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Efficacy and adverse effects of methotrexate compared with azathioprine in the antisynthetase syndrome

M. Casal-Dominguez[1,2], I. Pinal-Fernandez[1-3], J. Huapaya[2], J. Albayda[2], J.J. Paik[2], C. Johnson[2], L. Silhan[2], A.L. Mammen[1,2], S.K. Danoff[2], L. Christopher-Stine[2]

[1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD; [2]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [3]Faculty of Health Sciences, Universitat Oberta de Catalunya, Barcelona, Spain.

*Maria Casal-Dominguez, MD, PhD**
*Iago Pinal-Fernandez, MD, PhD**
Julio Huapaya, MD
Jemima Albayda, MD
Julie J. Paik, MD
Cheilonda Johnson, MD
Leann Silhan, MD
Andrew L. Mammen, MD, PhD
Sonye K. Danoff, MD, PhD
Lisa Christopher-Stine, MD, MPH

**These authors contributed equally.*

Please address correspondence to:
Dr Lisa Christopher-Stine,
5200 Eastern Avenue,
MFL Center Tower 4500,
Baltimore, MD 21224, USA.
E-mail: lchrist4@jhmi.edu

and to: Dr Sonye K. Danoff,
1800 E. Monument Street, 5th Floor,
Baltimore, MD 21287, USA.
E-mail: sdanoff@jhmi.edu

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ABSTRACT

Objective. *To study the efficacy in terms of muscle strength, and corticosteroid tapering as well as the prevalence of adverse effects in patients with the antisynthetase syndrome (ASyS) treated with azathioprine (AZA) compared to those treated with methotrexate (MTX).*

Methods. *We compared the clinical outcomes in ASyS patients treated with AZA versus MTX including change in corticosteroid dose, strength, and creatine kinase (CK) as well as the prevalence of adverse effects.*

Results. *Among 169 patients with ASyS, 102 were treated at some point exclusively with either AZA or MTX (± corticosteroids). There were no significant differences in the rate of muscle strength recovery, CK decrease or corticosteroid tapering between those ASyS patients treated with MTX versus AZA. The prevalence of adverse events in patients treated with AZA and MTX was similar (29% vs. 25%, p>0.05); elevated liver enzymes (17% AZA vs. 12% MTX) and gastrointestinal involvement (10% AZA vs. 8% MTX) were the most common adverse events. While no patients treated with AZA developed lung complications, two of the patients treated with MTX experienced reversible pneumonitis with MTX cessation.*

Conclusion. *AZA and MTX showed similar efficacy and adverse events in patients with ASyS. Pneumonitis is a rare but important event in patients receiving MTX.*

Introduction

The antisynthetase syndrome (ASyS), first described as an entity in 1990 (1), is characterised by the presence of an antisynthetase antibody which targets cytoplasmic enzymes that catalyse the formation of the aminoacyl-tRNA complex. Clinically, this syndrome is characterised by myositis, interstitial lung disease (ILD) or both. Other features including Raynaud's phenomenon, arthritis, fever and mechanic's hands are also common clinical features of the ASyS syndrome (2, 3).

Corticosteroids are considered first line treatment in the ASyS, but most of the time, other immunosuppressive agents are needed. Methotrexate (MTX) or Azathioprine (AZA) are common first line therapies in ASyS patients (4), but mycophenolate (5, 6), the calcineurin inhibitors, cyclosporine and tacrolimus (7-9), as well as cyclosphospamide (10) and rituximab (11, 12), have also been used for the treatment of these patients with good results.

The high risk of patients with the ASyS developing ILD makes MTX use controversial due its potential to induce hypersensitivity pneumonitis, which may be mistaken for ILD related to the underlying ASyS. Unlike ASyS associated ILD, MTX pneumonitis is typically reversible with MTX cessation. It has been suggested that MTX may be more beneficial than AZA in some groups of patients who are refractory to prednisone (13). Although MTX and azathioprine are two of the most widely used immunosuppressant drugs for the ASyS, the efficacy to treat the manifestations of the disease, comparative efficacy as steroid-sparing drugs and secondary effects are, to a large extent, unknown.

