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Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis

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Objectives. Results from open-label trials suggest that methotrexate (MTX) and leflunomide (LEF) are effective for maintenance of remission in Wegener's granulomatosis (WG), but data from randomized controlled clinical trails are not yet available.
Methods. In this multicentre, prospective randomized controlled clinical trial, patients with generalized WG were treated either with oral LEF 30 mg/day or oral MTX (starting with 7.5 mg/week reaching 20 mg/week after 8 weeks) for 2 yrs following induction of remission with cyclophosphamide. The primary endpoint was the incidence of relapses. Secondary outcome parameters were DEI, BVAS, SF-36, cANCA-titre, ESR and CRP.
Results. Fifty-four patients were included in the study, 26 in the LEF-limb, 28 in the MTX-limb. In the LEF-group, six patients relapsed after a median time of 7 months, thereof one major relapse with a new pulmonary manifestation. In the MTX-group, 13 relapses occurred in 6 months, of which seven were major: rapidly progressive glomerulonephritis ($n=4$), pulmonary haemorrhage ($n=2$) and one cerebral granuloma. The significantly higher incidence of major relapses in the MTX-limb ($P=0.037$) led to premature termination of the study. In the LEF-limb, four patients were withdrawn due to hypertension ($n=2$), peripheral neuropathy ($n=1$) and leucopenia ($n=1$).
Conclusion. LEF at a dosage of 30 mg/day appears to be effective in the prevention of major relapses in WG, however, this is associated with an increased frequency of adverse events. Further studies testing other dosing regimens of lower doses of LEF are needed to confirm these promising results in larger patients cohorts.

KEY WORDS: Wegener's granulomatosis, Remission, Relapse, Methotrexate, Leflunomide.

Introduction

During the last decade, different drug regimens have been designed in order to shorten the duration of cyclophosphamide (CYC) treatment in Wegener's granulomatosis (WG) and thereby to reduce cumulative CYC exposure. Nowadays, CYC is confined to the induction of a remission phase that rarely exceeds 6 months [1]. Thereafter, a less toxic remission maintenance regimen is applied for at least another year. For this purpose, Azathioprine (AZA) was evaluated *vs* CYC in a randomized controlled trial with a duration of 18 months. Interestingly, the relapse rates of for AZA (15.5%) and CYC (13.7%) were quite similar [2]. Relapse rates from open-label studies with methotrexate (MTX) are more variable ranging from 12.1% (4 out of 33 patients in 22 months) [3], to 16.1% (5 out of 31 patients in 13 months) [4] and 36.6% (26 out of 71 patients in 24 months) [5], respectively. The latter study included 15 patients (21.1%) relapsing with decreased renal function. A further study on MTX given for maintenance of remission in a cohort of 42 patients, reported 52.4% relapses during 32 months with glomerulonephritis occurring in 16 patients [6].

An alternative agent with similar immunosuppressive potency is leflunomide (LEF) [7] showing a more favourable profile of side effects as compared with conventional immunosuppressants [8]. Data from the pilot trial with LEF for maintenance of remission in WG revealed one major and eight minor relapses in 20 patients during an observation period of 24 months [7]. The present prospective randomized controlled multicentre trial was designed to evaluate the efficacy and safety of LEF for maintenance of remission in WG compared with MTX.

Methods

Study patients

Patients were recruited from five German rheumatological centres (Luebeck, Erlangen, Freiburg, Duesseldorf and Cuxhaven) all participating in the German Network for Rheumatic Diseases. The study had been approved by the local ethic committees, and all patients had given written informed consent.

Patients aged between 18 and 75 yrs with a diagnosis of generalized WG according to the ACR criteria [9] and CHC definition [10] were eligible for participation in the trial after successful induction therapy with oral CYC and prednisolone (PRD). Exclusion criteria were: bone marrow insufficiency (leucopenia $<4000\,\mu$l, haemoglobin <10 g/dl, or thrombocytopenia $<100.000\,\mu$l), serum creatinine >1.3 mg/dl ($115\,\mu$mol/l), malignancies, hepatitis B or C or HIV positivity, pregnancy or breast feeding, inadequate contraception, chronic liver disease or alcohol abuse, active gastric ulcer, lack of compliance, further coexisting autoimmune diseases or treatments interfering with the MTX/LEF medication.

