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 ischemic 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 hemorrhage, 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], “l affectin 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.

<table>
<thead>
<tr>
<th>Source</th>
<th>Study design</th>
<th>PMR Classification criteria</th>
<th>Number of patients</th>
<th>GC starting doses and tapering regimens (a)</th>
<th>GC cessation %</th>
<th>Time to stop GC, yrs</th>
<th>*Duration of therapy/ follow-up (a)</th>
<th>Relapses (b)</th>
<th>Recurrences (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonzalez-Gay et al. (8) (b)</td>
<td>Retrospective case series</td>
<td>Chuang et al. (40)</td>
<td>134</td>
<td>PDN, 14.5 (3.5) mg/d; speed of tapering (mg/mo) was analysed</td>
<td>91</td>
<td>11</td>
<td>20.2 (11.4) mo/ up to 11 yr (at least one yr after GC cessation)</td>
<td>23.1%; PDN was tapered faster in relapsers than in non relapsers (1.2 vs. 0.9 mg/mo; p&lt;0.05)</td>
<td>6.4% Rate of tapering not related to recurrences</td>
</tr>
<tr>
<td>Narvaez et al. (5) (b)</td>
<td>Retrospective case series</td>
<td>Chuang et al. (40)</td>
<td>69</td>
<td>PDN, 12.8 mg/d [10-20]; subsequent reductions made according to disease activity and ESR</td>
<td>50</td>
<td>2</td>
<td>27 mo (95% CI 21.1-32.8)/up to 10 yr (11 mo after PDN cessation)</td>
<td>29%</td>
<td>0%</td>
</tr>
<tr>
<td>Delecoeuillerie et al. (36) (b)</td>
<td>Retrospective case control</td>
<td>Authors’ own criteria</td>
<td>132</td>
<td>PDN, group 1 (74%), 10.2 [7-12] mg/d; group 2 (26%), 24.2 [15-30] mg/d</td>
<td>49</td>
<td>NR</td>
<td>25.7 mo (11.9)/ 43.2 mo (21.5) after GC cessation</td>
<td>NR</td>
<td>25% (26% in group 1 vs. 20% in group 2; the difference was not significant)</td>
</tr>
<tr>
<td>Ayoub et al. (6)</td>
<td>Retrospective case control</td>
<td>Authors’ own criteria</td>
<td>75</td>
<td>PDN, ≤20 mg/d (67%); &gt;20 mg/d (33%)</td>
<td>21</td>
<td>1</td>
<td>23.7 mo [6-54]/6 mo to 4.5 yr (16.5 mo after GC cessation)</td>
<td>56%</td>
<td>35% (mean 3.2 mo [1 to 13 mo] after GC discontinuation)</td>
</tr>
<tr>
<td>Weyand et al. (9)</td>
<td>Prospective cohort</td>
<td>Authors’ own criteria</td>
<td>27</td>
<td>PDN, 20 mg/d for 4 wk and then tapered by 2.5 mg every 2 wk as symptoms remained improved</td>
<td>30</td>
<td>1</td>
<td>4.5 to &gt;12 mo/1 to 2.7 yr (at least 6 mo after PDN cessation)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Myklebust and Gnan (38) (b)</td>
<td>Prospective cohort</td>
<td>Bird et al. (49)</td>
<td>217</td>
<td>PDL, 21.5 [5-80] mg/d; 2 groups, ≤15 mg/d (69%) and &gt;15 mg/d (31%)</td>
<td>10</td>
<td>1</td>
<td>&lt;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.</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kyle and Hazleman (10) (b)</td>
<td>Prospective randomised</td>
<td>Jones and Hazleman (50)</td>
<td>39</td>
<td>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</td>
<td>24</td>
<td>2</td>
<td>15 mo (median) up to 3 yr</td>
<td>61% (52% and 69% occurred within 6 and 12 mo, respectively; 50% of relapses occurred for PDL doses &lt;10 mg/d)</td>
<td>13% (25 mo after GC discontinuation)</td>
</tr>
<tr>
<td>Lundberg and Hedfors (22) (b)</td>
<td>Retrospective case series</td>
<td>Bird et al. (49)</td>
<td>40</td>
<td>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</td>
<td>85</td>
<td>2</td>
<td>17 mo [3-77]; 28 mo [1-83] after PDN cessation</td>
<td>55%</td>
<td>25% (1 to 65 mo after GC discontinuation)</td>
</tr>
<tr>
<td>Salvarani et al. (11) (b)</td>
<td>Retrospective case series</td>
<td>Healey (51)</td>
<td>24</td>
<td>PDN 20 mg/d</td>
<td>41</td>
<td>NR</td>
<td>12 mo (mean)/32 mo (32 mo after PDN cessation)</td>
<td>21%</td>
<td>23% (2 to 12 mo after GC discontinuation)</td>
</tr>
<tr>
<td>Bahlas et al. (7) (b)</td>
<td>Retrospective case series</td>
<td>Bird et al. (49)</td>
<td>136</td>
<td>PDN 23 (14) mg/d</td>
<td>21</td>
<td>1</td>
<td>28 mo (29)/3.7 yr (2)</td>
<td>27%</td>
<td>9%</td>
</tr>
<tr>
<td>Dasgupta et al. (52)</td>
<td>Prospective double blind randomised trial</td>
<td>Jones and Hazleman (50)</td>
<td>49</td>
<td>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)</td>
<td>33</td>
<td>2</td>
<td>20 vs. 21 mo (mean) /2 yr Similar remission rate. Higher cumulative doses and more GC related adverse effects in group 2</td>
<td>50% in both groups</td>
<td>NR</td>
</tr>
</tbody>
</table>

