Vision Loss in Patients with Giant Cell Arteritis Treated with Tocilizumab

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Abstract

Objectives: Giant cell arteritis (GCA) may lead to vision loss. To what extent tocilizumab (TCZ) is able to prevent vision loss is unknown. The aim was to analyze the occurrence of vision loss in a large GCA cohort treated with TCZ.

Methods: In this observational monocentric study, GCA patients treated with TCZ between the years 2010 and 2018 were studied. Demographic, clinical and laboratory data were analyzed.

Results: A total of 186 patients were included (62% female); 109 (59%) fulfilled the American College of Rheumatology (ACR) criteria, in 123 (66%) patients, large vessel vasculitis was diagnosed in magnetic resonance-angiography (MRA). Cumulative duration of TCZ treatment was 224 years, median treatment duration was 11.1 (IQR 5.6-17.9) months. Glucocorticoids (GC) were tapered over a median of 5.8 (IQR 3.0-8.5) months. At baseline, visual symptoms were present in 70 (38%) and vision loss in 21 (11%) patients. Patients with vision loss at baseline were older (p=0.032), had a lower C-reactive protein (p=0.002), more often cranial symptoms (p<0.001) or jaw claudication (p=0.031) and showed a negative association with MRA of the aorta (p=0.006). Two patients (1.1%) developed vision loss, both at initiation of TCZ treatment.

Conclusion: Our data show a very low incidence of vision loss in TCZ-treated patient. The two cases of AION occurred at initiation of therapy, they support the hypothesis that advanced, and established structural changes of arteries are key factors for this accident. Whether shorter duration of concomitant GC treatment is risky regarding vision loss needs to be studied.

Key Messages

- Vision loss is a rare event during therapy with tocilizumab
- The data suggest a lower incidence for tocilizumab than for glucocorticoid monotherapy
- The early events support the hypothesis that advanced structural changes with lumen narrowing define the risk for vision loss
- It is conceivable that glucocorticoids could be tapered more rapidly than studied in the two first RCTs

Introduction

Giant Cell Arteritis (GCA) is the most common vasculitis in Western populations at older age (1,2). Vision loss caused by ischemic events of the posterior ciliary arteries of the A. ophthalmica (anterior ischemic optic neuropathy, AION) or of the central retinal artery (central artery occlusion, CAO) is one of the most feared complication (3). It typically remains irreversible. To prevent it, glucocorticoids (GC) are prescribed immediately (4).

The rate of vision loss in patients with GCA seems to have decreased over the last decades, probably due to earlier diagnosis of GCA and prompt start of GC treatment (5). Nevertheless, a recent retrospective study
showed a prevalence of 2% of vision loss in 840 biopsy-proven GCA compared to the reference population of Skane (Sweden) with a prevalence of 0.6% (6). Further studies have documented vision loss mainly due to AION during treatment with GC at a quite variable rate of 0.7 to 10% (7, 8, 9, 10).

IL-6 plays a central role in the pathogenesis of GCA (11). Accordingly, tocilizumab (TCZ), a monoclonal antibody targeting the IL-6-receptor, was studied in the treatment of GCA. In addition to a remission-maintaining efficacy, the first two randomized controlled trials (RCTs) documented a steroid-sparing effect of approximately 50% compared with a conventional treatment with GC over one year (12, 13). While no ocular incidences were recorded in the first trial (12), one of 149 patients in the GIACTA trial suffered from AION while under TCZ treatment in the first 12 months (13). So far, no larger study has addressed the question, whether TCZ prevents vision loss comparable to GC monotherapy.

Therefore, we analyzed the frequency of vision loss in a large cohort of patients treated with TCZ and evaluated potential risk factors for vision loss.

**Patients And Methods**

Data of 186 patients with GCA treated with TCZ between 1\textsuperscript{st} January 2010 and 31\textsuperscript{th} December 2018 at the Division of Rheumatology and Clinical Immunology of the University Hospital (Inselspital) Bern, Switzerland, were extracted retrospectively from patient charts and entered in a REDCap database, which was prepared for this study and hosted at the Clinical Trial Unit (CTU) of the University of Bern, Switzerland. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. The patients fulfilled the criteria for GCA as defined in the two previously published RCTs (12, 13), i.e. patients either fulfilled the American College of Rheumatology (ACR) criteria of GCA and/or they suffered from symptoms of polymyalgia rheumatica (PMR) plus large vessel vasculitis (LVV) as diagnosed by magnetic resonance angiography (MRA).

