Treatment with methotrexate and risk of relapses in patients with giant cell arteritis in clinical practice

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ABSTRACT

Objective. *To assess the incidence and the risk of relapses in giant cell arteritis (GCA) patients treated with and without methotrexate (MTX) in clinical practice. Other associated factors were also investigated.*

Methods. *An inception cohort of GCA was assembled in the out-patient clinic at Hospital Clínico San Carlos, including patients from the date of diagnosis (Jan-1991 until Sept-2013), and followed-up until lost of follow up or Sept-2014. Main outcome: relapse defined as recurrence of symptoms or signs of GCA with high ESR and the need to increase glucocorticoids at least 10mg over the previous dose. The independent variable was exposure to MTX over time. Covariables: Sociodemographic, clinical, and treatment. Incidence rates of relapses (IR) per 100 patient-year with their 95% confidence intervals [CI] were estimated using survival techniques. MTX influence on relapses was analysed by Cox models.*

Results. *168 patients were included (675 patient-year). 31% of patients had relapses (IR of 12 [9.6-14.9]), and the median number of relapses was 1[1-2]. 65% of the patients were on MTX, (mean dose: 10mg). In the bivariate analysis, the risk of relapses in patients with and without MTX did not achieve statistical signification (p=0.1). After adjusting in the multivariate analysis, exposure to MTX had 72% less risk of relapse compared to those without MTX (p<0.05). Other variables included in the final model were: visual alterations and malaise at clinical presentation of GCA.*

Conclusion. *The use of MTX seems to decrease the risk of recurrences. We also found other factors influencing on relapses.*

Introduction

Giant cell arteritis (GCA) is a large vessel systemic vasculitis in the elderly, characterised by the granulomatous involvement of the aorta and its major branches, with predilection for the extracranial arteries of the carotid artery (1). It is the most common systemic vasculitis in Western countries (2, 3). GCA is a polygenic disease and novel contributions have recently demonstrated the central role for T cells in the pathogenesis (4).

Treatment with high doses of glucocorticoids usually suppresses inflammatory activity dramatically, thus improving clinical symptoms and preventing disease-related complications. It is accepted that patients should receive prednisone at an initial dosage of 40 to 60 mg/day, with subsequent tapering to a lower maintenance dose. However, adverse events related to glucocorticoids are frequent and disease relapses are common (up to 50%), especially within the first year (5, 6). Both are a major problem in the management of GCA in already frail patients (7). As a consequence, research towards other therapies for GCA management has been developed.

Regarding immunosuppressant drugs, several studies have been published. A small randomised double blind controlled study in GCA, showed a glucocorticoids-sparing effect of azathioprine (Aza), with drug toxicity in one third of the patients (8). Similar results were shown several years after in the observational study of Boureau *et al*. (9). Experience with cyclosporine has been scarce with poor results in terms of inefficacy and toxicity (10). Concerning cyclophosphamide, a systematic review has been published by De Boysson, concluding that it could be considered a sparing agent in GCA patients who were glucocorticoid-dependent or had a complicated disease with failure to methotrexate (MTX) or Aza. However, many adverse events have been described, highlighting the need for close monitoring (11).

Regarding MTX, several randomised, double-blind, placebo-controlled trials have been conducted in patients with GCA. They evaluated the effect of combining low-dose MTX and glucocorticoids at disease onset compared to glucocorticoids alone with conflicting results (12-14). A meta-analysis based on those clinical trials was developed few years after, by Mahr *et al*. (15) clarifying certain aspects. First of all, the study showed that the risk of relapses was lower in patients taking MTX compared to those receiving placebo up to 48 weeks. Moreover, MTX treatment was associated with a higher probability of achieving sustained discontinuation of glucocorticoids for at least 24 weeks. Finally, and regarding drug toxicity, MTX appeared to be well tolerated, without differences in adverse drug reactions between treatment groups (15). Yates *et al*. published another meta-analysis after that, showing a marginal decrease in the frequency of relapses using at disease onset either corticosteroid pulses or MTX as adjunctive treatment, with a greater risk of infections in those patients treated with glucocorticoids pulses compared to glucocorticoids alone (16). All these findings seem to indicate that MTX could be considered a feasible option in addition to standard-of-care treatment with oral glucocorticoids for selected patients with newly-diagnosed GCA.

