exception in our series and was not associated with a poor prognosis.[13] We noted that our patients with GPA-scleritis were rapidly treated with 3rd line treatment, which might explain their improved prognosis in our series. In contrast to previous findings, scleritis associated with RA was characterized by severe complications.[14,15] The longer delay in time to 3rd line treatment in our cohort might explain this finding.

The relevance of ANCA detection for systemic autoimmune vasculitis is generally accepted, as well as RF and ACPA (anti-CCP) for RA, and ANA, anti-ENA and anti-dsDNA for SLE.[4,6,7,16] In our series, the prevalence of these autoantibodies was slightly higher than previously reported.[17–19] This finding may be partly due to our tertiary referral center specialized in immunological disorders, or might in part be attributable to the use of different, more sensitive laboratory techniques for autoantibody detection.

In our series of patients with non-infectious scleritis, the presence of ANA was not associated with ocular clinical features or severity. In RA, the development of ANA during treatment with disease modifying anti-rheumatic drugs was associated with worse prognosis.[20] Further, the presence of

**Table 3.** Autoantibodies in scleritis and their clinical associations.

| | Overall (81) | ANA + (23/80) | Versus ANA - *P*-value | ANCA + (15/80) | Versus ANCA- *P*-value | Anti-PR3 + (11/71) | Versus anti-PR3- *P*-value | RF + (13/75) | Versus RF- *P*-value | ACPA+ (7/75) | Versus ACPA- *P*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Location | | | 0.31 | | 0.08 | | 0.03 | | 0.30 | | 0.48 |
| • Anterior | 42 (53) | 15 (65) | | 12 (80) | | 10 (91) | | 10 (77) | | 5 (71) | |
| • Posterior | 11 (14) | 2 (9) | | 1 (7) | | 0 (0) | | 1 (8) | | 0 (0) | |
| • Panscleritis | 15 (19) | 2 (9) | | 0 (0) | | 0 (0) | | 2 (15) | | 2 (29) | |
| • Sclerouveitis | 12 (15) | 4 (17) | | 2 (13) | | 1 (9) | | 0 (0) | | 0 (0) | |
| Subtype | | | 0.17 | | 0.19 | | 0.32 | | 0.38 | | 0.006 |
| • Diffuse | 38 (49) | 9 (39) | | 4 (31) | | 4 (44) | | 5 (39) | | 1 (14) | |
| • Nodular | 13 (17) | 7 (30) | | 3 (23) | | 3 (33) | | 2 (15) | | 1 (14) | |
| • Necrotizing | 15 (20) | 5 (22) | | 5 (39) | | 2 (22) | | 5 (39) | | 5 (71) | |
| Ocular complications [a] | 27 (35) | 9 (39) | 0.80 | 6 (43) | 0.55 | 4 (40) | 1.00 | 6 (50) | 0.34 | 6 (86) | 0.009 |
| Visual impairment (VA<0.5 at least one eye) | 15 (19) | 3 (13) | 0.53 | 3 (20) | 1.00 | 1 (9) | 0.44 | 5 (39) | 0.12 | 4 (57) | 0.03 |
| Highest systemic treatment [b] | 75 (93) | 22 (96) | 0.71 | 15 (100) | 0.01 | 10 (91) | 0.04 | 12 (92) | 0.09 | 7 (100) | 0.12 |
| | 16 (21) | 4 (18) | | 0 (0) | | 0 (0) | | 2 (15) | | | |
| • 1st line | 23 (31) | 8 (36) | | 3 (20) | | 1 (10) | | 1 (8) | | 0 (0) | |
| • 2nd line | 36 (48) | 10 (46) | | 12 (80) | | 9 (90) | | 10 (77) | | 1 (14) | |
| • 3rd line | | | | | | | | | | 6 (86) | |

ANA: anti-nuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibodies; PR3: proteinase 3; RF: IgM rheumatoid factor; ACPA: anti-citrullinated protein antibodies; VA: Visual acuity

[a]Includes cataract, glaucoma, cystoid macular edema, choroidal folds and effusion, papillary edema, subretinal fluid, pigment epithelial detachment, retinal detachment, peripheral ulcerative keratitis, scleral perforation, and enucleation.

[b]1st line (non-steroidal anti-inflammatory drugs/ corticosteroids <3 months), 2nd line (disease modifying anti-rheumatic drugs/ corticosteroids >3 months), 3rd line (biologicals/ cytostatics)

ANCA was previously associated with worse prognosis of scleritis, which could not be reproduced in our study.[6,19,21,22] As we discussed before, the rapid use of 3rd line treatment in ANCA positive patients with scleritis in our series might have prevented its severe complications, and explain the observed discrepancy. The high frequency of anterior scleritis in PR3 positive patients was notable, and to the best of our knowledge, not reported in previous articles.

