Review

The role of disease-modifying antirheumatic drugs in the treatment of giant cell arteritis

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ABSTRACT

Giant cell arteritis (GCA) is a vasculitis of unknown etiology that affects medium-sized and large arteries, and is the most common form of vasculitis in populations of predominantly Northern European ancestry. If left untreated, GCA can lead to significant morbidity including blindness, stroke, aortic aneurysm and dissection, as well as large-artery stenosis. Glucocorticosteroids are in general very effective in the treatment of GCA. Treatment with high dose glucocorticosteroids is associated with considerable morbidity and for some, but not all patients is required for prolonged periods sometimes exceeding several years.

Numerous efforts have been made over the decades to optimize therapeutic outcomes and reduce the side effects of glucocorticosteroids by enlisting adjuvant and alternative therapies. This review focuses primarily on evidence from randomized controlled trials with the objective of efficacy assessment of the respective drugs and dosing regimens in the treatment of GCA. Various glucocorticosteroid dosing regimens including alternate-day dosing, disease-modifying therapies including methotrexate and azathioprine, and the prospect of using monoclonal anti-cytokine or anti-cytokine receptor antibodies in the treatment of GCA are addressed. Thus far, no disease-modifying antirheumatic drug therapy or alternative to daily glucocorticosteroid therapy has been found to be unequivocally effective in the treatment of GCA.

Introduction

Giant cell arteritis (GCA) is a vasculitis of unknown etiology that affects medium-sized and large arteries, and is one of the most common forms of idiopathic vascular inflammation. The incidence of GCAhas been estimated to be as high as 15-33 cases per year per 100,000 persons over the age of 50 years in population-based epidemiologic studies of populations with predominantly Northern European ancestry (1-5). Classic symptoms related to the involvement of cranial arteries are a new headache, jaw claudication and visual disturbance (6), with risk of blindness when untreated (7). Other complications of GCA include stroke (8), aortic aneurysm and dissection (9), as well as large-artery stenosis (10). Over the past 50 years, glucocorticosteroid therapy has remained standard treatment for GCA(11).

Daily glucocorticosteroid monotherapy

Patients with GCA are conventionally initially treated with high dose oral glucocorticosteroid therapy consisting of prednisone equivalent in doses of 40-60 mg per day, which in most patients leads to rapid resolution of symptoms (11). Although the glucocorticosteroid dose subsequently can usually be gradually reduced, there is a high rate of relapses, especially when the dose is too vigorously tapered (12). The required duration of glucocorticosteroid therapy in the treatment of GCA is highly variable. Some patients may only require therapy with glucocorticosteroids for several months. In most patients, however, glucocorticosteroid therapy is needed for one to three years, but in some patients has to be extended for much longer periods. Similarly, the glucocorticosteroid dose needed to achieve adequate control of disease activity varies between patients (13-15).

Lower daily dose glucocorticosteroid therapy has been advocated by some in the initial treatment of GCA (12,16), but appears to be insufficient in a high proportion of patients, with frequent

relapses and disease related complications (17).

Initial high dose glucocorticosteroid therapy with pulses of methylprednisolone for treatment of newly diagnosed GCA has been assessed in a retrospective study with a limited number of patients (n = 15) and was generally well tolerated (18). The use of a single dose of intravenous methylprednisolone (240 mg) at the onset of therapy did not yield a significant glucocorticosteroid sparing effect in a large French randomized, multicenter, controlled phase III trial (19), which was not placebo-controlled and not blinded. A randomized, placebo-controlled, double-blinded trial comparing three daily pulses of 1000 mg of intravenous methylprednisolone to standard oral prednisone therapy at the initiation of treatment of newly diagnosed GCA is currently being conducted at Mayo Clinic. The primary outcome measure of this trial is the success rate of achieving disease control on a prednisone dose of 5 mg or less 34 weeks after trial entry. A possible rationale for use of high doses of glucocorticosteroids in the initial treatment of GCA is in part based on experiments in a human arteritis-SCID chimera mouse model, showing the need for extensive doses of glucocorticosteroids to effectively inhibit cytokine production in affected temporal arteries (20). This ongoing trial may determine the role of very high dose glucocorticosteroid use in the initial therapy of GCA.

Glucocorticosteroid-related side effects are common in patients on long-term glucocorticosteroid therapy and have a significant public health impact (21, 22). Consequently, there has long been interest in developing alternatives to daily glucocorticosteroid therapy of GCA which have a less severe side effect profile. These other treatment approaches have included the assessment of alternate-day glucocorticosteroid therapy as well as the addition of potential glucocorticosteroid sparing agents. The latter agents are conventionally called disease-modifying antirheumatic drugs, a term borrowed from the treatment of rheumatoid arthritis.

