Discontinuation of therapies in polymyalgia rheumatica and giant cell arteritis

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ABSTRACT

Glucocorticoids are highly effective in treating polymyalgia rheumatica and giant cell arteritis, but their use is associated with numerous adverse events. Therefore, it is important to use them for the shortest period of time possible. The published evidence suggests that discontinuation of GC is feasible in a substantial number of patients with polymyalgia rheumatica and giant cell arteritis after an adequate period of treatment, provided that glucocorticoids are tapered gradually. Recurrences are relatively infrequent in polymyalgia rheumatica and somewhat more common in giant cell arteritis. Immunosuppressive agents may be used in patients with frequently relapsing or recurring disease to decrease exposure to glucocorticoids.

Introduction

Glucocorticoids (GC) are the mainstay of treatment of both polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) because of their rapid onset of action and their capacity to effectively suppress inflammatory symptoms and prevent GCA-related ischaemic events (1). However, GC do have numerous, sometimes severe, adverse events. In a population-based study of 120 patients with GCA, as many as 86% of patients suffered side effects due to GC, including bone fractures, avascular necrosis of the hip, diabetes mellitus, infections, gastro-intestinal haemorrhage, posterior subcapsular cataract, and hypertension (2). Similarly, GC-related adverse events such as diabetes mellitus and fragility fractures have been shown to occur 2 to 5 times more commonly in patients with PMR than in matched controls (3), despite the fact that GC are used at lower doses in PMR compared with GCA (4). Strategies to optimise the benefit/risk ratio of GC include using the lowest effective daily GC dose and discontinuing GC therapy as soon as possible. A third, not mutually exclusive approach, consists of adding steroid-sparing treatment to GC.

In this article, we report how early GC can safely be discontinued after an adequate period of treatment in patients with GCA and/or PMR. We have also attempted to identify which factors, if any, might predict a successful drug-free survival after GC discontinuation. Finally, we have broadened our analysis to encompass patients treated with immunosuppressive agents , in order to establish if these agents could facilitate GC discontinuation.

Methods

We conducted a PubMed search (1963 to July 2013) using the following key words: "glucocorticoids"[Mesh], "polymyalgia rheumatica"[Mesh], "giant cell arteritis"[Mesh], "azathioprine"[Mesh], "methotrexate"[Mesh], "leflunomide", "tumor necrosis factor-α/subheading antagonists and inhibitors"[Mesh], "cyclophosphamide", "infliximab", "adalimumab", "etanercept", "rituximab" and "tocilizumab". We identified reports (in English) that specified the classification criteria used, the types and doses of treatment, the duration of GC treatment, the discontinuation rates, the time to drug discontinuation, and the follow-up duration. Case reports and studies that involved fewer than 10 patients were excluded from the analysis.

We defined "relapse" as the occurrence of clinical manifestations of PMR and/or GCA, associated with abnormal investigations in patients receiving GC that required an increase in GC dose, unless otherwise stated. We defined "recurrence" as the occurrence of clinical manifestations of PMR and/or GCA associated with abnormal investigations after discontinuation of therapy that required reinstitution of GC, unless otherwise stated.

Table I. Studies using glucocorticoids as starting treatment for polymyalgia rheumatica.