Our main objective was to study the differences in muscle strength and changes in the dose of corticosteroids, as well as the profile of adverse effects between ASyS patients treated with AZA *versus* those treated with MTX.

Materials and methods

In this longitudinal cohort study, we included all Johns Hopkins Myositis Center patients who were positive for one of the ASyS antibodies (anti-Jo1, anti-PL7, anti-PL12, anti-OJ or anti-EJ) and presented with at least two of the following clinical manifestations: myositis, ILD, polyarthritis or mechanic's hands. All the treatments administered at each clinical evaluation were recorded, and those patients treated with AZA or MTX without concomitant use of other steroid sparing agents were included for analysis. The sera from all patients was screened for anti-Jo1, anti-PL7, anti-PL12, anti-EJ, and anti-OJ by ELISA, line blotting (Euroline Myositis Profile 4; Euroimmun), by immunoprecipitation at the Oklahoma Medical Research Foundation and/or using Quest Diagnostics myositis panels.

This study was approved by the Johns Hopkins Institutional Review Board,

and written informed consent was obtained from each participant.

The change in strength, CK and dose of corticosteroids during the period that patients were exposed exclusively to AZA or MTX (± corticosteroids) were analysed using multilevel regression models adjusted for age at onset, sex, race, dose of corticosteroids, type of antisynthetase antibody and time from the onset to the clinical evaluation.

At each visit, arm abduction and hip flexion strength, were evaluated by the examining physician using the Medical Research Council (MRC) scale. This scale was transformed to Kendall's 0–10 scale for analysis purposes as previously described (14). Several investigators examined the patients, but serial strength measurements for each patient were made by the same physician.

Adverse effects were recorded as reported by the attending physician. Accordingly, laboratory abnormalities, like elevation of the liver enzymes, leukopenia or pancytopenia were based on the normality cut-off of the corresponding facility where the tests were performed. Also, MTX associated pneumonitis was defined by the occurrence of cough or dyspnea in a time course consistent with exposure to MTX which resolved with stopping this medication. All the episodes of possible MTX pneumonitis were reviewed by three of the authors (SD, MCD and IPF). The probability of the adverse effect was quantitated using Naranjo's method (15).

Dichotomous variables were expressed as percentages and absolute frequencies, and continuous features were reported as means and standard deviations (SD). Pairwise comparisons for dichotomous variables between groups were made using chi-square test or Fisher's exact test, as appropriate. Student's *t*-test was used to compare continuous variables among groups. CK, a highly positively skewed variable, was compared using Wilcoxon rank-sum test for the univariate analysis and transformed through a base-10 logarithm for regression analysis. Locally weighted regression was applied to analyse graphically the evolution of the strength and dose of corticostestoids over time.

All statistical analyses were performed using Stata/MP 14.1. A two-sided *p*-value of 0.05 or less was considered significant with no correction for multiple comparisons.

Table I. Adverse effects of methotrexate and azathioprine in patients with the antisynthetase syndrome.

	Azathioprine (n=89)	Methotrexate (n=52)	*p*-value
Elevated liver function tests	17% (15)	12% (6)	0.4
Gastrointestinal	10% (9)	8% (4)	0.8
Nausea	7% (6)	8% (4)	1.0
Diarrhoea	2% (2)	0% (0)	0.5
Abdominal pain	1% (1)	0% (0)	1.0
Leukopenia	4% (4)	2% (1)	0.7
Pancytopenia	1% (1)	2% (1)	1.0
Other adverse effects	6% (5)	13% (7)	0.1
Methotrexate pneumonitis	0% (0)	4% (2)	0.1
Rate of adverse effects	29% (26)	25% (13)	0.5

Dichotomous variables were compared using Chi-squared or Fisher's test as appropriate.

Results

Of 169 patients with the ASyS (73% women), 124 of them were positive for anti-Jo1, 23 for anti-PL12, 16 for anti-PL7 and 3 for anti-EJ and anti-OJ respectively. Of these patients, 63 (37%) were treated with AZA exclusively, 26 (15%) were treated with MTX exclusively and 26 (15%) were treated with both AZA and MTX at some point of their evolution (total of 115 patients). The average length of exposure to these medications was 24 months for AZA and 29 months for MTX. In general, AZA was administered to patients with less muscle involvement (lower CK and higher strength) and more severe lung involvement (lower FVC) while MTX was given to patients with milder lung involvement. MTX and AZA in combination were used in patients with more severe muscle disease (lower strength and higher CK). Patients treated with MTX were mostly white and presented anti-Jo1 autoantibodies more commonly than the other treatment groups (Supplementary Table I).

