Safety and efficacy of leflunomide in the treatment of lupus nephritis refractory or intolerant to traditional immunosuppressive therapy: an open label trial

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We evaluated the safety and efficacy of leflunomide in patients with lupus nephritis in a prospective open label study. Nineteen consecutive patients who fulfilled the revised American College of Rheumatology criteria for systemic lupus erythematosus (SLE)¹ and with proteinuria ≥ 2 g/day were invited to participate. The patients were chosen because of previous treatment related toxicities (six patients with severe sepsis) or a contraindication to the use of cyclophosphamide (one patient newly diagnosed with lupus nephritis and cryptococcal meningitis) or lack of response to immunosuppressive treatments including cyclophosphamide (mean (SD) cumulative dose 9 (6) g), azathioprine or ciclosporin for at least 6 months with persistent proteinuria ≥ 2 g/day for at least 3 months (12 patients). Two patients were excluded because of increased liver enzymes (one patient) and refusal to give consent (one patient). The study protocol was approved by the local ethics committee and consent forms were signed by all 17 subjects.

Previous immunosuppressive drugs were discontinued for 4 weeks before entering the study. All patients were given an initial loading dose of leflunomide 100 mg daily for 3 days, followed by 20 mg daily for the remainder of the study (52 weeks). Prednisolone dosage was tapered from an initial dose of 0.5 mg/kg/day (up to 30 mg daily) according to a standard protocol. Fourteen patients receiving angiotensin converting enzyme inhibitors at baseline were allowed to continue at the same dose. Clinical and laboratory evaluations

were assessed monthly for 6 months, then every 2 months up to 12 months. The primary end point was the number of patients achieving complete or partial response of nephritis (see table 1 for the definition of response). The secondary end points included changes in proteinuria, SLE Disease Activity Index (SLEDAI),² C3, C4, and anti-dsDNA levels (measured by enzyme linked immunosorbent assay (ELISA), Diastat; Axis-Shield Diagnostics, Dundee, UK), and prednisolone dosage after treatment.

At entry, the median (interquartile range (IQR)) duration between the last biopsy and starting leflunomide was 16 (11–44) months. Eleven (65%) of 17 patients had nephrotic syndrome and 8/17 (47%) patients had active sediments. Median (IQR) activity index and chronicity index were 3 (1–4) and 1 (0–2), respectively.

At the final visit, 13/17 (76%) patients had achieved a response (table 1). Complete response was seen in 5/17 (29%), partial response in 8/17 (47%), and treatment failure in 4/17 (24%). Figure 1 summarises the changes in proteinuria, creatinine clearance, and SLEDAI of all the 12 patients who completed the trial. Mean (SD) serum albumin increased significantly from 30.5 (5.8) g/l to 35.6 (8.6) g/l ($p = 0.012$). Serum complement 3 (C3) level increased from 0.59 (0.24) g/l to 0.78 (0.29) g/l ($p = 0.046$), serum C4 level increased from 0.11 (0.07) g/l to 0.17 (0.08) g/l ($p = 0.016$), and anti-dsDNA decreased from 350 (314) IU/ml to 84 (113) IU/ml ($p = 0.008$). Microscopic haematuria resolved

Table 1 Baseline clinical and laboratory characteristics and outcomes after leflunomide treatment

Patient No	Sex	Age	Disease duration (years)	Duration of nephritis (months)	WHO class	Previous immunosuppressive agents	SLEDAI	Proteinuria (g/day)	Duration on leflunomide	Response	Adverse events
1	F	43	23	122.7	4	CYC, AZA, CSA	17	2.1	12	TF	HT, WL
2	F	33	9	1.1	2, 5	NIL*	6	4.4	12	PR	
3	F	39	7	16.9	2, 5	CYC, AZA,	6	2.4	0.5	TF	§Transaminitis
4	F	49	5	46.1	3	AZA	16	2.2	12	CR	Warfarin od, GI bleed, HT
5	F	41	7	5.9	2, 5	CYC	14	2.3	12	CR	
6	M	55	1	19.1	5	AZA	12	3.2	6	PR	‡Vasculitis, died
7	F	21	4	4	4†	AZA	16	3.1	10	CR	§Severe pruritis
8	F	27	9	106	2, 5	AZA, CYC	12	5	12	PR	
9	M	35	7	11.2	5	CSA	16	4.4	12	PR	
10	F	30	9	15.7	3	CSA	16	3.6	12	PR	Herpes zoster, HT
11	F	43	13	11.7	3, 5	CYC, AZA	8	3.7	12	CR	Herpes zoster
12	F	33	4	2	3	CYC, AZA	16	5.1	12	CR	HT
13	F	53	5	39.4	3	CYC, AZA	10	4.7	12	PR	Herpes zoster, HT, WL
14	F	30	7	54.8	3, 5	AZA, CSA	4	3.6	0.5	TF	§Facial rash
15	F	41	4	29.9	4	CYC	4	2	12	TF	
16	F	46	15	11.6	5	CYC, AZA	12	2.4	12	PR	HT
17	F	34	14	10.7	5	AZA	10	6.7	6	PR	§Alopecia