Source	Study design	PMR Classification criteria	Number of patients	GC starting doses and tapering regimens (a)	GC cessation %	Time to stop GC, yrs	*Duration of therapy /follow-up (a)	Relapses#	Recurrences§
Gonzalez-Gay *et al*. (8) (b)	Retrospective case series	Chuang *et al*. (40)	134	PDN, 14.5 (3.5) mg/d; speed of tapering (mg/mo) was analysed	91	11	20.2 (11.4) mo/ up to 11 yr (at least one yr after GC cessation)	23.1%; PDN was tapered faster in relapsers than in non relapsers (1.2 *vs*. 0.9 mg/mo; $p<.05$)	6.4% Rate of tapering not related to recurrences
Narvaez *et al*. (5) (b)	Retrospective case series	Chuang *et al*. (40)	69	PDN, 12.8 mg/d [10-20]; subsequent reductions made according to disease activity and ESR	50 70 82	2 3 4	27 mo (95% CI 21.1-32.8)/up to 10 yr (11 mo after PDN cessation)	29%	0%
Delecoeuillerie *et al*. (36) (b)	Retrospective case control	Authors' own criteria	132	PDN, group 1 (74%), 10.2 [7-12] mg/d; group 2 (26%), 24.2 [15-30] mg/d	49	NR	25.7 mo (11.9)/ 43.2 mo (21.5) after GC cessation	NR	25% (26% in group 1 *vs*. 20% in group 2, the difference was not significant)
Ayoub *et al*. (6)	Retrospective case control	Authors' own criteria	75	PDN, ≤20 mg/d (67%); >20 mg/d (33%)	21 53 73 84	1 2 3 4	23.7 mo [6-54] /6 mo to 4.5 yr (16.5 mo after GC cessation)	56%	35%; (mean 3.2 mo [1 to 13 mo] after GC discontinuation)
Weyand *et al*. (9)	Prospective cohort	Authors' own criteria	27	PDN, 20 mg/d for 4 wk and then tapered by 2.5 mg every 2 wk as symptoms remained improved	30 50 96	1 1.3 2	4.5 to >12 mo/1 to 2.7 yr (at least 6 mo after PDN cessation)	NR Higher relapse rate in patients with more GC requirements; higher risk of relapse when reductions <10 mg/d	NR
Myklebust and Gran (38) (b)	Prospective cohort	Bird *et al*. (49)	217	PDL, 21.5 [5-80] mg/d; 2 groups, ≤15 mg/d (69%) and >15 mg/d (31%)	10 34	1 2	<1 to 2 yr/2 yr (6 mo after PDL cessation). Rate of GC cessation not influenced by initial PDL dose but by pretreatment ESR and haemoglobin.	NR	NR
Kyle and Hazleman (10) (b)	Prospective randomised	Jones and Hazleman (50)	39	PDL (2 groups), 10 mg/d and 20 mg/d for 4 wk, then reductions of 2.5 mg every 2 wk. After the first 2 mo, PDL reductions of 2.5 mg/mo (month 2–4), 1 mg/mo (month 4–12), and then 1 mg every 2 to 3 mo	24	2	15 mo (median)/ up to 3 yr	61% (52% and 69% occurred within 6 and 12 mo, respectively; 50% of relapses occurred for PDL doses <10 mg/d)	13% (25 mo after GC discontinuation)
Lundberg and Hedfors (22) (b)	Retrospective case series	Bird *et al*. (49)	40	PDL 18 mg/d [10-60]. PDL reduction of 2.5–5 mg/week to 10 mg/d, then of 1–1.25 mg/mo	85	2	17 mo [3–37]/43 mo [7–97], (28 mo [1-83] after PDL cessation)	55%	25% (1 to 65 mo after GC discontinuation)
Salvarani *et al*. (11) (b)	Retrospective case series	Healey (51)	24	PDN 20 mg/d	41	NR	12 mo (mean)/32 mo (32 mo after PDN cessation)	21%	23% (2 to 12 mo after GC discontinuation)
Bahlas *et al*. (7) (b)	Retrospective case series	Bird *et al*. (49)	136	PDN 23 (14) mg/d	21 43 61 69 77	1 2 3 4 5	28 mo (29)/3.7 yr (2)	27%	9%
Dasgupta *et al*. (52)	Prospective double blind randomised trial	Jones and Hazleman (50)	49	Group 1 (n=25): im MP acetate (120 mg every 2 wk for 12 wk, followed by monthly injections with dose reductions of 20 mg every 3 mo). Group 2 (n=24): oral PDL (15 mg/d for 3 wk, 12.5 mg/d for 3 wk, 10 mg/d for 6 wk, then reduction of 1 mg every 8 wk)	33 *vs*. 47	2	20 *vs*. 21 mo (mean) /2 yr Similar remission rate. Higher cumulative doses and more GC related adverse effects in group 2	50% in both groups	NR

