
Use of methotrexate in ANCA-associated vasculitides

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ABSTRACT

Since the introduction of combined immunosuppressive therapy consisting of oral cyclophosphamide (CYC) and glucocorticosteroids (GC) in the 1970s, the outcome of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides has improved dramatically over the last decades. However, the long-term follow-up of patients treated with CYC plus GC has revealed a high treatment-related morbidity and mortality and a high proportion of patients suffering from relapses (up to 50%), requiring CYC and GC again. Methotrexate (MTX) can replace CYC for induction of remission in patients with a non life-threatening disease course of ANCA associated vasculitides ("early systemic"). Furthermore, MTX can be used as a maintenance medication after induction of remission with CYC (plus GC), provided there is a decent renal function with a GFR >50 ml/min. As with any maintenance regimen, we do not know exactly for how long to continue MTX maintenance therapy. When using MTX as remission induction or maintenance regimen a tight control of urinary sediment and kidney function is mandatory in order to detect a potential renal relapse or de novo manifestation.

Introduction

Systemic necrotising vasculitides associated with antineutrophil cytoplasmic antibodies (ANCA) affect typically small to medium, rarely large size blood vessels and include Wegeners granulomatosis (WG), microscopic polyangiitis (MPA) and Churg Strauss Syndrome (CSS). The incidence of this group of vasculitides amounts to about 10–12 cases per million inhabitants per year (1) with 8 new cases for WG. Since the introduction of combined immunosuppressive therapy with oral cyclophosphamide (CYC) and glucocorticosteroids (GC) in the 1970s, the outcome improved over the last dec-

ades dramatically, also because of more sophisticated diagnostic procedures and therapeutic options. The improved outcome may be related to an earlier diagnosis as a result of an increased awareness of WG. This thus leads to the diagnosis of less severe courses of disease, for example the diagnosis of WG in the "localised stage" (symptoms restricted to the upper and/or lower respiratory tract) or the "early systemic stage" (generalised course without immediately life – or organ threatening manifestations, e.g. without significant kidney involvement). Furthermore, the long-term follow-up of patients treated with CYC plus GC has revealed a high treatment related morbidity and mortality (MDS, haemorrhagic cystitis, carcinoma, infections, infertility etc.) (2, 3). On the other hand, a high proportion of the patients, e.g. with WG suffering from disease relapses (up to 50%) require CYC plus GC again. This fact led to the concept of either shortening the oral CYC-therapy (maximum 3–6 months) or replacement of the oral CYC therapy by the dose saving and less aggressive CYC-pulse protocol or complete avoidance CYC usage in disease stages without immediately organ – or life-threatening manifestations. Since the first report about the successful remission induction with Methotrexate (MTX) in WG 40 years ago (4), it took more than 30 years until the first randomised trial compared MTX with oral CYC for induction of remission in "early systemic ANCA associated vasculitides" (NORAM). The trial showed that MTX is not inferior to daily oral CYC for induction of remission in this subset of ANCA-associated vasculitides (5). A further field for the use of MTX is the maintenance of remission after induction of remission with CYC (plus GC). The following review reports the use of MTX in the treatment of ANCA-associated vasculitides as induction of remission therapy as well as a maintenance strategy. Most published

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data on MTX use in ANCA-associated vasculitides relate to WG. Only a small number of patients with MPA were enrolled in the NORAM study (n=6) and only a small number of patients with CSS (n=11) were treated with MTX (6) for induction of remission.