Study design

This study was performed as a prospective, multicentre randomized controlled trial. All patients included in the study received the same standardized induction regimen with oral CYC [2 mg/kg body weight (BW)] and PRD for a period of 6 months. PRD was started with 1 mg/kg BW and tapered as follows: reduction of 10 mg every three days until 20 mg/day, followed by a 2.5 mg reduction weekly until 5 mg/day and thereafter 1 mg less per month. After successful induction of complete or stable partial remission, e.g. no change in disease activity for at least 3 months,

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patients were randomly assigned to treatment with MTX or LEF for a treatment period of two yrs. Partial remission was defined as partial improvement of the disease persisting for at least 3 months represented by a constant DEI and BVAS. Complete remission was defined as the absence of pathological findings in clinical, radiological and serological investigations, irrespective of the ANCA titre. Randomization was performed centrally (outside of all participating centres) with the use of permuted blocks of four.

Drug regimens

Patients in the MTX-group received 7.5 mg MTX/week orally during weeks 1–4, 15 mg MTX/week p.o. during weeks 5–8 and 20 mg MTX/week orally after week 8. Folic acid was applied at a dose of 10 mg on the day following MTX. This protocol was chosen in a consensus of the participating centres of the German Network for Rheumatic Diseases. It had been adapted from the EUVAS-protocol for induction of remission [11], reaching the target dose of MTX at week 9. The reduced starting dose of MTX during the first 8 weeks was chosen with respect to the preceding pre-treatment with CYC.

In agreement with study protocols in rheumatoid arthritis (RA), patients in the LEF-group were given a loading dose of 100 mg LEF/day orally for the first 3 days followed by 20 mg LEF/day p.o. between day 4 and week 4. Thereafter treatment was continued with 30 mg LEF daily. The 30 mg dose was adapted from the pilot trial, where this dose had been chosen in view of the severity of the disease. [7]

Concomitant PRD was allowed at a dose of 10 mg/day or below, and was tapered by 2.5 mg/month in absence of disease activity until 5 mg and by 1 mg/month thereafter. Calcium 1 g/day and vitamin D 1000 i.E./d were administered for the prevention of osteoporosis. Further immunosuppression was not allowed.

Evaluations

Clinical and serological staging of disease activity was performed at study entry—monthly for the first 3 months and every 3 months, thereafter. This included an interdisciplinary clinical examination by a rheumatologist, ENT-specialist and a chest X-ray for all patients. In addition, when clinically relevant, the patients were examined by an ophthalmologist and/or a neurologist. Additionally, a CT scan of the chest and/or a cranial MRI were performed, depending on the organ manifestations of the disease. These findings were compiled into the Disease Extent Index (DEI) [12] and the Birmingham Vasculitis Activity Index (BVAS) [13] for every patient at each visit. Laboratory parameters comprised ESR, CRP, blood counts with differential white cell count, liver enzymes, serum creatinine, cANCA-titre, glomerular filtration rate, quantitative proteinuria and urinary sediment. Thereafter these parameters were determined every two weeks for the first 3 months and monthly.

Efficacy outcomes

The primary efficacy outcome was the number of major and minor relapses. The (re)-occurrence of clinical symptoms attributable to active WG after complete or partial remission of at least 3 months was considered a relapse. A major relapse was defined as life- or organ-threatening disease activity requiring an increase in PRD and a switch to CYC. A minor relapse denoted a non-life-threatening flare, usually treated by a transient increase of the PRD and/or MTX/LEF dose. The relapse allocation was carried out by the local investigator.

Secondary outcome parameters were DEI, BVAS, patient self-assessment of quality of life (SF-36), cANCA-titre, ESR and CRP.

All data were collected in a case record book.