In recent years, various biological agents have been also investigated. Regarding infliximab and etanercept several studies have been shown to be inefficacious (16-19). Recently, it seems that patients with refractory GCA should be considered for tocilizumab therapy (20, 21). But the efficacy of biologic agents in GCA cannot be adequately judged on the basis of current data.

With the available evidence on the management of GCA patients, MTX can be considered the best choice as steroid-sparing treatment. In fact, EULAR, support the use of MTX as adjunctive therapy to glucocorticoids in GCA patients (22). Recently, Buttgereit *et al*. published a systematic review including a good summary of the current evidence regarding the treatment of GCA. They point out that adjunctive methotrexate might reduce cumulative glucocorticoid dosage and relapses (23).

It is important to note that all clinical trials have been conducted in selected patients, with close monitoring, in "ideal conditions" and with a maximum of two years of follow-up from disease onset, and a mean follow-up of 13 months (15, 16). Thus, despite the evidence, there is a need to evaluate and corroborate these results in real life conditions and, moreover, in the long term.

Regarding observational studies, several cohorts have assessed the nature, chronology, and clinical features of the clinical presentation and relapses in GCA patients, being constitutional symptoms, anaemia, malaise and systemic manifestations at diagnosis of GCA, (particularly visual alterations) clinical factors that increased the risk of relapses (24-28). Nevertheless, the therapeutic impact on the disease have been scarcely addressed in clinical practice.

Therefore, the purpose of this study is to assess the incidence of relapses in patients with recent diagnosis of GCA followed in clinical practice up to two decades, and to analyse the risk of relapses in these patients treated with and without MTX. Other sociodemographic, clinical and therapeutic associated factors will be also investigated.

Material and methods

Study design, patients, and data collection

This study was carried out in one of the tertiary public health hospitals of the Community of Madrid (Hospital Clínico San Carlos), covering a catchments area of approximately 400,000 people.

We carried out a retrospective observational study using an inception cohort of GCA patients attending the rheumatology outpatient clinic of our centre, from the time of diagnosis (January 1991 until September 2013) until loss of follow-up or September 2014. We selected all the patients that fulfilled the 1990 American College of Rheumatology classification criteria for GCA (29).

Patient's data in this project were obtained during routine clinical practice for 22 years with the oral informed consent of patients to be treated in a service that has clinical assistance and research work. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, and was approved by the institutional ethics committee (CEIC Hospital Clínico San Carlos, Madrid, Spain).

The investigators retrospectively reviewed all the medical records to obtain the variables. From the period between 1991 to December 2006, they were on paper and after that period, data were recorded in a departmental electronic health record (MEDI <log>) which integrates all the information collected during routine consultation by rheumatologists (30).

Variables

Our primary endpoint was relapses defined as recurrence of symptoms or signs of GCA after an objective improvement (absence of symptoms of GCA and normalisation of laboratory values), with high ESR and the need to increase glucocorticoids at least 10mg over the previous dose. The independent variable was exposure to MTX over time.

The following covariates were considered: 1) Sociodemographic baseline variables including sex and age. 2) Baseline comorbid medical conditions (hypertension, diabetes, hypercholesterolemia, cardiovascular disease (including cerebrovascular disease, peripheral artery disease and cardiovascular disease), congestive heart failure, cancer, depression, peptic ulcer disease, chronic obstructive pulmonary disease (COPD), liver disease, dementia, chronic renal failure, symptomatic vertebral fracture, tuberculosis and rheumatic disease including Polymyalgia Rheumatica). 3) Temporal artery biopsies positive, negative or indeterminate. 4) Clinical symptoms at diagnosis (headache, abnormal temporal artery in the exploration, cardiovascular symptoms, associated polymyalgia rheumatica, visual disturbances (transient visual disturbances, diplopia, blurred vision, loss of vision), jaw claudication, large vessel stenosis, thickening, tenderness, ulcers or nodules on temporal or occipital arteries, systemic

general manifestations (including constitutional symptoms [weight loss (yes/no in the last weeks), and fever (yes >=37.5ºC] and malaise) and analytical data as erythrocyte sedimentation rate (ESR) in mm/h and haemoglobin (Hb) in g/dl. 5) Treatment: a) glucocorticoids dosage in mg at diagnosis; taking aspirin at diagnosis, statins at diagnosis; taking Aza over time. 6) Calendar time: time of diagnosis grouped by five year intervals.

Data analysis

A description of the sociodemographic and clinical characteristics of patients were explored with frequency distribution and the mean and standard deviation or median and percentiles [p25–75].

