Glucocorticoid treatment of polymyalgia rheumatica

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Received and accepted on August 8, 2011.

Clin Exp Rheumatol 2011; 29 (Suppl. 68): S143-S147.

Key words: polymyalgia rheumatica, glucocorticoids, circadian rhythms, HPA, IL-6, dehydro-epiandrosterone sulphate (DHEA)

Competing interests: none declared.

Abstract

Glucocorticoids are the mainstay of treatment in patients with polymyalgia rheumatica (PMR). Moreover, lower serum cortisol levels have been reported in patients with PMR, suggesting an important role of impaired hypothalamus-pituitary-adrenal (HPA) axis in the pathogenesis of the disease.

Therefore, a good response to glucocorticoitds has been recognised as a feature of PMR, even if disagreement remains concerning an exact starting dose, duration of treatment and schedule of administration. The role of glucocorticoids in the pathogenesis of PMR, as well as the available evidence concerning different schedules of glucocorticoid treatment, including administration according to circadian rhythms, are discussed.

Introduction

Polymyalgia rheumatica (PMR) is a clinical entity of unknown etiology characterised by inflammatory pain and stiffness of the shoulder and/or pelvic girdles accompanied by laboratory evidence of inflammation in elderly patients (1, 2).

In patients with PMR, the mainstay of treatment is oral glucocorticoid: a good therapeutic response to glucocorticoid has been recognised as a feature of the condition, and constitutes one of Healey's diagnostic criteria (3). However, disagreement remains concerning an exact starting dose, duration of therapy and schedule of administration.

Role of glucocorticoids in the pathogenesis of polymyalgia rheumatica

Although one of the most striking features of PMR is the development of the disease in patients aged more than 50 years, the precise age-associated pathogenic factors are not yet known. The age-specific incidence rate increases from 2.6 per 100,000 in the age group 50-59 years to 44.7 per 100,000 in the age group 80 years and older, which strongly suggest the possibility of age-associated factors in etiology (4).

The natural decline in several hormones, including dehydro-epiandrosterone sulphate (DHEAS) and androstenedione during aging may represent one of these factors (5, 6). The interrelationship between inflammatory cytokines (IL-6, TNF) and adrenal hormones (cortisol, DHEAS, androstenedione) has been studied in more than 100 PMR patients with both recent onset and chronic disease (7).

As expected, IL-6 levels were found significantly higher in early PMR patients as compared to age-matched normal subjects and were positively correlated with serum cortisol, DHEAS and androstenedione levels, irrespective of glucocorticoid treatment. In addition, serum levels of cortisol in relation to IL-6 were significantly lower in patients with chronic disease and long-term glucocorticoid administration compared with patients with recent onset PMR without glucocorticoid therapy.

However, serum levels of cortisol in PMR patients with or without glucocorticoid were lower than would have been expected, considering their inflammatory status indicated by the increased concentration of IL-6.

These observations indicate a possible change in the responsiveness of the hypothalamus-pituitary-adrenal (HPA) axis to inflammatory stimuli such as IL-6 during active disease. IL-6, together with ACTH, acts synergistically to stimulate the direct release of corticosterone from the adrenal gland. This effect might explain the altered HPA axis responsiveness observed in PMR patients (8).

Healthy adrenal glands are capable of secreting the amount of endogenous cortisol necessary to control pathologic conditions under circumstances involving a strong activation of the hypothalamus, including acute stress, such as surgery, infections, and severe interpersonal stress (9). However, this does not happen in PMR patients: other

factors are thought to be responsible for the alteration of the HPA axis in PMR patients, including chronic systemic inflammatory stimuli with elevated IL-6 and TNF serum levels; age-related decreases in anti-inflammatory hormones, such as gonadal and adrenal hormones (*i.e.* testosterone, DHEA, androstenedione); and chronic activation of the defence system against stress (*i.e.* psychosocial stressors, and variables such as coping and personality) (10). Furthermore, glucocorticoid therapy alters the HPA axis, and most patients studied are taking these therapies.

