Low relapse rate in patients with giant cell arteritis in a multi-centre retrospective Turkish Registry

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Abstract

Objective

Glucocorticoids (GC) are widely accepted as the standard first-line treatment for giant cell arteritis (GCA). However, relapse rates are reported up to 80% on GC-only protocol arms in controlled trials of tocilizumab and abatacept in 12-24 months. Herein, we aimed to assess the real-life relapse rates retrospectively in patients with GCA from Turkey.

Methods

We assembled a retrospective cohort of patients with GCA diagnosed according to ACR 1990 criteria from tertiary rheumatology centres in Turkey. All clinical data were abstracted from medical records. Relapse was defined as any new manifestation or increased acute-phase response leading to the change of the GC dose or use of a new therapeutic agent by the treating physician.

Results

The study included 330 (F/M: 196/134) patients with GCA. The mean age at disease onset was 68.9±9 years. The most frequent symptom was headache. Polymyalgia rheumatica was also present in 81 (24.5%) patients. Elevation of acute phase reactants (ESR>50 mm/h or CRP>5 mg/l) was absent in 25 (7.6%) patients at diagnosis. Temporal artery biopsy was available in 241 (73%) patients, and 180 of them had positive histopathological findings for GCA. For remission induction, GC pulses (250-1000 methylprednisolone mg/3-7 days) were given to 69 (20.9%) patients, with further 0.5-1 mg/kg/day prednisolone continued in the whole group. Immunosuppressives as GC-sparing agents were used in 252 (76.4%) patients. During a follow-up of a median 26.5 (6-190) months, relapses occurred in 49 (18.8%) patients. No confounding factor was observed in relapse rates. GC treatment could be stopped in only 62 (23.8%) patients. Additionally, GC-related side effects developed in 64 (24.6%) patients, and 141 (66.2%) had at least one Vasculitis Damage Index (VDI) damage item present during follow-up.

Conclusion

In this first multi-centre series of GCA from Turkey, we observed that only one-fifth of patients had relapses during a mean follow-up of 26 months, with 76.4% given a GC-sparing IS agent at diagnosis. At the end of follow-up, GC-related side effects developed in one-fourth of patients. Our results suggest that patients with GCA had a low relapse rate in real-life experience of a multi-centre retrospective Turkish registry, however with a significant presence of GC-associated side effects during follow-up.

Key words

giant cell arteritis, relapse rate, glucocorticoids, glucocorticoid sparing agents

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Introduction

Giant cell arteritis (GCA) is a granulomatous large-vessel vasculitis that is characterised by the presence of ischaemic signs such as headache, visual manifestations, scalp tenderness, jaw claudication and stroke together with systemic symptoms such as weight loss, anorexia, fatigue and fever. GCA is the most frequent primary systemic vasculitis among patients ≥50 years of age (3), peaking in the seventh and eighth decade of life (9). In a recent systematic review, the pooled incidence of GCA was 10 [9.22, 10.78] cases per 100,000 people over 50 years old. The incidence was 3-6-fold higher in Scandinavia relative to the rest of Europe and East Asia. Mortality in GCA was found to generally decrease over time and showed no geographic variation (14).

Glucocorticoids (GC) are the mainstay of medical treatment in GCA. EULAR recommendations for the management of large-vessel vasculitis suggest starting with 40–60 mg/day prednisone-equivalent for induction of remission and tapering the GC dose to a target dose of 15–20 mg/day within 2-3 months and after 1 year to ≤5 mg/day. To avoid relapse, slow tapering of GCs with a withdrawal between 18 and 24 months is suggested (6). ACR 2021 guideline for GCA also recommends initiating treatment with high-dose oral GCs over moderate-dose oral GCs (16). However, despite slow tapering, 50-80% of patients with GCA relapse under GC treatment during follow-up (15). Though conventional ISs are suggested for selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC-related adverse effects or complications) by EULAR (6), recent ACR guideline conditionally recommended the usage of tocilizumab or methotrexate as GC-tapering agents, however routine use of ISs is still controversial (16).

In this first, large multicentre series from Turkey, we aimed to assess the real-life relapse rates retrospectively in patients with GCA. GC-associated side effects and damage are also surveyed.

