Methotrexate treatment in large vessel vasculitis and polymyalgia rheumatica

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ABSTRACT

In large vessel vasculitis, including giant cell arteritis and Takayasu arteritis, as well as in polymyalgia rheumatica, glucocorticoid therapy is the treatment of choice. However, there are two situations/questions for additional immunosuppressive therapies in these diseases: (i) therapy resistance to glucocorticoid mono-therapy; (ii) situations which call for sparing of glucocorticoids such as in complications of glucocorticoid therapy. This review summarises the current scientific debate on the effects of methotrexate in these diseases. Methotrexate at 10–15 mg/week appears to have a modest and delayed effect in GCA and PMR in reducing relapse rate and lowering the cumulative dose of glucocorticoid therapy. However, superiority of combination therapy in reducing the incidence of glucocorticoid-related complications has not been shown yet. The effects of higher doses and long-time effects as well as the efficacy in patients with glucocorticoid-resistance and complications are unclear. Methotrexate may thus be considered as adjunctive therapy to glucocorticoid therapy in glucocorticoid-resistance or complications. Further attempts should be made for a better identification of patients with glucocorticoid-refractory courses and a more precise formulation of guidelines on indication, optimal dosing and duration.

Introduction

In large vessel vasculitis, including giant cell arteritis (GCA) and Takayasu arteritis (TA), as well as in polymyalgia rheumatica (PMR), glucocorticoids actually are the treatment of choice (1, 2). The relative lack of efficacy of immunosuppressant agents other than glucocorticoids is remarkable and distinguishes these diseases from other auto-inflammatory syndromes (3). Treatment with medium to high doses of glucocorticoids (GC) usually suppresses inflammatory activity dramatically, leading to improvement of clinical symptoms and prevention of disease-related complications. It has been suggested that in the majority of cases, PMR and GCA are self-limiting disorders that burn out within an average of six months to two years from disease onset and, consequently, glucocorticoid therapy can be discontinued (4). However, there are two situations, where the question for additional immunosuppressive therapies arises in these diseases: (i) therapy resistance to glucocorticoid-mono-therapy; (ii) for sparing of glucocorticoids, for example in complications or difficult situations of glucocorticoid therapy.

In the absence of evidence, the European League against Rheumatism (EULAR) formulated recommendations for the management of large vessel vasculitis on the basis of a consensus opinion (1). It was recommended that an immunosuppressive agent should be considered for use in large vessel vasculitis as adjunctive therapy (1).

Methotrexate (MTX) is the drug that has been most widely used and best studied for potential disease-modifying and glucocorticoid sparing effects in the treatment of large vessel vasculitis and polymyalgia rheumatica (1, 5-9). This review summarises the available studies of the combined therapy of glucocorticoids and methotrexate in these diseases. We focus on the treatment of glucocorticoid-resistant patients and the question, whether the combined therapy is superior to glucocorticoid monotherapy. Alternatively, azathioprine is used (1, 10, 11); cyclophosphamide is not well investigated (12); anti-TNF-therapies were promising in refractory cases, but not effective in controlled trials (13-21); other biologic agents have been used sporadically (22).

Giant cell arteritis

Giant cell arteritis affects the aorta and its extracranial branches and occurs in

patients aged 50 years and older (2-4). It is the most common primary systemic vasculitis in adults with an estimated incidence of 32–290/million/year (1). It frequently occurs together with the inflammatory syndrome of polymyalgia rheumatica, around 40–60% of GCA patients having features of PMR (4). For treatment, 1mg/kg/day (maximum 60mg/day) prednisone equivalent as initial dose are recommended (1, 2). Approximately 50% of patients with GCA experience at least one severe disease flare that requires prolonged glucocorticoid therapy (23-25). About 25% of patients have a chronic-relapsing course and may require glucocorticoids for several years (4, 23, 25). Long-term glucocorticoid-therapy can lead to significant morbidity resulting from glucocorticoid-related side effects, including fractures, infections, diabetes, hypertension, cataracts and other problems (26). In GCA, glucocorticoid-related events have been observed in up to 86% of patients (25).

First case reports at the end of the 1980s (27) and subsequent small clinical pilot studies since the beginning of the 1990s reported on the efficacy of low-dose methotrexate in the therapy of glucocorticoid-resistant courses of giant cell arteritis and primary use of methotrexate in combination with conventional glucocorticoid-therapy aiming at glucocorticoid sparing and reduction of complications.

