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ORIGINAL RESEARCH

Rapid glucocorticoid tapering regimen in patients with giant cell arteritis: a single centre cohort study

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ABSTRACT

Objectives We evaluated the feasibility of a rapid glucocorticoid tapering regimen to reduce glucocorticoid exposure in patients with giant cell arteritis (GCA) treated with glucocorticoids only.

Methods Newly diagnosed patients with GCA treated with a planned 26-week glucocorticoid tapering regimen at the University Hospital Basel were included. Data on relapses, cumulative steroid doses (CSD) and therapy-related adverse effects were collected from patients' records.

Results Of 47 patients (64% women, median age 72 years), 32 patients (68%) had relapsed. Most relapses were minor (28/32) and 2/3 of those were isolated increased inflammatory markers (19/32). Among major relapses, one resulted in permanent vision loss. The median time until relapse was 99 days (IQR 71–127) and median glucocorticoid dose at relapse was 8 mg (IQR 5–16). Nine of 47 patients stopped glucocorticoids after a median duration of 35 weeks and did not relapse within 1 year. Median CSD at 12 months was 4164 mg which is lower compared with published data. Glucocorticoid-associated adverse effects occurred in 40% of patients, most frequently were new onset or worsening hypertension (19%), diabetes (11%) and severe infections (11%).

Conclusion We could demonstrate that 32% of patients remained relapse-free and 19% off glucocorticoids at 1 year after treatment with a rapid glucocorticoid tapering regimen. Most relapses were minor and could be handled with temporarily increased glucocorticoid doses. Consequently, the CSD at 12 months was much lower than reported in published cohorts. Thus, further reducing treatment-associated damage in patients with GCA by decreasing CSD seems to be possible.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The optimal steroid regimen for patients with giant cell arteritis is not known. Often high cumulative steroid doses (CSD) are reached with deleterious unwanted effects.

WHAT THIS STUDY ADDS

⇒ The application of a rapid glucocorticoid tapering regimen in clinical routine is feasible and leads to a low CSD and to a steroid-free remission at 12 months after diagnosis in around 20% of patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Approaches to lower CSD are needed and should be studied prospectively.

INTRODUCTION

Giant cell arteritis (GCA) is an inflammatory disease of large and medium-sized vessels. If GCA is suspected, glucocorticoid treatment must be started immediately to prevent the occurrence of ischaemic complications, for example, permanent vision loss.[1 2] Despite an overall high relapse rate in patients with GCA, vision loss and cerebrovascular events rarely occur after treatment has been initiated.[3–5] In order to avoid relapses, the European League Against Rheumatism (EULAR) recommends that after an immediate high dose glucocorticoid therapy (40–60 mg/day), glucocorticoids should be tapered slowly once the disease is controlled (to 15–20 mg/day within 2–3 months and to ≤5 mg/day in 1 year).[1] The Norwich protocol proposes an even slower tapering regimen with a logarithmic tapering over 2 years.[6] However, evidence for these recommendations is scarce.

Relapses of GCA are frequent, affecting 40–68% of patients, depending on dose and duration of glucocorticoid treatment.[7] They occur mainly within the first year after diagnosis often when glucocorticoids are tapered to below 10 mg daily.[8–10] EULAR defines a major relapse by the occurrence of clinical signs of ischaemia (ophthalmological damage, jaw claudication, scalp necrosis, stroke, limb ischaemia) or active aortic inflammation resulting in aortic damage. Recurrence of active disease not fulfilling these criteria define minor relapses.[1] By far,

most relapses reported in the literature are minor and include recurrence of headache, polymyalgia or isolated elevation of inflammatory markers, and can be treated with a temporary increase of the glucocorticoid dose.[11] The prevalence of major relapse is low (3.3%) and most major relapses are transient, for example, jaw claudication.[12] Hence, irreversible damage due to major relapses seems to be rare. Reliable prognostic markers for predicting relapses are lacking, precluding approaches of risk stratification to define individual treatment intensity and duration.[9 13]

