A French cohort of patients with giant cell arteritis: glucocorticoid treatment and its associated side effects

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ABSTRACT

Objective. *Giant cell arteritis (GCA) is the most common primary large-vessel vasculitis. Glucocorticoids (GC) therapy remains the standard of care for GCA despite frequent side effects (SEs). However, treatment modality changes, prophylactic treatment of osteoporosis, or vaccinations might have decreased the frequency of GC-related SEs. This study aims to describe GCA treatment and GC-related SEs in a recent cohort.*

Methods. *Patients with a diagnosis of GCA between May 2009 and March 2018 were included in this multicentric retrospective study. Characteristics of patients, treatment modalities and GC-related SEs were collected and analysed. Risk factors associated with the occurrence of SE were studied.*

Results. *We analysed the files from 206 patients (153 women, 53 men; median age 74 years). Median follow-up was 34 months. Patients received GC for a median of 25 months, starting at 0.7 mg/kg/day, with tapering to 5 mg/day after 11 months follow-up. Flares occurred in 83/201 (41%) patients. Among the 132 patients who stopped GC, 29 (22%) experienced a relapse. SEs occurred in 129 (64%) patients: bone fractures and infections in 13% each and hypertension onset in 9%. Age >75 years, treatment duration >2 years, past medical history of diabetes were risk factors associated with GC-related SEs.*

Conclusion. *Flares occur in 41% of patients during GC withdrawal. As much as 64% of patients had treatment related SEs. An age >75 year and a past medical history of diabetes were predictive of SEs during follow-up.*

Introduction

Giant cell arteritis (GCA) is the most frequent large-vessel vasculitis that occurs in individuals aged >50 years old (1). It affects the aorta and its main branches among which temporal artery (2). GCA is responsible for headaches, scalp tenderness, visual symptoms that can lead to blindness in almost 10% of cases (3), and polymyalgia rheumatica symptoms in a context of moderately impaired general status.

Glucocorticoids (GC) are the mainstay of treatment (4, 5) and typically trigger marked improvement within days (6). Although an alternate-day GC therapy increases the risk of relapse (7), the best GC therapeutic scheme for patients with GCA remains debated (8, 9). Long-term use of GC is associated with side effects (SE**s**) such as osteoporosis, infection or diabetes, which are a concern in older patients (10, 11). In 2003, Proven *et al*. reported such SEs in a retrospective cohort of 120 patients. Among them, GC-related SEs occurred in 86% patients, with ≥2 SEs occurring in 58% (12). Age and higher cumulative dose of GCs were associated with the development of adverse GC SE**s**. A nested case-control study realised on a GP database suggested that an average daily GC dose >30 mg/day during follow-up was associated with diabetes, osteoporosis, fracture and death, although the exact dosage instruction was missing for 80% of prescription (13).

Immunosuppressants and biologics have mainly been evaluated on the reduction of patient GC exposure or relapse rate. Despite the modest GC-sparing effect of methotrexate, we lack definite evidence that it can reduce treatment related SEs (14). Tocilizumab (TCZ) was recently shown to be an effective GC-sparing agent. It enabled sustained GC-free remission at week 52 for 56% of patients; however, 50% of patients experienced a relapse after TCZ withdrawal (15). Thus, the clinical benefit of immunosuppressant and biologics on SE**s** oc-

currence during long-term follow-up remains questionable.

Since the older studies (12, 16, 17), management of GC-related SEs has evolved, and preventive measures are now recommended for osteoporosis (18), hypertension, dyslipidaemia, diabetes (19) and infections (20).

This study aims to describe treatment modality/strategies, to evaluate the frequency of GC-induced SEs and identify the risk factors associated with GC-related SEs.

Materials and methods

Study design and population

This observational retrospective study was conducted in internal medicine departments of three French hospitals in Paris and Dijon, France. All consecutive patients with a clinical diagnosis of GCA between May 2009 and March 2018 were included. In patients without histology or imaging proof of vasculitis, files were carefully reviewed to confirm GCA diagnosis and a minimal follow-up of 6 months was mandatory in order to rule out another diagnosis. We retrospectively assessed i) the 1990 American College of Rheumatology (ACR) classification criteria (21), and ii) the inclusion criteria used in the GiACTA trial(22).

