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Brief communication

Leflunomide in Takayasu arteritis – A long term observational study

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ABSTRACT

Objective: To evaluate the extended follow-up data on efficacy and toxicity of leflunomide therapy in Takayasu arteritis (TA) patients previously enrolled in the original open-label study of short-term effects of leflunomide in TA.

Methods: An open-label long-term longitudinal study was performed in TA patients who fulfilled the 1990 American College of Rheumatology criteria for TA and had participated in a previous study that evaluated short-term efficacy of leflunomide in TA. Complete follow-up information could be retrieved from 12 out of 15 patients enrolled in the original study. Disease activity was evaluated by Kerr's criteria and by the Indian Takayasu Activity Score 2010 (ITAS2010).

Results: The mean follow up time was 43.0 ± 7.6 months and 5 (41.6%) TA patients remained on leflunomide therapy while 7 (58.3%) TA patients had to change to another therapy due to failure to prevent relapses in 6 patients and toxicity in one patient. No significant differences were found between patients who remained on leflunomide therapy and those who changed to another agent regarding age at study entry, time since diagnosis, prednisone daily dose at study entry, baseline ITAS2010, mean or maximum ESR and CRP, and cumulative prednisone dose at study end. Among TA patients who had changed leflunomide to another agent, two had an additional clinical relapse and needed to change therapy.

Conclusion: Leflunomide led to sustained remission in approximately half of patients at a mean time of 12 months and was well tolerated by TA patients.

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Leflunomida na arterite de Takayasu – Estudo observacional de longo prazo

R E S U M O

Palavras-chave:

Vasculites sistêmicas
Arterite de Takayasu
Leflunomida
Tratamento

Objetivo: Avaliar os dados de seguimento em longo prazo em relação à eficácia e toxicidade do tratamento com leflunomida em pacientes com arterite de Takayasu (AT) previamente recrutados no estudo aberto original dos efeitos de curto prazo da leflunomida na AT.

Métodos: Fez-se um estudo longitudinal aberto de longo prazo com pacientes que preencheram os critérios para AT da American College of Rheumatology de 1990 e que participaram de um estudo anterior que avaliou a eficácia em curto prazo da leflunomida na AT. Obtiveram-se informações completas de seguimento de 12 dos 15 pacientes incluídos no estudo original. A atividade da doença foi avaliada pelos critérios de Kerr e pelo Indian Takayasu Activity Score 2010 (ITAS2010).

Resultados: O tempo médio de seguimento foi de $43,0 \pm 7,6$ meses. Cinco (41,6%) pacientes com AT permaneceram em tratamento com leflunomida, enquanto sete (58,3%) tiveram de mudar para outro tratamento em razão da falha em prevenir recidivas em seis pacientes e toxicidade em um paciente. Não foram encontradas diferenças significativas entre os pacientes que continuaram o tratamento com leflunomida e aqueles que mudaram para outro agente em relação à idade no início do estudo, tempo desde o diagnóstico, dose diária de prednisona no início do estudo, ITAS2010 inicial, valor médio ou máximo de VHS e PCR, e dose de prednisona cumulativa no fim do estudo. Entre os pacientes com AT que mudaram de leflunomida para outro agente, dois tiveram nova recidiva clínica e precisaram mudar de tratamento.

Conclusão: A leflunomida levou à remissão sustentada em aproximadamente metade dos pacientes por um período médio de 12 meses e foi bem tolerada pelos pacientes com AT.

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Introduction

Takayasu arteritis (TA) is a large vessel vasculitis that is characterized by granulomatous inflammation involving the aorta, its main branches and pulmonary arteries.¹ TA affects more frequently females and the onset of symptoms usually occurs during the second and third decades of life. Although TA is described in all ethnic groups, it is more prevalent in Asians.² The assessment of disease activity in TA is usually problematic, because arterial inflammation may progress to fixed vascular injury even in the absence of overt signs and symptoms of disease activity.^{3,4}

In patients with active disease, medical therapy of TA includes high dose prednisone (0.5–1 mg/kg/day) or equivalent as the first line. However, relapses occur in up to 50% of TA patients during corticosteroid tapering and thus immunosuppressive agents are usually added to corticosteroid therapy in order to halt disease progression and to spare corticosteroid use.^{1,5} Conventional immunosuppressive agents used to treat TA include methotrexate, azathioprine, mycophenolate mofetil, leflunomide and cyclophosphamide. Recently, biological agents such as TNF α antagonists, tocilizumab and rituximab were added as treatment options for TA patients with refractory or severe disease.⁶

Our group showed a favorable short-term response (mean follow-up of 9.1 months) to leflunomide 20 mg/day in TA patients with active disease despite therapy with prednisone and immunosuppressive agents, mainly methotrexate.⁷ However, data about long-term efficacy and toxicity of leflunomide

in TA are lacking. Therefore, the aims of this study are to describe the extended follow-up data of efficacy and toxicity of leflunomide therapy in TA patients previously enrolled in the original open-label study of short-term effects of leflunomide in TA.