Modified from Hernandez-Rodriguez *et al*., Treatment of polymyalgia rheumatica. A systematic review (33).
ESR: erythrocyte sedimentation rate; GC: glucocorticoid therapy; MP: methyl-prednisolone; NR: not reported; NSAIDs: non-steroidal anti-inflammatory drugs; PDL: prednisolone therapy; PDN: prednisone therapy; PMR: polymyalgia rheumatica.
*Duration of therapy: only considering patients who discontinued GC; #Relapses: occurrence of clinical manifestation of PMR associated with abnormal investigation in patients receiving steroid that required increase in GC dose (expressed as % of all patients included in the study); §Recurrences: occurrence of clinical manifestation of PMR associated with abnormal investigation after discontinuation of therapy that required reinstitution of GC (expressed as % of patients who discontinued GC); (a) Unless otherwise indicated, data are reported as mean (SD) or median [range]; (b) Although the study initially included patients with GCA and PMR, only patients with isolated PMR were finally analysed; (c) This study used NSAIDs alone or in combination with GC to treat PMR.

Results

The results of our literature review are summarised in Tables I to IV.

These reports revealed significant heterogeneity across the published studies regarding GC discontinuation rates and time to GC discontinuation in both PMR and GCA.

Most of the studies conducted on PMR indicated, that after 2 years of treatment, about 50% of patients (with a wide range, 24% to 96%) were able to discontinue GC therapy, while about 20% needed GC therapy for longer than 4 years (5–7), and (according to another study) about 10% required GC for longer than 10 years (8). With regard to patients who discontinued GC, the mean duration of therapy was about 20 to 28 months, with some studies showing a shorter duration ranging between 4.5 and 15 months (9-11). Recurrences were reported in 10% to 30% of patients, usually during the first 12–24 months after GC discontinuation (Table I).

Most clinical trials of the use of immunosuppressive agents as GC-sparing agents in PMR evaluated methotrexate, with conflicting results. Studies with shorter follow-up duration (18 months) showed earlier GC discontinuation and lower cumulative GC doses in patients taking methotrexate compared to placebo (12, 13), but these results were not confirmed in an extension of a previous study (13) at longer-term follow-up (6.5 years) (14) (Table III).

Studies on GCA showed highly variable initial GC doses and wide differences in terms of duration of GC therapy, rate of GC discontinuation, and recurrences. At 2 years evaluation, 16% to 76% of patients could discontinue GC therapy, while 25-45% needed GC for longer than 3 years (2, 15). One study reported that as many as 25% of patients remained on GC therapy after 9 years of follow-up (15). In patients who were able to discontinue GC, mean duration of therapy ranged from 16 months to 5.8 years. Recurrences have been reported in 23% to 57% of patients, usually during the first 12-24 months after GC discontinuation (Table II). Most clinical trials and meta-analyses evaluating immunosuppressive agents as GC-sparing agents in GCA did not report data on GC discontinuation, and have thus not been included in our review (16-20). Only one study evaluated methotrexate as a GC-sparing agent, indicating earlier GC discontinuation in the methotrexate arm compared to placebo arm after 24 months of follow-up (21) (Table IV).

Fast tapering schemes (4), coexisting PMR and GCA (22) and highly elevated inflammatory markers at diagnosis (9, 11, 23) have been linked to longer GC requirements in PMR and GCA.

Discussion

Despite the lack of formal randomised controlled trials, empirical evidence suggests that GC are highly effective in treating PMR and GCA, and that GC therapy should be commenced as soon as the diagnosis of PMR and GCA is established (4). However, the optimal initial GC dosage and tapering scheme remain unclear, as well as how long GC should be continued (24). Because GC toxicity is largely related to their cumulative dose (25), it is important to use GC at the lowest effective dosage and for the shortest period of time.

In this review, we attempted to determine the discontinuation rates of GC therapy in PMR and GCA after an adequate period of treatment, and to identify prognostic factors that might favorably or adversely affect GC withdrawal. A related, ancillary aim was to investigate the role of immunosuppressive agents in facilitating GC discontinuation.

