Effectiveness and safety of medium-dose prednisone in giant cell arteritis: a retrospective cohort study of 103 patients

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ABSTRACT

Objective. *To compare the effectiveness and safety of medium-dose (MD) and high-dose (HD) prednisone regimens and to identify factors related to remission with a target maintenance dose of prednisone in patients with giant cell arteritis (GCA).*

Methods. *Retrospective cohort study conducted in an autoimmune diseases unit. Patients received ≤30 mg (MD group) or >30 mg (HD group) of daily prednisone as monotherapy or combined with methylprednisolone pulses and/or methotrexate, at the discretion of the physician. The primary endpoint was time to clinical and biological remission receiving a prednisone maintenance dose ≤7.5 mg/day. Factors related to the primary endpoint were identified by Cox regression analysis.*

Results. *Overall, 103 patients (MD=53, HD=50) were followed for a median (95%CI) of 2.85 (2.57-3.52) years. Both groups exhibited similar baseline features except for ocular ischaemic manifestations (MD=21%, HD=48%, p=0.004). Patients in the MD group had a shorter time to the primary endpoint (MD=186 [147-223], HD=236 [177-276] days, HR=1.70 [1.12-2.57], p=0.01) with no increase in relapses (MD=39%, HD=50%, p=0.29) or GCA complications (MD=11%, HD=16%, p=0.49). Cumulative prednisone doses at 6 months were 2.47±0.70 g for MD patients and 3.86±1.85 g for HD patients (p<0.001). Adverse effects were more frequent among HD recipients (MD=43%, HD=66%, p=0.02). The only independent factor associated with the primary endpoint was the use of methylprednisolone pulses (HR=2.21 [1.31-3.71], p=0.003).*

Conclusion. *MD prednisone regimen may be an effective and safe alternative to HD prednisone regimen in GCA. Induction with methylprednisolone pulses predicts a better response, allowing for a less intensive prednisone regimen.*

Introduction

Glucocorticoids (GCs) are still the mainstay of treatment for giant cell arteritis (GCA) (1, 2). However, the duration of GC treatment may range from several months to lifelong (3, 4). To date, few studies have identified baseline or follow-up predictors of a better therapeutic response (5, 6). On the other hand, it is well documented that the cumulative dose of GCs correlates with mortality and occurrence of adverse effects (7-9), especially in the elderly (10). Thus, a substantial proportion of GCA patients may be exposed to an excessive cumulative GC dose without proper consideration of the risk-benefit profile associated with this treatment (11, 12).

Current guidelines recommend a starting prednisone dose of 1 mg/kg/day (maximum, 60 mg/day) as the standard therapy for all patients with GCA (13), while other authors have suggested that this starting dose should be between 40 and 60 mg/day (14, 15). However, the fixed dose of 1 mg/kg/day has been criticised due to the risk of toxicity and the lack of supportive evidence (16). In addition, to date, the so-called high-dose prednisone regimen has not shown a clear benefit compared to lower doses. Nowadays, low, medium and high GC doses are respectively defined as ≤7.5 mg, between >7.5 and ≤30 mg and >30 mg of daily prednisone, regardless of patient weight (17). According to this nomenclature, previous studies comparing different GC regimens are difficult to interpret because researchers used different cut-off values for the prednisone doses (18-21). Further limitations of these studies are the inclusion of patients with isolated polymyalgia rheumatica without GCA, small sample sizes and short follow-up periods. Lastly, irrespective of the starting dose, achievement of a safe prednisone dose as soon as possible should be a therapeutic goal and this was not

adequately taken into account in the above-mentioned studies. Although the threshold below which prednisone can be considered safe is not well established, it is widely recommended that the daily maintenance dose should not exceed 7.5 mg (22, 23). Our hypothesis was that medium starting doses of prednisone could reduce time to remission achieved with a target dose of prednisone, without increasing GCA relapses and complications.

For these reasons, we designed this study aimed to compare the effectiveness and safety of medium (≤30 mg/day) and high (>30 mg/day) starting doses of prednisone in a large cohort of patients with GCA. In addition, we tried to identify factors associated with remission once the target maintenance dose of prednisone (≤7.5 mg/day) had been achieved.