Materials and methods

We assembled a retrospective cohort of patients with GCA diagnosed according to the American College of Rheumatology (ACR) 1990 criteria for GCA (7) from tertiary rheumatology centres in Turkey. The study included 330 (F/M: 196/134) patients. The demographics, clinical characteristics, therapeutic approaches, and outcomes of patients were abstracted from medical records. Relapse was defined as any new onset or reappearance of signs/symptoms compatible with GCA or increased acute-phase response leading to the change of the GC dose or use of a new therapeutic agent by the treating physician. Acute phase response was defined as a CRP level >10 mg/l and/or ESR by the Westergren method >50 mm/hour. Complete remission was defined as no new signs and symptoms of vascular disease assessed by a physician, normalised acute phase reactants, and reduction of GC dose under 10 mg/day of prednisolone or its equivalent at the third month of treatment.

The study was performed according to the Declaration of Helsinki and approved by the local ethical committee of Marmara University, Faculty of Medicine, Istanbul (no: 03.03.2023.415).

Statistical analysis

Statistical data were performed with Statistical Package for the Social Sciences 22.0 (SPSS, Chicago, IL, USA) program. Results were expressed as means and standard deviations or as median (minimum-maximum) according to the distribution of data. Mann-Whitney U-test, independent-samples t test, and chi-square test were used for comparisons of data. Spearman's rank-order correlation was used for correlation between continuous data. A *p*-value of less than 0.05 was considered statistically significant.

Results

The study included 330 (F/M: 196/134) patients with GCA. The mean age at disease onset was 68.9±9 years. The most frequent symptom was headache, with a duration longer than one month in 57.8% of patients (Table I). Polymyalgia rheumatica (PMR) was also present in 81 (24.5%) patients. Elevation of acute phase reactants (ESR>50 mm/h or CRP>5 mg/l) was absent in 25 (7.6%) patients at diagnosis.

Table I. Clinical characteristics of patients with giant cell arteritis at baseline.

	Giant cell arteritis (n=330)
Manifestations of systemic inflammation	
Anaemia * (n=327)	202 (61.8 %)
Erythrocyte sedimentation rate (mm/hour) (n=328)	79.7 ± 29.2 (9-159)
C-reactive protein (mg/l, n=325)	84.9 ± 69.3 (0.6-403)
Malaise (n, %)	261 (81.3 %)
Weight loss (n, %)	137 (41.5 %)
Fever (n, %)	80 (24.3 %)
Polymyalgia rheumatica (n, %)	81 (25.5 %)
Manifestations of vascular ischaemia	
Headache (n, %)	294 (89.1 %)
Scalp Tenderness (n, %)	156 (47.3 %)
Sensitivity on temporal artery region (n, %)	177 (53.6)
Jaw claudication (n, %)	128 (38.8 %)
Ocular symptoms (n, %)	139 (42.1 %)
Extremity claudication (n, %)	18 (5.9 %)
Absent or asymmetric pulses (n, %)	5 (1.5 %)
Asymmetric blood pressure (n, %)	4 (1.2 %)
Vascular bruit (n, %)	25 (7.6 %)
Neurological manifestations (n, %)	25 (7.9 %)
Comorbidities	
Hypertension (n=225)	177, 78.6%
Smoking, ever (n=239)	73, 30.7%
Diabetes Mellitus (n=224)	92, 41.1%
Hyperlipidaemia (n=300)	78, 26%
Ischaemic heart disease (n=317)	64, 20.2%
Chronic renal failure (n=323)	26, 8.1%
Malignity (n=330)	12, 3.6%
Other (n=330)	69, 20.9%

*<12 mg/dl for female, <13 mg/dl for male)