Baseline was defined as the time of diagnosis of GCA.

Changes in vision loss were assessed by determination of best corrected visual acuity (14): Amelioration was defined as gain of two or more Snellen lines on the visual acuity chart and deterioration as loss of two or more lines on the visual acuity chart.

Relapse was defined as the re-occurrence of disease activity attributable to active inflammation that was followed by an increase in GC treatment (15).

**Statistical analysis**

All analyses were done using Stata 15 (Stata Corporation, College Station, Texas). We compared baseline characteristics of patients with and without vision loss prior to baseline, using the chi-squared test and the non-parametric Kruskal-Wallis test as appropriate. We displayed the median durations of follow-up, tocilizumab, glucocorticoids and concomitant treatments. The patient-years of tocilizumab treatment
were also computed. Counts of visual impairment and vision loss during the follow-up were displayed. Number of relapses were also recorded and displayed regarding treatment time. We compared baseline characteristics of patients with and without relapses during follow-up, using the chi-squared test and the non-parametric Kruskal-Wallis test as appropriate. Association between permanent vision loss at baseline and the following baseline characteristics: age, first CRP, jaw claudication and abnormal MRA aorta status were shown in a table and estimated with a multivariate logistic regression model with all the variables presented in the table. Crude and adjusted Odds Ratio for all the other characteristics were computed, their 95%-confidence intervals and p-value were displayed.

**Ethical approval**

The cantonal ethical board of Bern, Switzerland has approved this retrospective study. All patients gave their written general informed consent for the evaluation of their data.

**Results**

**Patient characteristics**

A total of 186 patients diagnosed with GCA were treated with GC and TCZ according to published RCTs (12, 13), i.e., treatment was started with prednisone (PDN) at a dose of 1mg/kg body weight per day or three pulses of intravenous corticosteroid treatment depending of the ocular involvement followed by 1mg/kg body weight of PDN. TCZ was added intravenously in doses of 8 mg/kg bodyweight at 4-weekly intervals or at a dosage of 162 mg subcutaneously at weekly or bi-weekly intervals. 18 patients received a 3-day pulse of 500 or 1000mg methylprednisolon. Median duration of PDN treatment was 7.7 (IQR 5.2;12.0) months with a concomitant treatment duration with tocilizumab during tapering of PDN to 0mg/day of 5.8 (IQR 3.0;8.5) months; median duration of TCZ therapy was 11.1 (IQR 5.6;17.9) months with tapering of TCZ during the last months.

Patient characteristics at baseline are summarized in table 1. A total of 109 (59%) patients fulfilled the ACR criteria for GCA, and in 123 patients (66%) large vessel vasculitis was confirmed by MRA. The median age at diagnosis was 71 years. 124 (67%) patients suffered from cranial symptoms, 90 (48%) from polymyalgic symptoms. In 135 patients, temporal artery biopsies were performed, which revealed histological features of GCA in 73 (54%) patients. In 123 (72%) out of 170 performed thoracic or thoracic-abdominal MRA an aortitis was found (16).

**Vision loss**

A total of 21 patients (11%) had suffered from vision loss due to GCA already prior to baseline. Unilateral vision loss had occurred in 16 patients, whereas bilateral vision loss had occurred in 5 patients prior to baseline. At baseline, best corrected visual acuity (BCVA, decimal) in the eye with acute vision loss was $\geq 0.5$ in 11 eyes (42%), $<0.5$ and $\geq 0.3$ in 1 eye (4%), $<0.3$ and $\geq 0.1$ in 3 eyes (12%) and $<0.05$ in 9 eyes (35%). The visual acuity at baseline of two patients were not exactly determined.
In two patients vision loss occurred while under TCZ medication: One 69-years old male patient developed AION of the left eye (BCVA of 0.01). The immediate treatment consisted of pulses of 1 g methyl-prednisolone over 3 days, and, in addition, one TCZ infusion. As the AION did not improve, he received three more pulses of 500 mg methyl-prednisolone and was then switched to oral prednisolone of 1 mg/kg body weight. Two weeks later, while still on 75 mg PDN daily, he lost vision of the right eye too (BCVA of 0.003).