Patients and methods

Study design and setting

We conducted an observational retrospective study of an historical cohort recruited in the Autoimmune Diseases Unit of a tertiary care hospital between January 2004 and December 2012. Patients were scheduled for regular medical check-ups in a dedicated outpatient clinic for vasculitis (24).

Patient selection

All patients with GCA who received care in our unit were included in the study if they met the following inclusion criteria: 1. three of the five 1990 American College of Rheumatology classification criteria for GCA (25); and 2. acceptance of informed consent. Exclusion criteria were: 1. unavailability of data to determine dates of remission and doses of prednisone; and 2. loss to follow-up before 6 months.

The diagnosis of GCA was based on either a positive temporal artery biopsy (presence of cellular infiltration including lymphocytes, plasma cells and/or multinucleated giant cells in the media or the adventitia of the arterial wall) or the combination of at least one clinical criterion (new type of localised headache not explained by another cause, temporal artery abnormalities on physical examination not attributable to atheromatosis, new-onset jaw claudication, or ischaemic optic neuropathy not due to an atheroembolic or cardioembolic mechanism) and one analytical criterion (erythrocyte sedimentation rate [ESR] ≥50 mm/hour using the Westergren method, or C-reactive protein [CRP] ≥2 mg/dL, without an alternative origin), all of them in patients older than 50 years. We adopted this definition because of the low rate of positive temporal artery biopsies due to the segmental nature of the inflammatory infiltrate (26-28). Inconclusive temporal artery biopsies were reviewed by two independent pathologists before being classified by consensus as positive or negative for GCA.

Procedures

Initiation of therapy was decided on the basis of clinical and laboratory findings consistent with a diagnosis of GCA without waiting for the result of the temporal artery biopsy, which was performed within 15 days after the start of GCs (29). All patients were treated with oral prednisone as monotherapy or in combination with intravenous methylprednisolone (MP) pulses of 250-500 mg for 3 consecutive days on diagnosis and/or oral or intramuscular methotrexate (MTX, range dose: 7.5-20 mg/week) based on the clinical judgement of the physician. Depending on the starting dose of prednisone, patients were classified into 1) a medium-dose (MD) group (≤30 mg/day) or 2) a high-dose (HD) group (>30 mg/day), in accordance with current nomenclature (17). The rationale for choosing the MD instead of the HD regimen was based on a GC-sparing policy that has been shown effective in other autoimmune diseases (30), according to daily experience in our unit. The prednisone tapering did not follow a pre-specified protocol of time intervals but rather was adjusted by the physician on the basis of clinical and laboratory parameters irrespective of the starting dose. In the absence of contraindications, both groups received low-dose aspirin, calcium and vitamin D supplements, and bisphosphonate therapy if indicated (31-33). In addition, all patients underwent a systematic cardiovascular risk assessment based on recommendations (34), including periodical arterial pressure measures and blood tests at each scheduled visit and by their primary care physicians for screening of arterial hypertension, diabetes mellitus and hypercholesterolemia. During follow-up, patients who had a relapse were managed with an increase in prednisone of 5–10 mg/day until they recovered to their previous status (35). The follow-up consisted of regular visits every 1 to 3 weeks during the first 2 months, every 1 to 3 months until the first year and every 4 to 6 months thereafter, depending on the clinical status of patients.

Outcomes

The primary endpoint of the study was time to clinical and biological remission receiving a maintenance prednisone dose ≤7.5 mg/day. In the absence of standardised response criteria for large vessel vasculitis (36), this primary endpoint combined the achievement of both remission and a target prednisone dose. The secondary endpoints were: time to therapy withdrawal by the physician, percentage of patients who were withdrawn from treatment, cumulative prednisone dose at 6 and 12 months, and percentage of patients who had relapses, GC-related adverse effects, or GCA-related complications or who died, all of them after the treatment had been initiated.

Clinical remission was defined as complete absence of signs and symptoms of GCA for at least 1 week and biological remission as normalisation of ESR and CRP in two consecutive measurements at least 1 week apart (37, 38). Relapses were defined as any reappearance of signs and symptoms of GCA associated or not with a rise in ESR or CRP levels that required an increase in the prednisone or MTX doses. Asymptomatic laboratory abnormalities not involving treatment modifications and progressive increases in MTX dosage aimed to maximise the effect of the drug without clinical changes were not considered relapses.