Induction of remission with methotrexate in patients with WG

Forty years ago Capizzi and Bertino (4) reported on the first evidence of an effect of MTX in WG on two patients with histologically proven WG with involvement of the ENT tract, including retrobulbar masses, lung, skin, kidney without impaired function and gall bladder combined with severe constitutional symptoms, *e.g.* fever and weight loss. They were successfully treated with MTX 50mg per week intravenously, in one case over 6 months, with a subsequent dose reduction to 15 and 25mg per week orally. Both patients remained in remission for several years. Two decades later the NIH published the first open-label study on successful treatment of 29 patients with not immediately life-threatening WG with MTX 20–25mg orally per week plus concomitant GC, starting with 1mg/kg BW (mean: 51mg/day), tapering after the first month (7). When remission occurred and was sustained for one year the MTX dosage was tapered by 2.5mg per month. Nineteen out of twenty-nine had previously received cytotoxic drugs (*e.g.* CYC) and were enrolled because of relapsing WG or persistent activity and/or adverse events from their previous cytotoxic drugs. Ten patients were enrolled at their initial presentation of WG that had failed to respond to GC and/or cotrimoxazole. The mean duration of disease at the start of MTX was 6.4 years (3 months to 25 years). At this time 27/29 had permanent morbidity from their disease or treatment. At the time of MTX initiation 12/29 patients (41%) showed an active urinary sediment, 6 of them with renal impairment with a serum creatinine of 1.5–2.8 mg/dl. Within a mean period of 14.5 months (range: 6–25 months) 22/29 patients (76%) responded to the treatment, complete remission was achieved in 20/29 patients (69%) and

13/20 patients could discontinue their GC therapy. Two patients in remission later relapsed, one of them with a RPGN. Side effects occurred in 9/29 patients, 2 of them experienced a MTX pneumonitis and 3 patients suffered from pneumocystis pneumonia, in two of them with fatal outcome. Three years later the same group described the extended report on 42 patients with non life-threatening WG (serum creatinine <2.5mg/dl) treated with the same NIH protocol and including 20 patients from the first NIH study (8). One third of these 42 patients were newly diagnosed, two thirds were treated because of a relapse. In this extended report, similarly to the first report, 30/42 (71%) achieved a complete remission over a median time of 4.2 months (range: 1–17 months). Eleven of these 30 patients later relapsed, (36%) after a median time of 29 months. All relapses occurred after the discontinuation of GC, 4 patients relapsed after stopping MTX, 7 patients while still receiving MTX. There was a high rate of serious side effects, pneumocystis pneumonia in 4 patients (in 2 patients with lethal outcome), further three patients developed a MTX pneumonitis. In 2000, Langford (9) published separately the outcome of those 21 patients from the latter cohort who presented with an active renal involvement (mean serum creatinine 1.4mg/dl, max. 2.5mg/dl) after an extended follow-up of a median of 76 months (range: 20–108). Overall 20/21 patients achieved renal remission (one patient died after 14 weeks from an opportunistic infection). Eleven out of 20 patients experienced a relapse. However, only two patients had a rise in their serum creatinine of >0.2mg/dl. In our own study from 1998, comprising 17 WG patients with systemic but not life- or organ threatening disease – we studied the efficacy of MTX 0.3mg/kg BW once weekly intravenously as induction of remission, in 11 patients for initial diagnosis of WG (10). In this study patients with a serum creatinine >150mmol/l were excluded. At the start of MTX, 15/17 patients received additional GC at a median dose of 10mg/d (range: 5–50). Ten out of seventeen patients (59%) responded to MTX, 6

of them reached a complete remission over a median time of 24.5 months. Two of the 10 responders experienced a minor relapse that could be overcome by transient increase of GC dosage. As opposed to Langford's study, we discovered a *de novo* renal manifestation in 5 of the 7 non-responders. We did not observe any serious side effects.

In a further study by Stone *et al.*, beginning in 1999 (11), 19 patients with only newly diagnosed but non life-threatening WG were treated with MTX (maximum 22.5mg per week) plus GC, starting with 40mg/d, tapering at the end of the second month to 20mg/d. Forty-seven percent of these patients had renal involvement but none had a serum creatinine >1.2mg/dl. Seventeen out of nineteen responded to the therapy (89%) and 14 (74%) achieved a complete remission. However, half of them experienced a relapse. Only one patient developed a renal impairment that required a CYC therapy. Side effects leading to the discontinuation of MTX (elevated liver function tests) occurred in only two patients. For the first time all patients received folic acid supplementation, half of the patients also received a pneumocystis jiroveci prophylaxis.