The presence of ACPA and its levels were previously associated with more severe RA.[23–25] As a consequence, one might expect that scleritis occurs more often in RA patients with ACPA.[23,26] The exact prognostic value of ACPA in patients with scleritis remains unclear. In our study, we found that the presence of ACPA was clearly associated with worse prognosis of scleritis. Apparently, the presence of ACPA is associated with both more severe articular and extra-articular disease manifestation in RA. Pathogenically, ACPAs induce macrophage TNF-α production, osteoclastogenesis and complement activation. They also induce the formation of neutrophil extracellular traps (NETs). NETs, increased in RA, are a source of citrullinated autoantigens in RA and induce fibroblast interleukin-8 production.[27]

The levels of CRP and ESR determined during the first available laboratory evaluation after diagnosis were not associated with a more severe course of the disease or with its clinical parameters, although the number of examined patients was limited. We cannot exclude that some associations of these inflammatory markers could be found in larger cohorts. A reliable serological biomarker for inflammatory T-cell activation is sIL-2 R level.[28] Activation of T-cells results in the expression of IL-2 receptors on the cell surface, and shedding of sIL-2 R in the circulation. It is mainly used to support the diagnosis of sarcoidosis, however sIL-2 R levels are typically elevated in various autoimmune and inflammatory conditions.[28] We found no associations between sIL-2 R levels determined in the active phase of scleritis and its type, severity, or required treatment.

Our study is limited by the restricted number of patients, especially for the analysis of CRP, ESR, and sIL2R, as well by its retrospective design. In our retrospective setting we could not use the current grading systems for the severity of scleritis, and choose clear end points, such as the occurrence of specific complications and visual impairment.[29,30] However, our evaluation provides a comprehensive analysis of autoantibodies and inflammatory parameters in non-infectious scleritis.

In conclusion, we investigated the prevalence and clinical relevance of autoantibodies and commonly examined inflammatory parameters in non-infectious scleritis. Our main finding is that the presence of ACPA (anti-CCP) in patients with non-infectious scleritis in the context of RA was associated with the development of scleral necrosis. These patients might benefit from 3rd line treatment during the initial stages of the disease, preventing severe ocular damage. Further research using an expanded set of (novel) biomarkers might further improve clinical management of these patients.

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## Disclosure statement

No potential conflict of interest was reported by the author(s).

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**Supplementary table 1.** Characteristics and treatment of patients with non-infectious scleritis by etiology

| | Overall (80)[c] | GPA (12/80) | RA (6/80) | RPC (7/80) | Other systemic disease (12/80) | Idiopathic (43/80) | P-value |
|---|---|---|---|---|---|---|---|
| Age at onset (years) | 51.0 ± 16.4 | 57.3 ± 17.7 | 55.7 ± 7.2 | 57.7 ± 14.2 | 56.4 ± 11.9 | 46.1 ± 17.1 | 0.08 |
| Male | 31 (39) | 3 (25) | 1 (17) | 4 (57) | 6 (50) | 17 (40) | 0.43 |
| Caucasian | 68 (85) | 12 (100) | 5 (83) | 4 (57) | 11 (92) | 36 (84) | 0.14 |
| Laterality | 51 (64) | 9 (75) | 5 (83) | 4 (57) | 8 (67) | 25 (58) | 0.66 |
| Location | 42 (53) | 10 (83) | 4 (67) | 4 (57) | 3 (25) | 21 (50) | 0.18 |
| • Anterior | 11 (14) | 0 (0) | 0 (0) | 0 (0) | 4 (33) | 7 (17) | |
| • Posterior | 15 (19) | 0 (0) | 2 (33) | 2 (29) | 2 (17) | 8 (19) | |
| • Panscleritis | 12 (15) | 2 (17) | 0 (0) | 1 (14) | 3 (25) | 6 (14) | |
| • Sclerouveitis | | | | | | | |
| Subtype | 38 (49) | 4 (40) | 1 (17) | 3 (43) | 5 (42) | 25 (61) | 0.02 |
| • Diffuse | 13 (17) | 2 (20) | 1 (17) | 2 (29) | 1 (8) | 7 (17) | |
| • Nodular | 15 (20) | 4 (40) | 4 (67) | 2 (29) | 2 (17) | 2 (5) | |
| • Necrotizing | | | | | | | |
| Ocular complications [a] | 27 (36) | 4 (36) | 5 (83) | 1 (14) | 6 (50) | 11 (28) | 0.05 |
| Visual impairment (VA<0.5 at least one eye) | 14 (18) | 2 (17) | 3 (50) | 2 (29) | 2 (17) | 5 (13) | 0.24 |
| Highest systemic treatment [b] | 16 (22) | 0 (0) | 0 (0) | 1 (17) | 2 (18) | 13 (33) | 0.007 |
| • 1rd line | 22 (30) | 1 (8) | 1 (17) | 3 (50) | 2 (18) | 15 (39) | |
| • 2nd line | 36 (49) | 11 (92) | 5 (83) | 2 (33) | 7 (64) | 11 (28) | |
| • 3st line | | | | | | | |
| Time interval from onset scleritis to start 3rd line therapy (months) | 23.7 ± 37.9 | 4.0 ± 3.7[d] | 41.6 ± 77.8 | 11.0 ± 7.1 | 30.4 ± 19.1 | 34.2 ± 40.3 | 0.02 |