The following GC-related adverse effects were recorded: new-onset diabetes mellitus, arterial hypertension, hypercholesterolemia requiring lipid-lowering drugs, peptic ulcers, osteoporotic

fractures, avascular osteonecrosis, cataracts, appearance of Cushingoid clinical features, and infections requiring admission.

GCA-related complications were defined as occurrence of ocular ischaemic events (arteritic ischaemic optic neuropathy, amaurosis fugax, central retinal artery occlusion, and diplopia), aneurysm (39, 40), and ischaemic stroke.

Other variables assessed at baseline and, if appropriate, at each medical appointment during follow-up were: age, gender, previous comorbid conditions, clinical manifestations of GCA, haemoglobin levels, platelet count, ESR, CRP, histopathological findings on temporal artery biopsy, start of and successive maintenance prednisone doses, and association with MP pulses or MTX.

Ethical issues

The study protocol conformed to the Declaration of Helsinki and was approved by the local Institutional Review Board of Hospital Universitario Cruces, in accordance with the Spanish legislation. Written informed consent was obtained from all participants before being included in our database.

Statistical analysis

Time data were expressed as median (95% confidence interval [CI]), quantitative continuous data as mean ± standard deviation and categorical data as number (percentage). Quantitative continuous variables were compared between the two groups using the Student's *t*-test for unpaired data or the non-parametric Mann-Whitney *U* test if data did not follow a Gaussian distribution. Categorical variables were compared using Pearson's X^2 test or Fisher's exact test depending on the expected cell frequencies. The primary endpoint was described with the Kaplan-Meier estimator and the log-rank Mantel-Cox test was used for comparison between groups. Patients were censored for the analysis of the primary endpoint on death from non-GCA-related causes or loss to follow-up or absence of any event of interest at the end of the study period.

Multivariate analysis using a Cox regression model was performed to identify factors related to the primary endpoint and to obtain adjusted estimates of treatment effects. Using a manual, backward iterative process, the model was constructed from variables which either had a p value <0.2 in the univariate analysis or were considered clinically relevant on the basis of previous studies; the treatment group (MD or HD) was also included as a potential predictor. Potentially relevant interactions between predictors were tested through the use of cross products of main predictors. Bonferroni corrections were applied for multiple comparisons between different therapeutic subgroups (41). Two-sided hypothesis tests were performed, and the significance level was set at 5%. The analysis was conducted using Stata statistical software version 12.1 (StataCorp, College Station, Texas, USA).

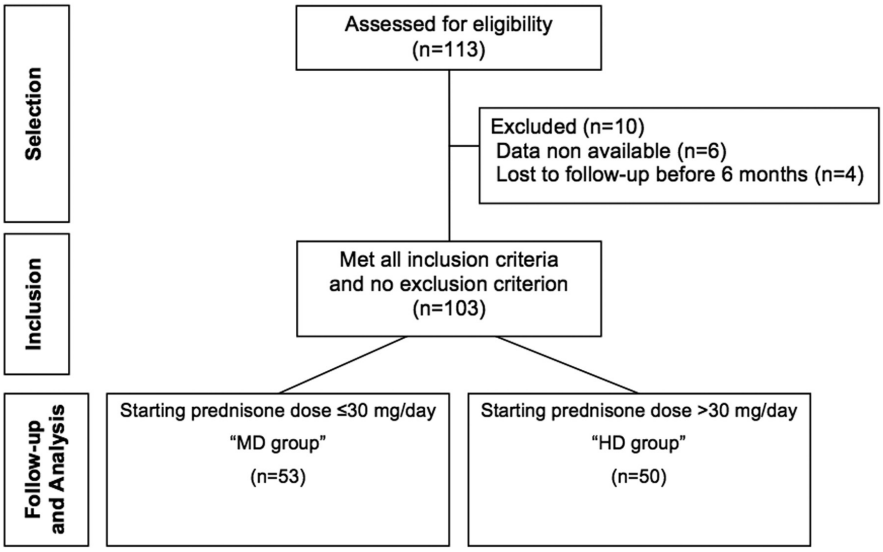

Fig. 1. Flow diagram of the participants of the study. Patients were selected from a vasculitis outpatient clinic. From a total of 113 potentially eligible patients with GCA, 103 patients were included in the study according to the inclusion and exclusion criteria. The cohort was divided into patients treated at baseline with medium-dose (MD group) and high-dose (HD group) prednisone. There were no significant differences between MD and HD groups in length of follow-up.
GCA: giant cell arteritis; MD: medium-dose; HD: high-dose.