The second patient, a woman of 68 years of age, participated in a TCZ study (NCT03745586). She received pulses of 500 mg methyl-prednisolone on three consecutive days followed by one infusion of TCZ (8mg/kg bodyweight) at day four and, thereafter, weekly subcutaneous injections of TCZ 162 mg. At day 18 (16 days after GC-pulse therapy) she suffered from an acute vision loss (BCVA of 0), which did not improve despite another three pulses of 1 g methyl-prednisolone pulse started within few hours and administrated over three days. Having reached lasting remission under GC, she was switched back to TCZ, GC were tapered and she remained symptom-free with a permanent vision loss (nulla lux).

A temporal biopsy was performed in 18 out of the 21 patients with vision loss at baseline, but was negative in 6 patients (33.3%). Positive histology was more frequent in patients with vision loss compared to those without. The patients with vision loss had lower CRP levels at baseline (p-value of adjusted OR 0.040), were older (p-value 0.021), had more often cranial symptoms (p-value <0.001) and jaw claudication (p-value 0.031) and less often fever (p-value 0.015). There was a negative association of vision loss with LVV of the aorta on MRA (p-value 0.028) (see table 2 and 3).

Median follow-up time of visual acuity was 17.5 (IQR 5.75-30) months. Visual acuity in the affected eyes remained stable in 15 eyes, decreased by ≥2 lines in 4 eyes and increased by ≥2 lines in 8 eyes. One patient was lost to follow-up.

**Relapses of GCA**

We identified 64/186 (34%) patients with either one or two relapses and 3 patients with more than 2 relapses. 27 (29.7%) relapses occurred before treatment with TCZ, 27 (29.7%) during treatment and 37 (40.6%) after discontinuation of TCZ. The relapses before start of TCZ occurred either under GC monotherapy or in combination with other conventional or biological disease-modifying anti-rheumatic drugs (DMARDs). Signs and symptoms between relapsing and non-relapsing patients did not differ significantly (table 4).

**Discussion**

Preventing vision loss remains one of the crucial aims in GCA treatment. As vision loss is irreversible in the vast majority of patients, long-term corticosteroid medication is still used commonly (17). The two RCTs investigating TCZ treatment in GCA reported only one patient with vision loss (12, 13). In the GIACTA trial, AION occurred in the lower dose treatment arm at week 24, i.e. under TCZ s.c. bi-weekly, while the patient was on concomitant prednisone at a dose of 2 mg/ day. However, the RCTs were not
powered to analyze the effect of TCZ on vision loss. Furthermore, the recently established national and international patient registries cannot yet answer the question either. As we started to treat GCA with TCZ around 10 years ago, we now have the opportunity to analyze the clinical course of a large cohort of GCA patients under therapy with TCZ.

The characteristics of the patients with vision loss in our cohort correspond to the data of other studies, i.e. the patients were older, the rate of positive histology of the temporal artery was higher and the CRP levels as well as the likelihood of aortitis were lower than in patients without vision loss (6, 9, 18, 19). Most patients were on GC treatment at initiation of TCZ therapy. The duration of GC co-medication corresponds to the periods in the cited RCTs.

A total of 22 out of 186 patients (12%) suffered from vision loss in our cohort, which is in line with the reported rates in previous publications ranging from about 2% – 19% (6, 10). In two cases only, vision loss occurred while patients were treated with TCZ. These two cases merit a more detailed analysis: One was in a clinical study (NCT03745586). AION developed 18 days after GC pulse therapy, while the patient was under TCZ monotherapy, and it remained non-responsive to immediate methylprednisolone pulse therapy. Notably, this patient complained of variably located and variably intense headache, which, retrospectively, had to be understood as ischemic. The second patient had suffered from AION in one eye and experienced vision loss in the second, despite immediate methyl-prednisolone treatment as standard of care. In this case, one infusion of TCZ was administered in the hope of having an additional effect. Thus, both cases presented with severe ischemic and treatment-resistant symptoms. It appears likely that structural changes were too advanced to respond to short term, intense immunosuppression. The fact that vision loss occurred early in the disease course supports this interpretation. Furthermore, in the first patient, treatment was successfully switched back to TCZ monotherapy, after stable remission under GC therapy was achieved, thus arguing against a non-response to TCZ. Advanced structural changes of extracranial arteries are well known from MRA and from arterial biopsies. If MRA of extracranial arteries are used for diagnostic purposes, a pitfall in interpretation is the loss of the “dark blood” sign. In case of intensely inflamed arterial walls, the lumen may be obliterated, the “dark blood” signal is lost and the vessel is misdiagnosed as a vein (20). In histology of temporal artery specimens, a fibrosis of the arterial wall together with a thickening of the intima and an obliteration of the lumen is also a well-known finding. Thus, regarding the two AION cases in our cohort, it appears likely that a critical narrowing of arterial blood vessels due to wall inflammation was the cause of AION.

