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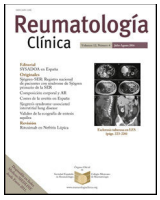

Brief report

Effect of combined treatment with prednisone and methotrexate versus prednisone alone over laboratory parameters in giant cell arteritis☆

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ABSTRACT

Objective: To compare the effect of combined treatment with prednisone and methotrexate (MTX) versus prednisone alone over laboratory parameters in giant cell arteritis (GCA).
Patients and methods: We performed a double-blind, placebo-controlled, randomized clinical trial about usefulness of treatment with prednisone and MTX versus prednisone and placebo in GCA (Ann Intern Med 2001;134:106–114). As a part of follow-up of patients ($n = 42$), we performed laboratory analysis in 20 time points during the two-year period of follow-up. To analyze differences, we calculated the area under the curve (AUC) for erythrocyte sedimentation rate (ESR), hemoglobin, and platelets, and compared the results in both groups adjusting by time of follow-up, existence of relapses and dose of prednisone.
Results: A total of 724 laboratory measurements were done. Median value of ESR was 33 [18–56] in patients with placebo and 26 [15–44] in patients with MTX ($P = 0.0002$). No significant differences were observed in ESR during relapses. The mean ESR value followed a parallel course in both groups, but was lower in the group with MTX than in the group with placebo in 18 of 20 time points of follow-up. The AUC of ESR by time of follow-up was 28,461.7 ± 12,326 in the group with placebo and 19,598.4 ± 8,117 in the group with MTX (mean difference 8,863, 95% CI 1.542–16.184; $P = 0.019$). The course of other laboratory parameters paralleled, without statistical significance, those observed for ESR.
Conclusions: These data, along with clinical data, suggest that MTX might play a role as a disease-modifying agent in the treatment of GCA.

Efecto del tratamiento combinado con prednisona y metotrexato versus prednisona sola sobre los parámetros de laboratorio en arteritis de células gigantes

Palabras clave:
Arteritis de células gigantes
Metotrexato

RESUMEN

Objetivo: Comparar el efecto del tratamiento combinado con prednisona y metotrexato (MTX) versus prednisona sola sobre parámetros de laboratorio en arteritis de células gigantes (ACG).
Pacientes y métodos: Realizamos un ensayo clínico aleatorizado, doble ciego, controlado con placebo sobre la utilidad del tratamiento con prednisona y MTX frente a prednisona y placebo en la ACG (Ann Intern Med. 2001;134:106-114). Como parte del seguimiento de los pacientes ($n = 42$), realizamos análisis de laboratorio en 20 puntos temporales durante el período de seguimiento de 2 años. Para analizar diferencias calculamos el área bajo la curva (AUC) de VSG, hemoglobina y plaquetas, y comparamos los resultados en ambos grupos ajustando por tiempo de seguimiento, existencia de recaídas y dosis de prednisona.

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Resultados: Se realizaron un total de 724 mediciones de laboratorio. El valor medio de la VSG fue de 33 (18-56) en pacientes con placebo y de 26 (15-44) en pacientes con MTX (p = 0,0002). No se observaron diferencias significativas en la VSG durante las recaídas. El valor medio de la VSG siguió un curso paralelo en ambos grupos, pero fue menor en el grupo con MTX que en el grupo con placebo en 18 de 20 puntos temporales de seguimiento. El AUC de la VSG por tiempo de seguimiento fue de 28.461,7 ± 12.326 en el grupo con placebo y de 19.598,4 ± 8.117 en el grupo con MTX (diferencia de medias 8.863; IC 95%: 1.542-16.184; p = 0,019). La evolución de los demás parámetros de laboratorio fue paralela, sin significación estadística, a la observada para la VSG.
Conclusiones: Estos datos, junto con los datos clínicos, sugieren que el MTX podría desempeñar un papel como agente modificador de la enfermedad en el tratamiento de la ACG.

Introduction

Giant cell (temporal) arteritis (GCA) is a systemic vasculitis primarily targeting large and medium-sized arteries in people over the age of 50 years. It is characterized by transmural inflammation of the arteries that induces luminal occlusion through intimal hyperplasia. Clinical symptoms are developed by end-organ ischemia and, in almost all patients with GCA, a syndrome of systemic inflammation. GCA is characterized by a vigorous acute-phase response that includes increased levels of C-reactive protein (PCR) and, particularly, a very high erythrocyte sedimentation rate (ESR).