Results

Baseline and therapeutic characteristics of the cohort

A total of 113 patients with GCA were assessed for eligibility. Of them, 103 patients (MD=53, HD=50 patients) were included in the study (Fig. 1) and followed for 2.85 (2.57–3.52) years. The starting prednisone dose was 27.45±5.51 mg/day in the MD group and 54.30±11.86 mg/day in the HD group ($p<0.001$).

Temporal artery biopsy was performed in 94 cases (MD=47 [88%], HD=47 [94%], $p=0.49$), with positive result in 49 patients (52%) and negative in 45 (48%). Reasons for omitting this biopsy (n=9 patients) were lack of consent (n=6), venous sampling in a previous attempt (n=2) and high risk of bleeding (n=1).

Except for ocular ischaemic manifestations (MD=11 [21%], HD=24 [48%], $p=0.004$), there were no statistically significant differences between the two groups in baseline characteristics (Table I) or in length of follow-up (MD=2.81 [2.42–3.54], HD=3.05 [2.47–4.55] years, $p=0.26$). Regarding treatment modalities (Table I), there was a trend towards a higher percentage of patients in the MD group being treated with MP pulses (MD=17 [32%], HD=8 [16%], $p=0.06$) and MTX (MD=26 [49%], HD=16 [32%], $p=0.08$).

Outcomes data

The product-limit estimate of the probability of achieving the primary endpoint was significantly higher in MD group patients (Fig. 2). Notably, most patients in the whole cohort achieved the primary endpoint during follow-up regard-

Table I. Baseline characteristics and therapeutic modalities of patients in the MD and HD groups.

Characteristics	MD group (n=53)	HD group (n=50)	*p*-value
Age (years)	74.7 ± 8.4	73.3 ± 7.9	0.39
Gender (male/female)	16 (30)/37(70)	19 (38)/31 (62)	0.40
Arterial hypertension	36 (68)	32 (64)	0.67
Diabetes mellitus	10 (19)	11 (22)	0.69
Tobacco use (prior or current)	18 (34)	13 (26)	0.38
Hypercholesterolemia	19 (36)	20 (40)	0.66
Polymyalgia rheumatica	18 (34)	14 (28)	0.51
Jaw claudication	14 (26.5)	21 (42)	0.09
Ocular ischaemic manifestations*	11 (21)	24 (48)	0.004
ESR (mm/hour)	88.7 ± 28.8	87.2 ± 25.0	0.77
CRP (mg/dL)	7.1 ± 9.8	8.9 ± 7.8	0.32
Haemoglobin (g/dL)	12.1 ± 1.4	11.9 ± 1.3	0.45
Platelets (10^3/μL)	323.6 ± 113.6	348.2 ± 144.1	0.34
Temporal artery biopsy (positive/negative)	26 (55)/21 (45)	23 (49)/24 (51)	0.68
Therapy			
Acetylsalicylic acid	40 (75.5)	37 (74)	0.86
Acenocoumarol	4 (7.5)	6 (12)	0.52
MP pulses	17 (32)	8 (16)	0.06
MTX	26 (49)	16 (32)	0.08

Data are expressed as mean ± standard deviation or number of patients (%).
*Ocular ischaemic manifestations were defined as arteritic ischaemic optic neuropathy, amaurosis fugax, central retinal artery occlusion or diplopia.
MD: medium-dose; HD: high-dose; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MP: methylprednisolone; MTX: methotrexate.