Subsequently more reports on cohorts of unselected WG patients were published, where 25% to 30% patients were treated in a stage-adapted manner with MTX induction of remission (12–14) in patients with non life-threatening course of disease.

The first randomised controlled study to compare MTX vs. oral CYC plus GC (NORAM) for the induction of remission by the EUVAS study group was published in 2005 (5). One hundred patients with newly diagnosed ANCA associated vasculitis (6 of them with MPA) with serum creatinine level <150mmol/l and without critical organ manifestations were enrolled. Fifty-one patients received MTX 20–25mg orally per week plus GC (starting with 1mg/kg BW/d, tapered to 15mg/d after 3 months and 7.5mg after 6 months), and 49 patients received oral CYC 2mg/kgBW per day and the same GC regimen for induction of remission. All drugs were discontinued after 12

Table I. Studies of methotrexate for induction of remission.

No. pts, (ref.)	Inclusion criteria	Renal involvement (%) Max. serum creatinine	Responders (%) Complete remission (%)	MTX-dose (weekly)	Concomitant GC at start of MTX
42 (7, 8, 9)	non life-threatening	50% 2.5mg/dl	71% 71%	20-25mg (orally)	GC 1mg/kg/d
17 (10)	non life-threatening	12% < 150mmol/l	59% 35%	20-25mg (i.v.)	GC 10mg/d
19 (11)	non-life threatening	47% < 1.2mg/dl	89% 74%	up to 22.5mg (orally)	GC 40mg/d
49 (5)	"early systemic"	27% < 150mmol/l	89.8%	20-25mg (orally)	GC 1mg/kg/d

months. Folic acid supplementation and pneumocystis jiroveci prophylaxis were optional. At six months, there were no differences in remission rates: 89.9% in the MTX-group vs. 93.5% in the CYC group. In the MTX-group the time to remission was significantly delayed among patients with more extended disease (measured by the Disease Extent Index, DEI > 10 vs. ≤10), $p=0.04$; or pulmonary involvement ($p=0.03$), but without differentiation between pulmonary infiltrates or nodules/cavities. The rate of severe side effects was not different between both groups.

All studies on the use of MTX for induction of remission in ANCA-associated vasculitides are summarised in Table I.

Induction of remission with Methotrexate in patients with Churg Strauss syndrome

There is only one report about the treatment of CSS with MTX for induction of remission (6). In this open-label study 11 patients with CSS without immediately critical organ involvement were treated with MTX (0.3mg/kg BW once a week intravenously), nine patients with initial disease manifestation and two patients with a relapse. The median GC dosage at the start of MTX was 10mg/d (range: 5–50). In these patients remission was achieved in 8/11 after a median time of 5 months (range: 2–9 months), a complete remission was seen in six of them. One patient suffered from MTX pneumonitis, two patients from upper airway infection and one patient of a urinary tract infection.

Methotrexate for maintenance of remission in patients with WG

Considering the high relapse rate in WG and the long-term toxicity associated with continued CYC treatment has prompted the search for less aggressive therapeutic alternatives since the 90s.

One of those concepts consisted of stopping the CYC containing induction of remission regimen rather early after 6–9 months, when remission is achieved, and continuing with a less aggressive regimen, that has proven its longer-term tolerability and safety in other fields such as rheumatoid arthritis or organ transplantation. The proof of concept study for this idea is the CYCAZAREM study (15) showing that azathioprine was not inferior to low-dose daily oral cyclophosphamide as remission maintenance treatment regarding relapse rates after 18 months from first presentation in patients with newly diagnosed AAV and renal involvement. Several studies have been undertaken to find out whether MTX could also be used as a remission maintenance drug. Already in 1996 we could observe (16) in an open-label study that the relapse rates in WG patients treated with MTX at 0.3mg/kgBW weekly alone ($n=22$) or in combination with low dose GC (median 3mg/d, $n=11$) as maintenance of remission therapy were 14% after a median of 16 months (range: 5–30), and 9% after a median period of 20 months (range: 4–34), respectively. Of note is that the median previous induction therapy with oral CYC was 27 and 22 months (up to 112 months), respectively. Side effects in this study were rare and resolved in 11 out of 12 patients