Twenty-nine percent of all the patients who were treated with AZA showed adverse effects to this drug, compared with 25% of the patients that were treated with MTX ($p>0.05$). The most common adverse effects with both drugs were elevated liver function tests (17% AZA *vs.* 12% MTX), gastrointestinal symptoms such as nausea and diarrhoea (10% AZA *vs.* 8% MTX) and cytopenias (6% AZA *vs.* 4% MTX), but none of these were significantly different between both drugs. Of note, most reported adverse effects were mild. While no patient with AZA experienced pulmonary adverse effects related to the use of the immunosuppressant treatment, four patients treated with MTX (8%) reported pulmonary events ($p=0.02$) but only two presented clear evidence of MTX pneumonitis ($p=0.1$). These two patients did not have pre-existing lung involvement. One had cough and lung CT involvement that reverted rapidly after MTX discontinuation and the other one was challenged twice with MTX developing cough and shortness of breath that reverted quickly after stopping the drug both times. (Table I). Both patients had a Naranja's score (15) of 5 which corresponds to a probable adverse effect. Complementarily, the two other patients that reported pulmonary events were patients with pre-existing ILD reporting worsening of their respiratory symptoms (one cough and one dyspnea) during MTX treatment. However, the time course was considered inconsistent with MTX pneumonitis and there were no objective tests available to show worsening of the ILD.

Of the 115 patients treated with AZA or MTX, 102 received either of the drugs combined with no other immunosuppressant drug than corticosteroids (59 AZA, 20 MTX and 23 AZA and MTX at different time points). These patients accounted for 450 visits under treatment with AZA or MTX ± corticosteroids (mean of 4.4 visits per patient) that were

