
Methotrexate plus leflunomide for the treatment of relapsing Wegener's granulomatosis. A retrospective uncontrolled study

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ABSTRACT

Objective. While remission is achieved in the majority of Wegener's granulomatosis (WG)-patients with cyclophosphamide, maintenance of remission remains a challenge due to the high rate of relapses. The purpose of this study was to evaluate the safety and efficacy of the combination of methotrexate (MTX) plus leflunomide (LEF) for the treatment of minor relapsing WG not warranting cyclophosphamide.

Methods. Retrospective chart analyses of 51 WG-patients with non-life-threatening relapses under MTX or LEF maintenance monotherapy. Relapsing patients were subsequently treated with a combination therapy of MTX+LEF.

Results. Fifty-one WG patients with relapses under MTX (n=36) or LEF (n=15) maintenance monotherapy were identified. They were subsequently treated with MTX+LEF to reintroduce remission. Mean follow-up was 26.0 (3–93) months. MTX+LEF controlled relapsing WG in 43/51 (84%) patients: 28/51 achieved a Birmingham Vasculitis activity index (BVAS)=0 and 15/51 a response (BVAS reduction of ≥50%). 8/51 patients did not respond to MTX+LEF (<50% BVAS reduction) and were switched to cyclophosphamide and/or a biological for ongoing disease activity. Follow up showed a sustained remission (BVAS=0 >3 months) in 14/51 patients, a minor relapse in 27/51, and a major relapse in 2/51 (subsequently switched to cyclophosphamide). Fifty adverse effects were observed. MTX+LEF therapy was discontinued in 18/51 patients because of adverse effects (main causes: gastro-intestinal complaints, hypertension, infections).

Conclusion. Although side effects limited the overall performance of MTX+LEF, this combination, if tolerated well, remains an effective treatment in patients not warranting cyclophosphamide.

Introduction

Wegener's granulomatosis (WG) is a chronic inflammatory and autoimmune disease of unknown etiology. WG may initially present with granulomatous inflammation of the upper and/or lower respiratory tract before generalised WG evolves, characterised by a necrotising small vessel vasculitis with multi organ involvement, e.g. pulmo-renal syndrome (1). Treatment with cyclophosphamide (CYC) and steroids induces remission in more than 90% of generalised WG-patients (2). Methotrexate (MTX) is an alternative to CYC for the induction of remission in early systemic WG (3). Despite immunosuppression for maintenance of remission with azathioprine, MTX or leflunomide (LEF), WG flares in more than 50% of the patients, resulting in inefficient control of disease activity (2, 4, 5). Repeated use of CYC may reintroduce remission in such situations, but is burdened with severe side-effects (e.g. myelodysplasia, hemorrhagic cystitis, bladder cancer) (6). Since combination therapy with MTX plus LEF has been shown to be efficacious in rheumatoid arthritis (7) we started to use MTX+LEF treatment in non-life threatening relapsing WG. Here we report our experiences.

Methods

The charts of 864 WG-patients from the Vasculitis Center University of Lübeck & Clinical Centre Bad Bramstedt between 1999–2008 were searched for a combination therapy with MTX+LEF. Diagnosis of WG was made according to ACR-classification criteria and Chapel Hill definitions for WG (8, 9). Medical history, previous immunosuppressants, glucocorticoid dosage, converted into prednisolone equivalents, serological parameters, adverse effects and disease activity (Birmingham Vasculitis Activity Score: BVAS) were analysed retrospectively for each visit (10). ANCA were determined by indi-

Competing interests: none declared.

rect-immunofluorescence technique, anti-PR3 specificity by ELISA, as described earlier (11). WG-subgroups and activity status were defined according to EUVAS and EULAR-recommendations (12). Remission is defined as the absence of any signs of active vasculitis with a dosage of prednisolone ≤ 7.5 mg/d. Response is defined as a BVAS-reduction $\geq 50\%$ and absence of new manifestations. Reoccurrence or new onset of potentially organ- or life-threatening disease is defined as major relapse requiring cyclophosphamide treatment. Reoccurrence or new onset of disease which is neither potentially organ- nor life-threatening is defined as minor relapse. Thus, a minor relapse warrants an intensification of treatment, but is not severe enough to be classified as major relapse. Furthermore low disease activity was defined as persistence of symptoms not warranting an escalation of therapy beyond a modest increase in the current medication (12).