Ethics statements

This study was conducted in compliance with the Good Clinical Practice guidelines and the Declaration of Helsinki principles. The study was approved by the ethical review committee for publications of the Cochin University hospital and was found to conform to scientific principles and research ethical standards (Decision AAA-2020-08008).

Study procedures

Medical records of the three departments where the patients had their medical follow-up were used to collect data by use of a standardised form. Past medical history, comorbidities and baseline characteristics including clinical symptoms, age, sex and weight were collected. Laboratory findings at diagnosis (erythrocyte sedimentation rate, and/or C-reactive-protein [CRP] level) were recorded. Results of temporal artery biopsy (TAB) and imaging studies were collected.

For therapeutic characteristics, we looked at GC management (initial dose, duration, tapering modality, withdrawal). Time to 7.5 and 5 mg were retrospectively determined as well as total GC therapy duration. For patients who received immunosuppressant, indication, initiation date and doses were recorded. Evolution and outcomes were recorded at each outpatient consultation and/or hospitalisation. Relapse and flare were defined according to clinical/biological symptoms attributable to vasculitis requiring a therapeutic increase. Flare was defined by an increase in GC daily dose during GC tapering and relapse as the need to re-introduce treatment after GC discontinuation. GC-withdrawal was defined by the discontinuation of GC therapy. GC-withdrawal was sustained if patients did not experience any relapse during subsequent follow-up. Patient outcome was analysed according to the initial daily GC dose that was used (≤ or ≥30 mg/day), the use of GC pulses and the evidence of an aortitis.

The major endpoint was the rate of new onset GC-related SEs. Infections were noted only if they were severe ie requiring hospitalisation (grade ≥3 according to CTCAE). Multiple vertebral/bone fractures occurring simultaneously were recorded as a single event. Excessive weight gain was defined as a gain of more than 10% of baseline weight. Diabetes, hypertension, and dyslipidaemia were noted if they appeared under GC therapy, according to international definitions. Gastrointestinal bleeding, cataract, psychiatric disorders, myopathy, trophic disorders, hypokalaemia, or osteonecrosis were reported as well. All SEs that occurred after the initiation of GC therapy were considered GC-related SEs. Patients at high risk for GC-related SEs were defined as having at least 2 different SEs. Data regarding infection or osteoporosis prophylaxis and gastrointestinal bleeding prevention were also recorded.

Statistical methods

Data are presented as median (with interquartile range [IQR]) for continuous variables and number (%) for categorical variables. To determine the risk factors associated with the occurrence of SEs, we used univariate and multivariate analysis of variables associated with the number of SEs. Chi-square, Student and Kruskal-Wallis tests were used for univariate analysis and logistic regression for multivariate analysis and subgroup analysis, estimating odds ratios (ORs) and 95% confidence intervals (CIs). Six subgroups were arbitrarily chosen a priori: age <75 or ≥75 years, sex, treatment duration <2 or ≥2 years, presence of aortitis, CRP level <5.0 or ≥5.0 mg/dL, and positive TAB or not. Statistical analyses were performed with R-3.4.2. $P \leq 0.05$ was considered statistically significant.

Analysis is made on the available data without imputation of missing data.

Results

Baseline characteristics

The entire cohort comprised 153 women and 53 men (median age of cohort 74 years [IQR 67–80] at diagnosis) (Table I). Among these 206 patients, one hundred and sixty-six patients (81%) had proven vasculitis on histology (134/203) or imaging (74/141). Overall, 187 (91%) patients met at least 3 ACR classification criteria, and 137 (67%) met GIACTA inclusion criteria. At diagnosis, 156 (76%) patients had a past medical history of arterial hypertension, dyslipidaemia, diabetes, cardiovascular events, osteoporosis and past or on-going smoking (Table I).

Treatment

All patients received GCs starting at a median dose of 45 mg/day [40–55]. Treatment started with methylprednisolone pulses (ranging from 100 mg once to 1g/d for 3 days) for 13 of them. Median patient follow-up was 34 months [IQR 21–62] (636 patient-years). Overall, GC median duration (including GC taken after relapse) was 25 months [IQR 17–29] at the time of the study (506 patient-years of GC exposure) (Table II). Tapering to 7.5 and 5 mg/day was achieved after a median of 9 [IQR 7–12] and 11 [IQR 9–16] months, respectively (Fig. 1). Flares occurred in 83/201 (41%) patients during GC wean-

Table I. Main characteristics of study population at the time of diagnosis (n=206).