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; 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 patients included in the study).
Recurrences: occurrence of clinical manifestation of PMR associated with abnormal investigation after discontinuation of therapy that required reinstoration 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
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Table II. Studies using glucocorticoids as starting treatment for giant cell arteritis.

<table>
<thead>
<tr>
<th>Source</th>
<th>Study design</th>
<th>n. patients/ GC starting doses and tapering regimens (a)</th>
<th>GC cessation</th>
<th>Time to discontinuation of therapy (follow-up (a))</th>
<th>Relapses§</th>
<th>Recurrences§</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fauchald et al. (53) (b)</td>
<td>Retrospective case series</td>
<td>61/100</td>
<td>PDN, 40 mg/d; reduction to 25-50 mg/d after 1-4 wk</td>
<td>67%</td>
<td>25%</td>
<td>(3 to 12 mo after GC discontinuation) All patients with visual or neurological symptoms at presentation received PDN &gt;60 mg/d (group 3)</td>
<td></td>
</tr>
<tr>
<td>Deleucaortin et al. (36) (b)</td>
<td>Retrospective case control series</td>
<td>78/77</td>
<td>PDN, group 1 (n=25): 16.2 [10-20] mg/d; group 2 (n=52): 39.1 [20-60] mg/d; group 3 (n=25): 66 [60-90] mg/d</td>
<td>51% (no significant difference between the 3 groups)</td>
<td>NR</td>
<td>NR</td>
<td>No correlation between relapses/ recurrences and initial GC dose or duration of GC treatment, but higher ESR at onset linked to more frequent relapses</td>
</tr>
<tr>
<td>Hachulla et al. (54) (c)</td>
<td>Retrospective case series</td>
<td>133/68</td>
<td>PDL: 35.5% or PDL: 64.5% &lt;0.5 mg/kg/d (n=29); 0.5 to 1 mg/kg/d (n=59); &gt;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</td>
<td>42%</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Salvarani et al. (11) (b)</td>
<td>Retrospective case series</td>
<td>30/50</td>
<td>PDN 40 mg/d (mean)</td>
<td>28%</td>
<td>20%</td>
<td>(3 mo after discontinuation)</td>
<td>5 variables predicted duration of therapy longer than 16 mo in 80% of patients.</td>
</tr>
<tr>
<td>Proven et al. (2)</td>
<td>Retrospective case series</td>
<td>120/70</td>
<td>PDL 60 mg/d [10-100]. Tapering regimen according to treating physician’s judgment of disease activity</td>
<td>75%</td>
<td>3</td>
<td>48%</td>
<td>86% of patients developed serious adverse side effects related to GC therapy</td>
</tr>
<tr>
<td>Lundberg and Hedfors (22) (b)</td>
<td>Retrospective case series</td>
<td>51/61</td>
<td>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 2.5-5.5 mg/wk to 10 mg/d, then 1-1.25 mg/month</td>
<td>76% (100% group 1; 60% group 2; 60% group 3)</td>
<td>2</td>
<td>49% (group 1 24%; group 2 68%; group 3 60%)</td>
<td>Patients with visual or neurological symptoms at presentation received higher PDN (30-60 mg/d). Patients with coexisting GCA and PMR required more treatment longer than 16 mo in 80% of patients.</td>
</tr>
<tr>