Patients and methods

This study is an open-label long-term longitudinal study to evaluate leflunomide in TA. TA patients included in this study fulfilled the 1990 American College of Rheumatology criteria for TA⁸ and had participated in a previous study that evaluated short-term efficacy of leflunomide in TA.⁷ From 15 TA patients enrolled in the original study, complete follow-up information could be retrieved from 12 patients, since 3 patients were lost to follow-up.

TA patients were divided into two groups: (A) TA patients who continued long-term use of leflunomide and (B) TA patients who had to change therapy to another immunosuppressive or biological agent. Disease activity was evaluated by the Kerr's criteria¹ and by the Indian Takayasu Activity Score 2010 (ITAS2010).⁹ Acute phase reactants used to evaluate systemic inflammation included the Westergren erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Arterial lesions were assessed by magnetic resonance angiography (MRA) or by computed tomography angiography (CTA) of the entire aorta and its main branches. Cumulative prednisone dose during the follow-up period was calculated for each study participant. Adverse events attributed to leflunomide therapy

were recorded. Study's protocol was approved by the Institutional Ethics Committee and all participants gave informed consent.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows, version 20.0 (Armonk, United States) and graphs were built with GraphPad Prism 5.0 software. Categorical data are presented as total number (percentage) and continuous data were presented as mean \pm standard deviation or as median and interquartile range as appropriate. Comparisons between groups were performed with the Fisher's exact test for categorical variables or with the Student's *t* test and Mann-Whitney *U* test for continuous data. A Kaplan-Meier curve was built to show the time curve of leflunomide withdrawal in TA patients. Accepted significance level was 5% ($p < 0.05$).

Results

The mean age of TA patients at study entry was 34.9 ± 12.5 years and 11 (91.7%) were females. The mean follow up time was 43.0 ± 7.6 months and 5 (41.6%) TA patients remained on leflunomide therapy whereas 7 (58.3%) TA patients had to change to another therapy due to failure to prevent disease relapses in 6 patients. Adverse events were observed in two patients and included diarrhea and gastrointestinal upset, but only one of them withdrew leflunomide due to these adverse events. Leflunomide was replaced by infliximab in 4 patients, by azathioprine in 2 patients and by adalimumab in 1 patient. Only one out of seven TA patients who changed therapy developed adverse events afterwards, she was on infliximab and presented manifested recurrent lower urinary tract infections. Fig. 1 illustrates the Kaplan-Meier curve for the time to replace leflunomide by other therapies. The mean time for leflunomide withdrawal was 12.8 ± 8.6 months. Groups A and B had similar time to prednisone withdrawal [20.8 (range 7.8–26.1) months vs. 34.1 (1.7–42.3) months; $p = 0.571$]. In group A, one patient refused to use prednisone since study entry and another could not taper prednisone below 20 mg/day, whereas in group B two patients could not taper prednisone as well.

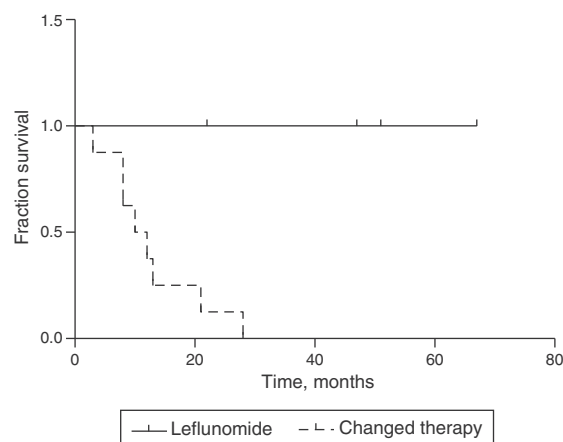


Fig. 1 – Time to replace leflunomide to another immunosuppressive or biological agent. Kaplan-Meier curve shows two groups of TA patients: group A (continuous line) comprising patients who continued leflunomide and group B (dashed line) with TA patients who changed therapy to other agents. The mean time to replace leflunomide to another agent was 12.8 ± 8.6 months.

No significant differences were found between group A and group B regarding age at study entry, time since diagnosis, prednisone daily dose at study entry, baseline ITAS2010, mean or maximum ESR and CRP, and cumulative prednisone dose at study end (Table 1). Amongst TA patients who changed leflunomide to another therapy, two had a clinical relapse and needed to change therapy with infliximab and adalimumab to etanercept and infliximab, respectively. New angiographic lesion was documented in 4 TA patients during the clinical relapse that led to leflunomide withdrawal. Nonetheless, two patients developed new angiographic lesions even after changing leflunomide to another agent, while no new angiographic lesion could be observed in patients who remained on leflunomide until follow up completion ($p = 0.469$).