Alternatives to daily glucocorticosteroid monotherapy

Alternate-day glucocorticosteroid therapy

The landmark study of alternate-day prednisone therapy compared to conventional daily prednisone use was a randomized controlled clinical trial performed at Mayo Clinic in the mid 1970s by Hunder *et al.* (23). In this trial, 60 patients were randomized to one of three treatment arms of oral prednisone for newly diagnosed, biopsy-proven GCA. All patients were initially treated with 60 mg of prednisone divided into three daily doses orally for 5 days. In one treatment arm prednisone was then given at 90 mg every other day, while in the other arms prednisone was given as either a 45 mg once daily dose, or as 45 mg divided into three daily doses. Over the first one month of therapy, the alternate-day prednisone regimen was associated with treatment failure in 70% of the patients, compared to a failure rate of only 20% and 10% in the once daily and the three times daily prednisone regimens, respectively. Clear-cut differences between the groups were supported by laboratory measures of disease activity (erythrocyte sedimentation rate, hemoglobin), in addition to clinical measures of disease activity. This lack of efficacy of alternate-day glucocorticosteroid therapy was regrettable, as adverse effects of prednisone were considerably fewer with the alternate-day regimen, but frequent with the other two regimens. A limitation of this trial is that it was neither placebo-controlled, nor double-blinded. However, the striking difference between the treatment arms is difficult to explain solely on the basis of bias due to lack of placebo-control or double-blinding.

The possible role of alternate-day glucocorticosteroid therapy one month into treatment of GCAwas assessed by Bengtsson *et al.* (24) in 27 patients with GCA, of whom only 17 had a biopsy diagnostic of the disease. Unlike in Hunder *et al.*'s study (23), once daily prednisolone was given for the first month, followed by a gradual transition to alternate-day therapy if disease activity was suppressed. The disease was not sufficiently controlled in 33% of their patients on the alternate-day regimen due to clinical symptoms on the "days off". Of interest, in the first month of treatment daily prednisolone was fairly rapidly tapered from initially 40 mg once a day the first week to 25 mg the second week, 20 mg the third, and 15 mg the fourth week. In spite of this rather quick taper, the disease was not sufficiently controlled in only 3 out of 27 patients. In contrast to the study of Hunder *et al.*, this was an uncontrolled trial, a study design weaker than the controlled trial. The studies differed in that Bengtsson *et al.* evaluated the potential role of alternate-day glucocorticosteroid therapy begun one month after initial daily dose therapy, while Hunder *et al.* evaluated alternate-day therapy begun after only 5 days of daily glucocorticosteroid therapy. The finding of a lower rate of symptoms occurring on the "off days" in Bengtsson *et al.*'s trial compared to Hunder *et al.*'s trial (33% versus 70%) suggests a possible role for alternate-day glucocorticosteroid therapy at a later point in the treatment course of GCA. However, the role of alternate-day glucocorticosteroid therapy in maintenance treatment of GCA has not been further addressed in a well designed, randomized, placebo-controlled study.

Experience with potential disease-modifying antirheumatic drugs

Numerous drugs have been assessed for their potential disease-modifying activity in the treatment of GCA. Azathioprine was evaluated for its potential to reduce maintenance doses of glucocorticosteroids in the treatment of established GCA or polymyalgia rheumatica (mean disease duration of more than 2 years) in a double-blinded, placebo-controlled, one-year study by De Silva *et al.* (25). The authors enrolled 31 patients, of whom only 11 had biopsy-proven GCA. De Silva *et al.* did not indicate how many patients underwent an arterial biopsy. The majority of their patients appear to have had isolated polymyalgia rheumatica and not necessarily clinical giant cell arteritis, although this is not clearly stated. Patients had to be on stable

prednisolone doses of 5 mg/day or more for at least 3 months prior to enrollment in the trial, a dose that had been reduced to a minimum sufficient to control symptoms. A completer analysis of 10 out of 16 patients randomized to azathioprine at doses up to 150 mg daily, and 12 out of 15 patients randomized to placebo was performed. Six patients on azathioprine withdrew within the first 3 months because of side effects, compared to only 1 patient on placebo. In the completer analysis, a statistically significant difference in the maintenance prednisolone dose between both treatment arms favoring the azathioprine group was seen only after 52 weeks ($p < 0.05$), but not at any earlier point during the trial (after 12, 24, or 36 weeks). The clinical significance of this difference is questionable, given that after 52 weeks the mean prednisone dose was 1.9 ± 0.84 mg in the azathioprine group compared to 4.2 ± 0.58 mg in the placebo group. Although not specifically addressed, the cumulative prednisolone dose likely did not differ significantly between the groups.

