Churg Strauss syndrome – Successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment

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ABSTRACT

Objective. *To examine the safety and efficacy of methotrexate (MTX) plus low-dose prednisolone for induction of remission in non life- or organ-threatening courses and for remission maintenance in Churg-Strauss syndrome (CSS).*

Methods. *In an open-label study 11 patients were treated with MTX for induction of remission at initial diagnosis and relapse. Twenty-five patients received MTX for maintenance of remission. Primary endpoints were the achievement of remission and the incidence of relapses, respectively. Doses of concomitant prednisolone (PRD) and side effects were secondary endpoints.*

Results. *Induction of remission was achieved in 8/11 patients with MTX/PRD. Median time to remission was 5 months (range 2 –9). Remission was maintained in 12 of 23 with available long-term follow-up (median 48 months). Eleven patients experienced 8 major and 3 minor relapses with a median time from remission to first relapse of 9 months. With MTX, the median cumulative PRD dose during the induction phase was 6.2 g. In the maintenance phase PRD could be reduced by 53% in responders. Apart from one case of MTX-induced pneumonitis, adverse events were confined to mild/moderate episodes of infection and leucopenia. No opportunistic infections occurred, neither did steroid-specific adverse events*

Conclusions. *MTX is safe and effective for the induction of remission in non-life-threatening CSS. It allows a considerable reduction of PRD and thus avoidance of PRD-related adverse events. However, the ability of MTX to prevent relapses in CSS appears limited. The identification of an optimal maintenance regimen and prognostic factors for treatment response requires trials with larger patient numbers.*

Introduction

Churg-Strauss syndrome was first described in 1951 as a disseminated vasculitis in patients with severe asthma, fever and hypereosinophilia (1). The clinical picture comprises allergic asthma, allergic rhinitis or polyposis nasi, preceding pulmonary infiltration, constitutional symptoms, palpable purpura of the skin, peripheral neuropathy, potentially life-threatening cardiac (rarely gastrointestinal or renal involvement), and arthralgias (2-4). Histologic characteristics are non-caseating extravascular granuloma, necrotizing vasculitis and tissue eosinophilia (1). Biochemical abnormalities encompass elevated serum IgE, hypereosinophilia, and a positive anti-neutrophil-cytoplasmatic autoantibody (ANCA) titer in 10% to 40% of the patients (5,6). Among the ANCA-associated vasculitides, CSS has the lowest incidence with 1 to 3.4 per million inhabitants per year in Western Europe (7,8). Thus, studying treatment regimens in CSS is difficult, as there are no larger patient cohorts including solely CSS that have been prospectively subjected to uniform and standardized treatment regimens.

Prednisolone (PRD) alone is considered to be effective to control the disease in most patients. However, in one series the long-term administration of 30-60 mg PRD/day over a median observation time of 24 months (range 6-140) was required to control the disease (9). Even doses of PRD above the Cushing threshold partly in conjunction with cytotoxic agents like azathioprine and cyclophosphamide (CYC) for the first year after treatment initiation (3) cannot reliably prevent relapses, which

still occur in 10-30% of patients (3,10, 11). Furthermore, deaths from uncontrollable disease despite high dose steroids with and without cytotoxics occur in up to 10% of patients with CSS (3, 11). Moreover, there is considerable morbidity from steroid-related adverse events with hypercortisolism, steroid-induced diabetes mellitus, osteoporotic fractures and avascular necrosis (3, 10, 11). Thus, the need for steroid-sparing agents in CSS is evident. CYC, the gold standard drug for induction of remissison in ANCA-associated vasculitis (12,13) should be confined to the induction of remission in disease courses with critical organ involvement because of its toxicity (12,14,15). In CSS there is only scarce experience with regimens for remission induction in less severe disease courses and especially for maintenance of remission (4). In Wegener's granulomatosis (WG) – a clinically and histopathologically related disorder – low-dose methotrexate (MTX) has proven safe and effective for the induction and maintenance of remission in patients with non-life-threatening manifestations and without renal involvement (16-21). Thus, its use in CSS seems reasonable. This study assesses the efficacy and safety of MTX for the induction and maintenance of remission in CSS.

Patients and methods

Patients

This study was performed as an open label, prospective, monocentric investigation. In the period between 1995 and January 2000 a total of 28 consecutive patients with CSS, fulfilling the CHC-definition (22) and ACR classification criteria (23) without immediately critical organ-threatening disease (e.g. pulmonary haemorrhage, perimyocarditis, coronaritis, CNS involvement, glomerulonephritis or mononeuritis multiplex) were included after written informed consent was obtained. Of these, 11 were treated with MTX for induction of remission (IR-group), 9 at the initial diagnosis and 2 after a relapse. Twenty-five patients were treated for maintenance of remission (MR-group), including the 8 in whom remission was successfully induced with MTX.