Survival techniques (allowing for multiple-failure per patient) were used to estimate the incidence rate of relapses (IR) in our cohort, expressed per 100 patient-years with their respective 95% confidence interval [CI]. Kaplan-Meier curves were set to account for relapses over time. Time of exposure comprised the period from the baseline visit (diagnosis visit) until the occurrence of any of the following cut off points: loss of follow-up, relapses or the end of the study (September 2014). It is important to note that real life conditions use complicated patterns of drug therapies. Thus, patients were included in different groups and contributed with patient-years at risk to both those exposed and those not exposed to MTX treatment.

Cox bivariate analyses were done to asses differences in relapses. Taking into account the observational nature of the design, cox multivariate regression models (adjusted for age, sex, calendar time, and all variables with a *p*-value less than 0.2 in the bivariate analysis) were run to examine the possible influence of MTX on relapses. Exposure to MTX and exposure to Aza were used in a time-dependent manner. Results were expressed by hazard ratio with the 95% confidence interval (HR [CI]), being interpreted as the relative risk of relapse per year with respect to the referent category. Proportional hazard assumption was tested using Schoenfeld residuals and the scaled Schoenfeld residuals. All analyses were performed using Stata v. 13 statistical software (Stata Corp., College Station, TX, USA). A two-tailed *p*-value under 0.05 was considered to indicate statistical significance.

Table I. Baseline demographic and clinical characteristics of patients.

Patients (n)	168
Total follow up patient*year	675.6
Women, n (%)	135 (80.3)
Mean age at diagnosis, mean ± SD	76.7 ± 7
Comorbilities, n (%)	
HTA	107 (64.1)
Hypercholesterolaemia	57 (34.1)
Cardiovascular disease	51 (30.5)
Diabetes Mellitus	31 (18.5)
Polymyalgia rheumatica	23 (13.8)
Depression	23 (13.7)
Congestive heart failure	21 (12.6)
Peptic ulcer disease	14 (8.4)
Chronic renal failure	14 (8.4)
COPD	14 (8.4)
Cancer	19 (7.2)
Liver disease	7 (4.2)
ESR (mm/h), median [p25-p75]	83 [60-102]
Hb (g/dl), median [p25-p75]	12 [11-13]
Temporal Positive artery biopsy, n(%)	77 (46.4)
Lag time in months from diagnosis to MTX, median [p25-p75]	1.0 [0.098-3.6]
Other immunosuppressive agents (azathioprine) at diagnosis, n (%)	2 (1.2)
Aspirin at diagnosis, n (%)	55 (33)
Statins at diagnosis, n (%)	36 (21.5)
Glucocorticoids, n (%)	166 (99.4)
Glucocorticoids dose (mg/day) at diagnosis, mean ± SD	50.7 ± 15
MTX maximum dose	10 [10-12.5]
Clinical symptoms at diagnosis:	
Headache	146 (87.4)
Systemic general manifestations	92 (55.1)
Polymyalgia rheumatica	83 (49.7)
Impaired occipital sensitivity	70 (42)
Jaw claudicating	62 (37.1)
Abnormal temporal artery	55 (32.9)
Visual alterations	54 (32.3)
Peripheral joint pain	28 (16.7)
Cardiovascular clinic	6 (3.6)

Results

We included 168 patients (675 patient-years), with a maximum follow up of 21 years. Most of the patients were females, with a mean age at diagnosis of 76±7 years old. At the beginning of the study (Table I), 87% of the patients had at least one basal comorbid condition, being HTA, hypercholesterolemia, and cardiovascular disease the most prevalent ones. The main clinical symptom at diagnosis was headache, followed by systemic general manifestations and associated polymyalgia rheumatica. 32% had visual alterations, including in 26 of them vision loss. Regarding temporal artery biopsy, 46.4% were positive, 33.7% were negative, 4.2% were indeterminate and it was not performed in the remaining 26 patients (15.6%). The median starting dose of glucocorticoids was 60 [p25–75: 40–60] mg/day. 65% of the patients were on MTX and the median duration on MTX was 1.7 [p25–75: 0.5–3] years, with a maximum of 8.4 years. Interestingly, 50% of them started in the first month after the diagnosis, being the median lag time to MTX 37 days [p25–75: 7 days–7 months]. The mean dose was 10mg/week, being 20mg/week the maximum dose used during the whole follow-up. Regarding other immunosuppressant drugs, 2 patients started with Aza at diagnosis and 16 during the follow-up. 1 started with Cyclophosphamide at diagnosis due to loss of vision, and 5 after relapses. Concerning biologic agents, throughout the disease course,

two of them tried Infliximab, and other started with tocilizumab (Tzl), these last one without relapses until the end of the study.