Statistical analysis

The study was designed in order to prove equivalence between two treatment regimens. In order to achieve this goal at a significance level of 0.05 and a power of 0.8, 145 patients were required. The effect of treatment on the time to the first relapse was examined by Kaplan–Meier Analysis. Categorical variables were analysed using the Student's *t*-test. Secondary outcome measures were the differences between start of maintenance treatment and study end with regard to the following parameters: DEI, BVAS, cANCA-titres, ESR and CRP which were analysed using the Student's *t*-test. A multi-factorial analysis for predictors of relapses or side effects at study entry was performed. Interim analyses were performed every 6 months.

Results

Patients

A total of 54 patients were included between August 2001 and September 2003. There was no significant difference between the two groups in demographic, clinical or laboratory features at the time of randomization (Table 1). Histological confirmation of the diagnosis was available for 36 patients, and 48 patients were cANCA/PR3-ANCA positive.

The study was terminated prematurely in September 2003 after the advisory board had decided that the high rate of major relapses in the MTX group was not acceptable.

Until study termination, median follow-up was 21 months (range 1–24). A total of 24 patients reached the scheduled time of 24 months on the study medication, 12 in each treatment group.

Withdrawals

In the MTX-limb, two patients were lost to follow-up. No patient had been withdrawn due to side effects. In the LEF-limb, six patients were withdrawn prematurely. In two of them, arterial hypertension worsened during LEF treatment and could not be controlled by conventional combination of antihypertensive medications after 15 and 12 months, respectively. One patient, who took 50 mg/day LEF accidentally for 6 months, developed peripheral neuropathy, potentially related to LEF. She received additional LEF prescribed by her general practitioner but failed to report this at the scheduled visits. One patient suffered from a newly diagnosed leiomyosarcoma 8 months after commencement of the study, in one patient, persisting leucopenia was the reason for withdrawal after 8 months and one patient was excluded due to a lack of compliance. (Fig. 1, Table 2)

Relapses

A total of 19 relapses occurred in the 54 patients during the follow-up of 21 months (median, range 1–24) with a median time from remission to relapse of 7 months (range 1–23). (Fig. 2). In the LEF-group, 6 out of 26 patients experienced a relapse, after 1, 3, 8, 15 and 23 months. Four of these flares occurred after complete, two, after partial remission. Included in these flares was one major relapse with a new pulmonary granuloma and infiltrations after 20 months. The other five relapses were minor, three with ENT granuloma and two with episcleritis. These patients were all treated with a transient increase in PRD and combination with MTX 15 mg/week parenterally in three cases.

In the MTX-group, 13 relapses were noted in 28 patients of which eight occurred after complete and, five after partial remission. Three of the 13 relapses appeared during the first 2 months of MTX-treatment with the reduced dose, the other 10 occurred after the final target dosage had been administered for at least 3 months. Seven relapses were classified as major: Four renal (all with nephritic sediment, and in three with an increase of serum creatinine), two pulmonary (both with new

TABLE 1. Characteristics at randomization of 54 patients with Wegener's granulomatosis, treated with leflunomide or methotrexate for maintenance of remission

Characteristics	Leflunomide-group $n=26$	Methotrexate-group $n=28$
Age (yrs) (median, range)	55 (27–76)	54 (25–67)
Sex (male/female)	16/10	16/12
ANCA (pos/neg)	23/3	25/3
Confirmatory biopsy (pos/neg)	18/8	18/10
Disease duration (months) (median, range)	8 (5–43)	9 (5–77)
Maximum DEI (median, range)	10 (3–11)	9 (5–14)
DEI (median, range)	0 (0–4)	0 (0–4)
BVAS		
(median, range)	0 (0–1)	0 (0–4)
[mean]	[2.6]	[2.9]
ANCA +/− [$P=0.14$]	15/11	21/7
Prednisolone (mg/day) (median, range)	5 (0–10)	5 (0–10)
ESR (mm/1st hour) (median, range)	20 (4–76)	18 (2–90)
CRP (mg/dl) (median, range)	0.5 (0.24–6.4)	0.5 (0.31–3.1)

