Methotrexate treatment in patients with adult onset Still's disease—retrospective study of 13 Japanese cases

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Abstract

Objective—To evaluate methotrexate treatment in patients with active adult onset Still's disease (AOSD).

Methods—Methotrexate was initially given as a single weekly oral dose of 5 mg and adjusted individually afterwards in 13 patients with active AOSD. Symptoms and laboratory findings were investigated.

Results—Signs of AOSD activity disappeared (remission) in eight patients between 3 and 16 weeks after starting methotrexate. In these patients, significant improvements in C reactive protein, erythrocyte sedimentation rate, white blood count, and serum ferritin were observed at 8, 12, 14, and 16 weeks after starting methotrexate, respectively. In six of these eight patients, steroids or non-steroidal anti-inflammatory drugs could be reduced or discontinued. In four patients methotrexate was not effective despite 12 or 16 weeks of treatment, and one patient discontinued treatment after 2 weeks because of severe nausea. Five patients suffered from adverse reactions, including acute interstitial pneumonia (one patient) and liver toxicity (two patients). Five out of eight patients successfully treated with methotrexate were HLA-DR4 positive (four homozygotes), and all the unsuccessfully treated patients were DR2 positive.

Conclusions—Methotrexate is useful for controlling disease activity in AOSD, not only for refractory patients but also for patients who have never taken steroids or for those with steroid associated toxicity. However, serious adverse reactions can occur, as with rheumatoid arthritis. It is important to determine the critical factors, such as the immunogenetic background, that are associated with response to methotrexate treatment.

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Adult onset Still's disease (AOSD) is a systemic inflammatory disease characterised by a high spiking fever, evanescent rash, polyarthralgia, leucocytosis, and hyperferritinaemia. Following the first description by Bywaters in 1971,[1] increasing numbers of patients with AOSD have been described in reports published worldwide, with detailed accounts of clinical and laboratory features.[2][3]

The mainstay of treatment in AOSD has been aspirin, non-steroidal anti-inflammatory drugs (NSAID) or steroids, or combinations of these; however, these agents are not always useful because high dose or long term treatment sometimes induces toxicity. Methotrexate has become a mainstay of treatment for patients with rheumatoid arthritis, and reports have suggested that it is effective in refractory cases of AOSD.[4][5] In the present study, we report our experiences with methotrexate treatment in 13 Japanese patients with AOSD.

Methods

PATIENTS

Thirteen patients were studied. They were diagnosed at the rheumatology clinic in the Keio University Hospital as having active AOSD. Detailed profiles of our patients at the start of methotrexate treatment are shown in table 1. Mean (SD) age was 35.6 (13.2) years (range 17 to 64 years). All met the preliminary criteria for a classification of adult Still's disease proposed by Yamaguchi *et al*.[6] Briefly, five or more criteria were required for diagnosis, including two or more major criteria: fever (39°C or higher), arthralgia (lasting more than two weeks), typical rash, and leucocytosis with granulocytosis; minor criteria include sore throat, lymphadenopathy and/or splenomegaly, liver dysfunction, and negative rheumatoid factor/antinuclear antibodies. Infections, malignancies, and other rheumatic diseases were excluded. In addition, our patients had active disease defined by the presence of three or more of nine activity signs or symptoms specific for AOSD (spiking fever, arthralgia or arthritis, typical rash, leucocytosis, sore throat, lymphadenopathy or splenomegaly, hepatomegaly or liver dysfunction, pleuritis, pericarditis), without other cause.

After prednisolone (10-20 mg daily for two to five weeks) was found to be ineffective in seven patients and diclofenac sodium (75 mg daily for three to four weeks) in the remaining six, methotrexate treatment was begun.

DOSE OF METHOTREXATE OR OTHER DRUGS, AND CLINICAL ASSESSMENTS

Methotrexate was initially given as a single weekly oral dose of 5 mg. The dose was adjusted individually according to both disease activity and adverse reactions. Other immunosuppressive drugs such as azathioprine, cyclophosphamide, or cyclosporine A were not used before or during methotrexate treatment.