Men/women (%)	53/153 (26/74%)
Age, median [IQR]	74 [67–80]
Past medical history	
Hypertension	90 (44%)
Dyslipidaemia	56 (27%)
Smoking (past or ongoing)	39 (19%)
Cardiovascular event	25 (10%)
Osteoporosis	23 (11%)
Diabetes	20 (10%)
Clinical symptoms	
Headache	153 (74%)
Asthenia/fever	143 (69%)
Joint pain	83 (40%)
Ocular symptoms	34 (17%)
Biology, median [IQR]	
ESR, mm (n=124)	79 [56–102]
CRP level, mg/l (n=202)	67 [36–119]
Positive temporal artery biopsy (n=203)	134 (65%)
Aortitis (n=141)	74 (36%)

IQR: interquartile range; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

ing. Sixty-four patients (32%) received an add-on treatment: methotrexate only (n=48/64, 75%), TCZ only (n=8/64, 13%) and combination therapy (Table II). These drugs were prescribed at the time of relapse/flare (n=48, 75%) or to reduce GC exposure in the others (25%) Patients also received bisphosphonates (n=161/201, 80%), calcium (n=174/201, 87%), and 25-OH vitamin D (n=180/201, 90%). Only 42% (n=84/201) had been vaccinated against pneumococci and/or influenza.

Among the 132 patients who achieved GC-withdrawal, 29 (22%) experienced a relapse (Table III). Thus, one hundred and three (51%) showed sustained GC-withdrawal after median treatment duration of 19 months [IQR 17-28]. Among the 29 patients who relapsed, a new GC withdrawal was obtained in 9 (31%) and twenty (69%) were still taking GC at the end of follow-up.

At the time of last available data, 89/203 (44%) patients were still taking GC and 112/203 (55%) of them were weaned off GC (Table III). The 11 patients who started GC at ≤30 mg stopped it in 21 months [IQR 13-42] with no significant difference (p=0.23) as compared with patients who started at doses of ≥30 mg/day. Patients with an aortitis at the time of diagnosis (n=74) or those who received initial GC pulses (n=13) were treated with similar GC duration: 22 [17–37] months (p=0.45 as compared to patients without aortitis) and 24 [18–40] (p=0.55 as compared to patients who did not receive methylprednisolone pulses) respectively.

Patients who achieved a sustained GC-withdrawal and never relapsed more often had headache and less often diabetes at baseline as compared with patients who relapsed or failed to achieve GC-withdrawal (83% *vs.* 66%, p<0.01, and 5% *vs.* 15%, p=0.03, respectively) (Supplementary Table S1). In addition, aortitis was less frequently evidenced in patients who achieved a sustained GC-withdrawal, although not significantly (32% *vs.* 41% respectively, p=0.18).

Table II. Treatment received during follow-up.

Follow-up, months, median [IQR]	34 [21–62]
Glucocorticoids (n=206)	
Prednisone	206 (100%)
Prednisone dose at M0, mg, median [IQR]	45 [40–55]
Prednisone dose at M0, mg/kg, median [IQR]	0.7 [0.7–0.7]
GC intravenous pulse	13 (6%)
Time before 7.5 mg/day prednisone, months, median [IQR]	9 [7–12]
Time before 5 mg/day prednisone, months, median [IQR]	11 [9–16]
Time before stopping prednisone, months median [IQR]	21 [17 -29]
Total prednisone time including relapses at the time of the study, months, median [IQR]	23 [18–39]
Add-on therapy (n=199)	
Patients receiving GC add-on therapy	64 (32%)
Methotrexate only	48 (75%)
Tocilizumab only	8 (13%)
Methotrexate + tocilizumab	6 (9%)
Methotrexate + azathioprine	1 (0.2%)
Methotrexate + tocilizumab + azathioprine	1 (0.2%)

IQR: interquartile range; GC: glucocorticoids.