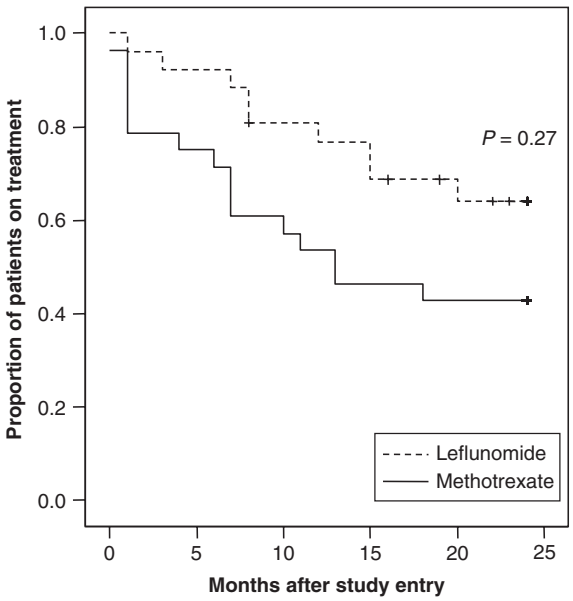

FIG. 1. Proportion of patients on treatment with methotrexate (MTX) or leflunomide (LEF).

infiltrates and haemoptysis) and one central nervous system manifestation in form of a cerebral granulomatous mass (Table 2). All major relapses required the reintroduction of CYC. The median time from remission to the major relapse was 6 six months (1–13) (Fig. 2). The minor relapses presented with the following manifestations: ENT-granulomata in three patients, and arthritis in one patient and constitutional symptoms in one patient. The total number of relapses tended to be higher in the MTX-group ($P=0.09$) while the incidence of major relapses was significantly higher in the MTX-group compared with the LEF-limb ($P=0.037$)

Concomitant PRD was ceased prior to a relapse in two patients in the MTX-group and in none of the LEF-patients, the median PRD at the time of major or minor relapse was 5 mg in both groups. Multivariate analysis revealed no factors predictive of disease flares or adverse events in both limbs. At study entry, cANCA was positive in 14/18 relapsing patients compared with 23/36 in relapse-free patients ($P=0.12$).

Adverse events

In 23 patients, a total of 51 adverse events were noted: 34 in the LEF-group and 17 in the MTX-group ($P=0.09$).

TABLE 2. Adverse events, withdrawals, infections and major relapses during treatment with methotrexate or leflunomide for Wegener's granulomatosis

($n=$)	Leflunomide group	Methotrexate group
Adverse events total	34	17
Severe side effects/ withdrawals	2 (hypertension) 1 (peripheral neuropathy) 1 (leucopenia) 1 (lack of compliance)	0
Infections	13	12
Major relapses	Pulmonary granuloma $n=1$	Renal involvement $n=4$ (3/4 with decrease of renal function) Pulmonary haemorrhage $n=2$ CNS-granuloma $n=1$

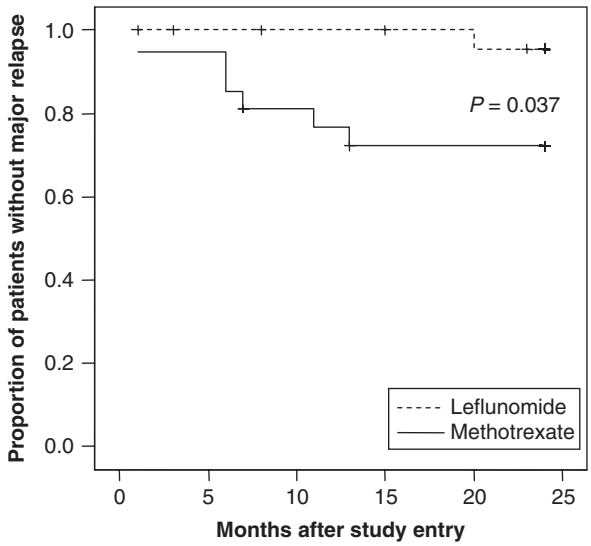

FIG. 2. Relapse Free Survival (major relapses) during treatment with methotrexate (MTX) or leflunomide (LEF).