Patients were followed up until combination therapy was stopped; otherwise end of follow-up was December 2008. All patients gave informed consent for the analysis of their data; the study protocol was approved by the local ethics committee.

All values are presented as mean values \pm SD. Statistical analysis was performed using SPSS 12.0 for windows. Differences were considered to be significant when p was < 0.05 .

Results

Patient characteristics

Out of 864 WG-patients, 51 were identified who received a combination therapy of MTX+LEF. Patient characteristics are summarised in Table I. C-ANCA with PR3-specificity were detected in 45/51 patients, P-ANCA with MPO-specificity was observed once, 5/51 patients remained ANCA negative. Minor relapses (e.g. worsening of ENT-symptoms, arthritis/arthralgia or constitutional symptoms) were the major indications for initiation of MTX+LEF-combination (Fig. 1). Single agent treatment with either MTX or LEF preceded MTX+LEF therapy in 36 respectively 15 patients (median dosage of MTX: 25 mg/week (15-30 mg/week), LEF:

Table I. Patient characteristics.

Characteristics	
Age (yrs, median, range)	55 (16-76)
male/female (n)	21/30
ANCA pos/neg. (n)	46/5
Biopsy proven (n)	40
Generalised (n)	41
Early systemic (n)	8
Localised (n)	2
Disease duration (month, median, range)	52 (0-290)
Cumulative cyclophosphamide (g, mean \pm SD)	62.8 \pm 76.6
Haemorrhagic cystitis (n)	8
Previous immunosuppressants (median, range)	2 (1-8)

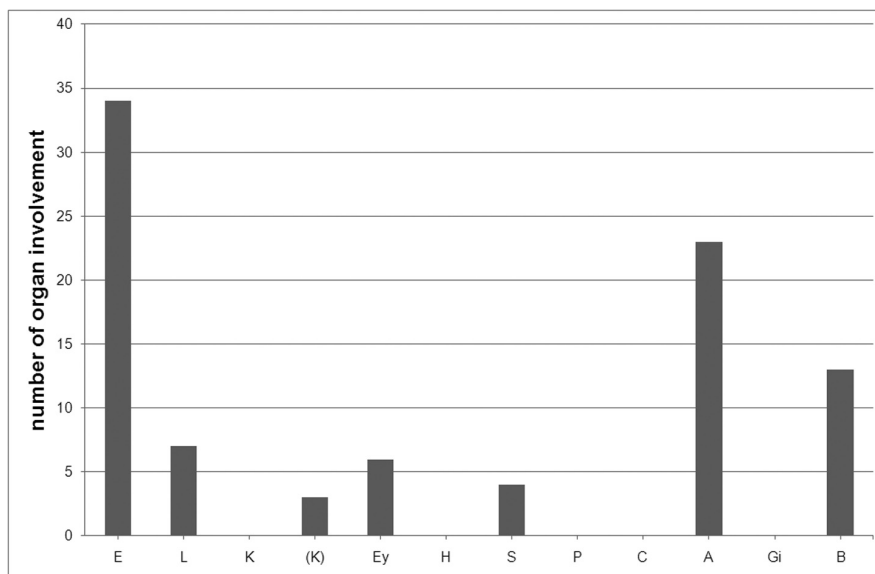


Fig. 1. Organ activity at initiation of combination therapy; E: ENT, L: lung, K: kidney with significant increment of creatinine, (K): kidney without sig. increment of creatinine, Ey: eye, H: heart, S: skin, P: peripheral nervous system, C: central nervous system, A: joints and musculature, GI: gastrointestinal-tract, B: constitutional symptoms.

30 mg/d (20-40 mg/d); mean duration of previous treatment: MTX: 23.3 \pm 28.3 months, LEF 26.5 \pm 26.9 months).

MTX was applied in the highest individually tolerated dosage not exceeding 0.3 mg/kg s.c. or i.v. weekly, followed by folid-acid in equal dosage 24 h after MTX at time of combination therapy and in cases of previous treatment. LEF was applied orally in a dosage of 10-40 mg/d without a loading dose in cases of former treatment or in cases of combination treatment. Dosages of prednisolone, MTX and LEF were adjusted to disease activity and tolerance. Mean dosages at the beginning of MTX+LEF combination were: prednisolone: 7.2 \pm 4.8 (0-25) mg/d; MTX: 18.9 \pm 6.8 (7.5-30) mg/week; LEF: 21.0 \pm 7.8 (10-40) mg/d. In six patients prednisolone was increased from

7.25 \pm 1.3 (5-9) mg/d to 11.5 \pm 7.4 (5-25) mg/d at time of initiation of MTX+LEF. Prednisolone was tapered according to disease activity.