Morbidity from GCA itself is substantial including vision loss, aortic aneurysms, aortic branch vessel stenoses, polymyalgia rheumatica (PMR), constitutional symptoms and stroke. Treatment with corticosteroids (CS) is mandatory,[1] initial dosage must be high (40–60 mg/d) with subsequent tapering to a lower maintenance dose that is given for an average of two years. Following initial improvement, up to 60% of patients experience disease relapse during CS tapering requiring reintroduction or dose escalation of CS.[2,3] This long-term CS therapy leads to CS-related adverse events in up 80% of patients being a major problem in the management of GCA in already frail patients.[4]

Current data reflect that standard CS regimens only partially suppress vascular inflammation and that ongoing subclinical disease activity may expose GCA patients to the risk of progressive vascular disease and chronic systemic complications.[5] Indeed, it has not been demonstrated that corticosteroid treatment induces changes in the course of the disease. This hypothesis is supported by the absence of revascularization of affected vessels, a higher incidence of aneurysms in previously GCA patients, the findings of positive artery biopsies after a successful course of treatment, and the fact that percentage of asymptomatic GCA patients present sustained ESR or CRP elevations after treatment.

In a previous study we have shown that methotrexate plus CS is a safe alternative to CS therapy alone in patients with GCA and is more effective in controlling disease than standard CS therapy.[6] Methotrexate plus CS was also more efficient than CS alone in maintaining disease remission supporting the notion that methotrexate may exert not only a role as steroid-sparing agent but also a role as disease-modifying agent in GCA.

In this work, we study the effect of combined treatment with prednisone and MTX versus prednisone alone over laboratory parameters, particularly ESR as a marker of inflammation, in GCA.

Patients and methods

Patients

Selection and randomization, follow-up, treatment protocol, assessments of disease activity and outcome measures are the same as the previously mentioned study.[6] Briefly, forty-two consecutive patients, newly diagnosed as having active GCA biopsy proven were included in the study and randomizing assigned to receive prednisone plus methotrexate or prednisone plus placebo.

A single weekly dose of four tablets of either oral methotrexate (total 10 mg/week) or placebo was started upon diagnosis, maintained throughout the treatment period, and finally interrupted after 24 months of follow-up if clinical signs of disease activity were absent. All patients received 60 mg/day of oral prednisone in three divided doses during the first week, and once daily during the second week. Then, prednisone dose was gradually tapered by 10 mg per week until reaching 40 mg/day at the end of the first month; by 5 mg per week until reaching 20 mg by the end of the second month; and by 2.5 mg every two weeks until complete withdrawn.

Relapses were defined as the recurrence of symptoms of GCA after definite, objective improvement followed by symptom reversal upon resumption of, or increases in, the prednisone dose.

Visits and laboratory parameters

Baseline and follow-up visits were scheduled weekly during the first month, monthly until completion of the first year of therapy, and quarterly during the second year of follow-up. In each scheduled visit routine blood tests were performed including erythrocyte sedimentation rate (ESR), red blood cells, platelets, white blood cells, serum chemistry studies and urinalysis. In presence of suspected relapse and other adverse events, additional analysis was obtained.

Statistical analysis

Laboratory parameters were compared between patients receiving methotrexate and those receiving placebo along the study period. In order to analyze differences in mean laboratory values over time, we calculated the area under the curve (AUC) and adjusted the results by treatment group, dose of prednisone and existence of a relapse. A two-sided *P* value of 0.05 was the criteria for statistical significance in all cases. Categorical variables are presented as frequency distribution and quantitative variables as means plus/minus standard deviation (SD) if they fit a normal distribution, and median plus/minus first and third quartile if distribution is non-normal. Differences between treatment groups were analyzed using the two-tailed Student's *t* test and the Mann–Whitney *U* test for normal and non-normal quantitative variables respectively, with their corresponding 95% confidence interval when appropriate. Statistical comparisons were made with Arcus Quickstat Biomedical 1.2 software.

Table 1
Baseline characteristics of the study patients.*

Characteristic	Methotrexate group $n=21$	Placebo group $n=21$
Age, y	78 ± 8.7	77.6 ± 7.6
Women, n	14 (66.7)	15 (71.4)
Body weight, kg	60.2 ± 11.7	58.1 ± 11.1
Weeks before diagnosis, n	14.3 ± 12.5	10.9 ± 8
Clinical features, n (%)		
Polymyalgia rheumatica	12 (57.1)	11 (52.3)
Abnormal temporal artery	16 (76.1)	15 (71.4)
Headache	21 (100)	20 (95.2)
Jaw claudication	12 (57.1)	17 (80.9)
Unilateral blindness†	4 (19)	5 (23.8)
Bilateral blindness‡	2 (9.5)	3 (14.2)
Amaurosis fugax	0 (0)	1 (4.7)
Laboratory values		
Hemoglobin level, g/L	117 ± 15	112 ± 15
Platelet count, $\times 10^9$ cells/L	371 ± 141	358 ± 115
Leukocyte count, $\times 10^9$ cells/L	9.5 ± 3.3	10.7 ± 63.9
Erythrocyte sedimentation rate, mm/h	91 ± 24	100 ± 26
Previous concomitant disease, n (%)		
Arterial hypertension	7 (33.3)	10 (47.6)
Diabetes mellitus	2 (9.5)	3 (14.2)
Cataracts	7 (33.3)	3 (14.2)
Glaucoma	2 (9.5)	0 (0)
Tuberculosis	4 (19)	2 (9.5)
Cerebrovascular disease	1 (4.7)	1 (4.7)