Our analyses indicated significant differences across the published studies relative to GC discontinuation rates and time to GC discontinuation in both PMR and GCA. Such differences can be accounted for, at least in part, by the heterogeneity of disease among different patients as well as of studies in terms of study designs, types of patients included, classification criteria, definition of outcomes, initial GC dose, GC tapering regimens, and length of follow-up.

Most studies were retrospective and often uncontrolled, and results are heterogeneous. Selection bias is also likely to affect the findings of many studies. For example, studies on patients with GCA carried out in tertiary referral centers (such as many European studies) and those performed by ophthalmologists usually reported higher GC doses, longer duration of treatment, or both, compared with population-based studies (which have been carried out mainly in the US), which may reflect a selection bias toward more severe cases (26). Practice habits may also play a role, since ophthalmologists tend to treat GCA at higher doses.

In virtually all studies included in our analyses, GC were administered daily. Alternate-day GC therapy has been investigated in GCA, but found to have excessively high rates of flares compared with daily treatment (70% versus 20%), and is thus not recommended for use in clinical practice (27). GC pulse therapy is sometimes empirically used in early GCA, especially in patients who are at risk of ischaemic complications. However, there is no evidence that pulse therapy is superior to high-dose oral GC in preventing GCA-related ischaemic events (28, 29). However, one small RCT showed that pulse methylprednisolone (15 mg/kg/day for three days) given at disease onset allowed more rapid tapering of GC dose, earlier GC discontinuation, and resulted in a lower cumulative GC dose (if the dose of the pulses was not taken into account) and a higher frequency of remission after discontinuation of oral GC therapy (30). Finally, a double-blind controlled trial of 12 weeks' duration, followed by an open phase that compared PMR patients treated with oral prednisone 15 mg daily tapering *versus* those treated with intramuscular methylprednisolone 120 mg every 3 weeks tapering, showed a lower cumulative GC dose, fewer fractures, and a trend for higher GC discontinuation rates in the methylprednisolone arm (31).

With regard to the initial dose of GC, the vast majority of patients with PMR are documented to respond to prednisone 15 mg/day (32, 33), while a dose of 40–60 mg daily of prednisone is adequate in most patients with GCA (26). However, patients at high risk

Table II. Studies using glucocorticoids as starting treatment for giant cell arteritis.