Balancing treatment-associated side effects against disease-related damage is critical. Glucocorticoid treatment is associated with multiple adverse effects (AE)[14] that depend on the daily and the cumulative steroid dose (CSD) as well as the treatment duration.[15] Osteoporosis, hyperglycaemia/diabetes mellitus, cardiovascular diseases and infections are most often reported during glucocorticoid treatment.[15 16] Glucocorticoid-associated AEs occur in up to 85% of patients with GCA and patients often suffer from more than one AE. Moreover, AEs may lead to hospitalisation and increased morbidity.[17] Despite awareness of glucocorticoid-associated AEs, Chandran *et al* showed a trend towards longer glucocorticoid treatment duration over the last decades.[18] In contrast, the Giant-Cell Arteritis Actemra (GiACTA)-trial applied a rapid 26-week glucocorticoid tapering regimen to demonstrate the superiority of tocilizumab over glucocorticoid treatment to prevent relapses. Notably, 20% of the patients treated with glucocorticoids for only 26 weeks remained relapse-free during the observation period.[19]

In 2020, we implemented a 26-week glucocorticoid tapering regimen in an attempt to reduce glucocorticoid exposure to our patients. We here report the patients' outcomes regarding relapses and CSD in patients treated with a glucocorticoid monotherapy.

MATERIALS AND METHODS

Patients

Retrospective analysis of patients with newly diagnosed GCA treated at the University Hospital Basel between January 2020 and April 2022. Clinical data, laboratory results, histology and imaging results were collected from electronic patient records and image acquisition was carried out as described before.[20 21]

Patients were included if treated with glucocorticoid monotherapy and glucocorticoid withdrawal was targeted after 6 months according to a 26-week protocol.[22] Starting dose for oral glucocorticoids was 1 mg/kg/day prednisone-equivalent to a maximum of 60 mg daily. Patients were excluded from the analysis if disease-modifying agents, for example, tocilizumab, were initially added in patients with strong risk factors for glucocorticoid-related AEs or glucocorticoid intolerability. All patients had a minimum follow-up of 12 months.

Methods

GCA was diagnosed as previously described.[21] Temporal artery involvement was defined by a positive temporal artery biopsy or 'vasculitic' findings of the temporal artery in at least one imaging method (ultrasound, ^{18}F-fluorodeoxyglucose positron emission tomography-CT or MRI) and large vessel involvement was defined by the presence of 'vasculitic' findings in at least one extracranial vessel in at least one of the above-mentioned imaging methods. Relapse was defined as the reappearance of GCA-related symptoms or increased inflammatory markers (not otherwise explained) requiring reinstitution or extension of the ongoing immune-suppressive therapy. Minor and major relapses were categorised according to the EULAR definitions.[1] We further subdivided major relapse into transient and irreversible ischaemic symptoms (eg, permanent vision loss, stroke).[1]

CSDs at relapse and at the 12-month endpoint were calculated from the daily glucocorticoid doses not including intravenous glucocorticoid pulse therapies.

Glucocorticoid-associated AEs were defined as newly diagnosed arterial hypertension, diabetes, severe infections requiring hospitalisation as well as osteoporotic fractures or intensification of the antihypertensive or antidiabetic treatment.

Statistics

Continuous variables were expressed as the median and IQR and categorical variables as counts with percentages. Quantitative variables were analysed using the Student's t-test for data with parametric distributions. Data with non-parametric distributions were analysed using the Mann-Whitney U test. Categorical variables were analysed using the Pearson or Fisher's exact test as appropriate.

Relapse-free time was analysed using the Kaplan-Meier method. Cox proportional hazards models were used to assess predictive factors associated with relapse-free survival. HR and 95% CI were computed for each predictor in the univariate analysis.

Statistical significance was defined as $p<0.05$. All statistical analyses were performed in RStudio V.2022.07.2.576 (2022-10-31).

RESULTS

Patients

From January 2020 to April 2022, 92 patients with a new diagnosis of GCA were followed at our clinics at the University Hospital Basel. Of those, 47 patients fulfilled the inclusion criteria. Reasons for study exclusion were as follows: therapy with tocilizumab initiated at diagnosis (n=15), missing follow-up at the University Hospital Basel (n=13), participation in phase 3 trials with blinded medication (n=7), glucocorticoid therapy deviating from the targeted regimen due to maladherence and comorbidities treated with glucocorticoids (n=9) and pre-existing glucocorticoid treatment >10 mg/day at the time of GCA diagnosis (n=1) (online supplemental figure S1). Tocilizumab was

Table 1 Baseline characteristics of patients with GCA with and without a relapse within the first 12 months after diagnosis