Treatment

In the IR group, MTX was administered at 0.3 mg/kg bodyweight (BW) i.v. once weekly, in accordance to the regimen used in WG (17). An equivalent dose of folinic acid was given on the day following MTX to avoid long-term toxicity (24). As all patients were pretreated with PRD at the study start, their individual PRD doses at that time were continued if possible. In cases of severe disease, represented by a BVAS ≥ 10 [the Birmingham Vasculitis Activity Score (25), in which a BVAS < 10 is predictive of a good outcome (11), and a Disease Extent Index (DEI) ≥ 6 (26)], PRD was increased to 1 mg/kg (BW) and gradually tapered as follows: reduction by 10 mg every 3 days until 20 mg/d, then by 2.5 mg every week until 5 mg/d, and thereafter by 1 mg/month, if clinically possible. In cases of worsening disease, manifested by a rise in the BVAS, PRD was increased to the last effective dosage and further reduction started 2 weeks later. Inhalative steroids were allowed as necessary for the treatment of asthmatic complains, such as topical nasal steroid for allergic rhinitis. The simultaneous use of other immunosuppressants was not allowed.

In the MR group, MTX therapy was initiated at a dose of 7.5 mg i.v. once weekly and increased by 2.5 mg steps to a weekly dose of 0.3 mg/kg BW i.v., provided there were no contraindications to dose escalation, e.g. leucopenia. An equivalent dose of folinic acid was given on the day following MTX. In patients already on MTX for the induction of remission, their current MTX dose was maintained after remission was achieved, until the complete cessation of concomitant PRD. If PRD had not been completely tapered off at the start of maintenance treatment, it was tapered by 2.5 mg every week until 5 mg, and thereafter by 1 mg/month. If a patient was off PRD and in complete remission after 6 months of MTX treatment for the maintenance of remission, the latter was tapered by 2.5 mg monthly and finally ceased.

Exclusion criteria for treatment with MTX were: chronic liver disease or alcohol abuse, renal insufficiency with a serum creatinine above 1.5 mg/dl at study start, bone marrow insufficiency (leucopenia < 4000/µl, hemoglobin < 10 g/dl, or thrombocytopenia < 100,000/µl), active infection and inadequate contraception.

Assessment of disease activity

Clinical and serological staging of disease activity was performed monthly at first in the IR group, and then every 3 months in both groups after the achievement of stable remission. This included an interdisciplinary clinical examination by a team consisting of an ENT specialist, an ophthalmologist, a neurologist, a dermatologist, and a cardiologist, plus a chest X-ray. Additionally, a CT scan of the chest and/or a cranial MRI (14) were performed, depending on the organ manifestations of the disease. These findings were compiled into the DEI (26) and the BVAS (25) for every patient at each visit. The Five Factor Score (FFS) for the prognosis was applied once prior to the induction of remission treatment (10). Laboratory parameters comprised ESR, CRP, blood counts with differential white cell counts, liver enzymes, serum creatinine and ANCA.

Complete remission was defined as the absence of pathologic findings in clinical, radiological and sero-immunological investigations, irrespective of the ANCA titer. Partial remission was defined as a partial improvement in the disease persisting for at least 3 months. The (re)-occurrence of clinical symptoms attributable to active CSS after complete or partial remission of at least 3 months was considered a relapse. Persisting asthma or an isolated rise in blood eosinophils had no influence on the remission or relapse allocation (3). ENT symptoms (e.g. polyposis nasi, sinusitis, anosmia) were included in the allocation to the remission or relapse groups, if there were signs of active disease (e.g., a new appearance or response to escalation of treatment). Major relapse was defined as life- or organ-threatening disease activity requiring an increase in PRD and cytotoxics or a switch to CYC or other immunomodulating substances [e.g. interferon-alpha (IFN-alpha)]. A minor relapse, denoted by a non-life-threaten-

ing flare of the vasculitis, was usually treated with a transient increase of the PRD and /or MTX dose.

Study endpoints

The primary endpoint in the IR group was the achievement of complete or partial remission; secondary endpoints were time until remission, dosage of concomitant PRD and side effects of MTX or PRD.

For the MR group, the primary endpoints were defined as the following: occurrence of the first relapse under MTX, or May 2004. Secondary endpoints were adverse effects and the dosage of PRD.

Statistical analysis

The Kolmogorov-Smirnov (27) Z test was used to analyze the distribution of the induction and maintenance samples. The Mann-Whitney U test was used to compare non-parametrically distributed values between 2 groups. The Wilcoxon rank test, Fisher's exact test and Student's t-test were applied, as appropriate. Values are given as medians and range. Statistical analysis was performed using SPSS for Windows, version 12.0 (SPSS, Chicago, IL).