* Values with the plus/minus sign are the mean ± SD. $P > 0.10$ for all paired comparisons between groups. No differences were observed between groups in either completion of follow-up or completion of treatment analysis.
† Includes complete (one patient) and partial (eight patients) unilateral blindness.
‡ Includes complete (two patients) and partial (three patients) bilateral blindness.
Ann Intern Med 2001;134:106–114.

Results

There were no significant differences among groups in terms of baseline characteristics (Table 1). All patients had an elevated ESR at baseline that normalized shortly after initiation of treatment.

Time-course analysis of ESR values demonstrated that mean values of ESR were higher in those patients treated with placebo than in patients treated with methotrexate and this difference was evident after the fifth week of treatment (Fig. 1). The mean ESR value followed a parallel course in both groups, but was lower in the group with MTX than in the group with placebo in 18 of 20 time points of follow-up. Median value of ESR was 33 [18–56] in patients with placebo and 26 [15–44] in patients with MTX ($P = 0.0002$). The area under the curve was significantly lower in patients treated with MTX than in patients treated with placebo (19,598.4 ± 8,117 vs. 28,461.7 ± 12,326, respectively; mean difference 8,863, 95% CI 1.542–16.184; $P < 0.01$). This result was independent of prednisone dose, relapse status, age and sex.

Time course of relapses along the study period and prednisone use in both groups of treatment is shown in Fig. 2. ESR was elevated in 90% of relapses, median value 59 mm/h, range 22–127 and no differences were observed in both groups. There was a peak of ESR between the third and fourth month that coincided with most relapses in both groups and with prednisone dose below 20 mg/day. Differences in ESR appeared few weeks after treatment initiation and were maintained all along the treatment course even after one year of therapy when the median dose of prednisone was below 10 mg in all patients.

The course of other laboratory parameters paralleled those observed for ESR but without statistical significance, with a trend to more normal parameters in patients treated with MTX, i.e., lower incidence of anemia, leucocytosis and thrombocytosis.

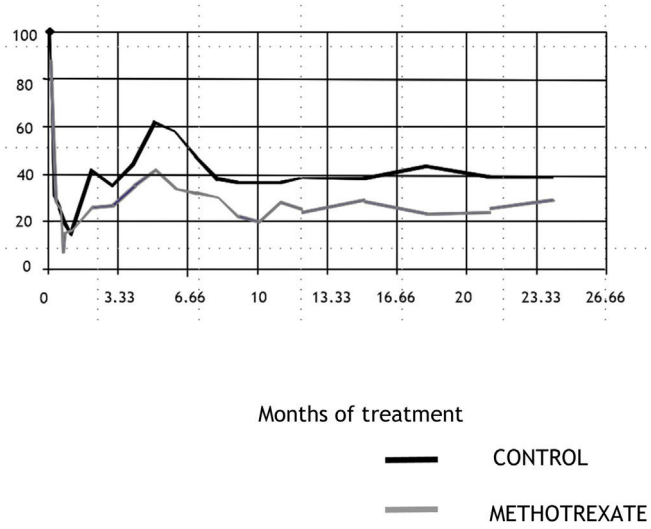

Fig. 1. Time course of ESR in each group. The gray line indicates the mean ESR in every time point for the patients treated with methotrexate and prednisone and the black line the same value for patients treated with prednisone alone. Differences are apparent after the first month of treatment, and from then on, the mean ESR value was higher in the group treated with prednisone alone.