	All patients (n=47)	Relapsing patients (n=32)	Non-relapsing patients (n=15)	P value
Female, n (%)	30 (64)	21 (66)	9 (60)	0.753
Age, years, median (IQR)	72 (66–76)	72 (66–76)	72 (65–76)	0.732
BMI, kg/m^2, median (IQR)	23 (21–26); N=32	24 (22–27); N=20	22 (20–25); N=12	0.211
Vascular involvement by imaging				
Temporal artery, n (%)	28 (60)	18 (56)	10 (67)	0.357
Large vessels, n (%)	31 (66)	23 (72)	8 (53)	0.719
Disease characteristics				
Fever, n (%)	6 (13)	4 (13)	2 (13)	1
Weight loss, n (%)	21 (45)	13 (41)	8 (53)	0.616
Stroke/TIA, n (%)	2(4)	1(3)	1(7)	0.541
Visual impairment, n (%)	12 (26)	7 (22)	5 (33)	0.481
Permanent vision loss, n (%)	3 (6)	3 (9)	0 (0)	0.541
Jaw claudication, n (%)	15 (32)	9 (28)	6 (40)	0.623
New onset headache, n (%)	35 (74)	24 (75)	11 (73)	1
Scalp tenderness, n (%)	16 (34)	12 (38)	4 (27)	0.528
Pathological temporal artery, n (%)	17 (36)	10 (31)	7 (47)	0.484
Polymyalgia, n (%)	18 (38)	12 (38)	4 (27)	1
ESR, mm/hour, median (IQR)	64 (35–90)	70 (46–95)	42 (28–71)	**0.027**
C-reactive protein, mg/L, median (IQR)	76 (42–110)	90 (48–145)	59 (40–90)	0.171
Haemoglobin, g/L, median (IQR)	120 (106–133)	118 (106–127)	127 (114–140)	0.077
Therapy				
GC pulse therapy (intravenous), n (%)	11 (23)	5 (16)	6 (40)	0.136
Initial GC dose (p.o.), mg/day, median (IQR)	60 (50–60)	60 (50–60)	60 (50–60)	0.908

All p values below 0.05 have been given in bold
BMI, body mass index; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; GCA, giant cell arteritis; n, number; p.o., peroral; TIA, transient ischaemic attack.

initially added in 15 patients due to the following reasons: pre-existing severe osteoporosis (n=4), decompensated diabetes mellitus (n=2), significant increase in blood pressure (n=2), steroid-induced psychosis (n=2), malignancy with indication for surgery (n=2), severe coronary heart disease (n=1), known glucocorticoid intolerability (n=1) and strong inflammation with fever (n=1). Patients receiving tocilizumab did not differ from those receiving a glucocorticoid monotherapy regarding their cardiovascular risk factors and disease characteristics (online supplemental table S1).

Median age of the 47 patients was 72 years (IQR 66–76) and 30 were women (64%). At diagnosis, imaging methods showed temporal artery involvement in 28 patients (60%), large vessel involvement in 31 patients (66%) and both in 19 patients (40%). The median initial oral glucocorticoid dose was 60 mg (IQR 50–60) for all 47 patients. A total of 11 patients (23%) received prior intravenous glucocorticoid pulse therapy with 125–1000 mg methylprednisolone (equivalent to 156–1250 mg prednisone) over 2–5 days (table 1).

Relapses of GCA within the first 12 months after diagnosis

Median relapse-free time for all patients was 121 days (95% CI 107 to 307 days) (figure 1). After 1 year, 32 patients (68%) had relapsed. Of these, 28 patients suffered a relapse during glucocorticoid tapering and the remaining 4 patients relapsed after glucocorticoid discontinuation. Of the 15 non-relapsing patients (32%), 9 (19%) were able to stop glucocorticoid therapy after a median of 35 weeks (IQR 26–46) and 6 patients were still on low dose (1–3 mg/day) glucocorticoid therapy at 12 months.

Patients with and without relapse did not differ regarding their disease characteristics except for the erythrocyte sedimentation rate (ESR, 70 vs 42 mm/hour, p=0.027) (table 1). Baseline characteristics were tested for association with relapse during glucocorticoid tapering and could not reveal any significant predictive factor for relapses (online supplemental table S2).