Glucocorticoid resistance in general and especially in GCA is not well defined. The phenomenon of glucocorticoid resistance, manifested by the absence of an expected response to treatment, is also known for rheumatoid arthritis and other inflammatory diseases and occurs in about 30% of these patients (28). Usually, waning of symptomatic relief has been considered a sign of GC resistance; however, in GCA the problem can be different. In a study with 41 patients with histologically confirmed giant cell arteritis, all patients initially received glucocorticoid treatment with 0.6 to 1mg/kg/day prednisone for three to four weeks, followed by a gradual reduction by a maximum of 5mg each week (29). When signs of activity occurred, no reduction was undertaken or the dose was increased to the previous level. After two years, the therapeutic status was investigated. Of the 41 patients, 9 patients (22%) were receiving more than 20mg/day of prednisone, due to clinical and/or laboratory exacerbation. It was suggested that patients who require more than 20mg of prednisone per day may be considered as having glucocorticoid resistant disease (29). Nowadays, this dose appears to be very high. In recent times, TNF inhibiting therapies have been investigated in GCA and PMR, and the first (successful) observations were made with infliximab in glucocorticoid-refractory patients (13, 14, 21). Here, glucocorticoid-refractory patients were defined as unable to reduce their prednisone dose below 7.5–12.5 mg/day and to have experienced multiple vertebral fractures (14, 19). However, in a larger group of patients, significant effects of infliximab could not be shown (15).

Table I. Possible "risk factors" for glucocorticoid resistance in GCA and PMR.

GCA	HLA DRB1*04 positive genotype (29)
	Strong initial systemic inflammatory response (30)
	Coexistance of PMR and GCA (9, 31, 32)
PMR	High pre-treatment ESR (40)
	Persistently increased IL-6 production (*e.g.* after 4 weeks of glucocorticoid therapy) (38, 41)
	Persistently increased CRP levels (41)
	Detection of subclinical large vessel vasculitis in PET (42)

There have been several attempts to identify those patients who are destined to develop glucocorticoid resistant disease in GCA/PMR in order to plan a rational alternative approach to treatment (Table I). In patients with giant cell arteritis a glucocorticoid requirement above 20mg/d of prednisone was found to be associated with the HLA DRB1*04 antigen (regardless of the subtype) (29). Patients with strong initial systemic inflammatory response (determined by sedimentation rate >100mm/h, thrombocytosis >400,000/mL, haemoglobin <11g/dL, leukocytosis >11000/mL, and fever >37.5 degrees C) have prolonged disease courses with more flares, requiring higher glucocorticoid doses (30). There is some evidence that patients with coexisting GCA and polymyalgia rheumatica may demand longer treatment compared with those with GCA or PMR alone (9, 31, 32).

In the past a glucocorticoid-sparing effect of MTX for *glucocorticoid-resistant GCA (and PMR)* at a dose of 12.5mg/week has been described in three case histories (27). However, a randomised controlled trial of the efficacy of MTX in glucocorticoid-resistant GCA is not available.

In 2001/2002 the efficacy of methotrexate in *newly diagnosed GCA* was assessed in 3 prospective, double-blind, randomised, placebo-controlled trials (33-35). These studies have yielded diverse results that led to discordant conclusions (Table II). Thus, the "methotrexate debate" is still going on (36). In 2007 Mahr *et al*. re-evaluated the data from these 3 RCTs in an individual patient data meta-analysis (24). The combined data set comprised 161 patients. This analysis could demonstrate that methotrexate was effective in preventing relapses, showing that adjunctive treatment with methotrexate in dosages of 7.5–15 mg/week in GCA reduces the risk of a first relapse by 35% and the risk of a second relapse by 51%. In addition, treatment with MTX decreased the cumulative exposure to glucocorticoids, at week 48 by 842mg and at week 96 by 1101mg. Use of MTX also increased the probability of achieving sustained discontinuation of glucocorticoids for >24 weeks. The superior effect of MTX treatment over placebo fully appeared only after 24–36 weeks. The rate of adverse events did not differ between treatment groups. In conclusion, methotrexate appears to be effective in GCA. Due to the delayed effect, it cannot be recommended as a replacement for glucocorticoids at disease onset. As the incidence of GC-related complications has not been shown to decrease, the clinical impact is finally questionable. Furthermore, it remains unclear whether a longer follow-up time would detect a difference in glucocorticoid-related side effects

Table II. Prospective, double-blind, randomised placebo-controlled trials (RCT) with methotrexate in newly diagnosed giant cell arteritis.