Source	Study design	n. patients/ TAB positive (%)	GC starting doses and tapering regimens (a)	GC cessation	Time to stop GC, yrs	*Duration of therapy/ follow-up (a)	Relapses#	Recurrences§	Comments
Fauchald *et al*. (53) (b)	Retrospective case series	61/(100)	PDN, 40 to 60 mg/d; reduction to 12.5–5.0 mg/d over 1–4 wk	61%	NR	22 mo [4–100]/24 mo [2–78]	26%	23% (3 to 12 mo after GC discontinuation)	
Delecoeuillerie *et al*. (36) (b)	Retrospective case control series	78/(77)	PDN, group 1 (n=25) 16.2 [10-20] mg/d; group 2 (n=28) 39.1 [20-60] mg/d; group 3 (n=25) 66 [60–90] mg/d	51% (no significant differences between the 3 groups)	NR	30.9 (14) mo (no difference in the 3 groups)/32.8 (17.9) mo after GC cessation	NR	57% in group 1, 53% in group 2, 45% in group 3 (the difference was not significant)	All patients with visual symptoms at presentation received PDN >60 mg/d (group 3)
Hachulla *et al*. (54) (c)	Retrospective case series	133/(68)	PDN (35.5%) or PDL (64.5%): <0.5 mg/kg/d (n=4); 0.5 mg/kg/d (n=29); 0.5 to 1 mg/kg/d (n=39); ≥1 mg/kg/d (n=61) for 3-4 wk. GC reduced by 10% of the doses every 10 days till 10 mg/d, then by 1 mg every mo	42%	NR	40 mo [7–138]/67 mo [0.5–215]; 52 mo [0.5–120] after GC cessation	62.5%	48% (1 to 25 mo after GC discontinuation)	No correlation between relapses/ recurrences and initial GC dose or duration of GC treatment, but higher ESR at onset linked to more frequent relapses
Salvarani *et al*. (11) (b)	Retrospective case series	30/(50)	PDN 40 mg/d (mean)	28%	NR	16.8 mo (mean)/ 32 mo (mean), 22 mo after PDN cessation	20%	36% (3 mo after GC discontinuation)	5 variables predicted duration of therapy longer than 16 mo in 80% of patients.
Proven *et al*. (2)	Retrospective case series	120/(NR)	PDN 60 mg/d [10–100]. Tapering regimen according to treating physician's judgment of disease activity	75%	3	21.6 mo [2.3–122]/ 120 mo [1–408]	48%	NR	86% of patients developed serious adverse side effects related to GC therapy
Lundberg and Hedfors (22) (b)	Retrospective case series	51/(61) 3 group: group 1 GCA (n=21); group 2 GCA + PMR (n=25); group 3 PMR → GCA (n=5)	PDL: group 1, 31 mg/d [20-60]; group 2, 28 mg/d [15-60]; group 3, 25 mg/d [10-60] PDL reduction of 2.5-5 mg/week to 10 mg/d, then of 1–1.25 mg/month	76% (100% group 1; 60% group 2; 60% group 3)	2	Group 1, 16 mo [8-24];Group 2, 24 mo [8-69]; Group 3, 28 mo [14–46]/43 mo [7–97], (27 mo [1–83] after PDL cessation	49% (group 1 24%; group 2 68%; group 3 60%)	23% (5% group 1; 47% group 2; 33% group 3) (1 to 65 mo after GC discontinuation)	Patients with visual or neurological symptoms at presentation received higher PDN (30–60 mg/d). Patients with coexisting GCA and PMR required longer treatment
Myklebust and Gran (38) (b)	Prospective cohort	56/(100) 2 group: group 1 GCA (n=37); group 2 GCA + PMR (n=19);	PDL: group 1, 48.8 mg/d [5–120]; group 2, 32.6 mg/d [10–80]	4% (5% group 1; 0% group 2) 16% (22% group 1; 5% group 2)	1 2	<1 to 2 yr/2 yr (6 mo after PDL cessation)	NR	NR	Positive correlation between initial and mainteinance doses of GC during follow-up Patients with coexisting GCA and PMR required longer treatment
Andersson *et al*. (15)	Retrospective case series	90/(NR)	PDL 33.2 mg/d [0-60]	57% 75%	5 9	5.8 yr [0-12.8] /11.3 yr [9-16]	53%	47% (1 to 12 mo after GC discontinuation)	
Chevalet *et al*. (28)	Randomised prospective controlled	164/(78)	Group 1: IV pulse of 240 mg MP once, then PDN 0.7 mg/kg/d (n=61); Group 2: PDN 0.7 mg/kg/d (n=53); Group 3: IV pulse of 240 mg MP once, then PDN 0.5 mg/kg/d (n=50). PDN reduced to half initial dose in group 1 and 2 within 1 mo and to 20 mg/d in group 3 within 2 wk. Then reduced by 1 mg every 2 wk.	16.5% (15% group 1; 23% group 2; 11% group 3)	1	12 mo for both duration of therapy and follow-up	51%	27%	IV MP pulses had no significant long-term GC sparing effect. No differences in GC discontinuation, GC adverse effects and GCA complication between the 3 study groups
Mazlumzadeh *et al*. (30) (c)	Randomised, double-blind, placebo-controlled	27/(100)	Group 1: IV pulse of 15 mg/kg of MP/day for 3 consecutive days (n=14); Group 2: IV pulse of placebo for 3 consecutive days (n=13); All patients were started on PDN 40 mg/d for 2 wk; subsequent doses, 30, 25, 20, 17.5, 15, 12.5 and 10 mg/d for 2-wk periods each. Then reduction of 1 mg/d every 2 wk	43% group 1; 0% group 2	1.5	18 mo for both duration of therapy and follow-up (at least 6 mo follow-up after GC discontinuation)	71% group 1 *vs*. 92% group 2	0%	Initial IV MP pulses allowed for more rapid tapering of oral GC, more GC discontinuation and lower oral GC cumulative doses after a follow-up of 18 mo