Results

Induction of remission

Six of 11 patients achieved complete and 2/11 achieved partial remission after a median time of 5 (2-12) months. The patients with partial remission had residual disease activity in the following organ systems: persisting ENT involvement with anosmia (a new manifestation 2 months prior to the start of MTX) and polyposis nasi in one and arthalgia in the other patient. A time-to-remission longer than 3 months was only accepted in patients without immediate life- or organ-threatening manifestations. Three patients stopped MTX prior to the achievement of remission. Two were switched to CYC (after 6 and 12 months, respectively); one had persisting pulmonary infiltrates on CT scan, eosinophilic pneumonia in BAL, malaise and elevated temperatures, while the other exhibited new peripheral neuropathy. The other patient experienced MTX-induced pneumonitis and was subsequently treated with azathioprine.

Concomitant PRD could be tapered in responding patients from 10 mg/d at the study start (5 – 50 mg/d) to 6.25 mg/d (3 – 7.5 mg/d) at remission (p = 0.014, t-test). Cumulative PRD until remission was 1.7 g (0.8 – 4.1 g). The 8 responders were switched to the MTX maintenance protocol (MR group).

Maintenance of remission

Twenty-five patients were treated with MTX for maintenance of remission of CSS. Their baseline characteristics are summarized in Table I and described in detail in Table II. Two of them were lost to follow-up after 3 and 4 months, respectively and were not included in the analysis due to the short follow-up. The diagnosis of CSS was confirmed by histology in 16 and by coronary angiogram in 1 patient.

The induction of the remission regimen consisted of daily oral CYC in 11 patients, i.v. pulse CYC in 3, AZAin one, PRD in a further 2 (at daily doses of 25 and 40 mg PRD) and MTX in 8 (Table II). In these patients the initial BVAS had been higher compared to the patients who had already received MTX for the induction of remission, while the DEI and FFS were similar in both groups (Table IV). When the patients were switched from their induction regimen to MTX for maintenance of remission, 15 patients were in complete and 8 were in partial remission. Their median DEI was 2 (0 – 4) and the corresponding BVAS was 0 (0 – 8). The median observation period for the 23 evaluable patients was 48 months from the start of the maintenance regimen.

Out of these 23 patients, 11 (47.8%) experienced a relapse after a median time of 9 months (1 – 80 months) while on maintenance with MTX, 4 after partial [DEI 2 (2 – 4), BVAS 2 (1 – 8)], and 7 after complete remission. Eight relapses were classified as major, presenting as follows: 3 patients had new ECG changes suggestive of cardiac ischemia, 2 with elevated cardiac enzymes and one with progressive cardiac failure and an ejection fraction of 11%. Five patients showed pulmonary activity, 2 with infiltrations on chest x-ray, 2 with eosinophilic pneumonia in the bronchoalveolar lavage, and one with bronchial granuloma on CT scan, all with a correlating rise in their CRP and eosinophil counts. Three relapses were minor (one with ENT involvement, one with constitutional symptoms, and one with arthritis) (Fig. 2b, Table II). At the time of relapse, all patients were still on an MTX dose of 20 mg/week and a median PRD dose of 9 mg/day (4 - 20 mg). The PRD dose had been reduced in only 2 of of the patients since start of the maintenance treatment.

Five patients with a major relapse (3 with pulmonary and 2 with cardiac manifestations) were treated with an increase in the MTX and PRD dose. Another 2 were switched to IFN-alpha and an increased dose of PRD, while one received oral CYC and subsequently died from cardiac failure.

Table I. Baseline characteristics of 11 patients with Churg-Strauss syndrome (CSS) treated with methotrexate (MTX) for induction of remission (IR) and 23 evaluable patients treated for maintenance of remission (MR). Values are presented as medians and (range).

		IR n = 11	MR n = 23
Male/female	(no.)	4/7	10/13
Age at diagnosis	(yrs.)	42 (17–62)	40 (17–76)
Maximum DEI		11 (4-13)	11 (4-13)
Biopsy proven (+/-)	(no.)	7/4	16/7
ACR 1990 criteria / CHC 1992 definition	(no.)	11/11	23/23
ANCA(+/-)	(no.)	0/11	4/19
Time from onset disease to study start	(mos.)	2 (0-236)	13 (2-241)
DEI at start of study		7 (2-13)	2 (0–8)
BVAS at start of study		6 (3-11)	0 (0-8)
FFS at start of study		0 (0-1)	
Prednisolone at start of study	(mg/d)	10 (5-50)	8 (0–15)

Table II. Patients history, treatment and side effects.