Leucopenia occurred in two patients in the LEF-group, in the first patient with a transient leucocyte count of 3.600 μl and in the second patient with persisting leucopenia between 3000 and 2500 μl, with subsequent cessation of treatment. LEF was also terminated in the two patients with intractable hypertension and the patient with peripheral neuropathy, mentioned above. Mild gastrointestinal side effects were seen in three patients in each group. In the MTX-group one patient suffered from nausea that responded well to symptomatic treatment. Twenty-five infectious episodes, 13 in the LEF-group and 12 in the MTX-group were noted, all responding well to conventional antibiotic treatment on out-patient basis. (Table 3)

Assessment of disease extent and activity

At randomization, all patients were in complete ($n=30$) or partial remission ($n=24$), represented by a median DEI and BVAS in both study groups of zero (DEI 0–4 and BVAS 0–4). There was no significant difference between the treatment groups and within each treatment group between those patients who flared and those who did not flare. The ESR and CRP levels at corresponding time points were also nearly normal, although the ANCA-titre was still positive in most of the patients ($n=37$). Within each treatment group, there was no remarkable change in the median values of any of the scoring or laboratory parameters. Only those patients suffering from a relapse showed an increase in median DEI from baseline 0 (range 0–4) to 4 (range 2–14) in the LEF-group and to 3.5 (2–7) in the MTX-group. This was paralleled by a rise in BVAS from 0 (range 0–1) at baseline to

7.5 (range 5–9) in the LEF-group and from 0 (range 0–4) to 10.5 (range 1–24) at relapse in the MTX-group. In the LEF-group, the ANCA titre in the patient suffering the major relapse remained stable. In the MTX-group, five of the patients with major relapse showed a 1–4-fold increase of the ANCA-titre.

In both groups, concomitant PRD could be reduced in the patients remaining in remission from median 5 mg/day (range 0–10) to 0 mg/day (range 0–5).

Discussion

This study is the first prospective randomized controlled trial for comparison of MTX and LEF as remission maintenance treatments in WG. Overall, results from the present study confirm data from an earlier open-label pilot trial [7] and provide further evidence that LEF has the potential to maintain remission in WG. We found a total relapse rate of 26.5/100 patient years (major relapses: 14.3/100 patient years; renal relapses 8.1/100 patient years) in the MTX-limb compared with a total of 13.1 relapses/100 per patient-yrs in the LEF-limb with 2.05/100 major relapses and no renal relapses. In view of the unacceptable difference in the major relapse rate between both study groups in an interim-analysis, the external advisory and safety board involving international experts and a biostatistician recommended cessation of the study prematurely. The patients who were still on oral MTX after the early termination of the study were recommended to switch to parenteral application or to LEF immediately.

TABLE 3. Total number of adverse events during treatment with methotrexate or leflunomide for Wegener's granulomatosis (disease activity excluded in all cases)

Side effect:	Leflunomide	Methotrexate
Cold/fever	3/1	2/0
Cough/bronchitis	2/1	
Chronic obstructive pulmonary disease	1	4
Gastroenteritis/diarrhoea/abdominal pain	1/1/1	1/1/0
Urinary tract infection	1	2
Sinusitis	1	1
Pneumonia	1	
Herpes zoster	1	
Erysipel	1	
Lumbalgia/disc-protrusion	1/1	1/0
Arthralgia/myalgia	4/1	1/0
Oedema	1	1
Cardiac insufficiency	**1**	
Tachycardia	1	
Weakness/nausea	1/0	0/1
Dry skin	1	
Thrombophlebitis		1
Hypertension	**2**	
Leucopenia	2 (**1**)	
Cholecystectomy		1
Removal of osteosynthetic material	1	
Peripheral neuropathy	**1**	
Leiomyosarcoma	**1**	

Severe adverse events with cessation of treatment in bold.