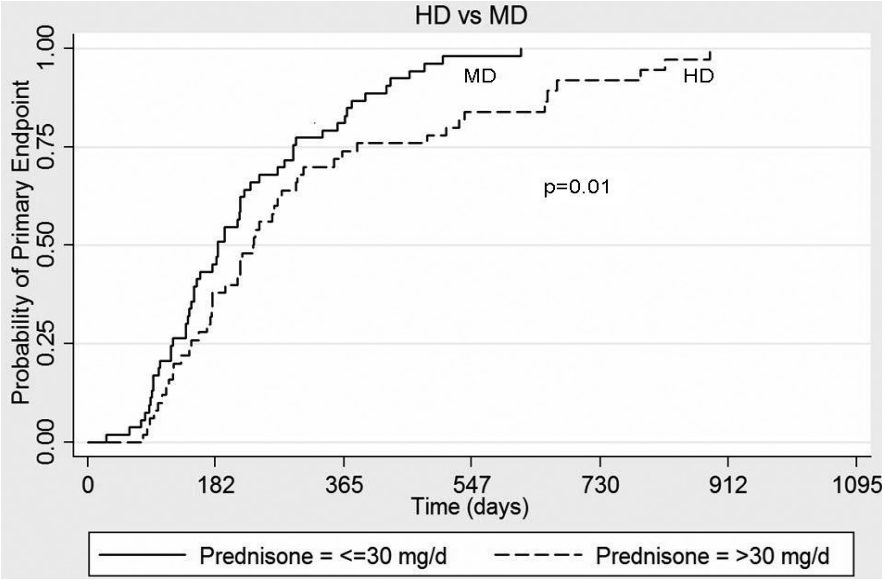

Fig. 2. Kaplan-Meier probability of achieving clinical and biological remission while receiving ≤7.5 mg/day of prednisone in MD and HD groups. The needed time to achieve the primary endpoint was shorter in MD group patients (MD=186 [147-223], HD=236 [177-276] days, log-rank test p=0.01).
MD: medium-dose; HD: high-dose.

less of treatment allocation (MD=53 [100%], HD=48 [96%], p=0.14).

The percentage of patients able to discontinue the immunosuppressive therapy including prednisone during the study period was similar in the two groups (MD=24 [45%], HD=21 [42%], p=0.67). There was a non significant difference in time to complete prednisone withdrawal (MD=2.20 [1.66-2.41], HD=2.34 [1.74–2.75] years, p=0.13).

Differences in the starting dose of prednisone were not associated with an increase in relapses (MD=21 [39%], HD=25 [50%], p=0.29) or GCA-related complications (MD=6 [11%], HD=8 [16%], p=0.49), none of which manifested in the form of ocular ischaemic events (Table II). In contrast, the cumulative prednisone dose was higher in the HD group at 6 months (MD = 2.47±0.70, HD=3.86±1.85 g, p<0.001) and 12 months (MD=3.65±1.11, HD= 5.23±2.54 g, p<0.001). Considering the MP pulses, the cumulative prednisone dose remained higher in the HD group at 6 months (MD = 2.75±0.77, HD=4.01±1.81 g, p<0.001) and 12 months (MD=3.93±1.07, HD= 5.38±2.50, p<0.001). This difference in the cumulative prednisone dose was in turn associated with a higher overall rate of GC-related adverse effects (MD=23 [43%], HD=33 [66%], p=0.02). New-onset hypercholesterolemia requiring lipid-lowering drugs was the most common adverse effect (Table II), especially in HD group patients (MD=5 [9%], HD=15 [30%], p=0.008). Infections requiring admission occurred in 9 patients (MD=6 [11%], HD=3 [6%], p=0.49); four of them corresponded to pneumonia, 3 to soft tissue infections and 2 to urinary tract infections. During follow-up, there were 4 deaths (MD=1 [2%], HD=3 [6%], p=0.35), none of them directly related to GCA.

Factors related to the primary endpoint

In the univariate analysis, significant factors related to the primary endpoint were MD group (HR=1.70, 95%CI=1.12–2.57, p=0.01) and MP pulse therapy (HR=2.34, 95%CI=1.45-3.77, p<0.001).