Spiera *et al*. 2001 (35); Patient number: 21; Duration of study: Approx. 12-18 months

Glucocorticoid (GC) treatment:
Initially 1mg/kg/d;
Tapering: By the treating physician according to the clinical response
Relapse: Increase of GC upon decision of treating physician

Methotrexate Dose:
Initially 7.5 mg p.o./week; folic acid supplementation 1 mg daily;
Start: When GC dose reached 30mg/d
Relapse: Increase of MTX up to 20mg/week
Taper off: After remission/discontinuation of GC therapy by 2.5mg/month

Results: No difference in cumulative GC dose (6469 *vs*. 5908mg), duration of GC treatment (68 *vs*. 60 weeks) and adverse events.
Conclusion: The combination of MTX and GC has no GC-sparing effect.
Limitations: Low patient number; no standardised GC treatment protocol; low initial MTX dose and late starting time point.

Jover *et al*. 2001 (34); Patient number: 42; Duration of study: Approx. 24 months

Glucocorticoid treatment:
Initially 60 mg/d; quick tapering
Relapse: Increase of GC to minimum amount that controlled disease

Methotrexate Dose:
Initially 10 mg p.o./week; folic acid supplementation 5 mg/d;
Start: Simultaneously to GC
Relapse: Increase of MTX by 2.5 mg/week

Results: Lower proportion of patients with at least one relapse (45 *vs*. 84%), lower cumulative GC dose (4187 *vs*. 5489 mg) and shorter duration of GC treatment (median 29 *vs*. 94 weeks) in MTX group. No difference in adverse events.
Conclusion: MTX is safe and more effective in controlling the disease than GC therapy alone.
Limitations: Low patient number; low MTX dose.

Hoffman *et al*. 2002 (33); Patient number: 98; Duration of study: Approx. 18-24 months

Glucocorticoid treatment:
Initially 1mg/kg/d, max. 60 mg/d; after 4 weeks tapering by 5 mg every 4 days; after 3 months every other day scheme; total duration of GC: 6 months
Relapse: Increase of GC to last effective dosage plus 10 mg/d

Methotrexate Dose:
Initially 0.15 mg/kg/week, increased to 0.25 mg/kg/week or max. 15 mg/week within 2 weeks; folic acid supplementation 5 mg/week
Start: Simultaneously to GC
Taper off: 12 months after achievement of remission by 2.5 mg/month

Results: No difference in proportion of patients with treatment failure (=2 distinct relapses or persistent disease activity after the first relapse despite increased GC therapy) (at 12 months 57.5 *vs*. 77.3%), cumulative GC dose (5375 *vs*. 5275 mg), duration of GC treatment (5.4 *vs*. 5.6 months) and adverse events.
Conclusion: The adjunctive use of MTX to control disease activity or GC sparing is not supported.
Limitations: Relatively rapid GC tapering scheme; follow-up only for 12 months.

or whether methotrexate at higher dosages of 15–25 mg/week would show a higher efficacy or a more rapid action. It is also unknown how effective methotrexate would be when given in patients with long-standing, glucocorticoid-resistant disease.

Polymyalgia rheumatica

Polymyalgia rheumatica is an inflammatory disorder characterised by aching and morning stiffness of the shoulder, neck and pelvic girdle (2-4). The symptoms appear to be related to synovitis of proximal joints and extra-articular synovial structures. Like giant-cell arteritis, polymyalgia rhematica affects patients aged 50 years and older. PMR is more frequent than GCA and a common disease, at least in Northern Europe and the USA with an estimated incidence of 17.8 cases per 100,000/year (2). About 16–21% of PMR patients have been reported as having coincident GCA (4). For treatment of PMR without GCA initial doses of 10–20 mg prednisolone equivalent are adequate in most cases (2, 6). In PMR glucocorticoid-related events have been observed in 65% of patients (37). The risk of adverse events is independently increased by older age at diagnosis, female sex and a cumulative dose of prednisone of 1800mg and more (37).

In regard to the disease course, PMR patients have been divided into 3 distinct groups: patients who respond rapidly and require glucocorticoids for less than 1 year with rare disease flares on glucocorticoid tapering (in the study 8/27 patients); patients who respond well initially but do not tolerate reduction to lower doses and have remitting disease of more than 1 year (12/27 patients); and patients who have only a partial response to the initial glucocorticoid regimen (7/27 patients) (38). This approach could be helpful defining subsets to identify patients that could benefit from adjunctive therapies in further studies.