31% of patients (n=52) had 81 relapses during the follow-up. The most common clinical symptom at relapses was polymyalgia rheumatica (53%), headache (47%), followed by general clinical symptoms (27%) and visual alterations (16%) with one patient with vision loss. The median ESR and Hb at relapse was 50 mm/h [28–68.5] and 12.3 gr/dl [11–13], respectively.

Interestingly, 69% of the patients had only one relapse, 22% had two and the remaining 8% had 3 or more, during the whole follow-up. The median number of relapses was 1[1–2] with a maximum of 6, with a median lag time of 1.6 [0.6–6.3] years. The median lag time until de first and second relapse was 0.8 [0.4–1.9] and 3.4 [2.0–6.7] years respectively. At the time of relapses 34% were out of glucocorticoids, and in those still on glucocorticoids, the median dose was 5 [5–10] mg. The median increase of glucocorticoids was 20 [12.5–30] mg, reaching a median dosage after relapses of 30 [20–30] mg.

From the total of relapses, 34% were on MTX and 65% were without MTX. Concerning the median dose of glucocorticoids at the time of flaring was 3.75 [1.25–5] for patients on MTX and 5[0–7.5] for patients without MTX. Regarding the increase of dosage after relapses, the median dose of glucocorticoids was 12.5 [10–20] mg for patients on MTX and 15 [10-30] mg for patients without MTX.

The IR of relapses was 12 [9.6–14.9] per 100 patient-years (Table II), being the rate of relapses over time 12% at 6 months, 27% at 12 months, 35% at 3 years, and 50% at 6.8 years (Fig. 1). The IR was higher for women and for those patients older than 67 years. The IR was rather stable with slight fluctuations over time (Table II).

In Table III the bivariate analysis is detailed. As we show in figure 1, the unadjusted hazard ratio for relapses was lower in those patients taking MTX compared to those without MTX (p=0.1). Finally, cox multivariate regression analysis was done to adjust for variables that were unevenly distributed between patients with and without MTX and with those variables which had an association with relapses. The final model is shown in Table IV. Exposure to MTX had 72% less risk of relapses compared to those without MTX. Other variables with statistical signification included in the final model were: diplopia, and malaise at clinical presentation of GCA. Mean dose of glucocorticoids at diagnosis (HR: 1.004 [0.98–1.02]; p=0.6), statins at diagnosis (HR: 0.71 [0.35–1.42]; p=0.33), and aspirin at diagnosis (HR: 0.84 [0.49–1.45]; p=0.5) dropped from the model.

Table II. Incidence rate (IR) of relapses by gender, age and calendar year.

	Patients*year	Events (n)	IR	95% CI
Total	675.6	81	12	9.6-14.9
Gender				
Women	523.1	71	13.7	10.7-17.1
Men	152.5	10	6.5	3.5-12.2
Age categories (interquartile ranks), years				
<67.5 (<P_{10})	88.7	6	6.7	3.04-15
67.5-71.5 (P_{10}-P_{25})	169.7	25	14.7	9.9-21.8
71.5-77.5 (P_{25}-P_{50})	143.4	19	13.2	8.4-20.7
77.5-81.3 (P_{50}-P_{75})	177.2	18	10.2	6.4-16.12
81.3-86 (P_{75}-P_{90})	64.5	9	13.9	7.3-26.8
>86 (>P_{90})	32.1	4	12.4	4.6-33.2
Calendar time				
1990 – 1995	125.4	15	11.9	7.2-19.8
1996 – 2000	145.5	26	17.8	12.1-26.2
2001 – 2005	158.6	15	9.4	5.7-15.6
2006 – 2010	213.7	22	10.3	6.7-15.6
>2011	32.3	3	9.3	2.9-28.8