There are several limitations to De Silva *et al.*'s study including the limited sample size, the small fraction (and absolute number) of patients with GCA, and the report of only the completer analysis in view of a high percentage of non-completers especially in the azathioprine group. Specific criteria for adjustment of the prednisolone doses on follow-up visits were not provided. These limitations in addition to the potential for an increased risk of lymphoproliferative disorders and other toxicities of azathioprine (26) probably explain why azathioprine has never been widely used as disease-modifying therapy in the treatment of GCA.

Use of dapsone (27-29) and cyclophosphamide (30) in the treatment of GCA has been the subject of case reports, but neither of these drugs has been assessed in a controlled clinical trial. These drugs have no demonstrated role in the treatment of GCA. Although cyclophosphamide has proven efficacy in the treatment of other life-threatening vasculitides, it has never gained an established place in the treatment of GCA. This is due to the fact that, in general, GCA can be adequately managed with glucocorticosteroids alone and does not require therapy with an alkylating agent such as cyclophosphamide with its associated toxicities (bladder cancer, myelo- and lymphoproliferative diseases, cytopenias).

Methotrexate is the drug that has been most widely used and best studied for its potential disease-modifying and steroid sparing effect in the treatment of GCA. There have been 3 randomized, placebo-controlled, double-blinded trials assessing its efficacy in newly diagnosed GCA in the recent past (31-33). These studies have yielded conflicting results.

In the early 1990s a group from Madrid, Spain, conducted an uncontrolled pilot study of 11 patients with newly diagnosed biopsy-proven GCA, initiating methotrexate at 10 mg once weekly at the time of diagnosis and continuing this for at least 20 months, in addition to prednisone which was quickly tapered (34). The patients required a mean cumulative dose of prednisone of 3.4 ± 1.03 grams (average follow-up 31.5 months). Only 2 out of 9 patients who completed the trial sustained a relapse. Based on this experience, this same group of Jover *et al.* then proceeded with a 2-year randomized, double-blinded, placebo-controlled trial of methotrexate. A total of 42 patients with newly diagnosed GCA were randomized to receive either methotrexate at 10 mg once weekly or placebo in addition to a standardized rapid prednisone taper (31). There was a significant decrease in the cumulative prednisone dose in the methotrexate group compared to the placebo group [4187 ± 1529 mg vs. 5489 ± 1396 mg; mean difference 1302 mg (95% CI 350 to 2253 mg); $p < 0.009$]. The proportion of patients who experienced at least one relapse was significantly lower in the methotrexate group compared to the placebo group (45.0% vs. 84.2%; $p = 0.02$), as was the proportion of patients who experienced multiple relapses ($p = 0.004$). First relapses occurred somewhat later in the methotrexate group at a median of 25 weeks (25th and 75th percentiles, 21 and 31.5 weeks) compared to the control group at 21 weeks (25th and 75th percentiles, 17 and 26.7 weeks), but the difference was not statistically significant ($p = 0.08$). Treatment had to be discontinued in 3 out of 21 patients in the methotrexate group due to methotrexate-related toxicity.

Although these results appear favorable for a clinically relevant disease-modifying effect of methotrexate in the treatment of GCA, this study had considerable limitations. The sample size was small. Only 15 out of 21 patients in the methotrexate group and 18 out of 21 patients in the placebo group completed treatment. The rapid prednisone tapering course, specifically at the lower doses by 2.5 mg every one week, was likely responsible for most of the relapses. Most relapses occurred after three months, when the prednisone dose was lowered to ≤ 10 mg/day per protocol. Conventionally, prednisone doses are much more slowly tapered below doses of 10 mg prednisone a day in the later course of treatment, a dose range that is associated with fewer side effects. A slower or later prednisone taper appears more likely to maintain disease control compared to a rapid or early taper. An aggressive glucocorticosteroid taper will likely be most useful in rigorously testing the hypothesis that methotrexate (or any other agent studied) can be used as a steroid sparing agent in the treatment of GCA. The occurrence of relapses after the prednisone dose was lowered to ≤ 10 mg suggests that methotrexate may have a glucocorticosteroid sparing role, mainly as these lower doses are reached. However, it is possible that the overall toxicity of methotrexate, which led to withdrawal of more than 10% of patients, outweighs the toxicity of low dose prednisone therapy that is tapered off more cautiously. Jover *et al.*'s study was unable to show differences in glucocorticosteroid related side effects between the two treatment groups, possibly due to the limited sample size.

