
Use of methotrexate in adult-onset Still's disease

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ABSTRACT

Adult-onset Still's disease, a febrile, multisystem rheumatic disease, has variable outcomes. Some patients experience remission after a single or multiple inflammatory episodes, while others progress to a chronic course with substantial joint destruction. Although no controlled clinical trials with immunosuppressive agents in this disease have been reported, a number of small uncontrolled studies and case reports describe the use of methotrexate therapy. Methotrexate has shown efficacy for the control of systemic and articular symptoms and its favourable safety profile appears similar to that seen in other rheumatic diseases, when for this indication. The combination of methotrexate and corticosteroids has, over the years, become the first step in the standard of care in adult-onset Still's disease. If the response to this treatment is incomplete, additional therapies, such as biologic agents may be appropriate.

History, classification, and epidemiology

Since the initial description of the systemic form of juvenile idiopathic arthritis by Sir George Frederick Still in 1897, the condition has also been known as Still's disease (1). In 1971, the British rheumatologist Eric Bywaters described 14 cases with an illness, which resembled Still's disease but began in adulthood. Characteristic features were remitting fever, rash, polyarthritis, serositis, and elevated sedimentation rate, but there was an absence of rheumatoid or antinuclear factors. Since then, the term "adult-onset Still's disease" (AOSD) has been used to describe this condition.

Already, in the first report, Bywaters recognised the necessity to differentiate AOSD from other febrile diseases, such as sepsis, "subsepsis (Wissler's syndrome)", Muckle-Wells-syndrome, and familial Mediterranean fever.

Since then, various attempts have been made to classify this disease, of which the Yamaguchi criteria from 1992 are the most widely used (2-4). The annual incidence of AOSD is 0.4 per 100,000 adults, the prevalence appears to be slowly increasing and was 6.9 per 100,000 in Norway in the year 2000 (5). The disease can occur in all age groups; a peak incidence is between the age of 18 and 30 years.

Prognosis

In his first description Bywaters pointed out that "...the prognosis is good, function usually being maintained and the symptoms remitting, often for years." Only two of the initially described 14 patients progressed to a destructive form of arthritis (1). A literature review from 1987 summarised 228 cases of AOSD published since the initial paper and found that 31% of these had developed deforming arthritis, with wrist involvement being a characteristic feature (6) (Fig. 1).

Over the last 20 years, many cohorts of AOSD patients from countries all over the world have been characterised with regard to their clinical features and outcome (5, 7-15). Table I summarises these findings and shows that a fairly consistent proportion of about one third of all AOSD patients progresses towards an erosive, RA-like polyarthritis.

MTX therapy in AOSD

No controlled trials are reported for any drug therapy to investigate its efficacy and safety in AOSD. The only available data in the literature come from case series and retrospective analyses. Empirically, first line therapy in AOSD is based on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. As NSAID monotherapy is usually not sufficient to control the symptoms, most patients will receive prednisone during their disease course. The response of inflammatory symptoms to steroids is usually fast

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Fig. 1: Cystic lesions and erosions in the distal ulna, the os pisiforme and at the bases of metacarpals II-V in a patient with an erosive form of AOSD.

prednisone therapy and they reported an excellent response of the systemic symptoms (21). Aydintug *et al.* treated 6 AOSD patients, who did not respond to or did not tolerate other therapies, with low dose weekly MTX for a mean follow-up period of 14 months (range 4–28 months). This led to a complete response in 3 patients, and a partial response in one. One patient did not respond and one had to discontinue therapy because of flares after each MTX administration (22).

In a multicentre study in France with 64 AOSD patients, corticosteroid therapy was required in 57 cases, 22 patients received an additional DMARD, 13 of them MTX (23). Eleven of those 13 thereafter were able to taper their steroid dose (23). In a later publication the same group of authors retrospectively analysed the effect of MTX as a second line drug in 26 patients, who were refractory to corticosteroids or required persistently high doses. The mean MTX dose was 11.5mg per week, average follow-up was 49 months (range 8–136 months). 23 patients (88%) exhibited a response to MTX, 18 of them (69%) achieved a complete remission. The overall prednisone could be reduced by 69% and 11 patients could stop steroid therapy altogether (24).

These data confirm similar observations by Fujii *et al.* in Japan, who treated 13 AOSD patients with persisting disease activity despite a prednisone therapy of 10–20 mg/d for several weeks. MTX therapy was started with 5mg/week and increased to a maximum of 20

and substantial. However, a prolonged therapy with 0.5 to 1mg/kg prednisone per day is frequently necessary and any attempt to taper the dose may lead to reactivation of the disease (16–18).

Therefore, a variety of disease-modifying antirheumatic drugs (DMARDs) have been used and examined for their steroid-sparing potential in AOSD, such as azathioprin, gold salts, hydroxychloroquine, and D-penicillamine (19). Other immunomodulatory treatments used successfully in individual

cases or small pilot studies include cyclophosphamide, cyclosporine, leflunomide, mycophenolate mofetil, and intravenous immunoglobulins (16–18). Sulfasalazine appears to be associated with a high frequency of side effects in AOSD and should be avoided (20).

The most extensive experience of all conventional DMARDs in AOSD is published for MTX. The first pilot study was described by Kraus and Alarcón-Segovia in 4 patients with persistent fever despite NSAID and

Table I. Prognosis and outcome in AOSD.