ESR: erythrocyte sedimentation rate; GC: glucocorticoid therapy; GCA: giant cell arteritis; MP: methyl-prednisolone; NR: not reported; PDL: prednisolone therapy; PDN: prednisone therapy; PMR: polymyalgia rheumatica; TAB: temporal artery biopsy.
*Duration of therapy: only considering patients who discontinued GC; #Relapses: occurrence of clinical manifestation of GCA associated with abnormal investigation in patients receiving steroid that required increase in GC dose (expressed as % of all patients included in the study); §Recurrences: occurrence of clinical manifestation of GCA associated with abnormal investigation after discontinuation of therapy that required reinstitution of GC (expressed as % of patients who discontinued GC); (a) Unless otherwise indicated, data are reported as mean (SD) or median [range]; (b) Although the study initially included patients with GCA and PMR, only patients with GCA (with or without PMR) were finally analysed; (c) In this study an isolated elevation of ESR and/or CRP without symptoms of GCA during steroid tapering or after steroid discontinuation was considered a relapse or a recurrence.

Table III. Studies using glucocorticoid-sparing agents in polymyalgia rheumatica.

Source	Study design	PMR classification criteria	Number of patients	Baseline situation and drug starting doses (a)	Drug modifications	GC Cessation/ GC cumulative dose (a)	Time to stop GC, yrs	*Duration of steroid therapy/ Follow-up (a)	Relapses#/ Recurrences§
				Initial Treatment with GC					
Van der Veen *et al*. (55)	Randomised, double-blind, placebo-controlled	Chuang *et al*. (40)	40	At PMR diagnosis, randomisation to PDN+ placebo (n=20) or PDN and oral MTX, 7.5 mg/wk (n=20) (all PDN doses, 20 mg/d)	PDN tapered 2.5 mg every 3 wk until 7.5 mg/d, then by 2.5 mg every 6 wk; after PDN cessation, the blinded capsule was taken once every 2 wk for 3 administration and then stopped	40% (no differences in the 2 groups) /No differences in cumulative PDN doses.	2	MTX 41 wk [3-63], *vs*. placebo 29 wk [2.5–81] /up to 2 yr (at least 1 yr after discontinuation of medication)	MTX, 50%, *vs*. placebo, 45%/ MTX 64% *vs*. placebo 22%
Ferraccioli *et al*. (12)	Randomised prospective	Authors' own criteria	24	After failure of NSAIDs to control PMR, randomisation to PDN alone, 15 mg/d for 3 months (n=12) or IM MTX, 10 mg/wk + PDN, 25 mg/d for 1 mo (n=12)	PDN alone, 10, 5, and 2.5 mg/d (1 mo each); IM MTX, 10 mg/wk + PDN, 12.5, 10, 6.25, 5, and 2.5 mg/d (1 mo each)	MTX 50%, *vs*. PDN 0% MTX 50%, *vs*. PDN 0% /PDN higher GC cumulative dose 1.8 *vs*. 3.2 g; (p<0.001)	0.5 1	6 to 12 mo/1 yr, extension of 6 mo	More relapses in patients treated with PDN alone *vs*. PDN + MTX (100% *vs*. 50%)
Caporali *et al*. (13)	Randomised, double-blind, placebo-controlled	Chuang *et al*. (40)	62	At PMR diagnosis, randomisation to PDN, 25 mg/d + oral MTX, 10 mg/wk (n=36) or PDN, 25 mg/d + placebo (n=36); all PDN was administered for 4 wk	PDN tapered to 0 in 24 wk in both groups (subsequent doses, 17.5, 12.5, 7.5, 5, and 2.5 mg/d for 4-wk periods each) MTX or placebo manteined for 48 wk	MTX 88% *vs*. placebo 53%; (p=0.003) /Lower median cumulative PDN dose in MTX *vs*. placebo (2.1 *vs*. 2.97 g; p=0.03)	1.5	MTX 30 [24-44] *vs*. placebo 56 [36-72] wk (p=0.007)/18 mo	≥1 relapses and/ or recurrences lower in MTX than in placebo (47% *vs*. 73%; p=0.04)
Salvarani *et al*. (56)	Randomised, double-blind, placebo-controlled	Healey (51)	47	At PMR diagnosis, randomisation to PDN + IFX (n=20) or PDN + placebo (n=27). All PDN doses were 15 mg/d for 4 wk; all IFX doses were 3 mg/kg given at week 0, 2, 6, 14, and 22	PDN tapered to 10, 5, and 2.5 mg/d for 4-wk periods each, and stopped if indicated by patient's clinical condition	IFX 50% vs placebo 54% /No differences in median cumulative PDN dose	1	IFX 26 [16-52] *vs*. placebo 22 [16-51] wk/12 mo	≥1 relapses and/ or recurrences 70% IFX *vs*. 63% placebo (the difference was not significant)
				Co-treatment for Remission Maintenance					
Feinberg *et al*. (57)	Observational prospective cohort	Authors' own criteria	43	All patients initially taking PDN, 10 mg/d (79% required ≥20 mg/d), treated with PDN + oral MTX; MTX doses started at 7.5 mg/wk for at least 3 mo	MTX was increased to 10 to 12.5 mg/wk if no response	0%	9 mo	9 mo for both treatment and follow-up	NR
Cimmino *et al*. (14)	Retrospective case-control study	Chuang *et al*. (40)	57	Retrospective review of patients with PMR from Caporali *et al*. (13) in 2 groups, 29 treated with PDN + MTX and 28 with PDN +placebo	Not described during the follow-up	MTX 69% *vs*. placebo 61% /No differences in cumulative PDN dose	6.5	NR/58.8 (11.1) mo	≥1 relapses and/ or recurrences 31% *vs*. 44% (the difference was not significant)