Out of all relapsing patients (n=32), 28 patients had a minor relapse (87.5%) and 4 patients suffered a major relapse (12.5%). The most common relapse

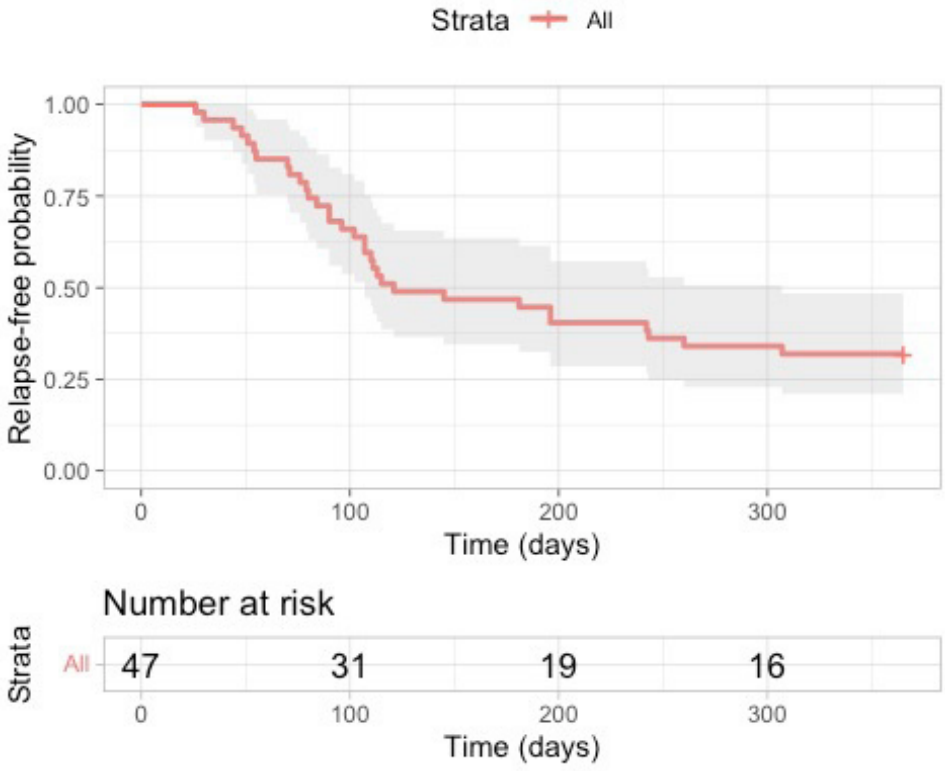

Figure 1 Kaplan-Meier curve for the occurrence of relapses within the first 12 months after diagnosis in patients with GCA. Within 47 newly diagnosed patients with GCA, the median relapse-free time was 121 days (95% CI 107 to 307 days, grey area). GCA, giant cell arteritis.

characteristics were increased inflammatory markers (n=30), headache (n=7) and polymyalgia (n=5). In 19/32 patients (59.5%), the sole characteristic of relapse was an increase of inflammatory markers and 2 patients (6%) presented with clinical signs without increased inflammatory markers.

Four relapses were classified as major, with jaw claudication in two, transient visual impairment (blurred vision) and a permanent vision loss due to an anterior ischaemic optic neuropathy (AION) in one patient, each (online supplemental table S3). AION occurred in a patient with AION of the contralateral eye at diagnosis. Of note, in this patient treatment was delayed after initial 3 days of glucocorticoid pulse therapy because of reasonable diagnostic doubt (AION was the only symptom and imaging was negative) and only resumed 4 weeks thereafter. Disease characteristics of patients with minor and major relapses were comparable (online supplemental table S4). Relapses occurred in a median of 99 days (IQR 71–127) and glucocorticoid dose at relapse was 8 mg (IQR 5–16) for all relapsing patients. Neither the time until relapse nor glucocorticoid dose at relapse were significantly different between minor and major relapses (99 vs 93 days, p=0.776, and 8 vs 8 mg, p=0.753). Figure 2 shows the time until relapse and the glucocorticoid dose at relapse for all minor and major relapsing patients.

Therapy at relapse

At relapse, 14/32 relapsing patients (44%) were treated by increasing glucocorticoid dose only, adjunctive tocilizumab was started in 18 patients (56%). The median glucocorticoid dose increment at relapse differed between minor and major relapsing patients (10 vs 40 mg, p=0.026). However, CSD at 12 months was not significantly higher in those with major compared with those with minor relapses (5016 vs 4640 mg, p=0.648) (table 2).