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Table 1   Profiles of 13 patients with adult onset Still's disease when methotrexate treatment was initiated

Patient	Sex/age	Disease duration (months)	Number of items of criteria[*]	Treatment before start of methotrexate (duration)	Number of active signs or symptoms[†]	Laboratory data before methotrexate treatment			
						Ferritin (ng ml⁻¹)	AST/ALT (IUl⁻¹)	RF/ANA	HLA-DR type
1	F/44	54	7	PSL 20 mg/d (2 weeks)	4	290	16/7	−/−	4/4
2	F/27	84	6	PSL 10 mg/d (4 weeks)	3	51	10/8	−/−	4/4
3	M/28	126	6	PSL 16 mg/d (2 weeks)	6	1025	17/24	−/−	2/2
4	F/21	66	7	DS 75 mg/d (3 weeks)	4	183	57/31	−/−	4/4
5	M/32	72	5	PSL 18 mg/d (2 weeks)	5	348	21/22	−/−	2/4
6	M/40	36	6	DS 75 mg/d (3 weeks)	4	3300	19/34	−/−	4/4
7	M/32	32	6	DS 75 mg/d (4 weeks)	3	68	20/30	−/−	2/2
8	M/46	8	5	DS 75 mg/d (4 weeks)	4	7500	141/89	−/+	2/9
9	F/22	24	5	DS 75 mg/d (4 weeks)	5	690	11/11	−/+	2/6
10	F/48	84	7	PSL 20 mg/d (4 weeks)	3	91	21/10	−/−	2/5
11	F/64	66	7	PSL 11 mg/d (5 weeks)	3	745	28/28	−/−	2/5
12	M/17	2	5	DS 75 mg/d (4 weeks)	4	860	31/51	−/−	2/8
13	F/42	148	7	PSL 10 mg/d (4 weeks)	4	14	9/9	−/−	4/9

[*]The number of items in preliminary criteria for a classification[6] at disease onset.
[†]The number of clinical findings associated with AOSD (spiking fever, arthralgia or arthritis, typical rash, leucocytosis, sore throat, lymphadenopathy or splenomegaly, hepatomegaly or liver dysfunction, pleuritis, pericarditis) which were present in our patients before methotrexate treatment.
WBC, white blood cell count; AST/ALT, aspartate aminotransferase/alanine aminotransferase; RF, rheumatoid factor; ANA, antinuclear antibodies; PSL, prednisolone; DS, diclofenac sodium.

Table 2   Results of methotrexate treatment in patients with adult onset Still's disease

Patient	Response	Duration to response or adverse reaction (weeks)	Maximum dose of methotrexate (mg/week)	Total dose of methotrexate (mg)	Adverse reactions	Dose of PSL (mg/d) or DS (mg/d)	
						Before MTX	After MTX
1	Remission	3	10	15		PSL 20	0
2	Remission	8	5	40		PSL10	10
3	Remission	8	20	120		PSL16	12.5
4	Remission	9	7.5	42.5		DS 75	DS 75
5	Remission	12	12.5	100		PSL18	8
6	Remission	12	7.5	90		DS 75	0
7	Remission	16	15	180		DS 75	0
8	Remission+AR	16	20	200	Moderate liver dysfunction	DS 75	0
9	Ineffective	12	7.5	75		DS 75	PSL pulse
10	Ineffective+AR	16	5	40	Nausea	PSL 20	PSL 30
11	Ineffective+AR	16	10	100	Mild liver dysfunction	PSL 11	PSL 15
12	Ineffective+AR	16	15	195	Acute interstitial pneumonia	DS 75	PSL pulse
13	AR	2	5	10	Severe nausea, appetite loss	PSL 10	PSL 15

AR, adverse reactions; PSL, prednisolone; DS, diclofenac sodium.

At each visit, activity signs or symptoms were sought. Complete absence of signs or symptoms of activity following methotrexate treatment was defined as a remission.