Group	Patient No	Sex	Age	Organ involvement at start of induction	BVAS at start of induction	FFS at start of induction	Induction regimen	Time to remission	Cumulative PRD	Organ manifestations at remission	BVAS at remission	Maintenance regimen	Time to relapse	Cumulative PRD from remission to relapse	Organ manifestation at relapse	BVAS at relapse	Side effects
IR- Resp.-No Rel	1	f	31	LSPB	11	0	MTX	2	1.7	0	0	MTX					
IR- Resp.-No Rel	3	f	52	EEyASPGiB	9	0	MTX	7	0.8	0	0	MTX					upper resp. tract inf.
IR- Resp.-No Rel	4	f	40	L	5	1	MTX	7	4.1	0	0	MTX					upper resp. tract inf
IR- Resp.-No Rel	6	m	40	Gi	6	0	MTX	3	0.8	0	0	MTX					
IR - Resp. - Rel.	7	f	17	L	4	0	MTX	5	2.7	0	0	MTX	9	1.2	H	6	
IR - Resp. - Rel	2	f	27	ELHGHB	11	1	MTX	3	1.7	0	0	MTX	90	12.0	L,E	8	
IR - Resp. - Rel	5	f	43	EByHB	5	1	MTX	4	1.5	E	2	MTX	29	5.8	H	4	cystitis
IR - Resp. - Rel	8	m	58	ELAPGHB	9	0	MTX	9	2.9	A	2	MTX	16	3.6	A	1	
IR – Non-Resp	9	m	46	LASB	11	0	MTX										
IR – Non-Resp	10	m	62	P	6	0	MTX										
IR – side effect	11	f	42	P	6	1	MTX										
MR – No Rel.	12	f	76	ELKASP	24	0	oCYC	98	15.3	0	0	MTX					upper resp. tract inf
MR – No Rel.	13	m	44	LH	10	1	oCYC	8	1.7	0	0	MTX					upper resp. tract inf
MR – No Rel.	14	m	49	ELAP	10	0	oCYC	8	1.9	E	4	MTX					leucopenia,
MR – No Rel.	15	m	39	ELASHPGHB	29	1	oCYC	2	4.7	P	6	MTX					
MR – No Rel.	16	m	60	ELP	10	0	ivCYC	11	6.8	P	2	MTX					upper resp. tract inf
MR – No Rel.	17	m	42	ELSPB	20	0	ivCYC	9	3.4	0	0	MTX					leucopenia, diarrhoea
MR – No Rel.	18	m	39	EPGHB	12	0	oCYC	12	4.2	0	0	MTX					
MR – Rel.	19	f	32	ELASP	19	1	oCYC	41	5.6	B	8	MTX	51	6.1	ELAB	7	
MR – Rel.	20	m	26	ELAHCB	19	1	oCYC	16	5.9	0	0	MTX	1	2.7	H	6	
MR – Rel.	21	f	33	ELASPGiB	15	1	oCYC	13	5.1	AP	1	MTX	9	1.7	L	4	
MR – Rel.	22	f	61	ELPCGHB	18	2	oCYC	13	5,6	0	0	MTX	6	1.4	L	4	
MR – Rel.	23	f	56	ELPB	13	0	oCYC	6	2,3	0	0	MTX	22	3,3	B	1	upper resp. tract inf
MR – Rel.	24	f	41	EL	6	0	ivCYC	10	2.5	0	0	MTX	10	1,5	L	8	upper resp. tract inf
MR – No Rel.	25	m	32	EEyLHB	12	1	PRD	7	3.5	L	1	MTX					upper resp. tract inf
MR – Rel.	26	f	20	EL	8	0	PRD	1	0.5	0	0	MTX	6	2.7	B	6	upper resp. tract inf
MR lost fol. up	27	f	43	ELSHGH		1	AZA			L		MTX					
MR lost fol. up	28	m	32	ELACB		1	oCYC			0		MTX					

IR–Resp.–No Rel: Induction treatment with MTX, responder, no relapse.
IR–Resp.–Rel: Induction treatment with MTX, responder, relapse.
IR–Non-Resp: Induction treatment with MTX, non-responder.
IR–side effect: Termination of MTX prior to remission due to side effect.
MR–No Rel.: Maintenance treatment with MTX, no relapse.
MR–Rel: Maintenance treatment with MTX, relapse.
MR lost fol. up: Maintenance treatment with MTX, lost to follow up.
BVAS: Birmingham Vasculitis Activity Score; FFS: Five Factor Score; MTX: methotrexate; oCYC: daily oral cyclophosphamide; ivCYC: pulse cyclophosphamide; PRD: corticosteroid monotherapy; AZA: azathioprine; upper resp. tract inf: upper respiratory tract infection; E: ENT involvement; L: pulmonary manifestation; K: kidney; EY: occular activity; A: musculo-skeletal activity; S: skin; H: cardiac involvement; P: peripheral neuropathy; C: central nervous symptoms; Gi: intestinal manifestation; B: constitutional symptoms.