Modified with permission from Hernandez-Rodriguez *et al*., Treatment of polymyalgia rheumatica. A systematic review (33).
GC: glucocorticoid therapy; IFX: infliximab; MTX: methotrexate; NR: not reported; NSAIDs: non-steroidal anti-inflammatory drugs; PDN: prednisone therapy; PMR: polymyalgia rheumatica. *Duration of therapy: only considering patients who discontinued GC; #Relapses: occurrence of clinical manifestation of PMR associated with abnormal investigation in patients receiving steroid that required increase in GC dose (expressed as % of all patients included in the study); §Recurrences: occurrence of clinical manifestation of PMR associated with abnormal investigation after discontinuation of therapy that required reinstitution of GC (expressed as % of patients who discontinued GC); (a) Unless otherwise indicated, data are reported as mean (SD) or median [range].

of developing GCA-related ischaemic complications usually receive higher prednisone dosages (~1 mg/kg/day) (34). Treatment of new-onset GCA with lower-dose GC (in the range of 10 to 40 mg/day) has also been advocated on the basis of retrospective data showing no differences in duration of GC therapy, rate of GC discontinuation and frequencies of relapses and recurrences in patients treated with lower GC doses *versus* those receiving higher GC doses (35, 36). However, because of the retrospective nature of the data, and because all patients with visual or neurologic ischaemic manifestations at onset received higher GC doses, there is insufficient evidence to endorse this approach in clinical practice.

It is unclear whether the initial GC dose may affect relapse or discontinu-

Table IV. Studies using glucocorticoid-sparing agents in giant cell arteritis.