EVALUATION OF LABORATORY TESTS
In all patients, assessments of the erythrocyte sedimentation rate (ESR), white blood cell count (WBC), C reactive protein, serum ferritin, and aspartate aminotransferase/alanine aminotransferase (AST/ALT) in peripheral blood were performed before and at each visit (every two or four weeks) following methotrexate treatment. When methotrexate treatment was initiated, serum ferritin level increased in nine patients (69%) (normal range 16-288 ng ml⁻¹ in males and 2-140 ng ml⁻¹ in females) (table 1). Abnormal liver function test values were seen in three patients (Nos 4, 8, and 12). Because patients 8 and 12 had abnormal values of AST or ALT before the administration of diclofenac sodium, both were considered to have hepatic dysfunction associated with AOSD activity. Furthermore, although low titres of antinuclear antibodies were detected by indirect immunofluorescence in sera from two patients (Nos 8 and 9), disease specific autoantibodies such as anti-Sm, anti-DNA, or anti-La/SS-B could not be identified by enzyme linked immunosorbent assay or immunoprecipitation assay. Evidence of SLE or other connective tissue disease such as Raynaud phenomenon was also lacking. MHC class II (HLA-DR) typing was performed in all patients.

STATISTICAL ANALYSIS
The Student *t* test was used for comparisons of laboratory findings before and after administration of methotrexate.

Results
RESULTS OF METHOTREXATE TREATMENT
Remission was observed in eight patients (Nos 1-8) between 3 and 16 weeks [mean (SD): 10.1 (4.0) weeks] after the start of methotrexate treatment (table 2). Relatively high doses of methotrexate (20 mg weekly) were required for remission in patients 3 and 8, whereas in the other six patients remissions were obtained with 15 mg or less weekly of methotrexate. The total dose of methotrexate [mean (SD)] used until remission in eight patients was 98.4 (62.3) mg (range 15-200 mg). Four patients (Nos 9-12) had fever or other symptoms for up to 12-16 weeks after treatment began; all were considered non-responders.

Overall, five patients—including patient 8, who had a remission—had adverse reactions during methotrexate treatment. Because patients 10 and 13 had nausea immediately after taking methotrexate, they could not tolerate more than 5 mg weekly; indeed patient 13 could not continue to take methotrexate for more than two weeks. Two patients had liver toxicity. Although the disease activity of patient

8 had been well controlled and diclofenac sodium was already discontinued, moderate liver toxicity was observed (AST/ALT: 146/194) at the 14 week evaluation after the start of methotrexate treatment. Afterwards, a gradual normalisation of AST/ALT was obtained by a reduction of methotrexate dosage. In patient 11, who had not used NSAID, mild liver toxicity also developed (AST/ALT: 38/69). When the dose of methotrexate was reduced, ALT values returned to normal. Unexpectedly, patient 12 developed acute interstitial pneumonia after four months of methotrexate treatment (total dose of methotrexate: 195 mg). During the development of acute respiratory failure, his laboratory findings did not suggest continued AOSD activity. He recovered from acute respiratory failure following pulse treatment with methylprednisolone (1000 mg for three days). Adverse reactions in patients 10, 12, and 13 were not ameliorated despite administration of folic acid.