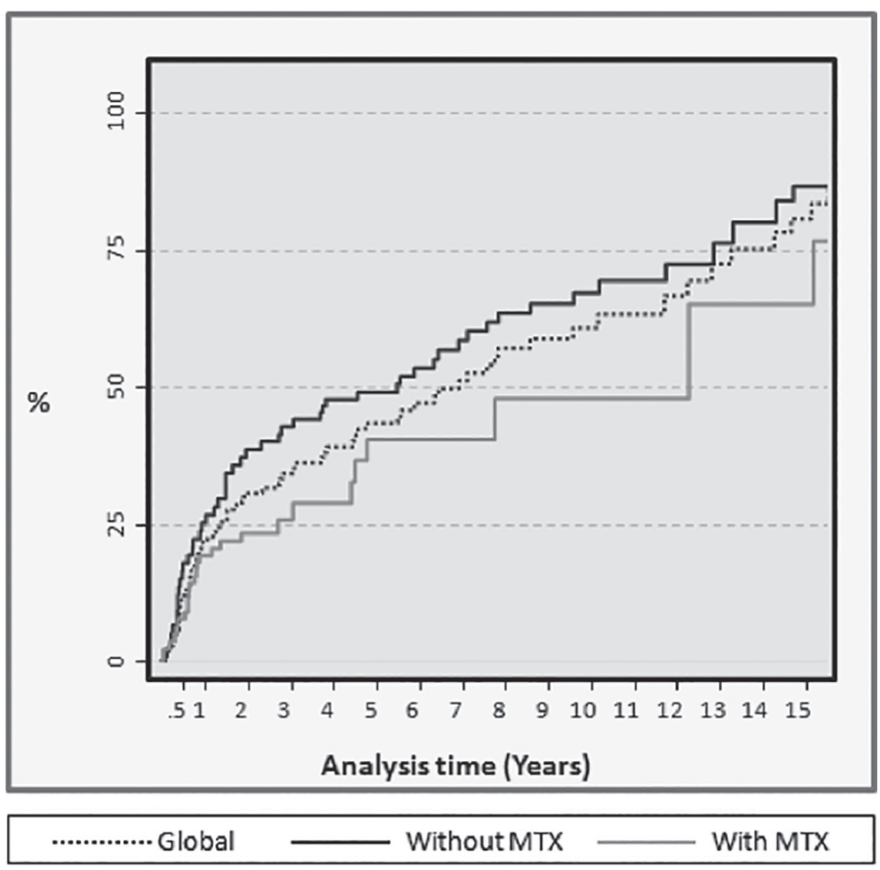

Fig. 1. Kaplan-Meier failure estimate curve of the probability of relapses over time.

Table III. Bivariate Cox regression analysis.

	HR	95%CI	p
Gender, male	0.50	[0.23-1.1]	0.08
Age categories, years			
<67.5	1	-	-
67.5-71.5	1.8	0.73-4.6	0.1
71.5-77.5	1.7	0.7-4.3	0.2
77.5-81.3	1.3	0.54-3.5	0.5
81.3-86	1.7	0.6-4.8	0.3
>86	1.4	0.4-5.1	0.5
Calendar time, years			
1990 – 1995	1	-	-
1996 – 2000	1.53	0.68-3.4	0.2
2001 – 2005	0.91	0.4-2.1	0.8
2006 – 2010	0.83	0.34-2.06	0.6
>2011	0.53	0.16-1.8	0.3
Comorbilities:			
HTA	0.99	0.57-1.73	0.9
Hypercholesterolemia	0.7	0.35-1.28	0.2
Cardiovascular disease	0.99	0.59-1.6	0.9
Diabetes Mellitus	0.8	0.4-1.6	0.5
Polymyalgia rheumatica	0.8	0.35-1.76	0.5
Depression	1.7	0.92-3.2	0.08
Congestive heart failure	0.7	0.3-2.04	0.6
Peptic ulcer disease	0.5	0.1-2.04	0.3
Renal insufficiency	0.6	0.14-2.4	0.4
COPD	1.15	0.4-3.5	0.8
Cancer	0.5	0.14-1.9	0.3
Liver disease	0.45	0.17-1.15	0.09
ESR (mm/h)	1.004	0.99-1.01	0.2
Hb (more than 12 g/dl)	0.56	0.38-1.03	0.06
Temporal Positive artery biopsy	1.01	0.6-1.7	0.9
Exposure to MTX (yes)	0.67	0.42-1.08	0.1
Aspirin at diagnosis (yes)	0.69	0.4-1.2	0.2
Statins at diagnosis (yes)	0.56	0.28-1.09	0.1
Glucocorticoids at diagnosis (dosage in mg)	1.007	0.9-1.02	0.3
Clinical symptoms:			
Headache	2.29	0.9-5.6	0.07
Malaise	1.6	1.01-2.7	0.04
Constitutional symptoms (fever/weight loss)	0.68	0.4-1.39	0.1
Polymyalgia rheumatica	1.18	0.7-1.9	0.5
Impaired occipital sensitivity	0.8	0.45-1.4	0.4
Jaw claudicating	0.8	0.47-1.5	0.5
Abnormal temporal artery	0.64	0.37-1.11	0.1
Visual alterations	1.5	0.87-2.6	0.1
Peripheral joint pain	1.3	0.7-2.4	0.3
Cardiovascular clinic	1.2	0.4-3.5	0.7
Exposure to Aza (yes)	1.6	0.69-4.0	0.2