<td>Myklebust and Gran (38) (b)</td>
<td>Prospective cohort</td>
<td>56/100</td>
<td>PDL: group 1, 48.8 mg/d [5-120]; group 2, 32.6 mg/d [10-80]</td>
<td>4% (5% group 1; 0% group 2)</td>
<td>1</td>
<td>23% in group 1 (25% group 1; 24% group 2; 33% group 3)</td>
<td>Positive correlation between initial and maintenance doses of GC during follow-up Patients with coexisting GCA and PMR required longer treatment</td>
</tr>
<tr>
<td>Andersson et al. (15)</td>
<td>Retrospective case series</td>
<td>90/70</td>
<td>PDL 33 mg/d [0-60]</td>
<td>57%</td>
<td>59</td>
<td>53%</td>
<td>(to 12 mo after GC discontinuation)</td>
</tr>
<tr>
<td>Chevalet et al. (28)</td>
<td>Randomised prospecitive controlled</td>
<td>164/78</td>
<td>Group 1: IV pulse of 240 mg MP once, then PDL 0.7 mg/kg/d (n=61); Group 2: PDL 0.7 mg/kg/d (n=35); Group 3: IV pulse of 240 mg MP once, then PDL 0.5 mg/kg/d (n=50); PDL 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.</td>
<td>16.5% (15% group 1; 23% group 2; 11% group 3)</td>
<td>1</td>
<td>51%</td>
<td>IV MP pulses had no significant long-term GC sparing effect. No discontinuation in GC discontinuation, GC adverse effects and GCA, complication between the 3 study groups</td>
</tr>
<tr>
<td>Mazlumzadeh et al. (50) (c)</td>
<td>Randomised, double-blind, placebo-controlled</td>
<td>27/100</td>
<td>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 PDL 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</td>
<td>43% group 1; 9% group 2</td>
<td>1.5</td>
<td>71% group 1 iv. 92% group 2</td>
<td>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</td>
</tr>
</tbody>
</table>
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-
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Table IV. Studies using glucocorticoid-sparing agents in giant cell arteritis.

<table>
<thead>
<tr>
<th>Source</th>
<th>Study design</th>
<th>n. patients/ TAB positive (%)</th>
<th>Baseline situation and drug starting doses (a)</th>
<th>Drug modifications</th>
<th>GC cessation/ GC cumulative dose (a)</th>
<th>Time to stop GC</th>
<th>*Duration of steroid therapy/ follow-up (a)</th>
<th>Relapses (§)</th>
<th>Recurrences (¶)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jover et al. (21)</td>
<td>Randomised, double-blind, placebo-controlled</td>
<td>333 (100)</td>
<td>At GCA diagnosis, randomisation to PDN + MTX, 10 mg/wk (n=15) or PDN + placebo (n=18), PDN initial dose, 60 mg/d</td>
<td>MTX 93% vs. placebo 72% Lower mean cumulative PDN dose in MTX vs. placebo (4024 ± 5360 mg; p=0.006)</td>
<td>MTX 29 wk vs. placebo 44 wk [64-103] p=0.0016/24 mo</td>
<td>≥1 relapses and/or recurrence: MTX 47% vs. placebo 83% (p=0.06)</td>
<td>High incidence of GC-related adverse events in both study group (MTX 90% vs. placebo 100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GC: glucocorticoid therapy; GCA: giant cell arteritis; MTX: methotrexate; PDN: prednisone therapy; TAB: temporal artery biopsy.

12. Ferraccioli G, Salaffi F, de Vitas S, Casatta L, Bartoli E: Methotrexate in