The 3 patients with minor relapses were primarily treated with an increase in the PRD dosage. Since a subsequent dose reduction of PRD proved impossible in 2 patients, one was switched to IFN-alpha, and in the other the MTX dosage was increased from 15 to 20 mg/week. Concomitant PRD could be reduced in the 12 patients who remained in remission throughout the study, from 7.5 mg/d at the study start (3 – 12.5 mg/d) to 4 mg/d at the study end (0 – 14 mg/d) (p = 0.056); additional inhaled glucocorticoids were administered in 9 patients.
No demographic or disease variable (DEI, BVAS, FFS, eosinophil count) qualified as a predictor for the response to MTX therapy. Furthermore, within the MR group there was no statistically significant difference in demographic or disease variables between patients who experienced a relapse and those without (Table III).

Table III. Characteristics of patients without / with relapse under maintenance of remission with MTX. Values are given as the median and (range).

		No relapse	Relapse	p
Male/female	(no.)	8/4	2/9	0.025
Age at diagnosis	(yrs.)	41 (31-76)	33 (17-61)	0.38
FFS at start of induction	(0 / 1 / 2)	8 / 4 / 0	5 / 4 / 2	0.209
DEI at start of induction		6 (2-13)	7 (2-13)	0.710
DEI at start of maintenance		2 (0-4)	2 (0-4)	0.392
DEI at relapse			2 (1-7)	
BVAS at start of induction		10.5 (3-29)	11 (4-19)	0.829
BVAS at start of maintenance		0 (0-6)	0 (0-8)	0.913
Induction regimen (MTX/CYC)		4/8	4/7	0.881
PRD at start of maintenance	(mg/d)	7.5 (3-12.5)	5 (0-15)	0.572
PRD at relapse	(mg/d)		8 (5-20)	
MTX at relapse	(mg/week)		20 (15-25)	
Eosinophils at start of study	(per nl)	82 (20-246)	124 (12-760)	0.358
Eosinophils at relapse (n < 580)	(per nl)		643 (27-2490)	
ANCA(+/-)	(no.)	3/9	1/10	0.999

Adverse events
In the IR group, one case of MTX-induced pneumonitis with interstitial pneumonia, reduction of pulmonary CO diffusion capacity and elevated lymphocytes on bronchoalveolar lavage in the absence of other signs of increased disease activity or infection occurred. In the MR group 2 patients had to reduce their MTX dosage due to leucopenia (both after pre-treatment with oral CYC).
Three infectious episodes (2 in the upper respiratory tract system, and one urinary tract infection) in the IR group and 7 upper respiratory infections in the MR group, all of mild to moderate severity, required antibiotic treatment on an out-patient basis. In both treatment groups neither opportunistic infections nor PRD-related side effects such as osteoporotic fractures or diabetes were observed during the entire follow-up period.

Table IV. Characteristics of 23 patients on MTX maintenance treatment according to induction of remission regimen. Values are given as median and (ranges).

		Induction with MTX	Induction with other than MTX	p
Male/female	(no.)	2/6	8/7	0.294
Age at diagnosis	(yrs.)	40 (17-58)	41 (20-61)	0.591
BVAS at start of induction		6 (3-11)	12 (6-29)	0.002
DEI at start of induction		7 (2-13)	9 (2-15)	0.298
FFS at start of induction		0 (0-1)	1 (0-2)	0.798
BVAS at start of maintenance therapy		0 (0-2)	0 (0-8)	0.447
DEI at start of maintenance therapy		2 (0-4)	1 (0-2)	0.213
Number of relapses	(no.)	4	7	0.881
PRD at start of maintenance therapy	(mg/d)	6.25 (3-7.5)	8 (0-15)	0.190
PRD at relapse	(mg/d)	7.75 (5-20)	9 (5-20)	0.513
MTX at relapse	(mg/week)	21.25 (15-25)	20 (15-22.5)	0.570
Eosinophils at start of maintenance therapy	(per nl)	112 (11-377)	82 (12-760)	0.7
Eosinophils at relapse (normal < 580)	(/nl)	505 (78-809)	643 (27-2490)	0.513
ANCA+/-	(no.)	0/8	4/13	0.169