In summary, these factors, which lead to the continuous stimulation of the HPA axis, could result in adaptive changes, *i.e.* the inadequately low secretion of adrenal and gonadal hormones in relation to systemic inflammation.

The adrenal glands of some elderly patients with PMR may not have the capacity to produce the amount of cortisol necessary to control inflammation. Age-related decline in adrenal gland function may be an important predisposing factor to explain the reduced responsiveness of the HPA axis to inflammatory stimuli in PMR patients.

Changes in steroidogenesis due to the direct effects of cytokines on the adrenal glands during inflammation may further increase adrenal insufficiency in chronic diseases (7).

A therapeutic question is whether or not, in the case of chronic inflammatory diseases such as PMR, immunosuppression with glucocorticoids should be accompanied by the additional administration of DHEA. These hormones are stimulated by an inflammation-induced increase in ACTH under normal circumstances; however, these responses are attenuated in chronic conditions such as PMR and rheumatoid arthritis (RA).

Glucocorticoid "replacement" therapy is the most effective approach to treat PMR and is also established for patients with other chronic immune-mediated diseases such as RA (11, 12).

Steroid regimens

Starting dosage

The optimal glucocorticoid starting dosage is not defined yet, and varies widely across different studies (13). A starting dosage of 15–20 mg/day of prednisone usually induces a dramatic clinical response, i.e. symptoms resolution within 48-96 hours and normalisation of acute-phase reactants. However, lower dosages have been suggested, in particular for those patients presenting contraindications to glucocorticoids, such as hypertension, glaucoma, diabetes, and severe osteoporosis. A starting dose at or below 10 mg/day is associated with fewer side effects, but many clinicians feel that it might be insufficient in most cases.

Delecoueuillerie *et al*. (14) compared high (15–30 mg/day) with low (7–12 mg/day) prednisone starting dose in two groups of PMR patients, and did not find significant difference in the relapse rate. However, due to the retrospective design of the study, confounding by indication could have been at work. In the only controlled comparison of two glucocorticoid dosages, Kyle and Hazleman (15) observed that 65% of patients who received an initial dosage of 10 mg/day prednisone experienced relapses in comparison with 26.3% of those receiving 15 to 20 mg/day.

Recently, a starting dose of 12.5 mg prednisone proved to be effective in 78.3% of patients, with a dose per kg of 0.2 mg prednisone appearing adequate (16). Nonetheless, the issue of the ideal starting dosage remains controversial because randomised, controlled studies are lacking (17). Table I summarises the main studies on glucocorticoid treatment of PMR.

Tapering and duration of treatment

No conclusive studies exist to determine the optimal tapering schedule of corticosteroid once the complete remission of symptoms is achieved and acute-phase reactants are normalised. To avoid relapses the dosage is usually decreased by 10% every 10–15 days, down to 10 mg/day. Then, a slower rate of decrease (1–2 mg every month or every two months) is used. Although disease flares occur more frequently when a rapid dose reduction is applied, spontaneous disease flares can occur independently of glucocorticoid dose (18).

Kremers *et al*. (19) showed that a higher starting dosage followed by a rapid tapering rate was associated with a greater risk of relapses. A direct comparison in a prospective design between high starting dose with fast tapering and low starting dose with slow tapering is not available.

To compare different studies and to appreciate the effect of treatment, it is important to agree on the definitions of relapse and remission, addressed in a recent report (20): features considered essential for definition of remission and relapse included morning stiffness, ESR, C-reactive protein (CRP), patients` pain assessment, shoulder and hip pain on clinical examination, limitation of upper limb elevation and assessment of glucocorticoid dose required to control symptoms.

These features form the primary basis for a decision to taper glucocorticoids or not, and/or to increase or re-start therapy. In general, an isolated elevation of ESR with no clinical change does not warrant an increase in glucocorticoid dosage.

CRP is considered to be a more reliable parameter to monitor the course of disease and guide therapy (2), although symptom recurrence is mandatory to define disease relapse. The same issue exists for tapering or stopping therapy: disease remission should be defined as absence of symptoms and normal level of acute-phase reactants. The role of the activity score for PMR (PMR-AS) (21) in tailoring glucocorticoid dose to the individual needs of each patient is still unknown.