*Patient newly diagnosed with lupus nephritis and cryptococcal meningitis; †patient presented with nephrotic syndrome did not have a renal biopsy owing to prolonged clotting time and the disease was managed as proliferative nephritis because of presence of active urine sediments.

CYC, cyclophosphamide; AZA, azathioprine; CSA, ciclosporin A; CR, complete response; PR, partial response; TF, treatment failure. Complete response (CR) was defined as proteinuria ≤ 0.5 g/day, with normal urinary sediment and normal values for both serum creatinine and creatinine clearance. Partial response (PR) was defined as either a reduction of $>30\%$ in proteinuria or proteinuria <2 g/day in a previously nephrotic patient with normal urinary sediment and stable renal function. Treatment failure (TF) was defined as no response at the end of follow up or requirement for additional immunosuppressant treatment. For those patients who could not complete the 12 months study, data at the last visit were assessed for response. ‡One patient withdrew because of inefficacy; §four patients withdrew owing to side effects. HT, arterial hypertension requiring additional anti-hypertensive drugs. WL, weight loss of 3–4 kg at the end of the trial owing to real body weight reduction because they remained nephrotic.

Figure 1 Changes in SLEDAI, proteinuria, and creatinine clearance after leflunomide treatment. Data are expressed as mean (SD). (A) The mean SLEDAI declined from 11.9 (4.8) to 5.4 (4.5) ($p=0.002$). (B) Proteinuria reduced significantly from 3.5 (1.3) g/day to 1.7 (1.5) g/day ($p=0.002$) for the whole group. A comparison of patients with proliferative and patients with membranous nephritis showed that proteinuria decreased significantly only in patients with membranous nephritis (proliferative nephritis: 3.3 (1.4) g/day to 1.9 (1.1) g/day; membranous nephritis: 3.7 (1.1) g/day to 1.3 (0.9) g/day, $p=0.000$). (C) The creatinine clearance rate remained stable and within the normal range (96 (37) ml/min at baseline v 96 (40) ml/min at the end of the study).

in 6/7 patients. Steroid dosages were reduced in 9/12 (75%) patients, with a significant reduction from a mean (SD) of 20.2 (9.4) mg/day to 11.6 (5.5) mg/day ($p=0.03$).

The obvious weakness in this study includes the relatively small numbers of patients who completed the trial, and the follow up was too short to examine the efficacy of leflunomide for long term renal preservation. In addition, our patients were a heterogeneous group with different renal histological classes who had been treated previously with multiple immunosuppressive agents for variable lengths of time. For these reasons, the possibility that the observed improvement, was due in part to corticosteroid or other immunosuppressant drugs given previously cannot be excluded in the absence of a control group. Another limitation includes the correlation of the clinical response with renal histological features that were obtained at a mean of 16 months before leflunomide treatment. Furthermore, repeat renal histology was not available after treatment. In conclusion, leflunomide is a safe and probably efficacious treatment in patients with lupus nephritis who do not respond or cannot tolerate conventional treatments.

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No evidence of parvovirus B19 in tissue samples from patients with polyarteritis nodosa and microscopic polyangiitis as assessed by the polymerase chain reaction

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Parvovirus B19 (B19) has been implicated in the aetiopathogenesis of some cases of systemic vasculitis, mainly giant cell arteritis.¹ A positive serological test for B19 has been reported in a few patients with polyarteritis nodosa (PAN).²⁻⁴

As far as we know no studies of B19 DNA in tissue samples of patients with PAN have been published, so we used a nested polymerase chain reaction (PCR) approach to screen for B19 DNA in fixed paraffin embedded tissue samples from

patients with PAN and microscopic polyangiitis (MPA). The diagnosis was based on the Chapel-Hill Consensus Conference guidelines.⁵ Only tissue samples from patients with vasculitis were used for DNA preparations.

DNA was extracted using a commercial kit (DNeasy tissue kit, Qiagen). A nested PCR for B19 was carried out using a previously published set of PCR primers.⁶ Positive and negative controls were included in every PCR run. A negative control consisted of a master mix without B19 DNA. DNA