Discussion

In this study, combined treatment with MTX and PRD resulted in the successful induction of remission in 8 of 11 CSS patients (72%). The concomitant PRD dose could be reduced significantly during the induction phase. The remission rate obtained and median time to remission are in line with those in Wegener's granulomatosis (12, 16, 17).
Studying treatment regimens in CSS is limited by the low incidence of this disease. There are no studies available in which a larger cohort of CSS patients has been subjected prospectively to one uniform treatment protocol, nor are there randomized controlled trials which only included CSS patients. Patients with CSS have been included in several randomized controlled trials in France together with other, pathophysiologically different vasculitis entities, but the outcome analyses were not stratified according to diagnosis (11),
The remission rate achieved in our patients with MTX plus low-dose PRD was slightly lower than the findings in two previous studies. In a Spanish cohort of 32 patients using a variety of treatments including azathioprin in 2 and CYC in 17 patients a remission rate of 81% (10) was observed. A long-term follow-up of 96 French CSS patients revealed an overall remission rate of 91.5% (3), again applying different treatment protocols including azathioprine, cyclophosphamide and plasmapheresis, and all using high dose concomitant steroids above the Cushing

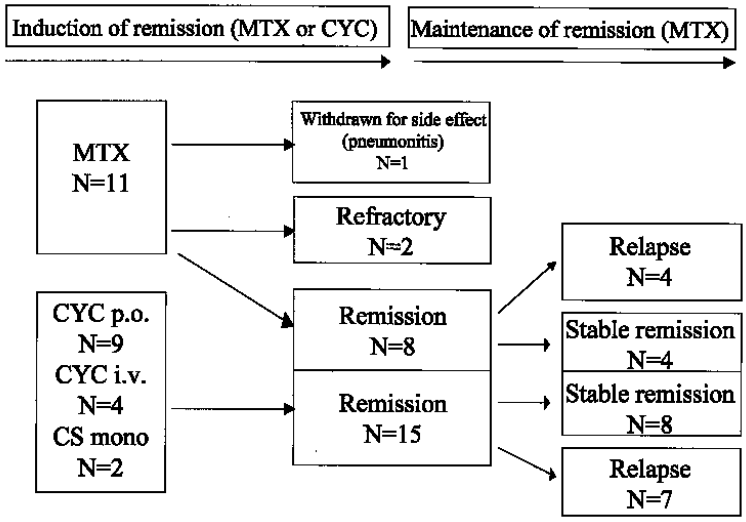
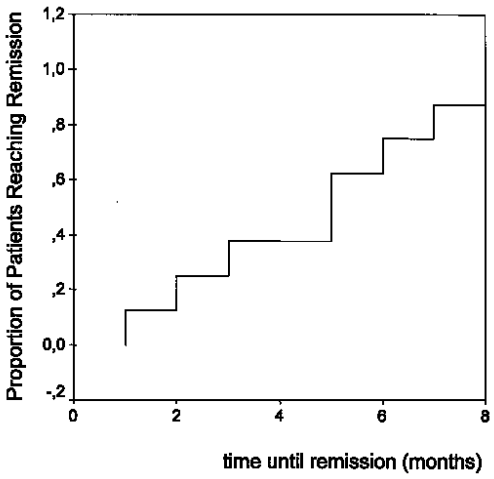


Fig. 1. Patient flow chart. For induction of remission, CSS patients received either MTX (for non organ- or life-threatening disease) or CYC (for organ- or life-threatening disease). All patients in remission from both groups then received MTX for maintenance of remission.

(**a**)



(**b**)

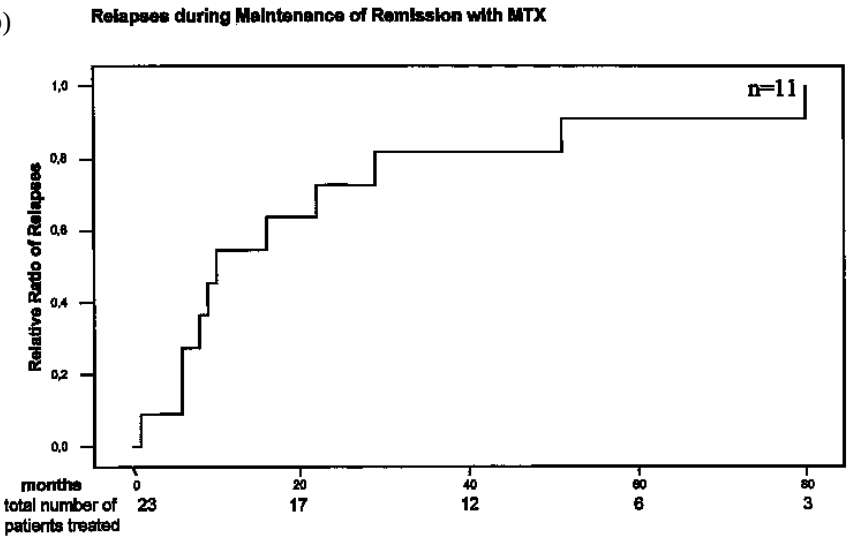


Fig. 2. (**a**) Proportion of responders to induction of remission with MTX; (**b**) Relapse ratio during maintenance of remission with MTX

threshold for more than 1 year.

