Efficacy and safety of leflunomide as an adjuvant drug in refractory dermatomyositis with primarily cutaneous activity

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ABSTRACT

Objective. *To evaluate leflunomide as an adjuvant drug in refractory dermatomyositis (DM) with primarily cutaneous activity.*

Methods. *A retrospective, single-centre, cohort study including 18 adult patients with DM (classical or clinically amyopathic DM) and cutaneous activity from 2001 to 2016 was conducted. Patients were dependent on glucocorticoid and refractory to at least two full-dose immunosuppressants/immunomodulators or presented previous adverse events with immunobiological drugs. One immunosuppressant was maintained and leflunomide added to the treatment. Patients were followed for six consecutive months.*

Results. *Leflunomide proved effective and safe in 12 (66.6%) out of the 18 patients. There was total control of cutaneous activity and prednisone was tapered from 17.5 to 6.0 mg/day (p<0.001). In addition, two of these patients that also had muscle involvement improved muscle strength after leflunomide treatment. Side effects or inefficacy were observed in six patients. There were no cases of serious infection or death.*

Conclusion. *Leflunomide therapy appears to be effective and safe as an adjuvant drug in refractory DM with primarily cutaneous activity. Further studies are needed to confirm this data.*

Introduction

Dermatomyositis (DM) is a rare systemic inflammatory myopathy characterised by progressive muscle weakness of limbs associated with typical cutaneous lesions, such as heliotrope and/or Gottron's papules (1-6). In addition, patients with DM may have constitutional symptoms and joint, cardiac, pulmonary and/or gastrointestinal tract involvement (1-7).

Despite the lack of randomised controlled trials, glucocorticoids have been used as first-line therapy in idiopathic inflammatory myopathies (8-10). Moreover, the use of different immunosuppressives (IS) or immunomodulatories (IM) drugs have been recommended as glucocorticoid-sparing agents, such as azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, cyclophosphamide, tacrolimus, leflunomide and intravenous human immunoglobulin, alone or in association (8-13).

Leflunomide is a pro-drug that, once activated, inhibits the synthesis of new pyrimidines by blocking cells proliferation and activation (14). Currently, only five studies investing leflunomide use in patients with DM are available in the literature, where these are limited to case or series reports (15-19).

Immunobiological drugs, such as rituximab (anti-CD20), have been recommended for refractory DM (20-25). However, in practice, some patients have contraindications, side effects or are refractory to these drugs. Thus, the objective of the present study was to evaluate the use of leflunomide as an adjuvant drug in DM patients with primarily cutaneous activity that are refractory or have contraindications to other IS/IM and/or rituximab.

Methods

This retrospective, single-centre, cohort study included 18 consecutive adult patients with classical DM, according to Bohan and Peter's criteria (4) or clinically amyopathic DM, according to Gerami *et al*. (26). In order to improve the homogeneity of the sample under study, only patients who were followed up at our tertiary service from 2001 to 2016 were included. The study was approved by the Local Ethics Committee. Patients with myositis overlap syndromes, neoplasia associated myositis, immune-mediated necrotising myopathies, and chronic infections were excluded.

All patients had primarily cutaneous activity, were dependent on glucocorticoid, showed inadequate response to at least two IS/IM drugs (azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, antimalarial and/or intravenous human immunoglobulin, at full-dose for a minimum period of three consecutive months) or had contraindications, inefficacy or adverse events for rituximab. Leflunomide was used in association with a previous IS/IM. For patients in use of two IS/IM concomitantly, one of these drugs was switched to leflunomide. Cutaneous disease can be associated or otherwise with muscle, pulmonary, joint and/or gastrointestinal involvement.

All patients were followed for six con-

Table I. General features of 12 patients with dermatomyositis with primarily cutaneous activity.