Regarding GC, most studies showed a higher percentage of vision loss during treatment. One recent case-control study with 104 GCA-patients showed new ischemic events (AION) in 4% after initiation of treatment with GC (21). An abstract of the ACR 2019 presented a cohort of 11'820 veterans in the United States with ophthalmologic complications of 6.2% within 1 year after diagnosis despite prednisone exposure (22). The lowest rate of vision loss under treatment with corticosteroids was reported in a cohort of 136 biopsy-proven GCA with one vision loss (0.7%) 14 months after start of treatment at a dose of 12.5mg/d prednisolone (10). One retrospective study found a percentage of 10% of patients with recurrent AION in the same eye during treatment with GC (3-60mg/d at 3-36 months of treatment) (23). In
summary, the percentage of vision loss reported by our data is below or equal to the data of ophthalmological studies with high-dose GC treatment (6,10). As vision loss occurs at a comparable rate and at a comparable time point of disease, the same cause of AION is likely responsible in GC and TCZ treatment.

Regarding evolution of vision loss, 15/28 eyes (54%) showed a stabilization of visual acuity while 8/28 eyes (29%) showed an improvement while treated with TCZ and GC. As the analysis of data was retrospective, these findings do not represent the whole cohort. Nevertheless, they argue for a stabilization of visual impairment during therapy, which is similar to an earlier study with GC treatment only. This prospective study of 34 biopsy proven GCA with vision loss and treatment with GC showed a deterioration of visual acuity by 2/more lines in 27% of the patients despite GC pulse treatment 1g iv for 3 days, followed by 60-80mg/d and tapering of GC (7). Another study showed an improvement in visual acuity in 5 of 39 eyes (13%) with vision loss from biopsy-proven GCA after administration of 3 iv GC-pules followed by 1mg/kg bodyweight prednison (24).

The relapse rate of GCA during TCZ treatment was expectedly lower in this cohort as compared to the follow-up data after cessation of TCZ treatment in the first RCT (25). We did not find any variables at baseline predicting relapse during therapy, whereas the follow-up data of the RCT identified younger age and more intense mural enhancement in MRA as risk factors for relapse.

Weaknesses of this study are the retrospective nature, the monocentric approach and the lack of a stringent protocol regarding GC-reduction. Strengths are the sample size, the long-term data and the meticulous data analysis of visual loss by an expert ophthalmologist.

**Conclusion**

This is the first study focusing on the occurrence of vision loss in patients with GCA receiving TCZ treatment according to the protocol of the first two RCTs. Only one percent of patients lost vision under TCZ treatment, a figure comparable to historic rates of 0.7-10% for standard GC therapy. Collectively, the data supports a central role of IL-6 and underlines the therapeutic benefit of TCZ in cranial GCA.

**List Of Abbreviations**

ACR American College of Rheumatology

AION Anterior Ischemic Optic Neuropathy

BCVA Best Corrected Visual Acuity

CAO Central Artery Occlusion

CRP C-Reactive Protein
CTU Clinical Trial Unit

DMARD Disease Modifying AntiRheumatic Drug

EULAR EUropean League Against Rheumatism

ESR Erythrocyte Sedimentation Rate

GC Glucocorticoids

GCA Giant Cell Arteritis

IQR Interquartile Range

LVV Large Vessel Vasculitis

MRA Magnetic Resonance Angiography

PDN Prednisone

TCZ Tocilizumab

Declarations

Ethics approval and consent to participate The cantonal ethical board of Bern, Switzerland, has approved this study. All patients gave their written general informed consent for the evaluation of their data.