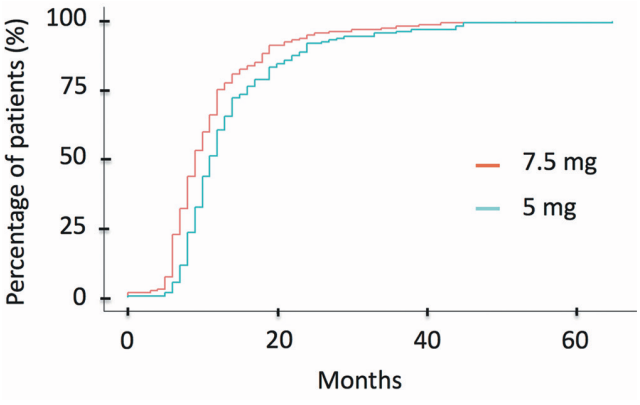

Fig. 1. Time to reach 7.5 and 5 mg/day prednisone in the overall population.

Proportion of patients with giant cell arteritis who achieved 7.5 or 5 mg daily prednisone dose.

Table III. Therapeutic outcome at the end of follow-up (n=203).

Patients stopped GC and never relapsed (sustained GC-withdrawal)	**103 (51%)**
Patients stopped GC and experienced ≥ 1 relapse	**29 (14%)**
No treatment at the end of follow-up	***9 (4%)***
Still under treatment at the end of follow-up	***20 (10%)***
Treatment on-going (GC never stopped)	**69 (34%)**
Remission with ≤5mg/day prednisone	***40 (20%)***
Treatment on-going 5 mg/day prednisone	***29 (14%)***
Death	***2 (1%)***

GC: glucocorticoids.

Side effects

SEs occurred in 129 (64%) patients: bone fractures and infection in 13% each

Table IV. GC-related side effects (SEs) occurring during follow-up.

SEs (n=203)	
Patients with SEs	129 (64%)
Number of SEs, median [IQR]	1 [0–1]
Type	
Bone fractures	26 (13%)
Hip	4 (2%)
Vertebra	16 (8%)
Wrist	3 (1%)
Other	8 (4%)
Severe infection*	26 (13%)
Weight gain (+10%)	21 (10%)
Cutaneous disorder	19 (9%)
Hypertension onset	18 (9%)
Psychiatric event	17 (8%)
Cataract	17 (8%)
Adrenal insufficiency	13 (6%)
Myopathy	12 (6%)
Dyslipidaemia onset	10 (5%)
Gastrointestinal bleeding	9 (4%)
Hypokalaemia	4 (2%)
Diabetes onset	4 (2%)
Osteonecrosis	3 (1%)

IQR: interquartile range.
*Severe infection: grade ≥3 according to CTCAE.

(n=26 each), arterial hypertension onset in 9% (n=18), cataract in 8% (n=17), GC-induced myopathy in 6% (n=12), gastrointestinal bleeding in 4% (n=9), diabetes mellitus onset in 2% (n=4), and osteonecrosis in 1% (n=3) (Table IV). People receiving add-on therapy also received longer GC treatment (35 months vs 21 months [p<0.01]) and tended to more frequently present ≥2 SEs (41% of patients with add-on therapy *vs*. 26% of patients without). Infectious SE occurred in 13/64 patients who received add-on therapy as compared to 13/139 in patients who did not (p=0.05). Patients who received bisphosphonates or were vaccinated more often experienced bone fracture and infection respectively, as these treatments might be prescribed to frailer patients or at the time of SE occurrence.

During follow-up, 49/203 (24%) had ≥2 SEs. As compared with patients with <2 SEs, these patients were significantly older (78 *vs*. 72 years, OR=1.32 per 5-year increase, 95% CI [1.07; 1.60]) and more often had a past medical history of diabetes (24% *vs*. 5%, OR=5.28, 95% CI [1.99; 14.04]) or cardiovascular event (24% *vs*. 9%, OR=2.89, 95% CI [1.21; 6.88]), received longer GC treatment (35 *vs*. 22 months, OR=1.43, 95% CI [1.15; 1.79]) and experienced more relapses and/or flares (65% *vs*. 43%, OR=2.52, 95% CI [1.27. 4.98]) (Table V).