Our regimen requires a considerably lower cumulative dose of PRD compared to the estimated dosage in the French protocols (median 2.8 g vs. estimated 11 g for a 70 kg patient for half a year) (11), and spared our patients severe steroid-related adverse events. In contrast, the Spanish protocol led to hypercortisolism in 25%, diabetes mellitus in 12.5%, osteoporotic fractures in 6.3% and avascular necrosis of the femoral head in 3.1% of the 32 treated patients (10).

Taking into account that patients with life- or organ-threatening disease were excluded in the present study, our results show that MTX constitutes a true therapeutic option for the induction of remission, with a substantially reduced concomitant PRD dose, in this particular patient cohort. Compared to the treatment of CSS with other drugs such as long-term high-dose PRD, daily oral or i.v. cyclophosphamide or IFN-alpha (28), MTX bears the advantages of being inexpensive and well tolerated.

When MTX was used for the maintenance of remission, nearly 50% of the patients experienced a relapse after a median time of 9 months. Due to the low incidence of CSS, comparable cohorts subjected to a uniform maintenance treatment regimen are not available. Relapses in our cohort were associated with a substantial number of critical cardiac and severe pulmonary manifestations with subsequent fatality in one patient. The French Vasculitis Study Group described 64 CSS patients within a group of 278 patients with different vasculitic disease entities (11). These patients were prospectively randomized to different treatment protocols at diagnosis of their active disease. After a median follow-up of 88 months in all patients, a relapse rate of 20.3% was found in the CSS subgroup irrespective of the treatment allocation. Mean time to relapse was comparable to our cohort (21 vs. 24.6 months).

In a larger cohort of French CSS patients (3), the mean time from remission to relapse was even longer (69 months). The severity of the relapses was not graded. Along this line, Solans found in his cohort of 32 CSS patients a

Table V. Clinical studies on treatment of CSS.

Author Year	Current data 2003	Lanham 1984
Number of patients BVAS	28 CSS No influence of initial BVAS on response/ non-response and relapse/non-relapse Initial BVAS at induction: 6 (3-11)	16 CSS Not applicable (not evaluated at time of study)
Follow up	21 months (1-60)	46 months (6-140)
Indication of treatment	Induction regimen: active, not life-threatening disease Maintenance regimen: successful partial or complete remission	PRD in all patients In case of non-response CYC/PE In case of relapse AZA/CAC
Induction regimen	MTX 0.3 mg/kg BWi.v./week + PRD 1 mg/kg BW	Induction and maintenance not distinguished
Cumulative prednisolone	6.2 g (2.8 – 21.9)	Not mentioned, initial PRD 30-60 mg/d
Maintenance regimen	MTX 7.5 mg iv. /week Increased to 0.3 mg/kg BW	Induction and maintenance regimen not separated
Endpoints	Induction: Achievement of remission Maintenance: First relapse, March 2002	Not defined
Definition of remission:	Complete remission: absence of pathologic findings Partial remission: partial improvement of the disease persisting for at least 3 months. Asthma or hypereosinophilia excluded.	Not defined
Remission rate	72%	15/16 (93.7%)
Relapse rate	47,8%	25%
Relapses	11 relapses in 11patients	6 relapses in 4 patients
Episodes of adverse events	Leucopenia: n=2	Not mentioned
Infections	n=11 (28%), not severe/life-threatening, no opportunistic infections	Not mentioned
Death	n=1, related to CSS	n=1, related to CSS

relapse rate of 28% (10) (Table V). In none of the above mentioned trials were patients placed on a specifically designed maintenance regimen, and in general there are no data available regarding immunosuppression at the time of their relapse. This makes the outcomes of the different trials not directly comparable.

However, most patients in the present study receiving MTX only for the maintenance of remission had severe disease with a high BVAS at the initial diagnosis (see Table IV), requiring CYC for induction of remission (12/23 patients). Thus, the more severe disease in this particular arm of the study is likely to have contributed to the higher