Consent for publication Not applicable

Availability of data and materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests JA, IK, CT, LS, GS, OS, SR declare that they have no competing interests. LC is a Consultant of BMS. FK is a Consultant of Actelion, BMS, Boehringer-Ingelheim, Pfizer. PV is a Consultant/Speaker of MSD, Abbvie, Roche, Pfizer, Sanofi, Gilead, Amgen, Novartis, Grünenthal, Mepha.

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Authors’ contributions JA and IK collected the global patient data, CT collected the data on visual acuity, OS and JA analyzed and interpreted the patient data. JA and PV were the major contributors in writing the manuscript. All authors read and approved the final manuscript.

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References

1. Smeeth L, Cook C, Hall AJ. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990–2001. Annals of the Rheumatic Diseases 2006;65:1093-1098.

2. Lawrence RC, Felson DT, Helmick CG et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. Arthritis & Rheumatism, 2008, 58: 26-35.

3. Gonzalez-Gay MA, Castaneda S & Llorca J. Giant cell arteritis: visual loss is our major concern. J. Rheumatol. 43, 1458–1461 (2016).

4. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Annals of the Rheumatic Diseases 2020;79:19-30.

5. Soriano A, Muratore F, Salvarani C et al. Visual loss and other cranial ischaemic complications in giant cell arteritis. Nat Rev Rheumatol. 2017 Aug;13(8):476-484.

6. Saleh M, Turesson C, Englund M et al. Visual Complications in Patients with Biopsy-proven Giant Cell Arteritis: A Population-based Study, J Rheumatol, 2016;43:1559–65;

7. Danesh-Meyer H, Savino P, Gamble G. Poor Prognosis of Visual Outcome after Visual Loss from Giant Cell Arteritis, Ophthalmology 2005;112:1098–1103

8. Singh Hayreh S, Zimmerman B, Visual Deterioration in Giant Cell Arteritis Patients While on High Doses of Corticosteroid Therapy, Ophthalmology 2003;110:1204–1215

9. Nesher G, Berkun Y, Mates M et al, Risk Factors for Cranial Ischemic Complications in Giant Cell Arteritis, Medicine 2004;83:114–122

10. Salvarani C, Cimino L, Macchioniet P al, Risk Factors for Visual Loss in an Italian Population-Based Cohort of Patients With Giant Cell Arteritis, Arthritis & Rheumatism (Arthritis Care & Research), Vol. 53, No. 2, April 15, 2005, pp 293–297,

11. Pulsatelli L, Boiardi L, Assirelli E, et al. Interleukin-6 and soluble interleukin-6 receptor are elevated in large-vessel vasculitis: a cross-sectional and longitudinal study. Clin Exp Rheumatol. 2017;35 Suppl 103(1):102-110.

12. Villiger P M, Adler S, Reichenbach S et al, Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial, Lancet 2016; 387: 1921–27

13. Stone JH, Tuckwell K, Collinson N et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med. 2017 Jul 27;377(4):317-328

14. Foroozan R, Deramo V, Buono L, Savino P et al, Recovery of visual function in patients with biopsy-proven giant cell arteritis, Ophthalmology, Volume 110, Issue 3, March 2003

15. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2020;79(1):19-30.

16. Reichenbach S, Adler S, Villiger P et al, Magnetic resonance angiography in giant cell arteritis: results of a randomized controlled trial of tocilizumab in giant cell arteritis, Rheumatology, Volume 57, Issue 6, June 2018
17. Vodopivec I, Rizzo JF 3rd. Ophthalmic manifestations of giant cell arteritis. Rheumatology (Oxford). 2018;57(suppl_2):ii63-ii72.

18. Liozon E, Herrmann F, Vidal E et al, Risk Factors for Visual Loss in Giant Cell (Temporal) Arteritis: A Prospective Study of 174 Patients, Am J Med. 2001;111:211–217.

19. Hočevar A, Ješe R, Rotar Ž. Risk factors for severe cranial ischaemic complications in giant cell arteritis. Rheumatology (Oxford). 2020 Mar 3.