GPA: Granulomatosis with polyangiitis; RA: Rheumatoid arthritis; RPC: Relapsing polychondritis; VA: Visual acuity

[a]Includes cataract, glaucoma, cystoid macular edema, choroidal folds and effusion, papillary edema, subretinal fluid, pigment epithelial detachment, retinal detachment, peripheral ulcerative keratitis, scleral perforation, and enucleation.

[b]1st line (non-steroidal anti-inflammatory drugs/ corticosteroids <3 months), 2nd line (disease modifying anti-rheumatic drugs/ corticosteroids >3 months), 3rd line (biologicals/ cytostatics)

[c]Surgically induced scleritis (N=1) was excluded from this analysis

[d]In our cohort 11/12 patients with GPA were treated with biologicals (all rituximab) of whom 6 also used DMARDS (4 azathioprine and 2 methotrexate) for some period during their course of disease. One case of scleritis was controlled with azathioprine alone.

**Supplementary table 2.** Inflammatory parameters in scleritis and their clinical associations.

| | Overall (21) | CRP >10mg/l (4/21) | P-value | ESR>30mm/h (6/21) | P-value | Overall (32) | sIL2R >2500pg/ml (25/32) | P-value |
|---|---|---|---|---|---|---|---|---|
| Male | 9 (43) | 2 (50) | 1.00 | 3 (50) | 1.00 | 16 (50) | 10 (40) | 0.08 |
| Location | 10 (48) | 2 (50) | 0.83 | 3 (50) | 0.29 | 14 (44) | 10 (40) | 0.87 |
| • Anterior | 1 (17) | 1 (25) | | 1 (17) | | 5 (16) | 4 (16) | |
| • Posterior | 2 (33) | 0 (0) | | 2 (33) | | 7 (22) | 6 (24) | |
| • Panscleritis | 0 (0) | 1 (25) | | 0 (0) | | 6 (19) | 5 (20) | |
| • Sclerouveitis | | | | | | | | |
| Subtype | 13 (62) | 2 (50) | 0.87 | 4 (67) | 0.29 | 14 (44) | 10 (40) | 0.85 |
| • Diffuse | 1 (5) | 0 (0) | | 1 (17) | | 8 (25) | 7 (28) | |
| • Nodular | 3 (14) | 1 (25) | | 0 (0) | | 5 (16) | 4 (16) | |
| • Necrotizing | | | | | | | | |
| Ocular complications[a] | 7 (37) | 1 (33) | 1.00 | 1 (20) | 0.60 | 11 (36) | 8 (32) | 0.64 |
| Visual impairment (VA<0.5 at least one eye) | 4 (19) | 1 (25) | 1.00 | 1 (17) | 1.00 | 8 (25) | 6 (24) | 1.00 |
| Highest systemic treatment [b] | 7 (35) | 1 (25) | 0.86 | 1 (17) | 0.53 | 10 (33) | 9 (38) | 0.44 |
| • 1$^{rd}$ line | 5 (25) | 1 (25) | | 2 (33) | | 9 (30) | 6 (25) | |
| • 2$^{nd}$ line | 8 (40) | 2 (50) | | 3 (50) | | 11 (37) | 9 (38) | |
| • 3$^{st}$ line | | | | | | | | |

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; sIL2R: soluble IL-2 receptor; VA: Visual acuity

[a]Includes cataract, glaucoma, cystoid macular edema, choroidal folds and effusion, papillary edema, subretinal fluid, pigment epithelial detachment, retinal detachment, peripheral ulcerative keratitis, scleral perforation, and enucleation.

[b]1st line (non-steroidal anti-inflammatory drugs/ corticosteroids <3 months), 2nd line (disease modifying anti-rheumatic drugs/ corticosteroids >3 months), 3rd line (biologicals/ cytostatics)