On multivariate analysis, three factors remained independently associated with the occurrence of 2 or more SEs: past medical history of diabetes (OR=5.09, 95% CI [1.64; 16.6]); occurrence of flares and or relapses (OR=2.41, 95% CI [1.06; 5.68]) and older age (OR per 5-year increase = 4.76, 95% CI [1.66; 16.31]). Patients aged ≥75 years with a past medical history of diabetes had a 7.37-fold increased risk of having ≥2 SEs (95% CI [2.16–28.78]).

Prespecified subgroup analysis showed a significant difference in ≥2 *vs*. <2 SEs for 2 subgroups: age ≥75 years (OR=3.19, 95% CI [1.41; 8.95]) and treatment length ≥2 years (OR=3.22, 95% CI [1.56; 6.65]). For TAB, sex, CRP level and aortitis, we did not find significant differences (Suppl. Table S2).

Discussion

In this retrospective study, GC-related SEs in GCA remained a concern. SEs more frequently occurred in patients ≥75 years old with past medical history of diabetes. The initial GC dose and tapering were mainly prescribed in accordance with the French recommendations (23), these practice is responsible for a higher GC cumulative dose as compared to the tapering regimens used in randomised controlled trials. Along this line, we observed flares in 41% of our patients. This is to be compared with the 1 year-long prospective trials that found 86% of flares/relapses when evaluating TCZ add-on therapy in patients treated with 6 months GC (22), and 50% of flares/relapses when evaluating adalimumab add-on therapy in patients treated with 1 year GC (24). More consistently, we observed a similar flare rate as what was observed in the study by Proven *et al*. (12) and in a systematic review (25), although definition of flares and relapses vary from one study to another and do not align with the definition of relapses stated in the EULAR recommendation by Hellmich *et al*. (4). Indeed, our definition was based on clinical data, due to the retrospective design of our study. At the end of the follow-up, 55% of patients were free of GCs. These results are similar to recent findings for TCZ added to GCs (15).

Among patients who stopped GCs, only 22% relapsed. This low relapse rate is possibly a result of the sustained GC therapy and/or the concomitant use of add-on therapy. Indeed, time to reach 7.5 and 5 mg/day prednisone was longer than previously reported (12, 26). However, in Proven's study, as much as 39/87 (45%) patients experienced a relapse before sustained remission (12). At the opposite, we cannot exclude that some patients may have

Table V. Univariate and multivariate analysis of factors associated with number of SEs (<2 or ≥2) (n=203).

	<2 SEs n=154	≥2 SEs n=49	OR [95%CI]	aOR [95% CI]
Age, years, median [IQR], OR: per 5 years, median [IQR]	72 [66-79]	78 [71-83]	1.32 [1.07; 1.60]	4.76 [1.66; 16.31]
History of cardiovascular event	14 (9%)	11 (24%)	2.89 [1.21; 6.88]	2.26 [0.79; 6.27]
History of diabetes	8 (5%)	11 (24%)	5.28 [1.99; 14.04]	5.09 [1.64; 16.6]
Time before stopping prednisone, months, median [IQR], OR: per 10 months	22 [17-32]	35 [22-65]	1.43 [1.15; 1.79]	2.76 [0.73; 10.4]
Flare and/or relapse	66 (43%)	32 (65%)	2.52 [1.27. 4.98]	2.41 [1.06; 5.68]

IQR: interquartile range; OR: odds ratio; aOR: adjusted odds ratio (adjusted for age, history of cardiovascular event, history of diabetes, time before stopping prednisone, and flare and/or relapse); CI: confidence interval.

achieved sustained GC-withdrawal with shorter treatment duration. In this retrospective study, we were unable to evaluate the benefit of steroid sparing agents on the relapse rate.

In our study, we evidenced that sustained GC-withdrawal was more frequent in patients with headaches. In addition, we observed a trend toward a prolonged treatment and a less curable disease in patients with aortitis, as was previously reported (27, 28). Overall, these data suggest that subgroups with different outcomes might be identified in GCA, although additional data are required to support this hypothesis and better identify prognostic factors. We can hypothesise that patients with a past medical history of diabetes received shorter GC therapeutic scheme thus explaining the reduced GC-withdrawal rate observed in this subgroup.