20. Seitz L, Wagner F, Christ L et al. No blood for dark-blood: false-negative MRI in a patient with giant cell arteritis and occluded left temporal artery. Clinical vignette in press. Rheumatology

21. Dumont A, Lecannuet A, de Boysson H et al. Characteristics and outcomes of patients with ophthalmologic involvement in giant-cell arteritis: A case-control study. Semin Arthritis Rheum. 2020 Apr;50(2):335-341.

22. Chung S, Morcos M and Bernard Ng, The Veterans Health Administration (VHA) National Database Cohort: Incident Ophthalmic Complications in Giant Cell Arteritis (GCA) Patients with a Negative Temporal Artery Biopsy, Abstract from the 2019 ACR/ARP Annual Meeting

23. Chan C K, Paine M, O'Day J, Predictors of Recurrent Ischemic Optic Neuropathy, in Giant Cell Arteritis, J Neuro-Ophthalmol 2005;25: 14–17

24. Foroozan R, Deramo V A, Savino PJ et al, Recovery of Visual Function in Patients with Biopsy-proven Giant Cell Arteritis, Ophthalmology 2003;110:539–542

25. Adler S, Reichenbach S, Villiger PM et al. Risk of relapse after discontinuation of tocilizumab therapy in giant cell arteritis. Rheumatology (Oxford). 2019 Sep 1

Tables
Table 1
Baseline characteristics

|                                | All          |
|--------------------------------|--------------|
|                                | n (%) or median (IQ-range) |
| Total N                        | N = 186      |
| Female                         | 116 (62%)    |
| Age at diagnosis               | 71.0 (63.0; 77.0) |
| Weight [kg]                    | 70.0 (59.0; 83.4) |
| BMI [kg/m2]                    | 24.9 (22.0; 28.4) |
| CRP (mg/L)                     | 50.0 (20.0; 99.0) |
| ESR (mm/h)                     | 70.0 (40.0; 86.3) |
| ACR Criteria 1990              | 109 (59%)    |
| Cranial symptoms (including visual symptoms) | 124 (67%) |
| Visual symptoms                | 70 (38%)     |
| vision loss                    | 21 (11%)     |
| Headache                       | 93 (50%)     |
| Jaw claudication               | 48 (26%)     |
| Scalp tenderness               | 42 (23%)     |
| Claudicatio of tongue          | 2 (1%)       |
| Fever ≥ 38 °C                  | 35 (19%)     |
| Weight loss > 2 kg within 4 weeks | 50 (27%) |
| Night sweat                    | 33 (18%)     |
| Polymyalgia rheumatica         | 90 (48%)     |
| Biopsy of the temporal artery performed/ positive* | 135 (73%)/ 73 (54%) |
| MR angiography of aorta performed/ positive * | 170 (91%)/ 123 (72%) |
| MR angiography of extracranical arties performed/ positive* | 132 (71%)/ 63 (48%) |
| PET Imaging performed/ positive* | 20 (11%)/ 12 (60% ) |
| Duplex ultrasound of extracranial arteries performed/ positive* | 43 (23%)/ 18 (42%) |