Three of the four patients with major relapses subsequently received tocilizumab. In minor relapses, tocilizumab was preferentially given if the relapse occurred early under higher glucocorticoid doses (13 vs 7 mg, p value=0.319). Patients with minor relapses receiving tocilizumab had lower CSD at 12 months compared with those who did not receive tocilizumab (4133 vs 5020 mg, p=0.041) (online supplemental table S5).

Cumulative steroid doses at 12 months

The median CSD at 12 months for all patients was 4164 mg (IQR 3614–4961) and was higher in relapsing patients compared with non-relapsing patients (4640 vs 3889 mg, p value=0.011).

Compared with established glucocorticoid tapering regimens, a significantly lower CSD was seen within our cohort regardless of whether relapses occurred.[11 18] Compared with data from a recent systematic review

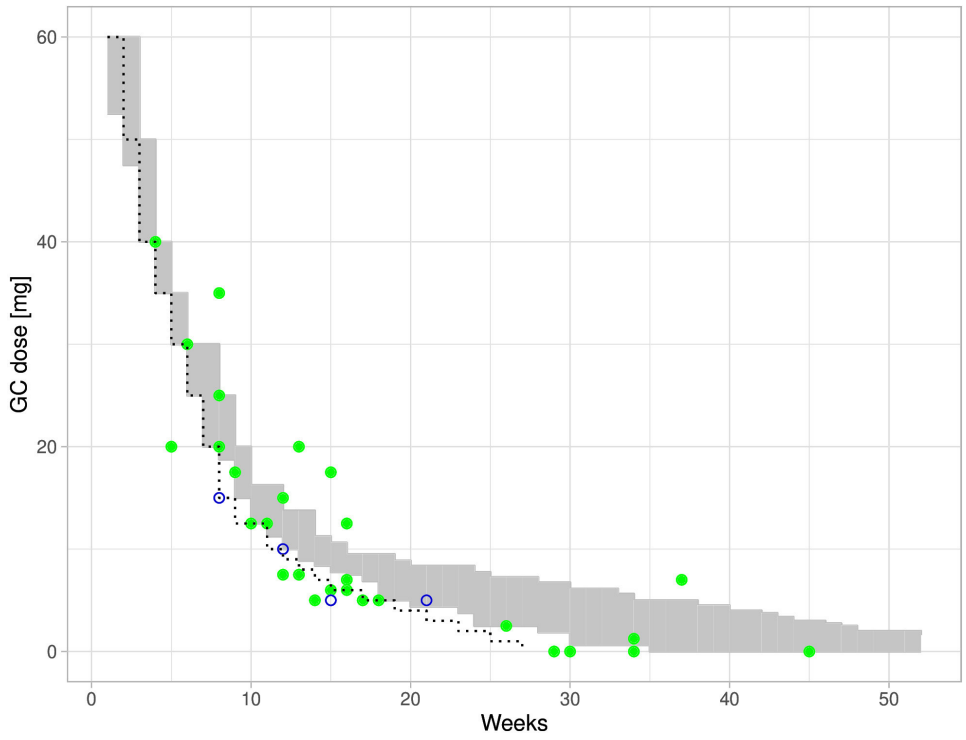

Figure 2 Glucocorticoid tapering regimen in major and minor relapsing patients. The grey shaded area depicts the IQR of the glucocorticoid dose of the non-relapsing patients. Dotted line shows the planned 26-week tapering regimen doses. Blue circles mark patients with major relapses (n=4) and green dots indicate patients with minor relapses (n=28). Four patients suffered a relapse after glucocorticoid discontinuation (GC dose is 0 mg). GC, glucocorticoid.

and meta-analysis, CSD was slightly below the CSD of the patients in the 26-week placebo-controlled arm of the GiACTA protocol (4325 mg)[19 23] and much lower than in the control group from Villiger *et al* (8468 mg)[23 24] (figure 3).