after adaptation of the MTX dose. In this study the MTX groups (without and with low-dose GC) were compared with a maintenance therapy with cotrimoxazole, also without ($n=24$) and with low-dose GC ($n=8$) in an uncontrolled fashion. In the latter two subgroups, the relapse rates were conspicuously higher with 48% and 100%. In a further study from the NIH 1999 Langford *et al.* (17) report on 31 WG patients who received MTX maintenance therapy for a median of 16 months (range: 4–49) after induction of remission with oral CYC (plus GC) was achieved, mostly after 3 months. The MTX dosage was 0.3mg/kgBW orally per week, however did not exceed 15mg a week at the start, being increased to up to 20–25mg per week thereafter. After a median of 13 months (range: 10–15 months) from remission only 5 patients (16%) had a relapse without having had concomitant GC at that time. Two patients had to stop MTX, because MTX pneumonitis was suspected. All patients had received pneumocystis prophylaxis with cotrimoxazole 3 times per week; no patient developed an opportunistic infection. The authors have found similar relapse rates when comparing with their own historical data of 60 patients who were continuously treated with daily oral CYC for at least one year after achieving remission. When extending the follow-up to 32 months the same group reported in 2003 (18) that 22/42 WG patients (52%) experienced a relapse using the same MTX regimen. In 16 of them signs of a glomerulonephritis were observed, in 6 of them as *de novo* manifestation, while four experienced an increase of their serum creatinine of >0.2mg/dl (maximum 0.4mg/dl). The median time from remission to relapse was 15 months (range: 5–60). At the time of relapse, GC had been ceased for a median time of 9 months in all patients. We could confirm (19) a comparable rate of relapses studying 71 patients from our centre using MTX as maintenance therapy (mean 22.5mg MTX weekly i.v. with an equivalent dose of folic acid after 24 hours) over a median follow up period of 25 months. Fifty-five of these 71 patients (77.5%) were

Table II. Studies of methotrexate for maintenance of remission in ANCA associated vasculitides.

No. pts, (ref.)	Follo- up (months) Median (range)	concomitant GC (at start of maintenance)	relapse (%)	renal relapse (% of relapses)
22 (16)	16 (5-30)	no	14%	n.i.
11 (16)	20 (4-34)	3mg/d	9%	n.i.
31 (17)	16 (4-49)	n.i.	16%	n.i.
42 (9)	32 (5-71)	n.i.	52%	73%
71 (19)	25 (1-71)	in 77.5%: 5.9mg/d	36.6%	61.5%
28 (20)	21 (1-24)	5mg/d	46.4%	31
63 (21)	mean 29 (+13)*	13.4mg/d (+ 3.8)	33.3%	n.i.

Exception of study (21) (MPA n=15) in all other studies only WG patients were included.

*MTX-therapy only for 12 months. n.i. no information.

on low dose GC (median: 5.9mg/d) at the start of MTX; 26 patients (36.6%) developed a relapse after a median of 19.4 months. Again, the majority of the patients (65.4%) had ceased their GC medication at the time of relapse, and 16 of the 26 patients with relapses had signs of renal activity with an increase of serum creatinine in 14 of them; one patient died in the course of RPGN. No serious adverse events occurred.

In a multicentre randomised controlled study to compare MTX with leflunomide for maintenance of remission in WG, 28 patients received MTX (20mg per week orally plus in the median GC 5mg/d) after induction of remission with CYC (20). Thirteen of the 28 MTX patients relapsed within six months; seven of them were classified as a major relapse requiring CYC again, 4 of them with glomerulonephritis and 2 with pulmonary haemorrhage. Compared to the leflunomide group (30mg/d) the incidence of major relapses under MTX was significantly higher ($p=0.037$) and led to premature termination of this study. However, the frequency of serious side effects was higher in the leflunomide group and led to the discontinuation (hypertension, peripheral neuropathy, leucopenia) in four patients, whereas no patient had to cease MTX because of drug side effects.