Although well tolerated, MTX given for maintenance treatment in uncontrolled open-label trials was associated with a significant number of relapses, particularly in the kidney [5, 3]. In a previous study, we observed renal relapses in 16 out of 71 patients within 24 months of treatment with MTX at a dosage of 0.3 mg/kg BW given parenterally; and 15 of these renal flares were associated with a significant decrease in renal function [5]. In that study, the relapse ratio of 17.6 relapses/100 patient years for all types of relapses, 12.67 major/100 patient years ($n = 18$) and 10.68 for renal relapses was modestly lower compared to that of the MTX-limb in the present study. In a cohort treated at the NIH with MTX at 20–25 mg/week p.o., 22 out of 42 (52.%) patients relapsed during an extended follow-up and 16 of these 22 cases had active glomerulonephritis [4, 6]. Although the comparison of these previous studies is limited by differences in disease assessment and definitions for activity states, the incidence of renal flares was in a similar range of 10.62 relapses in 100 patient years [5] *vs* 14.28 relapses in 100 patient years [6]. Our experience with oral MTX is supported by recent data from the EUVAS group on the use of oral MTX for induction of remission in early systemic WG and MPA. Compared with CYC, remission was attained at similar rates but was delayed in the MTX group and the number of relapses was significantly higher in the MTX group during follow-up after complete cessation of all drugs [11].

The unexpected high relapse rate in the MTX-group in the present trial might be explained by potentially lower bioavailability of the oral application [14, 15] and the low starting dosage of 7.5 mg/week, which was progressively increased to 20 mg/week until week 8, which is possibly responsible for three early relapses that occurred during the first 2 months. In contrast, the full dosage of LEF with 30 mg/day was already reached after week 5. The 30 mg dose of LEF was chosen based on the experience gained from the pilot trial where this dose was used, and only one major relapse was observed in 20 patients within 24 months. Furthermore, in the aforementioned study, minor flares responded to an increase to 40 mg. In addition, pharmacokinetic studies have demonstrated plasma levels of LEF below the therapeutic level in some patients with an oral administration of 20 mg/day [16].

The relapse rates in LEF-treated patients in the present study, are comparable with the data from the open-label trial [7] and with relapse rates found in AZA-treated patients in the CYCAZAREM-trial (Table 4) [2]. However, the shorter follow-up of 18 months from first diagnosis and the inclusion of patients with microscopic polyangiitis that had a lower relapse rate in the latter trial and the small number of LEF-treated patients in the present trial, allow no definite conclusions on the comparative efficacy of both agents.

The disappointing results for MTX must be weighted against the low rate of side effects that had not led to any treatment withdrawal in the MTX-group. In contrast, in the LEF-group four patients were prematurely withdrawn due to hypertension ($n = 2$), leucopenia ($n = 1$) and peripheral neuropathy ($n = 1$). All adverse events were completely reversible after cessation of LEF. The mechanism of hypertension with LEF treatment is still

TABLE 4. Comparison of relapse-ratios (*n*/100 patient-yrs) for maintenance of remission treatments in Wegener's granulomatosis

Medication	Author	Observation time (months)	Total Relapses	Major Relapses	Minor Relapses
Azathioprine	Jayne [2003][a]	18	10.32	4.68	5,64
Methotrexate	De Groot [1996]	22	26.44	n.a.	n.a.
Methotrexate	Reinhold-Keller [2002]	24	17.6	12.67	10.68
Methotrexate	Langford [2003]	32	19.64	5.36	14.28
Leflunomide	Metzler [2004]	21	25.71	2.85	22.86
Leflunomide	This study	21	13.1	2.05	10.9
Methotrexate	This study	21	26.5	14.3	12.3

[a]including patients with Wegener's granulomatosis and microscopic polyangiitis.

unknown and seems to be independent of the renal function. Although the data quoted may suggest that the higher number of adverse events might be due to the higher 30 mg dose, dose escalating studies in patients with RA have shown that doses of up to 40 mg LEF were not associated with increased toxicity [17]. Unfortunately, a multi-factorial analysis could not identify significant predictors for relapses or side effects with MTX or LEF in this study.

In view of the good experience with MTX after parenteral application in RA [14, 15], we see further need for controlled studies using different protocols especially for MTX, since the premature stop of this study was possibly due to the low starting dose of MTX. Although a dose-dependent increase in side effects with LEF at doses up to 40 mg/day is not documented [17], the use of LEF in the standard dose of 20 mg/day should also be evaluated.

Although the relatively small number of patients due to the premature termination of this trial precludes definite conclusions on the relative potency of LEF compared to MTX, the data confirm the potential of LEF for the prevention of relapses in WG. Thus, further comparative studies of existing maintenance treatments including AZA, MTX, LEF and mycophenolate mofetil are warranted.

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