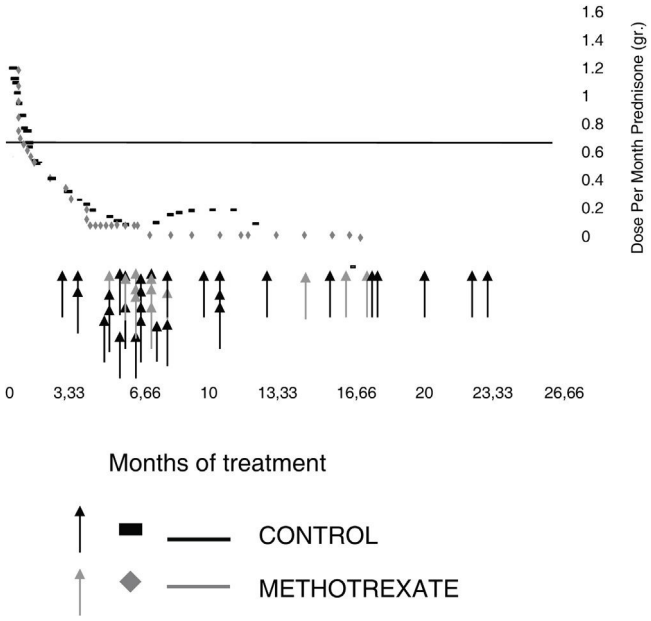

Fig. 2. Relationship between ESR and prednisone dose in each group. The gray line and gray rhombs indicate the mean ESR and median prednisone dose respectively in every time point for the patients treated with methotrexate and prednisone. The black line and black rectangles indicate the mean ESR and median prednisone dose in every time point for patients treated with prednisone alone. Arrows indicate the time at which relapses occurred in both groups. As you can see, relapses were more frequent in the first year of treatment in both groups and were accompanied by a significant rise in the mean ESR value.

Discussion

We presented the analysis of the laboratory parameters in a group of patients with GCA treated with an identical schedule of prednisone plus methotrexate or placebo along a two-year study period. These patients were participants in a randomized, double-blind, placebo-controlled study that showed that combined treatment with prednisone and methotrexate reduced the proportions of patients suffering relapses and the mean cumulative dose of prednisone suggesting that methotrexate in association with CS are

more effective in disease control than standard CS therapy. In this report, we go further suggesting that methotrexate may act as an anti-inflammatory modulator, and probably a disease-modifying factor, for GCA due to the observed decrease in acute-phase reactants.

The differences appeared few weeks after treatment initiation and were maintained all along the treatment course even after one year of therapy when the mean dose of prednisone was below 10 mg in all patients. Although not statistically significant, the course of other laboratory parameters paralleled those of ESR, with a better trend in patients treated with MTX. Due to the year of the original protocol design, 1992, neither CRP nor IL-6 or other pro-inflammatory cytokine levels were routinely considered, what would have been useful at the light of these results. However, differences observed point toward MTX not merely as a steroid-sparing agent but an anti-inflammatory modulator, and probably a disease-modifying factor, for GCA.

The anti-inflammatory modulator concept is not new for rheumatologists but is a challenging new hypothesis for GCA.[7] None will now discuss that CS alone is not a proper treatment for chronic inflammatory diseases such as rheumatoid arthritis (RA). In fact, the concept of modification of inflammation versus symptoms modification has extended from RA to other several rheumatic and non-rheumatic diseases. Trials with MTX in GCA and polymyalgia rheumatica have been more that anecdotical in the literature.[8–13]

Although clinical results of other studies with MTX have been conflicting with ours and difficult to interpret,[14–19,1] ESR showed also a trend favoring MTX in previous studies.[20,21] Anti-TNF-α have also been studied and used in patients with GCA[22–24] and failed to show efficacy in GCA, thus, anti-TNF therapies have not shown benefit in GCA.

Other DMDs have been studied such as azathioprine[25] and leflunomide.[26,27]

Activated T cells have also been implicated in the pathogenesis of GCA, hence, abatacept (ABA) has been studied in a multicentre, randomized study[28] with promising results.

IL-12 and IL-23 in the Th1 and Th17 responses are also recognized actors in the pathogenesis of GCA, therefore, ustekinumab, was studied in an open-label study of 14 patients with CGA.[29]

The new prospects for GCA as well as polymyalgia rheumatica (PMR) include fairly evidence for a role of IL-6 in both GCA and PMR. Interleukin-6 includes acute-phase response and has a central role in the pathogenesis of GCA.[30–32] The tocilizumab has been reported to be effective in several published randomized clinical trials.[33,34]

Although there is evidence in favor of treatment with other immunosuppressive drugs, in this article, we want to point out/emphasize the role of methotrexate as an anti-inflammatory modulator just decreasing VSG. Probably MTX could also act as a disease-modifying drug on its own taking into account the widespread evidence supporting/showing that MTX is safe and effective in the treatment of GCA and, in the background, it decreases acute-phase reactants.

Conflict of interest

The authors declare that they have no conflict of interest.

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