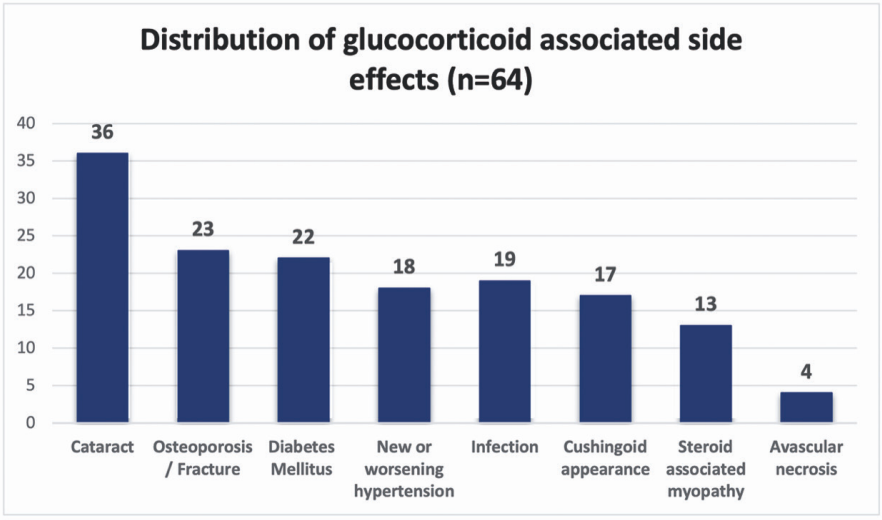

Fig. 1. Distribution of glucocorticoid-associated side effects.

Among patients with low acute phase reactants: 7 had biopsy positivity, 1 had PET positivity, and 3 had halo sign by ultrasonography.

Different diagnostic modalities were used according to the availability and the choice of treating physicians in each study centre. Temporal artery US was performed in 132 patients, with 42 (31.9%) of them having a "halo sign" compatible with GCA diagnosis. Temporal artery biopsy was available in 241 (73%) patients with 180 (74.6%) having positive histopathological findings for GCA diagnosis. Imaging of large vessels with PET/CT showed increased FDG uptake in the aorta and/or its main branches in 57.1% (28/49) which was compatible with vasculitis. Large-vessel involvement was detected in 4 patients by CT or MR angiography.

Treatment at diagnosis

While all patients received 0.5-1 mg/kg/day GC treatment for remission induction, additional GC pulses (250–1000 mg/d 3–7 days) were given to 69 (20.9 %) patients with sudden vision zloss. Patients with or without GC pulses were given a steroid-tapering protocol according to each study centre's own practice. ISs as a steroid-sparing agent were used in 252 (76.4%) patients (methotrexate=187, azathioprine=54, tocilizumab=9 cyclophosphamide=2) at the diagnosis. Aspirin usage rate was 62.1% (n=205) and statin 18.2% (n=60) (either previously or added at diagnosis).

Follow-up data

At the third month after diagnosis, 92.7% of patients achieved remission (280/302). Data for follow-up of more than 6 months was available for 260 (78.8%) patients, and the median follow-up duration was 26.5 (6-190) months (mean 40.9±26.5). During follow-up, relapses occurred in 49 (18.8%) patients after a median of 14 months (4-110). A second relapse was also reported in 3 patients. Gender, CRP or ESR levels, and age at diagnosis were similar between relapsing and not relapsing patients (NS for all). We also did not find any effect of pulse GC, aspirin, and statin usage on relapse development (p>0.05 for all). The relapse rate was significantly higher in patients using additional ISs on GC compared to the GC-alone group (22% *vs*. 4%, p=0.001). However, the follow-up duration was significantly shorter in the GC-alone group (38.5 ±36 *vs*. 51.1±38 months p=0.03).

At the end of the follow-up, 236 (90.8%) patients were in clinical remission, and 13 (5%) were still accepted to have active disease (treatment failure) by the treating physician. Permanent visual loss developed in 49 (18.8%) patients. GC treatment could be stopped in only 62 (23.8%) patients at the end of the follow-up due to GCA-related symptoms or acute phase elevation when GC was tried to be tapered or

Table II. Distribution of reported VDI items in patients with GCA (n=213).