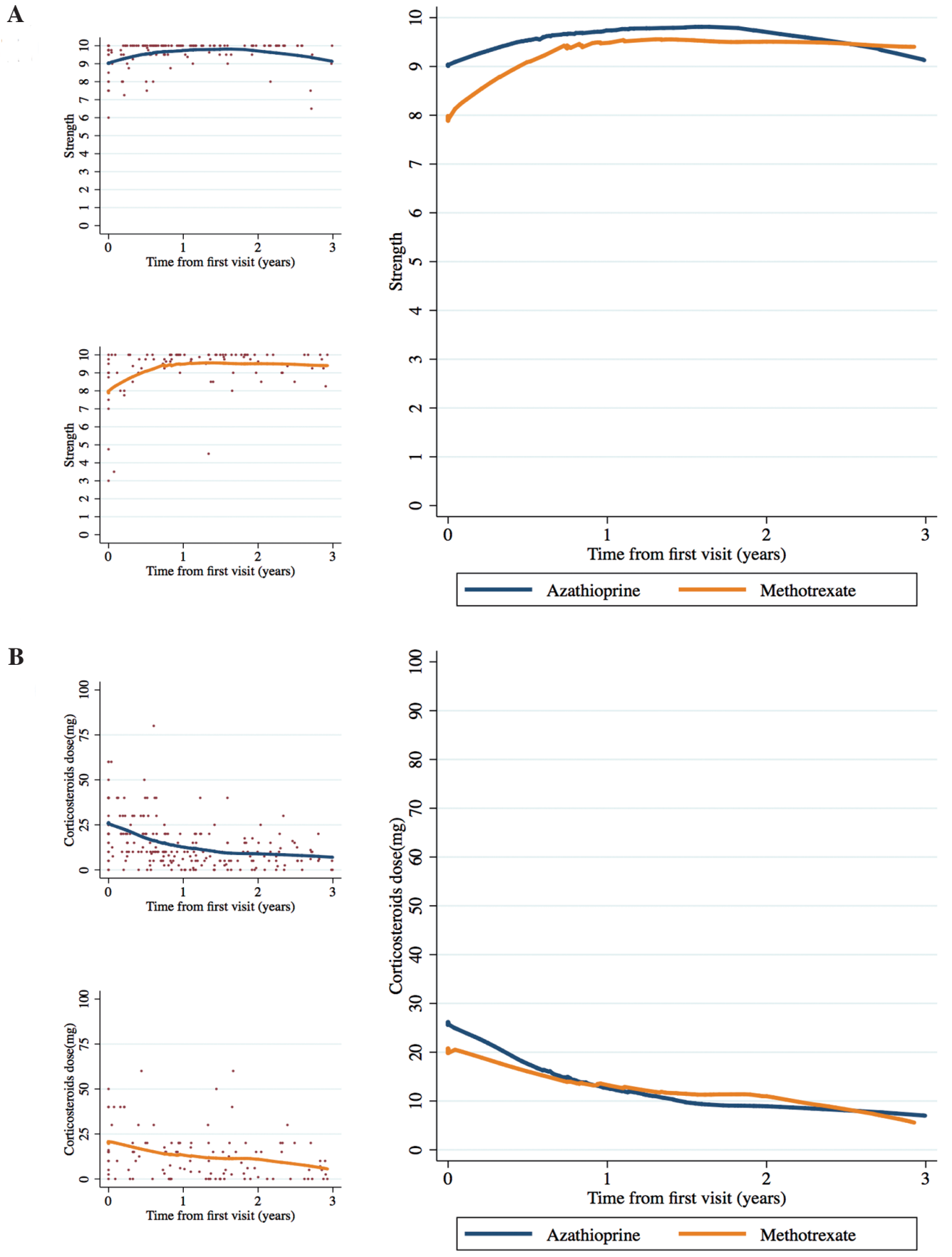

Fig. 1. Strength recovery (**A**) and corticosteroid tapering (**B**) in patients with the antisynthetase syndrome treated with azathioprine and methotrexate.

used to compare the rate of change of strength, and corticosteroid tapering. There were no significant differences in the rate of muscle strength recovery (p=0.9), CK decrease (p=0.6) or corticosteroid tapering (p=0.9) during treatment with AZA or MTX (Fig. 1).

Discussion

This study demonstrated that MTX and AZA are comparable in terms of rate of muscle strength recovery, rate of corticosteroid tapering, and rate of CK decrease with similar rates of adverse events. We did identify two episodes of MTX pneumonitis which reversed with discontinuation of therapy.

MTX has been reported to cause pneumonitis in 4–8% of the patients exposed to this drug (16) and this may dissuade clinicians from prescribing MTX in patients with ASyS autoantibodies or pre-existing ILD (17). Our study confirms previous data regarding the low prevalence of MTX pneumonitis (4%).

Some authors have suggested an increased efficacy of MTX over AZA in selected groups of patients (13). Our study found that MTX was comparable to AZA in terms of efficacy in patients with the ASyS.

The data that we report is based on a cohort study followed longitudinally in the context of routine clinical care and not a clinical trial. The assignment of therapy to the individual patient was based on physician preference, thus, it is possible that some of the analyses were subject to unaccounted bias. Patients underwent PFTs and CT imaging as part of clinical care, therefore, we cannot comment on the appearance of some features such as ILD except as detected based on clinical symptoms and findings. Likewise, adverse events were both patient-reported and surveyed by the treating clinicians but not necessarily in a routine manner for all patients. Moreover, the small number of patients in each group precludes a cautious interpretation of our results.

In conclusion, in our real-world clinical experience, we found that compared with AZA, MTX had a similar prevalence of adverse effects and efficacy. MTX pneumonitis occurred in 4% of patients started on this medication, but was entirely reversible with stopping therapy, thus, attention to this potential adverse event is important with rapid discontinuation of therapy if symptoms occur.

Competing interests

S. Danoff has received grant/research support from Bristol-Meyers Squibb, Genentech/Roche and Boehringer-Inghelheim; L. Christopher-Stine has received royalties related to the licensure of anti-HMGCR antibody testing to Inova Diagnostics, and receives research support from CSL Behring and Novartis; the other co-authors have declared no competing interests.

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