Potentially glucocorticoid-associated AEs

Despite the relatively low CSD, 19 patients (40%) were affected by potentially glucocorticoid-associated AEs within 12 months after diagnosis. Seven of 23 patients with pre-existing hypertension needed an intensification of the antihypertensive therapy. Two additional patients were newly diagnosed with arterial hypertension during therapy. Two of five patients with diabetes required an intensified therapy, and three patients developed diabetes during therapy. Within the first 12 months, five patients suffered a severe infection requiring intravenous antibiotics (n=4) or antimycotics (n=1, thrush oesophagitis). Diagnosis of osteoporosis or osteopenia prior to glucocorticoid therapy was only known in seven patients. Within 1–2 months after starting glucocorticoids, baseline bone density measurement was performed detecting central or peripheral osteoporosis in 6 additional patients and osteopenia in 15 patients. One patient with newly diagnosed osteoporosis suffered an osteoporotic fracture under glucocorticoid treatment.

DISCUSSION

Current tapering regimens for newly diagnosed GCA propose glucocorticoid monotherapy for at least 1 year

Table 2 Therapeutic details of patients with GCA with a relapse within 12 months after diagnosis

	All relapses (n=32)	Minor relapses (n=28)	Major relapses (n=4)	P value
Therapy at relapse				
Increment in GC dose, mg/day, median (IQR) *	15 (8–26)	10 (8–23)	40 (30–46)	**0.026**
Initiation of TCZ, n (%)	18 (56)	15 (54)	3 (75)	0.656
Cumulative steroid dose				
CSD at relapse, mg, median (IQR) *	2303 (2100–3104)	2303 (2100–3136)	2284 (2161–2472)	0.711
CSD at 12 months, mg, median (IQR) *	4640 (3834–5296); N=29	4640 (3834–5173); N=25	5016 (3957–6092); N=4	0.648

*Without intravenous glucocorticoid pulse therapy.
CSD, cumulative steroid dose; GC, glucocorticoid; GCA, giant cell arteritis; n, number; TCZ, tocilizumab.

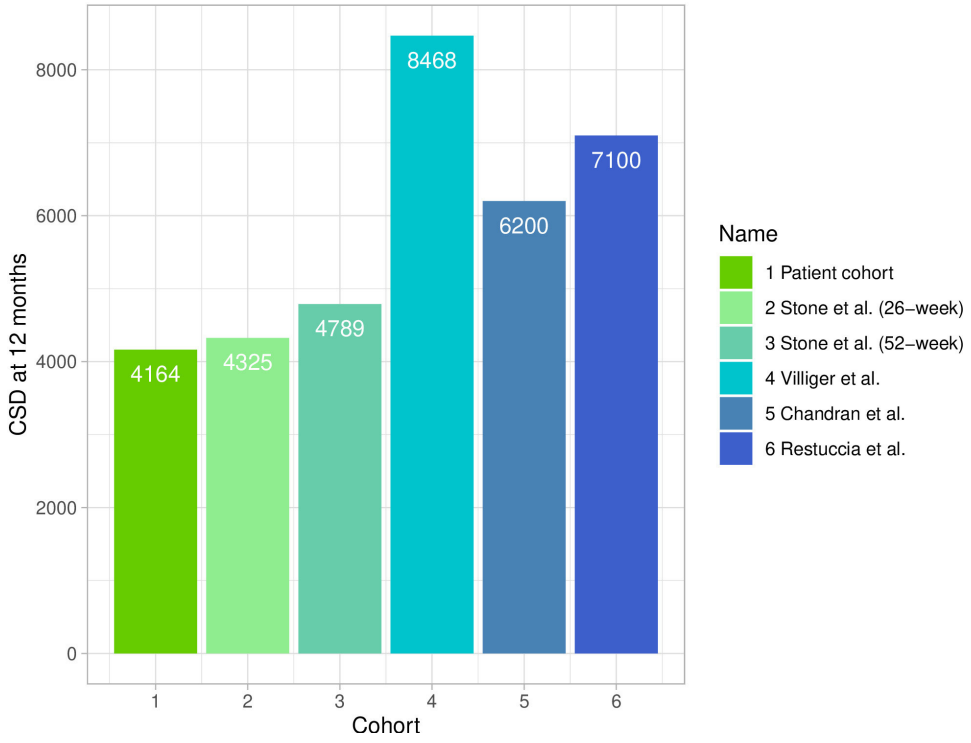

Figure 3 CSD at 12 months in our patient cohort compared with published data. CSD at 12 months in published GCA cohorts with targeted glucocorticoid withdrawal ≤12 months (Stone *et al** and Villiger *et al**) and >12 months (Chandran *et al* and, Restuccia *et al*). *Including patients with new-onset and relapsing GCA. CSD, cumulative steroid dose; GCA, giant cell arteritis.