While Jover *et al.* had a standard treatment protocol for tapering the prednisone dose in the event that no relapse occurred, there were only vague guide-

lines about how to adjust the prednisone dose in case of a relapse ["the dose of prednisone was increased to the minimum amount that controlled symptoms" (31)]. Thus, the frequency of a second relapse was difficult to interpret. Especially in view of the small sample size, variability in the interpretation of this guideline between study physicians may have introduced unknown bias.

The apparently favorable results for methotrexate as a glucocorticosteroid sparing agent in the Spanish studies were contradicted by two US studies (32,33). Spiera *et al*. (32) enrolled 21 patients into a randomized, double-blinded, placebo-controlled trial comparing methotrexate in addition to prednisone therapy in the treatment of newly diagnosed GCAto standard therapy with prednisone alone. This study had important limitations even beyond its small sample size with inherently limited power. There was no standardized protocol for prednisone therapy. Starting doses of prednisone equivalents ranged from 40 to 1000 mg a day. There was no requirement to follow a pre-defined tapering schedule, and there were no guidelines for prednisone therapy adjustments in the case of a relapse. Methotrexate was not initiated until the daily glucocorticosteroid dose was tapered down to 30 mg/day. The starting dose of methotrexate was low at only 7.5 mg a week, and only increased by 2.5 mg if a relapse occurred. Of 171 patients approached to participate in the study, only 21 were finally enrolled. The diagnosis of GCA was biopsy-proven in only 17 out of the 21 patients. The study was considerably underpowered, with only a 60% chance of detecting a difference in the cumulative prednisone dose of 30% or more. It was powered (at 92%) to detect a difference in the cumulative prednisone dose of 50% or more. It was unlikely that this expectation could be met, because of the late initiation of methotrexate and the low methotrexate doses used, and also in view of the results of previous studies on methotrexate use in GCA (34, 35). Because of these study design and conduct issues, conclusions from this study cannot be regarded as definitive.

The largest randomized, placebo-controlled, double-blinded study of methotrexate use in the treatment of newly diagnosed GCA was a multicenter US study of 98 patients (33). A clear strength of this study by Hoffman *et al.* compared to that of Jover *et al*. was the larger sample size. A potential weakness of Hoffman *et al.*'s study was the use of alternate-day prednisone dosing. After the initial 4 weeks of daily prednisone, the alternate-day prednisone was tapered so that patients were taking 60 mg of prednisone on one day, alternating with no prednisone the next day by 3 months after trial entry. The alternate-day dosing scheme was initiated later than in Hunder *et al*.'s study (who started it 5 days after trial entry) (23). Hoffman *et al.* employed a higher glucocorticosteroid dose both in the first month of daily dosing and during the following months of alternate-day dosing than Bengtsson *et al.* (24). In our view, based on the evidence of the previous studies (23, 24), alternate-day prednisone therapy has no role in the treatment of GCA, even though the dosing schedule in Hoffman *et al*.'s trial differed from the previous studies. Treatment with prednisone within 3 weeks prior to trial entry was allowed, and it is unclear whether there were significant differences in the cumulative glucocorticosteroid doses prior to trial entry between the two treatment groups. This compares to the exclusion of patients taking prednisone in doses of more than 10 mg per day or the equivalent for more than 2 weeks prior to trial entry in Jover *et al.*'s study. The methotrexate dose used by Hoffman *et al*. was higher than in Jover *et al*.'s study, so that underdosing with methotrexate would less likely explain its apparent lack of efficacy.

The primary outcome measure in Hoffman *et al*.'s trial was the rate of relapses of GCA. The study was designed to detect a 50% reduction in relapses with a power of 80%. These researchers initially assumed a relapse rate in the placebo group of 30%, which later proved to be much higher at 60%. The higher than previously expected relapse rate may have been at least partially explained by the use of alternate-day prednisone therapy. A clear strength of this study was the well defined treatment protocol with exact guidelines for prednisone dosing, including dosing for relapse, in contrast to Jover *et al*.'s study. GCAwas biopsy-proven in 83% of patients in the Hoffman *et al*. study compared to a required positive temporal artery biopsy in Jover *et al*.'s study, although the strict enrollment criteria make it unlikely that this had any effect on the study results.