Guillevin 1999	Solans 2001	Gayraud 2001
96 CSS < or > 23 without prognostic value Initial BVAS: 22.1 ± 6.3	32 CSS Not calculated	64 CSS CSS: 22.1
Not mentioned 78-month survival ratio calculated	4 months to 17 years	88.3 months (3 days – 192 months)
Patients randomised and partly stratified for good and poor prognosis (Five Factor Score ≥ 2)	PRD in all patients Immunosuppression in severe organ involvement	Patients randomised and partly devided in good and poor prognosis (Five Factor Score ≥ 1)
Induction and maintenance not distinguished Different study arms with PRD, PE, oCYC, i.v.CYC and AZA,	No division between induction and maintenance regimens: All patients: PRD 1 mg/kgBW Severe organ involvement: 15 x oCYC 2 x ivCYC 2 x AZA	Induction and maintenance assessed separately. Different study arms with PRD, PE, oCYC, i.v.CYC and AZA,
Not mentioned, initial PRD 1 mg/kgBW, estimated 11g for a 70 kg patient	Not mentioned, initial PRD 1 mg/kgBW	Not mentioned, initial PRD 1 mg/kgBW, estimated 11g for a 70 kg patient
Induction and maintenance regimen not separated	Induction and maintenance regimen not separated	Induction and maintenance regimen not separated
Not defined	Not defined	Not defined
Clinical manifestations, except asthma and eosinophilia, no longer present for 6 months Neurological sequelae or mononeuritis multiplex may persist	Clinical manifestations, except asthma or neurological sequelae, no longer present for 6 months	Not defined
91.5%	81.3% after 14 months (median)	Not described
25.6%	28.1%	20.3%
28 relapses in 22 patients	14 relapses in 9 patients	13 after 24.6 months
n=50 Related to PRD: osteoporosis, psycologic disorders, cataract, diabetes, myopathy, Related to CYC: amenorrhea, cystitis, bladder cancer	n=16 Hypercorticism, PRD induced diabetes mellitus, PRD induced myopathy, osteoporosis with vertebral fracture, avascular necrosis of the femoral head, gastrointestinal haemorrhage, CYC-induced cystitis, colon neoplasm	Osteoporotic fractures in 8.6%
n=15 including 4 severe: 2 pneumonia, 2 septicemia	9.4% in all patients 1 PCP, 1 CMV	13.3%
n=23 11 related to CSS 4 related to treatment	n=4 3 related to CSS	20 in CSS 4 related to vasculitis

relapse rate compared to the above mentioned cohorts in which the percentage of patients requiring CYC for induction of remission was substantially lower [56.0% in this study, 53% in the Spanish cohort (10) and approximately 35% in the French cohort (3)]. A referral bias is a likely explanation for the more severe disease in our cohort, since our center is a nationwide tertiary referral center for vasculitis patients, while other studies recruited patients from large community-based and university hospitals.

The high relapse rate in our cohort with a rather short median time of 9 months from remission to relapse may indicate that steroid tapering took place too ra-

pidly and/or was introduced too early during the maintenance phase, despite concomitant cytotoxic treatment with MTX. Demasking of CSS disease activity by a reduction of anti-asthmatic drugs including PRD may contribute to an elevated relapse rate (4).

Regrettably, a reliable predictor for an elevated risk of relapse did not emerge from this study, most likely due to the small patient number. However, our patients were subjected to a 3- to 6-monthly standardized follow-up examination, including clinical, serological, immunological and specialist (ENT, neurologist, opthalmologist, dermatologist, cardiologist) examinations. Whether this had an impact on the number of diagnosed relapses needs to be elucidated. The incidence of at least minor relapses may therefore have been higher in our cohort than in others; however, these can then be treated immediately before they threaten critical organ functions. The fact that we had only one fatality due to uncontrolled disease activity may accord with this concept.

Our remission induction and maintenance regimen with MTX showed very few treatment-related adverse events, comprising one case of MTX-associated pneumopathy, a total of 10 airway or urinary tract infections and some epidsodes of cytopenia, the latter only in patients who were pre-treated with CYC. All of these adverse events were of mild or moderate severity. This is in contrast to the profile of side effects reported in immunosuppressive regimens other than MTX and low-dose PRD (3, 10, 11). Remarkably, we observed hardly any overt steroid-associated severe adverse events. This may represent a clear advantage of our protocol, as a large proportion of treatment side effects (3,10, 11) can be ascribed to the use of cyclophosphamide and high-dose PRD, which renders the long-term or repeated usage of both drugs difficult. The optimal concomitant steroid regimen for the treatment of CSS remains to be studied. The value of maintaining remission treatment must be assessed by weighing the potential damage from persistent immunosuppression including PRD against the potential damage accumulating from relapsing disease. This issue has not been addressed in CSS as yet.

In conclusion, MTX with concomitant low-dose PRD is a safe and successful regimen for induction of remission in non life-threatening CSS and has a significant steroid-sparing potential. For maintenance of remission, however, our MTX/PRD regimen was not convincing, despite its excellent long-term tolerability, due to the unsatisfactorily high relapse rate with critical organ manifestations. If MTX is used for maintenance of remission, close surveillance of the patients is mandatory and PRD should be tapered more slowly than in our protocol. Further work on maintenance regimens in CSS should include the identification of an optimal steroid regimen in conjunction with a well tolerated cytotoxic, and determination of potential predictors of relapse. In view of the low incidence of the disease, this should form the subject of a multi-center effort.

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