Relapses are most likely over the first 18 months of treatment, but they can occur after apparently successful treatment, when glucocorticoids have been discontinued for a long period. In a retrospective evaluation of 256 PMR patients, 40% of the relapses were observed after 6 months from treatment discontinuation (22). At present, there is no way of predicting which patient is most at risk.

The optimal length of therapy as well as the rate of drug cessation remain unknown, as do the optimal initial dose and tapering strategies. The length of glucocorticoid therapy varies in different studies: while some authors report a mean duration of therapy of 11–17

Table I. Main clinical studies highlighting different steroid starting dose in patients with polymyalgia rheumatica (MTX: methotrexate; CRP: C-reactive protein).

Reference	Study	Starting dose	Follow-up	Notes
Behn AR, *et al*. (24)	Prospective, 114 patients	10 mg	—	Relapse after corticosteroid withdrawal is common
Delecoeuillerie G, *et al*. (14)	Retrospective 132 patients	7–12 mg 15–30 mg	—	No significant difference between the two subgroups
Lundberg I, *et al*. (45)	Retrospective 40 patients	18 mg (mean)	43 months (mean)	Corticosteroid treatment can be terminated within 24 months
Van der Veen MJ, *et al*. (46)	Prospective 34 patients	20 mg + 7.5 mg MTX/ placebo	24 months	There is no steroid sparing effect of MTX in a dosage of 7.5 mg/week
Bahlas S, *et al*. (47)	Retrospective 133 patients	23 mg ± 14	43±24 months	
Narvaez J, *et al*. (48)	Retrospective 69 patients	10–20 mg	until death or to December 31, 1995	Prolonged therapy is required for a significant number of patients
Cantini F, *et al*. (49)	Prospective 177 patients	17.5–20 mg	60 months	
Myklebust G, *et al*. (50)	Prospective 217 patients	21.5 mg	24 months	Low initial dose associated with low maintenance dose
Caporali R, *et al*. (51)	Prospective 72 patients	25 mg + 10 mg MTX/ placebo	18 months	High relapse rate in placebo group
Kremers HM (19)	Retrospective 284 patients	15 mg (median)	61 months (median)	Higher steroid doses and faster tapering predict relapses
Salvarani C, *et al*. (52)	Prospective 94 patients	17.5 mg (mean)	48 months	patients with elevated CRP and IL-6 have a higher risk of relapse
Pease CT, *et al*. (53)	Prospective 147 patients	15 mg	24 months (minimum)	Long-term follow up is essential to establish correct diagnosis
Salvarani C, *et al*. (54).	Prospective 51 patients	15 mg + 3 mg/kg infliximab/ placebo	12 months	
Bogliolo L, *et al*. (22)	Retrospective 320 patients	12.5 (median)	58 months (median)	60% discontinued treatment after 15.5 months (median). 38% of those who discontinued had at least 1 recurrence and restarted treatment

months (23), others report a mean duration of therapy of up to 31 months (24). The same variability may be encountered when assessing the rate of patients who were able to interrupt therapy.

Most European studies reported that between 33% and 50% of patients are able to discontinue steroids after two years of treatment. Other studies from the USA reported a higher frequency of discontinuation (75% of patients discontinued therapy after two years). However, a large study from the Mayo Clinic confirmed the European view (25), with a median duration of therapy of 1.8 years and a cumulative dose of prednisone between 4.5 and 5.4 g.

Glucocorticoid side effects

Long-term medium-high dose glucocorticoid therapy is associated with serious side effects in 20–50% of patients. In women over the age of 50, PMR and rheumatoid arthritis are the conditions in which glucocorticoids are used at the highest dose for the longest time (26).

Compared to age-matched controls, PMR patients had a 2 to 5 times greater risk of developing diabetes, and vertebral and hip fractures (26). Another long-term follow-up study found that 65% of the patients undergoing treatment developed at least one adverse event (25). Older age at diagnosis, a higher cumulative dose, and female sex are independent predictors of the risk of adverse events (1). Bisphosphonates, vitamin D and calcium have been found to be effective for preventing bone loss in glucocorticoid-treated patients (27) (see also *Glucocorticoid-induced osteoporosis* p. S-93). Various alternatives have been proposed, such as possibly safer compounds, different treatment modalities, and steroid-sparing agents, in order to avoid side effects due to long-term glucocorticoid therapy.