In recent times anti-TNF therapies have also been investigated in PMR, and successful observations were made with infliximab in glucocorticoid-refractory patients (however not in the whole group), who were not able to reduce their prednis(ol)one-dose below 7.5–12.5 mg/day and had experienced multiple vertebral fractures (19, 20).

Which patients do respond poorly to glucocorticoid therapy? There are no established criteria for monitoring treatment and comparing alternative treatments regimens in PMR (and GCA). However, EULAR has developed a core set of response criteria for PMR including erythrocyte sedimentation rate or C-reactive protein concentrations, pain, physician's global assessment, early morning stiffness and degree of elevation of the upper limbs allowing to assess 90%, 70%, 50%, and 20% improvements, which occurred in 54%, 81%, 89%, and 95% of patients, respectively (39). High pre-treatment ESRs have been shown to correlate with duration of treatment in PMR, thus also being a prognostic factor (Table I) (40). In the subset of PMR patients, who responded only partially to the initial glucocorticoid dose and who also required glucocorticoids for longer than 1 year, Interleukin-6 production remained elevated even after 4 weeks of glucocorticoid therapy (although their ESR had normalised) (38). Also, in another study, persistently elevated CRP and IL-6 levels were significantly

associated with an increased risk of relapse/recurrence (whereas no patient had persistently elevated ESRs) (41). In a study using positron emission tomography (PET) it was shown that a third of PMR patients with *glucocorticoid-resistant* disease have underlying subclinical large vessel vasculitis in PET (42). A high ESR and the presence of systemic manifestations are predictors of coexistent silent giant-cell arteritis in polymyalgia rheumatica (2).

There is no controlled trial of methotrexate in patients with defined *glucocorticoid-resistant PMR.* In patients with PMR previously receiving glucocorticoids where most patients required prednisone ≥20mg/d for 3 months oral methotrexate doses of 7.5mg/week (increased to 10.0–12.5mg/week, according to clinical response) used as combination therapy for remission maintenance did not show clinical or laboratory benefit after 9 months of follow-up (43). There is one recently published letter reporting on 5 patients with *glucocorticoid-resistant PMR* which had been shown to have subclinical large vessel vasculitis by positron emission tomography (42, 44). Glucocorticoid resistance was defined as the impossibility to withdraw prednisolone treatment before 2 years and to taper its dosage to <7.5mg daily without exacerbations (42). These patients were treated with methotrexate 10 to 15mg/week in addition to the ongoing dose of prednisone (7.5–18.75 mg/d). The combined treatment with MTX and glucocorticoids markedly improved the clinical condition of all patients allowing mean prednisone tapering from 13.1mg/d to 7.9mg/d. Also, laboratory parameters and PET-CT uptake declined, however not significantly, which is most probably due to the low patient number. The results support the efficacy of MTX in vasculitis, especially in the subset of patients with PMR or GCA who are also affected by large vessel vasculitis (44).

The efficacy of methotrexate in *newly diagnosed PMR* has been investigated in 2 randomised controlled trials, also with conflicting results and conclusions (45-46) (Table III).

The results of the latter study, which was based on a pilot study with intramuscular methotrexate with positive outcomes (47) suggest that oral methotrexate started at disease onset and given for at least 1 year at a dose of at least 10mg/week may be effective in reducing the time to discontinuation of glucocorticoid therapy, the incidence of relapses and the cumulative glucocorticoid dose required to maintain remission (45). However, like in GCA a decreased rate and severity of glucocorticoid-related adverse events could not be demonstrated, questioning the superiority of the combined therapy. It is unclear whether methotrexate at higher doses would be of higher efficacy or more rapid action and how effective methotrexate would be in patients with long-standing, GC-resistant disease. Thus, the "tantalising" debate in PMR seems to go on (48).

Concerning the similar rate of side effects it was argued that a general limitation might have been that patients at the highest risk for glucocorticoid toxicity were excluded by the exclusion criteria as well as 12–24 months of follow-up may be insufficient to detect many glucocorticoid-related side effects (45). The average time from starting glucocorticoid treatment to a first side effect had been reported as 1.6 years (37). Recently, long-term follow-up data of 57 polymyalgia rheumatica patients enrolled in the previous study were presented (49). The patients were reviewed again after 5 years. MTX-treated patients had lower ESR (17 *vs.* 2mm/h, p=0.08) and CRP (2.7 *vs.* 10.2 mg/L, p=0.04) 6 years from initiation of therapy. However, there was no significant difference in the rate of side effects. There was also no significant difference in the mean cumulative glucocorticoid dosage and the frequency of flare-ups. One third of patients of both groups still needed glucocorticoid treatment after 6 years (31% *vs.* 39.3% in controls), demonstrating that PMR is not an unproblematic condition.