Discussion

In this long-term follow up study, we observed that leflunomide had to be replaced by another therapy, mostly biological

Table 1 – Comparisons between TA patients who remained on leflunomide (group A) and those who needed to change therapy (group B).

Variables	Group A (n = 5)	Group B (n = 7)	<i>p</i>
Age at study entry, years	41.4 ± 12.7	30.3 ± 11.1	0.138
Disease duration, months	95.0 (73.0–144.0)	77.0 (62.0–112.0)	0.465
Prednisone dose at study entry, mg	11.0 ± 8.9	31.4 ± 19.5	0.056
ITAS2010 at baseline	6.0 ± 3.5	5.6 ± 3.3	0.864
Mean ESR during study, mm/h	21.5 ± 15.8	31.4 ± 21.5	0.407
Mean CRP during study, mg/L	5.6 ± 4.5	10.3 ± 10.6	0.379
Maximum ESR during study, mm/h	38.8 ± 28.6	56.0 ± 31.2	0.354
Maximum CRP during study, mg/L	9.4 ± 9.9	25.3 ± 15.3	0.072
Cumulative prednisone at study end, mg	$6,324.8 \pm 5,023.2$	$13,366.1 \pm 10,492.6$	0.247

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ITAS2010, Indian Takayasu's arteritis activity score.

agents, in more than half of TA patients. The main reason for leflunomide withdrawal was failure to prevent disease relapses, even though a good disease control had been achieved on the short-term open-label study.⁷ Moreover, leflunomide was shown to be relatively safe and only one patient could not tolerate this agent due to diarrhea and gastrointestinal upset. Limitations of this study include the low number of patients evaluated and the lack of a control group.

Indeed, a subgroup of TA patients presented a sustained response to leflunomide with long-term remission leading to prednisone withdrawal while the development of new arterial lesions was halted. Although no significant differences could be found between TA patients who remained on leflunomide and those who needed to change therapy, it is possible that the latter group presented a more severe disease course, since a trend to higher prednisone dose at study entry and higher maximum CRP levels were observed in these patients from group B as well as after changing therapy, 2 patients developed new angiographic lesions despite the use of a TNF α antagonist.

To date, no randomized controlled trials have evaluated medical therapy in TA.⁶ Immunosuppressive and biological agents were assessed in TA only by open-label studies with a small number of patients what may be a potential source of bias. Furthermore, studies that evaluated therapy in TA used different criteria to assess disease activity and head-to-head comparisons are not possible.^{3,10} Recently, the ITAS2010 has been validated to evaluate disease activity in TA and this outcome measure yields a numeric score that is useful for patient monitoring.⁹ The OMERACT Vasculitis Working Group is developing a validated set of outcome measures for disease activity in TA.¹⁰ In this study, we preferred to use Kerr's criteria and ITAS2010 to assess disease activity in order to increase sensitivity by using two different outcome measures. Actually, in some cases we detected a disease relapse when patients presented new angiographic lesion and elevated ESR despite the absence of new complains or changes in physical examination, in other words ITAS2010 score did not change in some of the silent relapses of our TA patients.

Regarding immunosuppressive agents, the rate of remission induction in TA patients for methotrexate, azathioprine and mycophenolate mofetil was 81.0%, 76.7% and 90.0%, respectively.¹¹⁻¹³ In another study, the use of mycophenolate mofetil in TA patients with active disease led to a decrease in median ITAS2010 from 7.0 (range 0.0-19.0) to 1.0 (range 0.0-7.0), $p=0.001$, as well as a significant reduction of steroid dose, ESR and CRP values.¹⁴ These rates of remission in TA observed with the use of other immunosuppressive agents are similar to our findings with short-term leflunomide therapy for TA (80% of patients in remission at 9.1 months of follow up).⁷ However, those studies do not report the relapse rate for the long-term follow up. The follow up period of our study is slightly higher (3.6 years) than in the above mentioned studies (i.e. 2.8, 1.0 and 3.0 years, respectively). The reasons for this apparently lower efficacy of leflunomide in keeping sustained remission might be the inclusion of more severely ill TA patients or the absence of information about relapses after remission was attained in other studies.¹¹⁻¹³

The use of biological agents in TA has also been evaluated in open-label studies. Studies that evaluated TNF α antagonists in TA (i.e. infliximab, etanercept and adalimumab) report a response rate of 89% but a relapse rate of 37% whereas for tocilizumab the response rate was 100% and a relapse rate of 18%.¹⁵ Thus, leflunomide induces remission in active TA similarly to TNF α antagonists but seems to be inferior to biological agents in preventing disease relapses in TA.

In conclusion, leflunomide leads to sustained remission and prevents the development of new arterial lesions in approximately 41% of TA patients at a mean follow up time of 43 months. Leflunomide therapy was well tolerated by TA patients and the main reason for withdrawal leflunomide therapy is the failure to prevent disease relapses rather than adverse events.

Conflicts of interest

The authors declare no conflicts of interest.

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