Year (reference)	1990 (7)	1991 (8)	1997 (9)	2006 (10)	2006 (5)	2006 (11)	2007 (12)	2008 (13)	2009 (14)	2009 (15)	
Country	Japan	France	Germany	Greece	Norway	Turkey	Kuwait	India	China	South Korea	Total
Patients	74*	62	10	11	13	75**	28	14	61	71	419
<i>Disease course</i>											
Remitting-monocyclic	18	21	6	9	6	20	4	4	27	30	145 34.7 %
Relapsing-polycyclic	30	15	2	2	3	16	16	6	18	9	11 27.9 %
Chronic-articular	26	22	1	0	3	39	8	3	10	23	135 32.2 %
Lethal	4 (of 90)*	4	1	0	1	ND	0	1	6	9	22 5.9 % (of 370)

*Only 74 of a total of 90 patients were classified with regard to their disease course.

**Only 75 of a total of 95 Patients were classified with regard to their disease course.

mg/week. Average final dose was 10.7 mg per week, the mean observation period until response or adverse effects was 11.2 months (range 2–16 months). Remission of clinical symptoms and marked reduction of inflammatory parameters was observed in eight of 13 patients, five of them could completely stop their prednisone therapy. Four patients did not respond and one had to discontinue MTX because of severe nausea (25).

In addition to these small case series, a number of case reports describe the efficacy of MTX therapy in AOSD in special clinical circumstances. In two cases of AOSD associated with myositis a suppression of disease activity was achieved with a combination of MTX and corticosteroids (26, 27). MTX therapy also showed efficacy when thrombocytopenia or a recalcitrant rash were the predominant clinical features (28, 29). And two cases of a 83 and a 76-year-old AOSD patients demonstrate that low dose (6 or 7.5 mg/week respectively) MTX can be used safely and effectively in this age group (30, 31). Therapy with MTX plus prednisone also has the potential to maintain disease remission after life-threatening AOSD complications such as alveolar haemorrhage or haemophagocytic syndrome had been brought under control with more aggressive therapy regimens (32–34).

Safety of MTX in AOSD

The favourable safety profile of low dose MTX therapy in AOSD appears similar to that in RA. Nonetheless, due to the highly inflammatory and systemic nature of AOSD and the difficulty to differentiate flares from infectious episodes, close clinical and laboratory monitoring is essential.

In the report by Fujii *et al.*, 5 of 13 patients experienced adverse events during MTX therapy, one developed acute interstitial pneumonitis, two each had nausea or reversible elevations of liver enzymes (25). An AOSD-induced pre-existing elevation of transaminases *per se* is not a contraindication for the initiation of MTX treatment, however, close follow-up is advised (18). In the study by Fautrel *et al.* one patient with

additional AA-amyloidosis died from renal failure and neutropenia. No further severe adverse events were reported among 26 patients (24).

Yet another publication describes two cases of fatal infectious complications, which occurred, when AOSD patients were treated with increasing doses of MTX and steroids, because their disease was not adequately controlled. One patient was diagnosed with *Legionella* pneumonitis on 40 mg MTX per week plus 20 mg/d of prednisone, the other developed multiple brain abscesses with *Nocardia asteroides* on 55 mg MTX per week and 34 mg prednisone/d (35).

A recent report describes the first case of a MTX-associated lymphoproliferative disorder in a patient with AOSD. After eight years of treatment with 10 mg MTX per week plus betamethasone, this patient developed a maxillary tumour. Histology revealed CD20, CD30, and CD79a positive atypical lymphoid cells positive for EBV-encoded small RNA. As in other cases of MTX-induced, EBV-positive lymphoproliferative disorders, the tumour regressed completely after termination of MTX therapy (36).

Combination therapies

As described before, MTX in AOSD is usually used together with corticosteroids. A treatment with MTX/DMARD combinations has been described sporadically (16). In more recent case reports, combination therapies of MTX plus biologics usually follow the same pattern: After an insufficient response to MTX and steroids a step-up strategy by adding infliximab, etanercept, adalimumab, anakinra, or tocilizumab usually leads to improvement or remission of systemic and/or articular symptoms (16, 37, 38). However, due to low numbers and a natural publication bias, no firm conclusions about efficacy or safety of combination therapies, which include MTX, can be drawn from these data.

Pathogenesis and rationale for the use of MTX

Although the initial use of MTX in AOSD has been empirically based mainly on the RA-like appearance of chronic articular disease courses (Fig. 1),

in retrospect there may also be a pathogenetic background to support this approach. Over the recent years, and with the knowledge about the effect of anakinra therapy in AOSD, it has become increasingly clear that interleukin-1 (IL-1) and IL-1-triggered events in the inflammatory cascade play a key role in the pathogenesis of AOSD (18, 39). The inhibitory effects of MTX on IL-1 production and activity described more than 15 years ago offers one possible explanation for the clinically observed efficacy of MTX therapy in AOSD (40–43).

Conclusion

Despite the absence of controlled trials the combination of MTX and low dose steroid has over the years become the standard of care in AOSD (39). Different treatment algorithms have been published and they all propose to start an adequate therapy with corticosteroids and MTX as the first steps after the diagnosis of AOSD (17, 18). Only when this strategy does not elicit the desired response additional measures such as adding a biological therapy are recommended.

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