Overall mean duration of follow up, as the equivalent duration of MTX+LEF combination therapy was 26.0 \pm 24.3 (3-93) months, the mean time interval between follow up visits was 6 months. Combination therapy was stopped, individually reduced either due to remission, significant reduction of steroid demand or adverse effects.

Outcome

- Adverse effects

In summary, 50 adverse effects in 31 patients during 110.42 patient-years were registered (Table II), mainly minor infections (n=12). Additionally, in one patient with progressive fever, a

Table II. Cumulative adverse effects (AE) during combination therapy; severe adverse events (SAE) are defined as death, AEs leading to hospitalisation or prolonged hospitalisation; (*) AEs likely unrelated to MTX+LEF.

Side effects	n.	AE	SAE
Hypertension	11	9	2
Bronchitis	5	5	0
Nausea	5	4	1
Diarrhoea	4	4	0
ASAT/ALAT>3x	3	1	2
Psychic	3	3	0
Neoplasia	2	0	2
Skin infection	2	1	1
Pneumonia	2	0	2
Wound healing disorder	2	1	1
Leukopenia	1	0	1
Erysipel	1	0	1
Allergic reaction (*)	1	1	0
Skin nodule	1	1	0
Conjunctivitis	1	1	0
MTX-pneumopathia (*)	1	0	1
CMV-reactivation	1	0	1
PJ-pneumonia	1	0	1
Letal myocardial infarction (*)	1	0	1
Bacterial sinusitis	1	1	0
Polyneuropathy (*)	1	1	0
Total	50	33	17

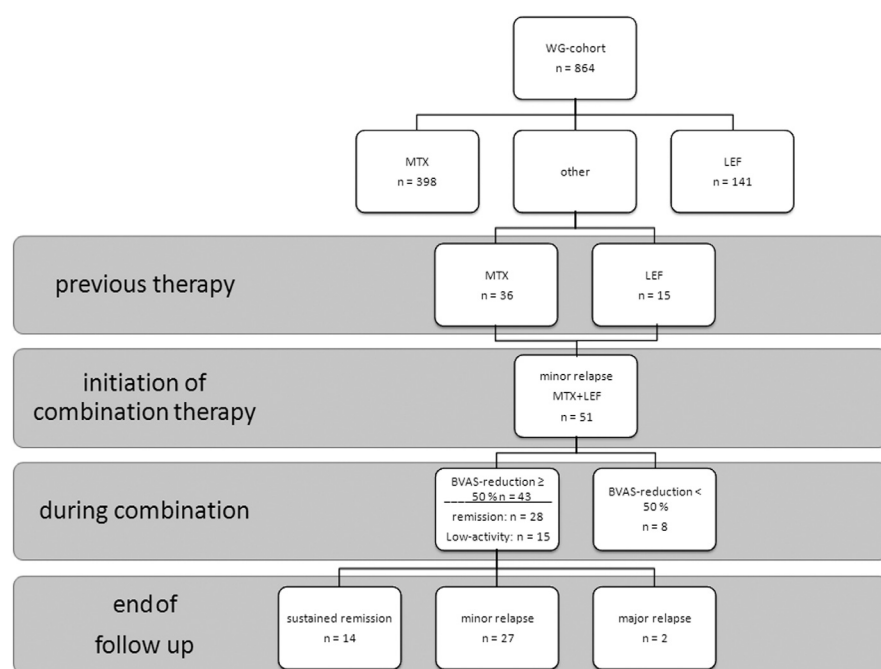


Fig. 2. Outcome of MTX+LEF combination therapy for minor relapsing WG; definitions according (12).

CMV-reactivation after 37 months of MTX+LEF was identified. Subsequent to treatment with Foscarnet, maintenance therapy was continued with MTX alone. One Pneumocystis jiroveci pneumonia leading to discontinuation of MTX+LEF and induction of cotrimoxazole-therapy was diagnosed after 5 months of MTX+LEF.