Proportionality of these the regression models was tested with a *p*-value=0.9.

Discussion

To our knowledge, the current study constitutes the first cohort of GCA assessing the potential efficacy of long-term MTX in the disease course. It seems that exposure MTX had less risk to relapse compared to those without MTX. Although, the use of methotrexate did not significantly reduce the risk of relapses in the bivariate analysis, it did so in the multivariate analysis. The study also gives a detailed description of relapses in clinical practice and discloses and corroborates the influence of other factors in relapses.

This cohort included all patients with recent diagnosis of GCA from the early nineties until 2014, with a maximum follow up of 21 years. They are representative of the GCA population in Europe (31-33), most of them women in their 70s, being headache, systemic general manifestations and polymyalgia rheumatica the most prevalent symptoms at disease onset (24, 25, 34). From those patients with temporal artery biopsy, 64% were positive and almost 30% negative (31, 35).

In all patients, the starting dosage of prednisone was 1 mg/kg/day, regardless whether they were on MTX or not. Two-thirds were on MTX, and most of them with a dosage of 10 mg/week. In fact only two patients increased up to 20mg/week during the whole follow-up. This dose could be considered low, if we take into account that the optimal dose in other rheumatic diseases such as rheumatoid arthritis is much higher (25mg). But GCA patients are old people, some of them with chronic renal failure, other associated comorbidities and with concomitant use of glucocorticoids. We must take into account that at this dosages, MTX can be considered safe in the treatment of GCA as previous studies have shown (15, 36).

In our study 31% of the patients had relapses during follow-up with an IR of 12 [9.6–14.9] per 100 patient-years. The frequency of relapses was overall similar to that reported in other cohorts (24, 26, 37), but lower than that reported in the study of Alba (25) and Proven (5) that evaluated a frequency of relapses in 64% and 48% respectively. These discrepancies are mainly related to differences in the definition of relapse. We used a strict definition, as the study of Restuccia *et al*. (24), considering relapses as the reappearance of GCA-related clinical manifestations, with elevated ESR, that required treatment adjustment for at least 10 mg of glucocorticoids over the previous dose. The majority of our patients with relapses only developed one, and 22% two. Our study also confirms that relapses may occur at any time; however, as in other studies, 50% of patients experienced the first relapse during the initial 12 months (25, 33, 38), and 75% of patients before the first two years (24). Besides, we corroborate (28, 39) that relapses were favoured at low prednisone doses (median in our study was 5 [0–7.5] mg).

In agreement with other observational studies (24-26, 28, 33, 40) the most frequent clinical manifestations at the time of relapse were PMR, headache, and systemic general manifestations,

Table IV. Multivariate Cox regression analysis.

	HR	95%CI	*p*
Gender, male	0.54	0.25-1.16	0.1
Age categories, years			
<67.5	1	-	-
67.5-71.5	2.07	0.78-5.47	0.1
71.5-77.5	1.63	0.54-4.90	0.3
77.5-81.3	2.05	0.71-5.90	0.1
81.3-86	1.95	0.69-5.50	0.2
>86	1.00	0.28-3.61	0.9
Calendar time, years			
1990 – 1995	1	-	-
1996 – 2000	2.14	0.92-4.94	0.07
2001 – 2005	1.23	0.51-2.97	0.6
2006 – 2010	1.06	0.44-2.56	0.8
>2011	0.78	0.21-2.96	0.7
Hb (more than 12 g/dl)	0.60	0.29-1.25	0.1
Malaise	1.93	1.08-3.42	0.024
Visual alterations			
Transient visual disturbances	-	-	-
Blurred vision	-	-	-
Diplopia	3.96	2.21-7.07	0.000
Loss of vision	1.90	0.88-4.11	0.09
Depression (yes)	1.51	0.81-2.80	0.1
Exposure to MTX (yes)	0.58	0.35-0.94	0.029

whereas cardiovascular involvement was rarely observed. We also corroborate that despite the frequency at diagnosis of visual alterations, this manifestations declined considerably at disease relapses (25, 26, 41). In our cohort we found one visual loss during the whole follow-up.