DOSE OF CONCOMITANT DRUGS
In three of four patients (Nos 1, 3, and 5) successfully treated with methotrexate together with prednisolone, the daily dose of prednisolone could be discontinued or reduced
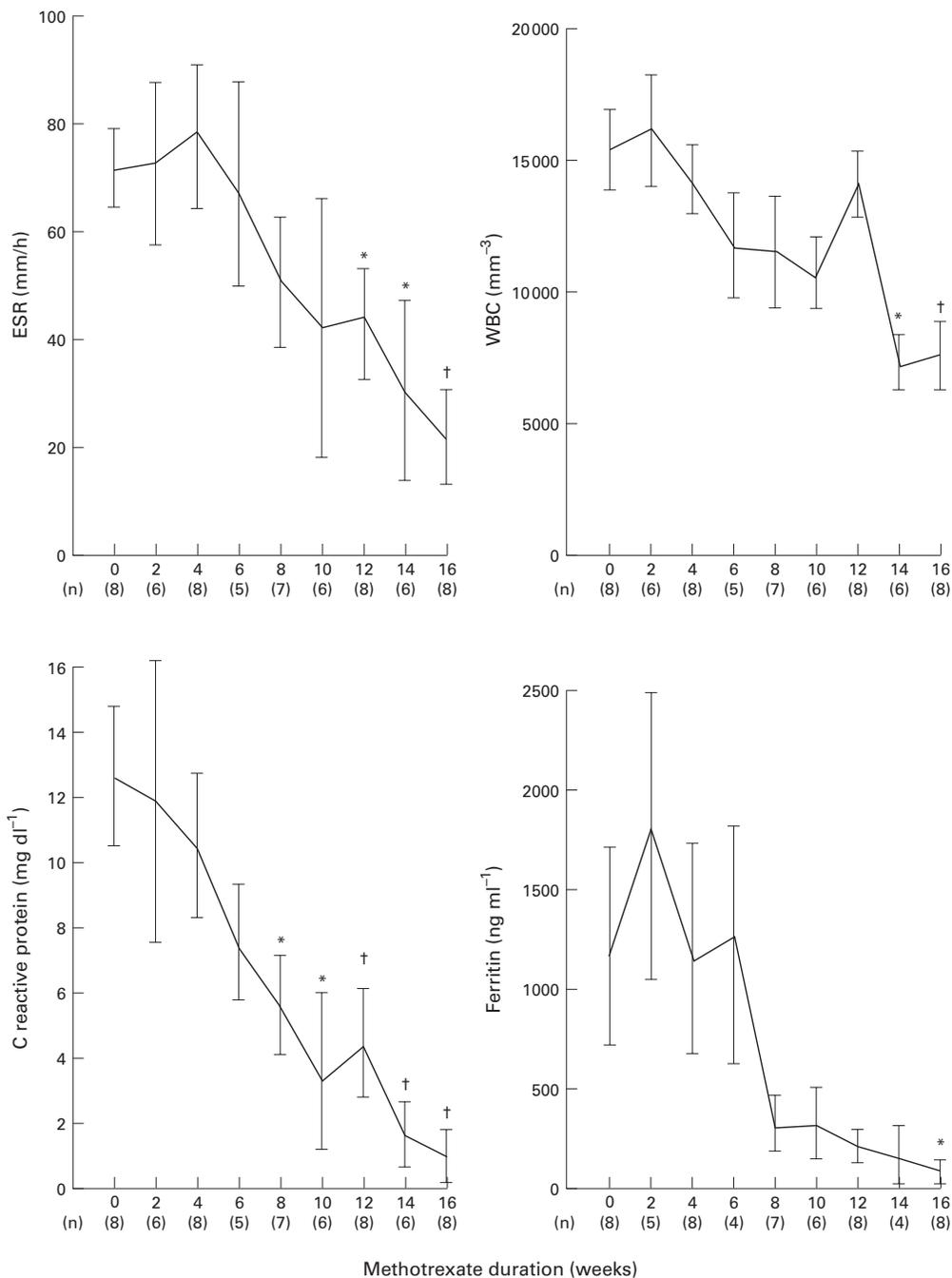
*Changes in laboratory findings in eight patients with AOSD who had remission following methotrexate treatment. Values are means (bars = SEM), and values at the start of methotrexate treatment are designated 0 weeks. The number of patients is shown in parentheses below methotrexate duration. ESR, erythrocyte sedimentation rate; WBC, white blood cell count. *P < 0.05; †P < 0.01, v the time of the methotrexate administration.*

following the introduction of methotrexate (table 2). Three other patients were able to discontinue diclofenac sodium following the introduction of methotrexate. In contrast, in patients 9 and 12 pulse treatment with methylprednisolone (1000 mg for three days) was required for severe pericarditis (associated with increased disease activity) and methotrexate induced pneumonia, respectively. Additionally, the doses of prednisolone were increased in three patients (Nos 10, 11, and 13) who failed to respond to methotrexate.