We found far fewer SEs than previously reported: 64% vs 86% of patients with at least 1SE and 25% vs 58% of patients with ≥2 SEs in our study and Proven's study respectively (12). This was observed despite an increased time above 7.5 and 5 mg/day of GC during GC weaning in our study compared to Proven's study (9 and 11 months versus 6.5 and 7.5 months respectively).

Last, according to the definition of SEs by Proven *et al*., only 36% of our patients would have presented SEs during follow-up. GC-related SEs are known to be associated with age (7, 12), high initial daily GC dose (13, 16) or high cumulative GC dose (12, 13, 29). It is consistent with our finding that age >75 years treatment length ≥2 years predicted SEs. In our study, past medical history of diabetes was a predictor of SEs, especially in older people. In addition, a history of cardiovascular event tended to predict GC-related SEs.

The benefit of intravenous pulses of methylprednisolone used as GC-sparing therapy is controversial (30, 31). Methotrexate and TCZ are the only treatments with a proven GC-sparing effect (14, 22). However, the long-term benefit of these treatments for preventing treatment-related SEs has not been properly evaluated. In our study, neither immunosuppressant nor TCZ were associated with fewer SEs or reduced relapse rate. This might be due to the retrospective design and initiation of an add-on therapy in patients with a high GC cumulative dose and relapsing disease and the small proportion of patients who received TCZ (8 patients). These GC-sparing agents might also lead to SEs, and their long-term benefit is questionable (32). TCZ could be a good option as a first-line regimen in high-risk patients, but TCZ-specific SEs have been poorly evaluated in "real-life" patients. Therefore, better identifying high-risk SE patients is crucial. We do not know how prevention guidelines for GC-induced osteoporosis, hypertension, dyslipidaemia, diabetes, or vaccinations and lifestyle interventions in the past 20 years (18–20,33,34) could have explained the differences in the occurrence of SEs between our study and previous ones (12, 26). Nevertheless, only 42% of our patients were vaccinated against pneumococci and/or influenza and 80% received bisphosphonates despite recommendations (35). Improvements are still needed in vaccination coverage or osteoporosis prophylaxis. Better preventive care would probably further reduce SE occurrence. In our study, bisphosphonates intake and vaccination were associated with an increased SE rate. We assume that these treatments may have been prescribed to frail patients. Unfortunately, this hypothesis could not be confirmed in this retrospective study.

The main strength of our study is its size, with a long median follow-up of nearly 3 years. This is one of the largest studies focusing on GC therapy and GC-related SEs in patients with a stringent definition of GCA (81% of proven vasculitis on histology or imaging). Diagnosis, GC therapy and SEs were checked with medical records, which allowed for a proper estimation of the GC-related SE rate, and we were able to evaluate the number of flares/relapses and GC-withdrawal. Moreover, we have few missing data.

Because of its retrospective design, this study also has limitations. First, there is possible selection bias despite the recruitment from different hospitals. We decided to focus on new-onset SEs and excluded worsening of previous medical conditions, not-well-defined data that are difficult to assess. We did not estimate the GC cumulative dose, which is difficult to calculate in retrospective studies, or according to adherence. Some long-term SEs may not yet have occurred for patients still under treatment. Furthermore, some SEs, such as cataract, may not have been reported in medical reports. Nevertheless, serious SEs such as infections or fractures were well reported. However, the median follow-up of 3 years limits this bias because most SEs usually occur within the first 2 years after treatment initiation (8). Finally, the initial GC dose and tapering followed French recommendations and practices; such recommendations differ by country, so our results may not be representative in all countries. Finally, age could have been a confounding factor for SEs. Therefore, prospective studies focusing on SEs are needed to better evaluate the real benefit of GC-sparing therapies.

In conclusion, in this large cohort of GCA patients, the SE rate seems to have decreased as compared with previous studies. Age ≥75 years, treatment duration ≥2 years and a past medical history of diabetes predicted an increased number of SEs. Although alternative options to GC are important, these results show that the exact place of GC-sparing agents in the treatment strategy should be evaluated for each patient individually.

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Competing interests

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