* % positive refers to number performed
Table 2
Baseline table of vision loss

|                          | All        | Normal vision at baseline | Vision loss before baseline | p-value |
|--------------------------|------------|---------------------------|----------------------------|---------|
|                          | n (%) or median (IQ-range) | n (%) or median (IQ-range) | n (%) or median (IQ-range) |         |
| Total N                  | N = 186    | N = 165                   | N = 21                     |         |
| Female                   | 116 (62%)  | 101 (61%)                 | 15 (71%)                   | 0.475   |
| Age at diagnosis         | 71.0 (63.0; 77.0) | 70.0 (63.0; 76.0)       | 74.0 (69.5; 82.0)          | 0.032   |
| Weight [kg]              | 70.0 (59.0; 83.4) | 71.9 (59.1; 83.3)        | 61.6 (54.1; 85.5)          | 0.178   |
| BMI [kg/m2]              | 24.9 (22.0; 28.4) | 25.2 (22.0; 28.4)        | 23.7 (21.3; 27.7)          | 0.237   |
| First CRP (mg/L)         | 50.0 (20.0; 99.0) | 54.5 (21.0; 101.3)       | 20.0 (3.5; 47.5)           | 0.002   |
| First ESR (mm/h)         | 70.0 (40.0; 86.3) | 70.0 (40.0; 87.5)        | 50.0 (34.0; 78.0)          | 0.197   |
| ACR Criteria 1990        | 109 (59%)  | 94 (57%)                  | 15 (71%)                   | 0.245   |
| Cranial symptoms (incl. visual symp.) | 124 (67%) | 103 (62%) | 21 (100%) | < 0.001 |
| Visual symptoms          | 70 (38%)  | 49 (30%)                  | 21 (100%)                  | < 0.001 |
| Permanent vision loss    | 21 (11%)  | 0 (0%)                    | 21 (100%)                  | < 0.001 |
| Headache                 | 93 (50%)  | 83 (50%)                  | 10 (48%)                   | 1.000   |
| Jaw claudication         | 48 (26%)  | 38 (23%)                  | 10 (48%)                   | 0.031   |
| Scalp tenderness         | 42 (23%)  | 36 (22%)                  | 6 (29%)                    | 0.579   |
| Claudicatio of tongue    | 2 (1%)    | 1 (1%)                    | 1 (5%)                     | 0.214   |
| Fever ≥ 38 °C            | 35 (19%)  | 35 (21%)                  | 0 (0%)                     | 0.015   |
| Weight loss > 2 kg within 4 weeks | 50 (27%) | 42 (25%) | 8 (38%) | 0.295 |
| Night sweat              | 33 (18%)  | 29 (18%)                  | 4 (19%)                    | 1.000   |
| Polymyalgia rheumatica   | 90 (48%)  | 84 (51%)                  | 6 (29%)                    | 0.062   |
### Table 3
adjusted OR for all the other variables

| Permanent vision loss at baseline | Crude OR (95%-CI) | p-value | Adjusted OR (95%-CI) | p-value |
|----------------------------------|-------------------|---------|----------------------|---------|
| Age at diagnosis                 | 1.07 (1.01 to 1.14) | 0.018   | 1.07 (1.01 to 1.14) | 0.021   |
| CRP (mg/L)                       | 0.98 (0.97 to 1.00) | 0.015   | 0.99 (0.97 to 1.00) | 0.040   |
| Jaw claudication                 | 3.04 (1.20 to 7.70) | 0.019   | 2.34 (0.85 to 6.43) | 0.099   |
| Abnormal MRA aorta               | 0.27 (0.10 to 0.69) | 0.006   | 0.32 (0.12 to 0.89) | 0.028   |

### Table 4
Patient characteristics by relapse

|                           | All               | No relapse       | Relapse          | p-value |
|----------------------------|-------------------|------------------|------------------|---------|
| n (%) or median (IQ-range)|                   |                   |                  |         |
| Total N                    | N = 186           | N = 119          | N = 67           |         |
| Female                     | 116 (62%)         | 77 (65%)         | 39 (58%)         | 0.432   |
| Age at diagnosis           | 71.0 (63.0; 77.0) | 71.0 (66.0; 77.0)| 69.0 (62.0; 76.0)| 0.174   |
| Cranial symptoms (incl. visual imp.) | 124 (67%) | 81 (68%) | 43 (64%) | 0.629   |
| Visual symptoms            | 70 (38%)          | 49 (41%)         | 21 (31%)         | 0.209   |
| Vision loss                | 21 (11%)          | 15 (13%)         | 6 (9%)           | 0.630   |
| Headache                   | 93 (50%)          | 58 (49%)         | 35 (52%)         | 0.760   |
| Jaw claudication           | 48 (26%)          | 33 (28%)         | 15 (22%)         | 0.487   |
| Scalp tenderness           | 42 (23%)          | 23 (19%)         | 19 (28%)         | 0.201   |
| Claudicatio of tongue      | 2 (1%)            | 2 (2%)           | 0 (0%)           | 0.537   |
| Fever ≥ 38 °C              | 35 (19%)          | 20 (17%)         | 15 (22%)         | 0.435   |
| Weight loss > 2 kg within 4 weeks | 50 (27%) | 29 (24%) | 21 (31%) | 0.389   |
| Night sweat                | 33 (18%)          | 22 (18%)         | 11 (16%)         | 0.843   |
| Polymyalgia rheumatica     | 90 (48%)          | 58 (49%)         | 32 (48%)         | 0.878   |