or even 2 years.[1 6] In contrast, data from the control group of the randomised controlled trial of tocilizumab, showed that almost 20% of patients remain in sustained remission if treated with a rapid glucocorticoid tapering regimen.[19] Those patients would clearly be overtreated with the standard tapering regimens and would be at risk to experience unnecessary and potentially severe glucocorticoid therapy-associated AEs.[25] Glucocorticoid-associated AEs depend on the daily dose, the CSD and the therapy duration.[15] In an attempt to reduce glucocorticoid exposure, we, therefore, implemented a rapid 6-month tapering regimen in 2020.

Our data show that one-third of all newly diagnosed patients with GCA (15/47) were relapse-free within the first year after diagnosis, and 9 patients (19%) were in glucocorticoid-free remission at 12 months. This resulted in a very low CSD in the latter group (3211 mg). The occurrence of relapses was identical to the one reported in the GiACTA-trial for the 26-week regimen group (68%), and accordingly higher than in the corresponding 52-week regimen group (68% vs 49%), as well as compared with the cohort from Restuccia *et al* (68% vs 36%) with a mean corticosteroid duration of 40 months. However, most relapses were minor and an increase of inflammatory markers without clinical symptoms was the most often reported relapse characteristic. Consistent with Aussedat *et al*,[12] major relapses were uncommon and vision loss occurred in one patient during treatment. Relapses occurred in median after 3–4 months, earlier than reported previously (9–12 months).[9 26] However, the median glucocorticoid dose at the time of relapse ranged within the reported doses (10–5 mg)[8 10] indicating that the occurrence of relapses is more strongly impacted by the daily glucocorticoid dose than the duration of treatment with a critical dose around 10 mg/day. Distinctive predictors for relapse are still missing. Univariate analysis could not confirm the ESR value at diagnosis as risk factor for relapse, although the median ESR was higher in relapsing patients. Contrary to previous reports,[9 13] Large Vessel vasculitis was not associated with a higher risk for relapse. Clearly, developing biomarkers for relapse prediction would be important, especially for predicting irreversible ischaemic relapses, which are rare but feared.

With the use of a rapid glucocorticoid tapering regimen, the overall (relapsing and non-relapsing patients) median CSD at 12 months in our patient cohort was much lower compared with published data. Both >12 months and ≤12 months glucocorticoid tapering regimens are associated with an up to twofold higher CSD at 12 months than presented in our cohort[11 18 23 24] (figure 3). The comparison should be treated with caution as the cohorts have different patient inclusion criteria (eg, newly diagnosed vs relapsing patients) and different study settings (prospective vs retrospective). Of note, the CSD calculated with the Norwich regimen would be around 6500 mg after 12 months, not considering relapses.[6]

Although the prevalence of AEs in our cohort seems to be lower than previously reported,[17] it still occurred in almost half of the patients, with five patients requiring hospitalisation for severe infections and one patient suffering an osteoporotic fracture.

Finding an optimal balance between disease control, minimising CSD and coping with side effects remains challenging, even with the advent of tocilizumab. The strength of our study lies in the application of a fast glucocorticoid tapering regimen in clinical routine outside of highly controlled study settings. Nevertheless, our study has several limitations. Given the retrospective approach, the relatively small sample size, the limited observation time and the lack of controls, the results need to be verified in a controlled setting.

In conclusion, we showed that a rapid glucocorticoid tapering regimen applied in clinical routine leads to a consistent remission rate with low CSDs at 12 months after diagnosis, protecting these patients from unnecessary high glucocorticoid exposure. Biomarkers predicting the glucocorticoid response would be helpful in identifying patients who are at high risk of relapse and require more extended glucocorticoid treatment.

Contributors Conceptualisation: NM, AKH and TD. Acquisition of data: NM, AKH, MA, SI and TD. Manuscript preparation: NM, AKH, MA, SI and TD. Preparation of figures and tables: NM. Statistical analysis: NM, AKH and TD. Interpretation of the data: All authors. All authors commented on the manuscript draft and approved the final version of the manuscript. TD accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethikkommission Nordwest- und Zentralschweiz (EKNZ), #239/09. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. The data used and analysed during this study are available from the corresponding author upon reasonable request.

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