Table III. Prospective, double-blind, randomised placebo-controlled trials (RCT) with methotrexate in newly diagnosed polymyalgia rheumatica.

Van der Veen *et al*. 1996 (46); Patient number: 40 (6 with GCA); Duration of study: 12-24 months
Glucocorticoid treatment: Initially 20 mg/d; rapid tapering
Methotrexate dose: 7.5 mg p.o./week
Results: No difference in time to remission, duration of remission, number of relapses and cumulative prednisone doses.
Conclusion: MTX in a dosage of 7.5 mg/week has no glucocorticoid-sparing effect
Limitations: Low MTX dose; high number of dropouts (19/40); inclusion of GCA patients (15%).
Carporali *et al*. 2004 (45); Patient number: 62; Duration of study: 18 months
Glucocorticoid treatment: Initially 25 mg/d; tapering to 0 mg/d within 24 weeks
Methotrexate dose: 10 mg p.o./week for 48 weeks; folic acid supplementation 7.5 mg/week
Results: Higher proportion of patients who discontinued GC therapy at 76 weeks (88 *vs*. 53%), lower number of patients who had at least 1 flare-up (47 *vs*. 73%), lower total number of flare-ups (27 *vs*. 50), lower cumulative GC dose (2.1 *vs*. 2.97 g) in MTX group. No difference in adverse events. The adjunctive effect was seen only after 48–76 weeks.
Conclusion: The combination of GC and MTX is associated with shorter glucocorticoid treatment and glucocorticoid sparing.
Limitations: Low MTX dose.

Takayasu arteritis

Takayasu arteritis typically occurs in females under the age of 40 years and is less common than giant cell arteritis with an annual incidence of 0.4–2/million/year (1). About 50 % of all patients with Takayasu arteritis have chronic active disease for which glucocorticoid therapy alone does not provide sustained remission (50). Methotrexate has been investigated in Takayasu arteritis in one open-label study in refractory cases only (50). Weekly administration of MTX 15–25 mg/week (mean stable dose of 17.1mg) and glucocorticoids resulted in a high remission rate of 81% (13 of 16 patients) (50). Of those patients who achieved remission, 8 (50%) had sustained remissions of 4–34 months (mean 18 months), and 4 of this group did not require GC or MTX therapy for 7–18 months (mean 11.3 months). Three patients experienced disease progression in spite of treatment. Patients were followed up for a mean period of 2.8 years. Randomised

double-blind placebo-controlled trials and long-term studies to confirm the results are lacking.

Conclusion

Methotrexate at 10–15 mg/week seems to have a modest and delayed effect in patients with giant cell arteritis and polymyalgia rheumatica in reducing relapse rate and lowering the cumulative dose of glucocorticoid therapy. However, superiority of combination therapy in reducing the incidence of glucocorticoid-related complications has not been shown yet. Due to the delayed effect, MTX cannot be recommended as a replacement for glucocorticoids at disease onset. It is unclear yet whether a longer follow-up time would detect a difference in glucocorticoid-related side effects or whether methotrexate at higher dosages of 15–25mg/week would show a higher efficacy or a more rapid action. It is also unknown how effective methotrexate would be when given in patients with long-standing, glucocorticoid-resistant disease or patients with glucocorticoid-induced complications. The evidence for the (probably existing) efficacy of methotrexate in Takayasu arteritis is weak. Methotrexate may be thus considered as adjunctive therapy to glucocorticoid therapy in glucocorticoid-refractory courses or complications due to glucocorticoid therapy in patients with large-vessel vasculitis and polymyalgia rheumatica. Attempts should be made for a further development of response criteria as well as a precise definition of glucocorticoid-resistance and differentially responding subsets of patients in order to identify patients in which an adjunctive therapy is indicated. Risk factors for glucocorticoid-resistance should be evaluated systematically. Further randomised controlled studies on indications, optimal dosing and duration of methotrexate therapy are required, in order to be able to formulate more precise guidelines on treatment.

Methods

A literature research was conducted for papers published up to May 2010 in MEDLINE and/or PubMed (National Center for Biotechnology Information, National Institutes of Health). Only papers in English language were reviewed. The search strategy included the key word methotrexate combined with the keywords polymyalgia rheumatica, giant cell arteritis, large vessel vasculitis, Takayasu arteritis, respectively.

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