Categories	VDI, n (%)
Musculoskeletal	40 (18%)
Muscle atrophy or weakness	13
Osteoporosis/osteoporotic fracture	23
Avascular necrosis	4
Arthritis	2
Skin	9 (4.2%)
Alopecia	3
Cutaneous ulcers	2
Mouth ulcers	4
Ocular	100 (46.9%)
Cataract	36
Retinal change/optic atrophy	36
Blindness	30
Visual impairment/diplopia	23
ENT	7 (3.9%)
Hearing loss	7
Pulmonary	16 (7.5%)
Pulmonary hypertension / fibrosis	3
Pulmonary Infarction	2
Chronic asthma/breathlessness	8
Impaired lung function	5
Cardiovascular	22 (10.3)
Cardiomyopathy/valvular disease	6
Angina / angioplasty	5
Myocardial infarction	8
Diastolic blood pressure > 95 mmHg	8
Peripheral vascular disease	8 (3.7%)
Absent pulses in one limb	3
Major vessel stenosis	4
Claudication >3 months	3
Venous thrombosis	1
Gastrointestinal	4 (1.8%)
Mesenteric insufficiency	2
Gut Infarction	2
Renal	14 (6.5%)
Estimated/measured GFR<50 ml/min	10
Proteinuria ≥0.5 gram/24 hour	2
End-stage renal failure	2
Neuropsychiatric	12 (5.6%)
Cognitive impairment	5
Stroke	4
Cranial nerve lesion	v
Peripheral neuropathy	2
Other	32 (15.1%)
Diabetes mellitus	22
Malignancy	3
Others	7

VDI: Vasculitis Damage Index; GFR: glomerular filtration rate; TADS: Takayasu Arteritis Damage Score; ENT: eye-nose-throat.

stopped. The cumulative GC dose was a median of 4743 (120-46000) mg. It was similar between relapsing and not relapsing patients (p=0.198). There was no difference regarding cumulative GC dose in patients with or without pulse GC treatment. GC-related side effects developed in 64 (24.6%) patients during follow-up. The distribution of side effects is given in Figure 1. Mortality was 4.2% (n=11) during follow-up. Causes of death were cardiovascular events in 3, malignancy in 3, infection in 1, gastrointestinal bleeding in 1, active vasculitis in 1, and unknown reasons in 2 patients.

Damage assessment

VDI scores at the last visit were available in 213 of the patients with a median score of 1 (0–13). In 141 (66.2%) patients, at least one damage item was present. The main causes of damage were cataract (16.9%), retinal changes (16.9%), blindness (16.9%), osteoporosis (10.7%), and diabetes (10.3%) (Table II). The median VDI score was similar between relapsing and not relapsing patients (p=0.641). It also did not correlate with cumulative GC doses.

Discussion

In this first multi-centre, retrospective series of GCA from Turkey, we observed that only one-fifth of patients had relapses during a median follow-up of 26.5 months. All patients were treated with GCs, and 76.4% of our patients were also given a GC-sparing IS agent at diagnosis. In a recent meta-analysis, the relapse rate was 47% in GCA patients receiving GC alone without improvement across decades. The relapse rate was significantly higher in patients with the cessation of GCs before 12 months than cessation after >12 months (65.8% *vs*. 34.5%, p<0.0001). The meta-analysis did not detect any association between initial GC dose and relapse prevalence (15). Relapses were also found more frequent in RCTs than in observational studies, probably due to shorter GC duration. A randomised controlled trial of tocilizumab demonstrated a relapse rate of 86% in patients on rapidly tapered GC-only protocols in 12 months (13). In our study, only one-fourth of patients with GCA relapsed during the median 2 years of follow-up in real-life experience.

However, GCs could be stopped in only 23.8% of our patients during follow-up. This can be another reason for the low relapse rate in our cohort compared to the literature. In our study, the relapse rate was also similar between patients taking pulse GC and not taking similar to results detected in previously mentioned meta-analysis (15). Although ACR 2021 guideline did not address the optimal duration of GC tapering due to a lack of randomised controlled data (16), the majority of panel members in EULAR recommendations reported that cessation of GCs usually takes about 2 years or more (6). In a large retrospective cohort from the French Vasculitis Study Group, 89/203 (44%) patients were still under GC treatment after a median of 34 months follow-up (18).