In the multivariate analysis, the model included use of MTX because this drug was close to statistical significance in the univariate analysis (p=0.16) with a favourable effect (HR=1.33, 95%CI=0.89–1.99) and had been shown to be of benefit in previous studies (42). Finally, the only independent factor related to the primary endpoint was use of MP pulses (HR=2.21, 95%CI=1.31–3.71, p=0.003).

Table II. Therapy-related adverse effects, relapses and GCA-related complications in patients of MD and HD groups.

	MD group (n=53)	HD group (n=50)	*p*-value
Adverse effects	23 (43)	33 (66)	0.02
Diabetes mellitus	6 (11)	10 (20)	0.22
Arterial hypertension	2 (3)	2 (4)	0.95
Hypercholesterolemia	5 (9)	15 (30)	0.008
Osteoporotic fracture	5 (9)	7 (14)	0.47
Cataract	4 (7)	5 (10)	0.74
Infections requiring admission	6 (11)	3 (6)	0.49
Cushingoid clinical features	1 (2)	4 (8)	0.19
Relapses	21 (39)	25 (50)	0.29
GCA complications	6 (11)	8 (16)	0.49
Ocular ischaemic events*	0 (0)	0 (0)	1.00
Ischaemic stroke	1 (2)	1 (2)	0.97
Aneurysm	2 (3)	0 (0)	0.49
Death	1 (2)	3 (6)	0.35

Data are expressed as number of patients (%).
*Ocular ischaemic events were defined as arteritic ischaemic optic neuropathy, amaurosis fugax, central retinal artery occlusion or diplopia.
MD: medium-dose; HD: high-dose; GCA: giant cell arteritis.

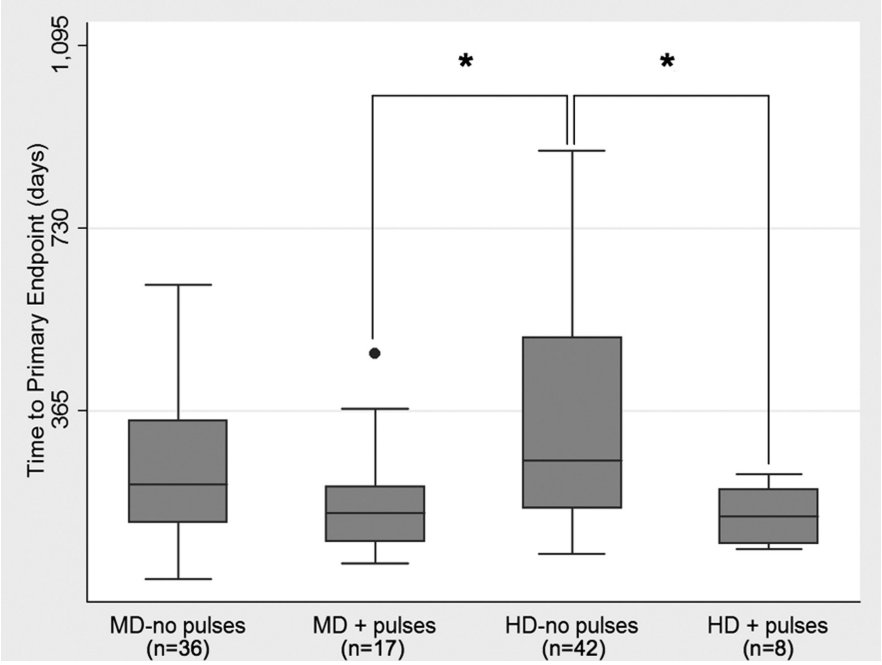

Fig. 3. Box plot comparing time to the primary endpoint between MD and HD groups with or without MP pulse therapy. The time to the primary endpoint in days for the MD without pulses subgroup was 262.5 (93-426); for the MD with pulses subgroup, 164.5 (103-213); for the HD without pulses subgroup, 263 (177-550); and for the HD with pulses subgroup, 176.5 (88-238).
*p=0.001 (Bonferroni-adjusted significance threshold p=0.008).
MD: medium-dose; HD: high-dose; MP: methylprednisolone.