LABORATORY FINDINGS FOLLOWING
METHOTREXATE TREATMENT
Laboratory data in eight patients with remissions after methotrexate treatment are shown in the figure. Compared with baseline levels (week 0, at the start of methotrexate treatment), ESR was significantly decreased at 12 weeks, WBC at 14 weeks, C reactive protein at eight weeks, and serum ferritin at 16 weeks. Additionally, the means of WBC (normal range = 4000-8000 mm^{-3}) and serum ferritin (normal range 16-288 ng ml^{-1} in males and 2-140 ng ml^{-1} in females) decreased into the normal range at the 14 and 8 week observation points, respectively. ESR (< 20 mm/h) and C reactive protein (< 0.15 mg dl^{-1}) also decreased to the upper limit of normal range at the 16 week observation.

Discussion

We have examined the value of methotrexate treatment in Japanese patients with AOSD. Kraus *et al* [4] and Aydintug *et al* [5] discussed patients in whom conventional treatment failed but who were successfully treated with methotrexate, and suggested that the use of methotrexate should be considered in refractory patients. Our results are consistent with those reports. However, we suggest that methotrexate is useful not only for refractory patients but also for patients who have not previously been treated with conventional agents, such as steroids. In addition, methotrexate may be helpful for long term steroid users with adverse reactions (for example, diabetes mellitus, severe osteoporosis). Although it remains controversial whether methotrexate should become a first line treatment for patients with AOSD because of its side effects, it has the potential to control disease activity. Up to now, we have had experience with 26 patients with AOSD in our hospital. Besides the 13 patients in the present study, other antirheumatic drugs were used in five patients (auranofin in four, salazosulphapyridine in one), and azathioprine (100 mg daily) was used in another patient. Their disease activity was not suppressed successfully with these agents. The aim of our next study will be to determine whether methotrexate is of more value for patients with AOSD than other immunosuppressive agents.

Adverse reactions following methotrexate treatment were relatively common (five patients, 38.4%), included the unexpected development of acute interstitial pneumonia in one patient (No 12). The risk factors associated with methotrexate induced pneu-monitis that are found in patients with rheumatoid arthritis (smoking history or previous lung diseases[7]) were not present in this patient. In the context, it should be noted that relatively rare manifestation of AOSD include adult respiratory distress syndrome (ARDS)[8] and chronic restrictive pulmonary disorders.[9 10] Nonetheless, the pulmonary manifestation of patient No 12 seemed to be caused by methotrexate induced pneumonitis, since the laboratory findings were not consistent with the AOSD activity. Liver toxicity following methotrexate treatment was also observed. While it is well known that AOSD itself can induce liver dysfunction, we did not find any evidence that methotrexate treatment worsened pre-existing liver function abnormalities associated with AOSD activity. Overall, these experiences indicate that severe adverse reactions, as described in patients with rheumatoid arthritis following methotrexate administration, can also occur in patients with AOSD. Further studies will be necessary to determine whether pulmonary or liver toxicity is more frequent in patients with AOSD than in rheumatoid arthritis.

Interestingly, five out of eight patients successfully treated with methotrexate were HLA-DR4 positive (four were homozygous for DR4). This result suggests that AOSD with DR4 resembles rheumatoid arthritis, because the type of rheumatoid arthritis which frequently responds to methotrexate is closely associated with DR4. On the other hand, all the patients without remission had the DR2 gene. While it is not possible within the constraints of the present small study to identify associations between HLA-DR and response to methotrexate, the factors that indicate a likelihood for response to methotrexate should be clarified in future studies.

Although hyperferritinaemia is only seen in 60-75% of patients with AOSD, it can be a specific marker of disease activity.[11] It has been hypothesised that methotrexate may inhibit interleukin-1 (IL-1).[12 13] Rogers *et al* [14] have postulated that IL-1 in the acute phase response may modulate ferritin synthesis at the level of translation. In our cases, serum IL-1 concentration was not measured; therefore, the relation between methotrexate treatment and ferritin synthesis may warrant further investigation.

In conclusion, methotrexate appears to be a useful agent for controlling the activity of AOSD. However, serious adverse reactions following methotrexate treatment may occur, as described in rheumatoid arthritis. To establish methotrexate as a treatment mainstay, it will be important to determine whether adverse reactions are more frequent in patients with AOSD than in rheumatoid arthritis, and to investigate critical factors associated with methotrexate response.

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