The EULAR recommendation had limited the usage of adjunctive therapy for selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC-related adverse effects or complications) (6). However, the recent ACR 2021 guideline for GCA conditionally recommended the usage of oral GCs with tocilizumab over oral glucocorticoids alone. Also, methotrexate was addressed as another option (16). In a recent retrospective study, half of the GCA patients with large vessel involvement were treated with a GC-sparing IS agent at baseline, while the other half were given GC monotherapy. The patients with GC monotherapy relapsed sooner (relapse-free survival, HR = 0.56, 95% CI 0.41–0.78, p<0.001) and had a higher relapse rate (relapses per 10 person-years, 6.73±11.50 *vs*. 3.82±10.83, p=0.011) (22) .In a recent meta-analysis including 16 studies (1068 participants), when the impact of GC-tapering agents compared to GC only group was assessed, tocilizumab significantly reduced the relapse risk. However, sirukumab (anti-IL6), TNF inhibitors, methotrexate, and abatacept did not significantly reduce the risk of relapse. An observational study also showed the potential benefit of leflunomide on relapse rate compared to the GC-only group (RR=0.34, 95%CI 0.13 to 0.91) (5). In a recent open prospective non-randomised study, a biologic agent was added to oral GC treatment in 28 of 33 patients with GCA (85%) (17 tocilizumab and 16 abatacept). After 12 months of the follow-up period, all patients in the TCZ group and 7 (43%) of the ABA group achieved an oral prednisone dosage below 7.5 mg/day as a maintenance regimen (p=0.0003) (19).

In our study, 76.4% of GCA patients were given a GC-sparing IS agent at diagnosis. Longer GC treatment duration may have caused lower relapse rates in our study compared to the literature.

We did not find any association between clinical characteristics and relapse rates. There are controversial data for relapse predictors in GCA, mostly from retrospective series. A negative temporal artery biopsy (1, 4), large vessel involvement, and peripheral musculoskeletal manifestations were previously found as predictive factors for relapse in GCA (4). However, in a meta-analysis, gender and age at diagnosis were not risk factors for relapses (15). High acute-phase response was also not found to be associated with relapses (2, 4, 12). General descriptive clinical characteristics of our multi-centre large GCA cohort are similar to the literature at the time of diagnosis. However, PMR presence is lower than the published series (2, 12). Normal ESR and CRP at the diagnosis were reported below 5% (10), similar to our observations (7.6%). At the end of the follow-up period, permanent vision loss was present in 18.8% of patients, which is again similar to the literature (17, 20).

It is well-known that long-term use of GCs is associated with side effects such as osteoporosis, infection, or diabetes. These are major concerns in GCA patients who are an older population with mostly multiple comorbidities. In a recent study, GC-related side effects developed in 129 (64%) of 206 patients (18). The most frequent side effects were cataract, osteoporotic fractures, and infections, and their presence significantly correlated with age and cumulative GC dosage. In our study, GC-related side effects were developed in one-fourth of patients which is lower than the published series. Our lower GC side effect rate may be due to lower cumulative dosage, higher GC-sparing agent usage, and lower relapse rate during follow-up. In a recent study, it was also reported that GCA patients had a higher risk of death due to infections, diabetes, and gastrointestinal ulcers, which were again GC-related complications (21). Therefore, reducing the cumulative GC dose with effective GC-sparing IS agents in GCA patients who are older and often have comorbidities is essential to prevent morbidity and mortality.

There is limited data assessing damage in GCA. Kermani *et al*. reported that 80% (n=161) of 204 patients had one or more items of damage assessed with VDI after a mean follow-up of 3.5 years (11). In a recent study from Turkey including 89 GCA patients, 60% of patients had damage with one or more VDI damage items (8). In the present study, 141 (66.2%) patients had at least one damage item. The majority of damage was GC-associated, such as ocular complications, osteoporosis, and diabetes. Our results were compatible with Kermani's and Ince's study. The median VDI score was similar between relapsing and not relapsing patients in our study. It also did not correlate with cumulative GC dose. In Ince *et al*. study, the damage was found to be associated with relapses, but not with cumulative GC dose (8).

Retrospective design is the major limitation of our study. The presence of some missing data and the lack of follow-up data of all patients are other limitations. However, our first, large multi-centre cohort from Turkey, in a country with lower GCA prevalence. is an important strength of the present study.

In conclusion, we observed that only one-fifth of GCA patients had relapses during a median follow-up of about 2 years in a multi-centre real-life experience from Turkey. A GC-sparing agent was given to 76.4% of our patients at diagnosis. At the end of follow-up, GC-related side effects were observed in one-fourth of patients, with 66.2% having at least one damage item. The most frequently detected damage items were GC-associated ones. Our results suggest that patients with GCA had lower relapse rates in the real-life experience of a multi-centre retrospective Turkish registry, however, with a significant GC-associated side effect rate during follow-up.

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