An interaction between the starting prednisone dose and receiving MP pulses was found to have a close to significant effect on the primary endpoint (p=0.07). That is, the estimated effect of the initial prednisone dose regimen upon the achievement of the primary endpoint seemed to vary according to whether additional MP pulses were administered (Fig. 3). Applying the Bonferroni-adjusted significance threshold (p=0.008), only the comparisons between HD with pulses *versus* HD without pulses (HR=3.89, 95%CI=1.74-8.71, p=0.001) and MD with pulses *versus* HD without pulses (HR=2.86, 95%CI=1.56–3.32, p=0.001) showed statistically significant differences (Fig. 3).

Subgroup analysis

Figure 4 summarises the relative probability of achieving the primary endpoint in different subgroups. In the subgroups of patients with positive temporal artery biopsy result (n=49, MD=26, HD=23 patients) or with ocular ischaemic manifestations at baseline (n=35, MD=11, HD=24 patients), the time to the primary endpoint was also shorter in MD regimen patients (MD=183 [142–280], HD=236 [147–384] days, p=0.05; MD=160 [76–213], HD=220 [175–308] days, p=0.005; respectively). In both subgroups, the cumulative prednisone doses at 6 months and 12 months were higher in HD regimen patients; relapses were more common only in HD regimen patients with biopsy-proven GCA, while the rate of prednisone-related adverse effects and GCA-related complications did not differ between MD and HD groups (data not shown).

Discussion

The present study investigated the effect of two different GC regimens (MD and HD groups) on the therapeutic response of a cohort of patients with GCA. In terms of effectiveness, the most important finding is that patients in the MD group exhibited a response at least as favourable as those in the HD group. Specifically, there was a higher probability of achieving the primary endpoint in the MD group without an increase in the risk of GCA relapses or complications. Further, clinical benefits in favour of the MD regimen largely remained when analysing different subgroups of patients. However, the effect of the starting prednisone dose on the primary endpoint was strongly influenced by the administration of MP pulses.

In terms of safety, our data confirm what has been shown previously, in that patients in the HD group showed higher overall levels of toxicity because of a more intensive GC regimen (4, 7, 18, 19). Probably due to the limited sample size and time of exposure to GCs, the single prednisone-related adverse effect that accounted for the observed benefit

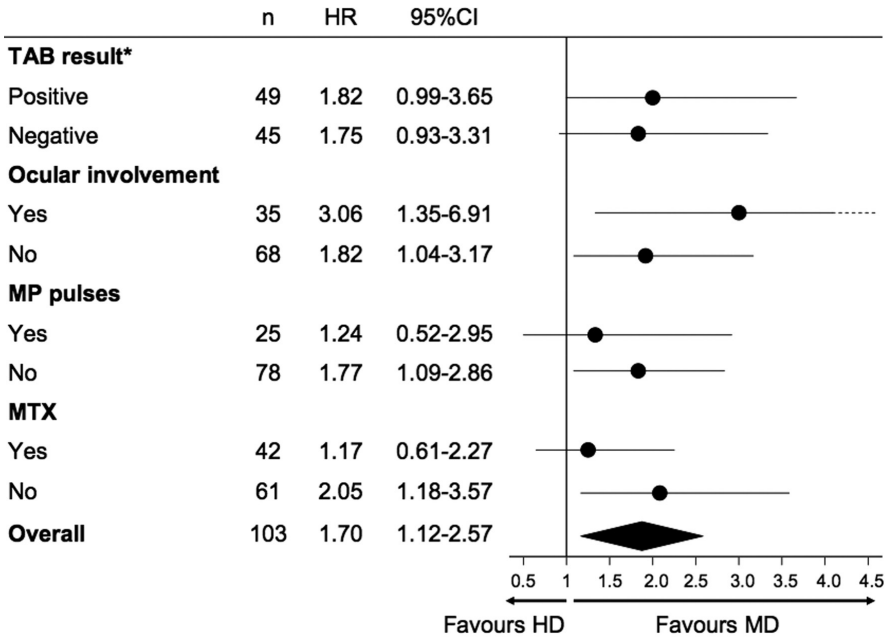

Fig. 4. Forest plot representing the relative probability of achieving the primary endpoint in MD group *versus* HD group depending on the positive or negative result of TAB, the presence or absence of ocular ischaemic involvement at baseline and the use or not of MP pulses and MTX.
*TAB was performed in 94 patients (MD=47 [88%], HD=47 [94%], p=0.49).
TAB: temporal artery biopsy; MP: methylprednisolone; MTX: methotrexate; MD: medium-dose; HD: high-dose.

in favour of the MD group was hypercholesterolemia requiring lipid-lowering drugs. Even so, our results suggest that a therapeutic approach focused on a GC-sparing strategy may be valid. In our opinion, optimising the cumulative prednisone dose is of critical importance in the elderly, who are especially susceptible to GC-related toxicity and represent a major subgroup of patients with GCA (43).