Hypertension, a known side effect of LEF (13), was observed in 11 cases (after 31.4±17.2 (5-60) months) leading to dose reduction of LEF (n=6), discontinuation of LEF (n=4) or intensification of antihypertensives (n=1). Nausea and diarrhoea either caused by MTX or LEF was observed in 9 patients leading to discontinuation of immunosuppres-

sion (n=5), deescalation to single agent treatment (n=4), or dose reduction of MTX or LEF (n=2).

Elevation of liver enzymes (ASAT/ALAT>3x norm) appeared in 3 patients (after 5.67±6.66 (0-13) months), successfully treated either by discontinuation of combination therapy (n=1), adjustment of dosage (n=1) or de-escalation to single agent treatment (n=1). MTX was stopped because of mild leucopenia (leucocytes: 3-4/nl) in one patient, afterwards leukocytes returned to formally known values.

One case of MTX-pneumopathia and hypertension likely unrelated to MTX+LEF caused a switch to azathioprine after 35 months.

LEF medication was stopped after 93 months in one patient due to polyneuropathy likely unrelated to LEF.

After 10 months of combination therapy a 75 year-old patient with several cardiovascular risk factors (hypertension, diabetes, hyperlipoproteinaemia) and manifest coronary artery disease died of myocardial infarction, not clearly related to MTX+LEF treatment, which had been well tolerated so far.

A myelodysplastic syndrome was diagnosed subsequent to 71 months of MTX+LEF; combination therapy was switches to mycophenolate. One case of oesophagus-carcinoma was diagnosed 21 months after initiation of MTX+LEF; LEF was stopped because of remission.

- Response

Fifty-one WG patients with relapses under MTX or LEF maintenance monotherapy were treated with MTX+LEF to reintroduce remission. MTX+LEF controlled relapsing WG in 43/51 (84%) patients: 27/51 achieved a remission (BVAS=0), in one patient active vasculitis was not present but prednisolone dosage yield 9 mg/d, and in 15/51 response (BVAS-reduction ≥50%) was achieved.

Follow-up showed a sustained remission (BVAS=0 >3 months) in 14/51 patients, a minor relapse in 27/51, and a major relapse in 2/51 (subsequently switched to cyclophosphamide).

In 8 patients, the combination of MTX+LEF was not effective (BVAS-reduction <50%) (Data summarised

in Fig. 2). Subsequently the immunosuppressive treatment was switched to cyclophosphamide and/or a biological after a mean follow up of 7.8 ± 7.5 (2-25) months.

At the end of follow-up, MTX+LEF therapy was continued in 17/51 patients (mean follow up: 32.7 ± 25.69). In the remaining 34 patients immunosuppressive treatment was modified because of remission in 8 patients, adverse effects in 15 patients, insufficient disease control in 8 patients and a combination of adverse effects and insufficient disease control in 3 patients (Fig. 3). De-escalation towards a single agent treatment with MTX (8 patients), or LEF (11 patients) was performed in 19 patients. In 15 patients MTX+LEF was switched towards mycophenolate, rituximab, cyclophosphamide-pulse, anti-TNF α , desoxyspergualine, azathioprine or cotrimoxazole.

- Cumulative analysis

Overall MTX+LEF resulted in a significant decrease of the BVAS (6.3 ± 2.5 to 2.9 ± 3.1), while the dosage of prednisolone kept stable (7.2 ± 4.8 vs. 6.7 ± 4.8 mg/d) (Fig. 4).

Discussion

Adverse events limit the usage of MTX+LEF combination, since we observed several adverse effects, mainly minor infections. However, combination therapy, if tolerated, seems to be efficient in minor relapsing WG despite MTX or LEF-monotherapy, resulting in an overall reduction of the BVAS, while stable dosage of prednisolone. In 43/51 patients MTX+LEF was efficient to control disease activity, and only 8 patients did not reach criteria for remission or response.