Source	Study design	n. patients/ TAB positive (%)	Baseline situation and drug starting doses (a)	Drug modifications	GC cessation/ GC cumulative dose (a)	Time to stop GC, yr	*Duration of steroid therapy/ follow-up (a)	Relapses#/ Recurrences§	Comments
				Initial Treatment with GC					
Jover *et al*. (21)	Randomised, double-blind, placebo-controlled	33/(100)	At GCA diagnosis, randomisation to PDN + MTX, 10 mg/wk (n=15) or PDN + placebo (n=18). PDN initial dose, 60 mg/d	PDN tapered by 10 mg per wk until 40 mg/d, then by 5 mg per wk until 20 mg/d, then by 2.5 mg every 2 wk until discontinuation	MTX 93% *vs*. placebo 72% Lower mean cumulative PDN dose in MTX *vs*. placebo (4024 *vs*. 5360 mg; p=0.006)	2	MTX 29 wk [22.2-65] *vs*. placebo 94 wk [64-103] p=0.0016/24 mo	≥1 relapses and/or recurrences: MTX 47% *vs*. placebo 83% (p=0.06)	High incidence of GC-related adverse events in both study group (MTX 90% *vs*. placebo 100%)

GC: glucocorticoid therapy; GCA: giant cell arteritis; MTX: methotrexate; PDN: prednisone therapy; TAB: temporal artery biopsy.
*Duration of therapy: only considering patients who discontinued GC; #Relapses: occurrence of clinical manifestation of GCA associated with abnormal investigation in patients receiving steroid that required increase in GC dose (expressed as % of all patients included in the study); §Recurrences: occurrence of clinical manifestation of GCA associated with abnormal investigation after discontinuation of therapy that required reinstitution of GC (expressed as % of patients who discontinued GC); (a) Unless otherwise indicated, data are reported as mean (SD) or median [range].

ation rates, since published data are controversial (6, 30, 37, 38). By contrast, there is reasonably good evidence suggesting that fast tapering schemes, especially for doses lower than 10 mg/day of prednisone, are associated with higher rates of flares, thus probably impeding earlier GC discontinuation (4). At the same time, it should be borne in mind that flares may sometimes occur despite cautious tapering (26). Other factors that are associated with longer GC requirements are coexisting PMR and GCA (22) and highly elevated inflammatory markers at diagnosis (9, 11, 23). Female gender has been also linked in newly diagnosed PMR to a higher risk of relapses, but not of recurrences or length of GC treatment (39), while other studies have reported longer treatment duration in women with PMR (6, 40) and GCA (41) compared with men.

Our approach in treating patients with PMR and GCA is similar to that suggested by the British Society for Rheumatology (BSR). Specifically, the treatment regimen suggested by the BSR for PMR is prednisolone (or its equivalent) 15 mg per day for 3 weeks, then 12.5 mg for 3 weeks, then 10 mg for 4–6 weeks, and then tapering by 1 mg every 4–8 weeks provided no flares occur (42). For GCA, the BSR recommends that after treatment with high-dose glucocorticoids for 3-4 weeks, the prednisolone dosage can be reduced by 10 mg every 2 weeks to 20 mg, then by 2.5 mg every 2–4 weeks to 10 mg, and then by 1 mg every 1–2 months if no flare occurs (43).

A sizeable proportion of patients with PMR and/or GCA may require long-term GC treatment, sometimes indefinitely (6, 44, 45). This subset of patients probably have smoldering inflammation rather than adrenal insufficiency and can often be managed with low doses of GC (9). Adrenal insufficiency causing PMR-like myalgia has been reported after long-standing GC therapy in GCA, but unlike true relapses is not associated with elevated serum inflammatory markers (46).

Immunosuppressive agents have been proposed for use in both PMR and GCA, but their efficacy is not as impressive as in arthritis. Methotrexate is probably the most widely used synthetic immunosuppressive agents and has been shown to increase the probability of achieving a sustained discontinuation of GC in GCA (20) and in PMR (13), but not to decrease the incidence of GC-related adverse events. Emerging data also suggest a role for biological immunosuppressive agents in patients with PMR and GCA who incur repeated flares upon reduction of the GC dose (47, 48).

In conclusion, the published evidence suggests that discontinuation of GC is feasible in a substantial number of patients with PMR and GCA after an adequate period of treatment, provided that GC are tapered gradually. Recurrences are relatively infrequent in PMR and somewhat more common in GCA. Immunosuppressive agents may be given a trial in patients with frequently relapsing or recurring PMR and GCA, to decrease exposure to GC.

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