Another notable finding is that remission was a common event in our cohort regardless of the prednisone dose at baseline. Despite being frequent, achievement of a safe prednisone maintenance dose occurred after prolonged treatment periods in order to reduce GCA relapses and complications. Concerning relapses, the rate of which was not higher in our series than in previous reports (8, 44), they usually manifested in the form of headache or polymyalgia rheumatica, and were easily managed with small and short-term increases in the prednisone dose. Regarding complications, our data are consistent with prior studies that have shown a low frequency of ischaemic events once GCs have been initiated (3, 44, 45), especially if they are provided as pulse therapy.

Furthermore, our multivariate analysis identified the use of MP pulses as the only factor that had an impact on the therapeutic response in GCA. Despite conflicting preliminary results (46), the benefit of three MP pulses as induction therapy has been observed in a prior clinical trial (47), which provides external validity for our results. Since this study by Mazlumzadeh *et al*. was published, we have gradually incorporated MP pulses in our therapeutic protocol. With only 24% of all our patients receiving MP pulses, we found a positive effect similar to the one previously reported by Mazlumzadeh *et al*.

In addition, the benefit derived from MP pulses cannot be separated from the effect of the starting dose of prednisone due to the existence of an interaction between these two factors. Specifically, the impact of the starting prednisone dose depends on its combination or not with MP pulses (Fig. 3). Given the lack of differences in terms of effectiveness between MD and HD prednisone in patients receiving adjunctive MP pulses, safety considerations seem to be a sensible justification for prioritising the MD over the HD regimen. Nevertheless, we note that a recent meta-analysis has raised doubts about the benefit of adjunctive agents (including MP pulses) other than prednisone in GCA (48).

Several methodological limitations of the current study should be recognised. First, the observational retrospective design does not allow us to draw firm conclusions regarding causality, and does not ensure protection against a potential confounding by indication bias related to the physician's underlying reasons to choose the MD or HD regimen. Second, ocular ischaemic manifestations at baseline, despite not being associated with a poorer outcome in our analysis, were more common in the HD group. Thus, the tendency among physicians towards using a slow-tapering prednisone schedule in these patients with the most severe forms of GCA might in part explain the better response to the MD regimen. However, the benefit in favour of the MD regimen was observed both in patients with and without ocular ischaemic involvement at baseline (Fig. 4). Third, the percentage of patients in the MD group being treated with MP pulses and/or MTX tended to be higher than in HD group. However, among patients who did not receive MP pulses or MTX, the MD regimen was related to an earlier achievement of the primary endpoint (Fig. 4). Further, the presumed superiority in terms of safety derived from a more restrictive use of GCs was not as clinically significant as might be expected given the differences in the cumulative prednisone doses. Insufficient statistical power, long-term nature of much of GC-related toxicity and retrospective data collection may have led to an underestimation of the rate of adverse effects. Lastly, prescription of MP pulses on three consecutive days may not be applicable to all patients due to comorbidities or to logistical factors. We underline that the fact that visual ischaemic deterioration was not detected during follow-up does not rule out the risk of this complication, particularly within the first week of treatment (49, 50). Based on our data, a randomised controlled trial comparing MD prednisone preferably in combination with MP pulses *versus* HD prednisone may be warranted.

In conclusion, our results suggest that in patients with GCA starting MD prednisone has a better safety profile than HD prednisone and is similarly effective in achieving both remission and a target maintenance dose of prednisone. One well-defined factor namely the use of MP pulses has a substantial impact on the therapeutic response. Combined treatment with MP pulses followed by MD prednisone appears to be a valid therapeutic approach that optimises the risk-benefit ratio.

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