A major issue in the management of GCA would be to identify effective immunosuppressant adjunctive treatment in these patients. In this sense, this study shows that concomitant treatment with MTX decreases the risk of relapses compared to those without MTX, supporting the clinical trial of Jover (13) and other meta-analysis (15, 16), but with the advantage of non selected patients from clinical practice and during the long term. The advantage of patients on MTX is the possibility of decrease glucocorticoids quickly, avoiding the risk of adverse drug reactions related to glucocorticoids, and increasing the likelihood of a better course of the disease in the context of elderly and comorbid patients.

The present study also has investigated the role of other clinical, sociodemographic and therapeutic factors at the time of GCA diagnosis in the development of relapses. As in other studies, we show that higher activity at diagnosis might imply a higher risk of relapses (38, 39). Specifically, the presence of malaise and systemic manifestations, and particularly visual alterations (24, 38) increased the hazard of flaring. In this sense the model achieved statistical signification for diplopia. Concerning other aspects of activity, several studies have exposed the role of anaemia on relapses (24, 26). In this sense, Hb was included in our final model, showing that lower levels at diagnosis achieved a trend of flaring. Finally regarding constitutional symptoms, and specifically focusing on fever, Restuccia *et al*. (24) showed that this parameter increased the risk of relapses. In our study, fever and weight loss dropped from the final model. Disparity may be related to the way of collecting these variables and the retrospective nature of the study. In our study weight loss had many missing values, and fever was registered as "yes" when the patient had at least 37.5ºC instead of a numeric value (24)**.**

It has been suggested that the presence of atherosclerosis risk factors at the time of diagnosis of GCA, might influence the development of severe ischaemic manifestations of the disease (42). But the role of statins in GCA is still unknown (43). Pugnet *et al*. exposed that these drugs might favour a quicker corticosteroid tapering (44). Whereas, in accordance with our results, other studies concluded that statin use did not appear to modify the disease course (27, 45).

Concerning aspirin, several studies have attempted to determine whether antiplatelet therapy would reduce the risk of relapses and specifically the ischaemic complications in patients with GCA. In general, clinical trails failed to demonstrate the efficacy of low-dose aspirin as an adjunctive treatment in GCA (46). Observational studies have been also published with conflicting results (31, 47-49). Some of them found significant reduction in the incidence of ischaemic manifestations and in the frequency of relapses in the group of aspirin patients (47, 48), whereas others, like our study, did not (31, 49). A recent meta-analysis including six retrospective studies, has showed a marginal benefit of antiplatelet therapy in patients with established GCA and without associated bleeding risk (50). Clinicians who are considering the use of low-dose aspirin as an adjunctive treatment in GCA should recognise the haemorrhagic risks, especially in the context of frailty and comorbid patients taking concurrent treatment with corticosteroids.

Our study has several limitations. First, given the retrospective nature of the design, data obtained relies on documentation available in the medical records. Thus, we did not have the tapering regimens of glucocorticoids in all visits, and in this aspect we were not able to directly demonstrate the effect of MTX as a corticoid sparing agent. But at time of relapses the median corticoid dosage, and also the frequency and risk of relapses was lower in the MTX group, making understandable this premise. Another limitation is the low number of patients included, but we have to keep in mind the low prevalence of this disease. In fact, we have included all patients with GCA from our catchments area. Otherwise, one of the greatest strengths of this study is the long-term follow up of non selected patients from clinical practice, with and without immunosuppressant agents, adjusted for multiple confounders.

In conclusion, we can say, and supported by previous clinical trials, that MTX can be useful for the treatment of GCA. Our cohort provides further evidence of the potential efficacy of long-term MTX in the management of patients with GCA. We think the point should be to start with MTX at least 7.5-10 mg in early stages of disease, with recommended dosages of glucocorticoids. We have also seen that in addition to MTX, severity of inflammation at clinical debut might predict the development of disease relapses. Further studies in multicentre settings should be required to corroborate our findings.

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