Gastrointestinal side effects, infections and arterial hypertension are known side effects of MTX and LEF (4, 13, 14). During follow up, 50 adverse effects were registered, mainly minor infections. One CMV-reactivation and one *Pneumocystis jiroveci* pneumonia were recorded. The number of infectious complications related to MTX+LEF treatment appeared to be higher in our WG cohort, compared to earlier studies in RA (7). This might be related to the

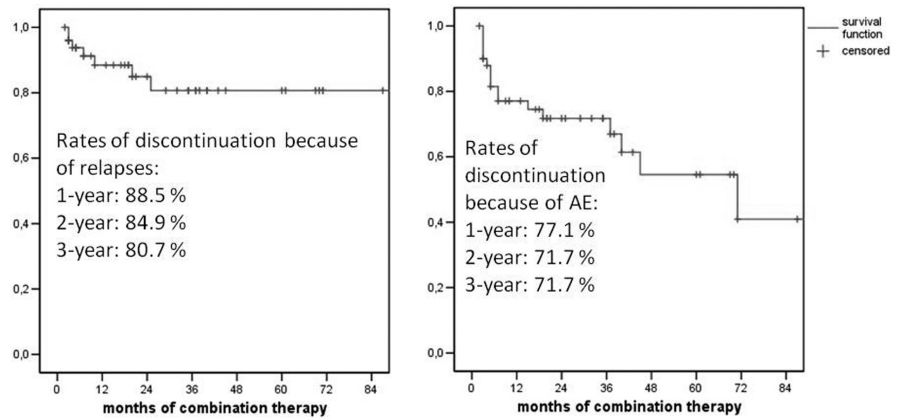
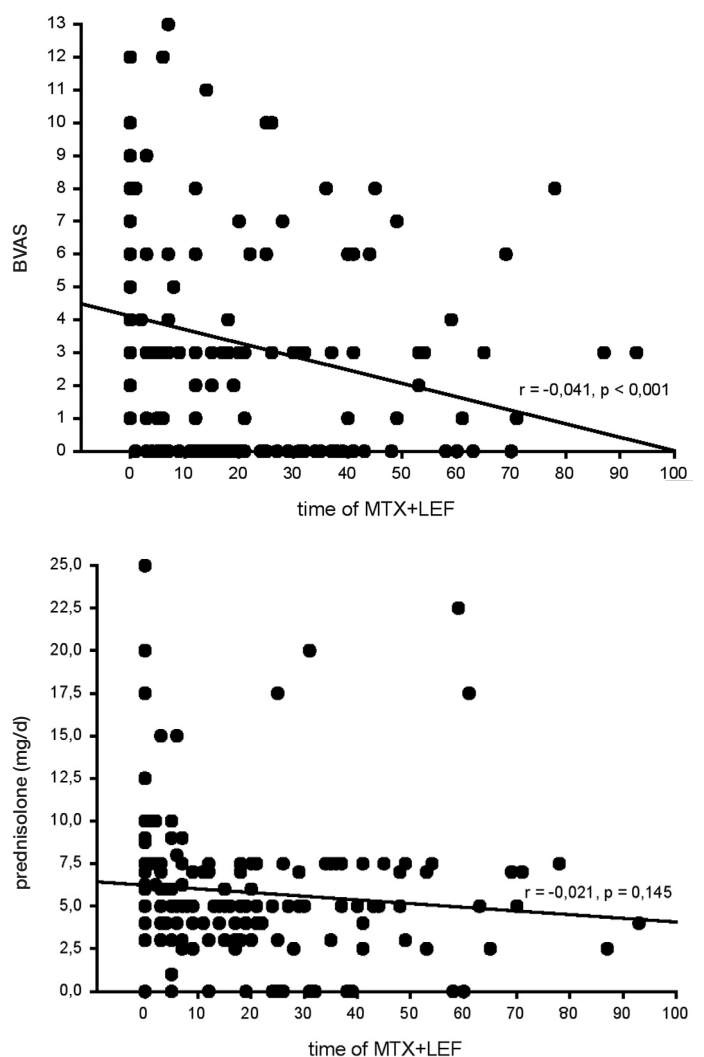


Fig. 3. Kaplan-Meier analysis regarding relapses and adverse events leading to discontinuation of combination therapy.

Fig. 4. Significant reduction of BVAS, while dosage of prednisolone kept stable (linear regression analysis).



extent of earlier immunosuppressive treatment (median 2 immunosuppressants), including the repeated use of cyclophosphamide with high cumulative dosages of 62.8 ± 76.6 g. Thus, WG patients might be more vulnerable to

airway infections, as mechanisms of local defence seem to be altered by WG itself (15).

Our analysis demonstrates that the combination of MTX+LEF is effective in minor relapsing WG, but is burdened

with several adverse events. Therefore combination therapy might be an alternative in patients with minor relapsing WG not warranting cyclophosphamide. Since this study was retrospective and uncontrolled, data concerning effectiveness and adverse effects are preliminary and must be specified by a controlled clinical trial.

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