Alternative glucocorticoid treatments

Deflazacort, an oxazoline derivative of prednisolone, has been proposed as an alternative to prednisolone with fewer side effects affecting bone and glucose metabolism (28-30). It proved to be as effective as prednisone in treating PMR (31-33) but the purported increased safety has been questioned (34-36).

Intermittent steroid treatment could be useful to reduce steroid-related side effects. In a multicentre prospective study involving 60 patients, intramus-

cular methylprednisolone at a dosage of 120 mg every three weeks led to a remission rate similar to oral prednisolone, but with a significantly lower fracture rate and a lower proportion of patients with weight gain (37, 38). This increased safety profile was associated with a significantly reduced cumulative dose of steroids.

Similarly, it has been suggested that methylprednisolone acetate injections into the glenohumeral joints (40 mg, four times at one-week interval) may be a valid alternative to systemic corticosteroid therapy (39). Limited experience exists for pulse intravenous steroid regimens in PMR: in a pilot study on four patients, Cimmino *et al*. (40) did not demonstrate any steroid-sparing effect of three intravenous methyprednisolone boli (250 mg each on three consecutive days) used as first-line therapy.

Timing of glucocorticoid administration in PMR

Night pain and morning stiffness are generally accepted core symptoms of PMR and, similar to RA, a link with night-time increase in cytokine production is suggested (41).

These results may support a circadian variation of TNF-α and IL-6 secretion in PMR with peak values in the early morning hours, but data are much less extensive than in RA (42). One of the few published studies in the literature concerning the kinetics of IL-6 in polymyalgia rheumatica/giant cell arteritis showed a 24-hour cycle of IL-6 plasma levels following a single oral dose of prednisone (60 mg) in two patients with giant cell arteritis, a clinical syndrome closely related to PMR (43).

IL-6 concentrations were found to decrease abruptly, but showed a rebound toward pre-treatment concentrations before the next dose of prednisone was given 24 hours later, during the night. When glucocorticoid therapy was suddenly withdrawn, the rebound of IL-6 was paralleled by the reappearance of clinical symptoms.

These results appear to indicate that a time-adapted glucocorticoid therapy, administered prior to the flare of cytokine synthesis and inflammatory activity, may be more effective than administration in the morning, as in RA. Modified-release prednisone for night-time "replacement" therapy, already a reality in RA treatment (44), will be soon tested in PMR patients.

Conclusions

Glucocorticoid treatment is essential in PMR, although there is a lack of controlled studies and observational data to show the optimal dosage and tapering schedule. PMR patients demonstrate altered HPA axis functioning at disease onset, before glucocorticoid treatment, and during the course of the disease. This is indicative of a reduced responsiveness of the HPA axis and reinforces the hypothesis that PMR and elderly-onset RA are similar diseases.

Several factors could be involved in this adrenal hypofunction, such as the concomitant physiological decline in adrenal steroidogenesis during aging, chronic stress system activation (with consequent adrenal hypofunction), chronic infections (for example, by *Chlamydia pneumoniae* or herpes viruses), altered adrenal hormonal pathways (inter-individual and genetic differences), and age-related changes in gonadal hormone biosynthesis (*i.e*. oestrogens).

The relatively abrupt onset of PMR, with symptoms reminiscent of the steroid withdrawal syndrome (i.e., myalgia, malaise, fever, pain, depression, sleepiness, anorexia, etc.) and of adrenal insufficiency, and the dramatic and rapid disappearance of these symptoms following glucocorticoid administration, could very well represent further strong clinical evidence that PMR is an HPA axis-driven disease.

Glucocorticoid-replacement therapy addressing circadian rhythms of the disease and of cytokine production should optimise treatment by increasing its efficacy and by reducing both doses and side effects.

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