Hoffman *et al*. analyzed their data at 6 months and 1 year after initiation of therapy, while Jover *et al*.'s study extended over 2 years. At 12 months they found that treatment failed in 57.5% of patients in the methotrexate group (95% CI 41.6 to 73.4%) compared to 77.3% in the placebo group (95% CI 61.9 to 92.8%; p = 0.26 by long-rank test). Treatment failure was defined as the occurrence of either two distinct disease relapses, or a relapse not responding to treatment with a prednisone dose 10 mg higher than the previously effective dose. Of patients in the methotrexate group, 74.8% experienced a first relapse within one year (95% CI 61.2 to 88.4%) compared to 91.3% in the placebo group (95% CI 80.6 to 100.0%; p = 0.31 by log-rank test). Even though the differences were not considered to be statistically significant with the methods employed, there was a trend toward a benefit from methotrexate. Hoffman *et al*. were unable to detect a difference in the cumulative prednisone dose between the groups (median cumulative prednisone dose in the methotrexate group was 5,375 mg (range 1,980 to 8,270 mg; IQR 1,560 mg) compared to 5,275 mg in the placebo group (95% CI 1,020 to 8,605 mg; IQR 1,695 mg) (p = 0.5). It remains uncertain whether prolonged follow-up over an additional one year with final analysis at 2 years would have demonstrated a difference between the treatment arms in favor of methotrexate. It is possible that a higher dose of methotrexate than that chosen for the trial may have led to more striking differences between the treatment groups. In any case, there is still no unequivocal evidence for the effica-

cy of methotrexate as a disease-modifying drug in the treatment of GCA.

In these clinical trials evaluating methotrexate, the drug was started early in the treatment of GCA while patients were receiving the initial higher dose glucocorticosteroid therapy (31-34). In the community, rheumatologists frequently consider methotrexate use for patients who experience multiple relapses and are unable to successfully taper off glucocorticosteroids. While this strategy has not been sufficiently addressed in clinical trials, it appears reasonable to extrapolate the equivocal results in the setting of methotrexate use early on during the disease course to the setting of refractory cases who have experienced multiple relapses.

To date neither a clearly effective glucocorticosteroid sparing therapy nor an alternative to glucocorticosteroid therapy for the treatment of GCA has been found. Methotrexate had perhaps been the most appealing of the disease-modifying drugs assessed thus far, but its benefit has not been definitely demonstrated to this point. The search for glucocorticosteroid sparing therapies is ongoing, and much hope has been evoked by recently developed and newly evolving biologic designer drugs.

Future prospects in the treatment of GCA

With the advent of a new class of therapeutic agents, the monoclonal anti-cytokine antibodies or anti-cytokine receptor antibodies, including the tumor necrosis factor (TNF) alpha antagonists infliximab and etanercept and others on the horizon, and the interleukin-1 receptor antagonist anakinra, has come consideration of the use of these agents in the treatment of GCA. TNF has been suggested to play a role in the inflammatory lesions of GCA. Immunohistochemistry for TNF of temporal artery biopsy specimens from patients with GCA revealed significantly more cells staining positive for TNF than in control tissues (36). However, tissue cytokine patterns assessed by measuring messenger RNA suggested a significant increase of interleukin-1 and interleukin-6 production, but not of TNF-alpha production (37). A recent study using human temporal artery cultures found that specimens from patients with GCA had an increased production of interleukin-1 beta, but a decreased production of TNF alpha after stimulation with lipopolysaccharide (38). Based on the evidence from these studies elucidating the pathophysiology of GCA, monoclonal interleukin-1 receptor antagonist therapy might be a more promising approach than anti-TNF-alpha therapy in the treatment of GCA(37, 38).

Use of TNF-alpha antagonist therapy with infliximab has been reported in a case series of four patients treated for longstanding refractory GCA (39). Three out of the four patients had a good response to three consecutive intravenous infusions of infliximab (3 mg/kg) at weeks 0, 2, and 6, the current regimen used in rheumatoid arthritis (40), and one did not. The three patients achieved complete remission after the second infliximab infusion and continued to be in remission without repeated infusions and off prednisone up to 6 months after the third infliximab infusion. It is too early to conclude from this small case series that infliximab has a therapeutic effect in GCA.

As of yet, there have been no clinical trials using any of these new monoclonal cytokine antagonists in the treatment of GCA, but such trials are being planned.

It merits consideration that the high cost of the new monoclonal cytokine antagonists may not justify their use in a disease for which an inexpensive alternative in the form of glucocorticosteroid therapy is available. However, long-term prednisone therapy is associated with significant morbidity (21, 22). From a public health standpoint a more expensive, but less toxic drug therapy could result in less utilization of health care resources. A lowering of the cost of these therapies, assuming an acceptable risk/benefit profile, would certainly make them attractive as adjuncts and alternatives to standard glucocorticosteroid treatment.

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