In 2008, the French vasculitis study group published a multicentre prospective open-label study to compare azathioprine (2mg/kgBW/d) with methotrexate (0.3mg BW up to 25mg weekly plus folic acid) over 12 months for remission maintenance in ANCA-associated vasculitides after induction of remission with CYC pulses (21). Each

group comprised 63 patients; in both groups 76% of the patients had WG while the other patients had MPA. The primary end-point of this study was to determine the safety of both drugs, the primary hypothesis was that MTX would be less toxic than azathioprine. After a mean study period of 29 months (± 13 months), there was no difference in the incidence of side effects. Patients with fewer than 250 CD4+ T-lymphocytes/ml received a pneumocystis prophylaxis with cotrimoxazole in the AZA-group, in the MTX group with pentamidine aerosol. Twenty-three out of sixty-three (36.5%) patients in the Azathioprine group and 21/63 patients (33.3%, n.s.) in the MTX group had a relapse, 73% of them experienced the relapse after discontinuation of the study drug after 12 months. In the MTX-group, two cases with a MTX pneumonitis occurred.

All studies with MTX for maintenance of remission in ANCA-associated vasculitides are summarised in Table II.

Discussion

Among conventional cytotoxics, CYC remains the treatment of choice in cases of ANCA associated vasculitides, preferably WG, with a severe course, comprising life or organ threatening disease manifestations or a seriously compromised renal function. However, MTX can replace CYC for induction of remission in patients with non life-threatening course of disease of ANCA associated vasculitides ("early systemic"), possibly less effective in patients with lung involvement and patients with a high Disease Extent Index, e.g. more than 5 organ systems (DEI >10).

If MTX has to be used with a high dose concomitant corticosteroid regimen for serious organ manifestations (e.g. glomerulonephritis with renal impairment and serum creatinine >2mg/dl) as in the first study from the NIH, a high rate of adverse events can be anticipated, all the more, if a prophylaxis against pneumocystis jiroveci is not performed (2, 8). From today's perspective and with the rheumatologists' long-standing experience with the treatment of rheumatoid arthritis with MTX, folic acid supplementation is generally recommended when using MTX. At any rate, when using MTX as remission induction regimen a tight control of urinary sediment and kidney function is mandatory in order to detect a potential renal relapse or *de novo* manifestation. The design of the optimal maintenance of remission regimen remains still a matter of debate. The relapse rate in WG patients amounts to twice that of MPA patients (15). However, apart from PR3-ANCA positivity and pulmonary involvement (22) no further predictors of a future relapse could be identified. Certainly, the course of the ANCA titer did not qualify as a predictor of a relapse in a recent subanalysis of a large placebo-controlled randomised therapeutic trial in WG patients in the US (23).

The question on the optimal duration of the MTX treatment for remission maintenance has also not yet been answered. As a secondary result of the NORAM study (5), an extraordinarily high relapse rate (69.5% in the MTX induction group and 46.5% in the CYC induction group) following complete termination of the immunosuppressive therapy after one year was observed until the end of follow-up at month 18. Thus, it must be concluded, that at least in WG patients that represented the vast majority of the NORAM patients, the maintenance therapy should be continued beyond 12 months, especially when induction of remission was achieved without CYC (24).

Concerning the differential indication of MTX and other equipotent immunosuppressives for maintenance of remission, concomitant diseases and especially renal function must be taken

into account. Azathioprine, MTX and leflunomide have proven to be of similar efficacy. However MTX should not be administered below a glomerular filtration rate of 50ml/min, in order to avoid drug accumulation and subsequent mucositis and/or cytopenia. Thus for grossly impaired renal function after induction of remission, azathioprine remains the drug of choice, in cases of intolerability leflunomide may be an alternative, provided new onset of or worsening of a pre-existent arterial hypertension presents a problem.

A current meta-analysis of recent large controlled trials showed (25) that the concomitant GC regimen may also influence the risk of relapse, in that the relapse rate was significantly higher in those patients who had a scheduled stop of the GC within the first 12 months of treatment (43%) as opposed to those who remained on low-dose GC beyond year one of treatment (14%). Trials that primarily evaluate different corticosteroid regimens do not exist to date.

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