Patient	Gender	Age (years)	Disease (years)	Immunosuppressant/immunomodulatory		Activities	Current		6 months	
				Previous	Current		Pred (mg/day)	CPK (U/L)	Pred (mg/day)	CPK (U/L)
1	F	30	5	MP, Pred, Aza, MTX	Aza	Cut, mm	60	6051	10	120
2	F	67	3	MP, Pred, IVIg, RTX, Aza, MTX, CP, MMF	RTX*, Aza	Cut, mm	5	1130	0	258
3	F	71	4	MP, Pred, AM, Aza, MTX	MTX	Cut	20	206	15	43
4	M	25	7	MP, Pred, AM, IVIg, TCZ, Aza, MTX, CP	TCZ*, Aza	Cut	15	176	5	148
5	F	78	10	MP, Pred, AM, Aza, MTX, CP, MMF	CP*, Aza	Cut	20	59	15	62
6	F	32	4	Pred, Aza, MTX	Aza	Cut	20	68	5	115
7	F	29	2	MP, Pred, AM, Aza, MTX	Aza	Cut	10	110	10	83
8	F	63	1	MP, Pred, AM, Aza, MTX	Aza	Cut	30	44	5	227
9	F	56	1	MP, Pred, IVIg, Aza, MTX, CP	CP	Cut	20	72	20	50
10	F	39	12	MP, Pred, AM, Aza	Aza	Cut	5	105	0	80
11	F	43	1	MP, Pred, AM, Aza, MTX, CP, MMF	MMF*, MTX	Cut	15	57	7.5	48
12	F	41	7	Pred, Aza, MTX	Aza*, MTX	Cut	15	186	0	186
		47.8±18.3	4.8±3.6				17.5	108	6.0	99
							(11.3-20.0)	(62-201)	(1-14)	(53-177)

Statistical data are expressed as mean ± standard deviation, median (interquartile 25th–75th). AM: antimalarial; Aza: azathioprine; CP: cyclosporine; CPK: creatinine phosphokinase; Cut: cutaneous; IVIg: human intravenous immunoglobulin pulse therapy; F: female; M: male; mm: muscular; MMF: mycophenolate mofetil; MP: methylprednisolone pulse therapy; MTX: methotrexate; Pred: prednisone. *Suspended.

secutive months after leflunomide introduction. Data were obtained from the standardised and parameterised ongoing electronic database protocol carried out for all patients at 1 - 6 month intervals that consists of an extensive clinical and laboratory evaluation, including those relevant for this study.

The following disease activities were analysed: cutaneous (heliotrope rash, Gottron's papules/signal associated or not with "V-neck" sign, "Shawl" sign, vasculitis, ulcers, facial rash, "mechanic" hands); muscle (objective muscle weakness and graded according to Medical Research Council classification (27)); pulmonary (pulmonary alterations in computed tomography: incipient pneumopathy, ground-glass lesions and/or basal pulmonary fibrosis); joint (arthritis); and gastrointestinal involvement (upper dysphagia). In cases with muscle involvement, serum creatinine phosphokinase level (reference value: 24–173 U/L) was also analysed.

At six months, leflunomide treatment was defined as effective when the drug promoted over 50% improvement in the initial cutaneous disease activity of the patient – evaluated clinically by the rheumatologists from our service; and allowing prednisone dose tapering.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the distribution of each parameter. The demographic and clinical features are expressed as the means ± standard deviations (SD) for the continuous variables or as frequencies and percentages (%) for the categorical variables. The medians (25th–75th percentiles) were calculated for the continuous variables that were not normally distributed. Comparisons between the patients at initial and after six months of leflunomide were performed using Student's *t*-test or the Mann-Whitney U-test for continuous variables. $p<0.05$ was considered significant. All of the analyses were performed with the SPSS 15.0 statistics software (Chicago, USA).

Results

Eighteen consecutive patients were initially included in the present study.

Leflunomide was suspended within the first two months of follow up in six (33.3%) cases: four without improvement (or worsening) of cutaneous activity; one without improvement of cutaneous activity and with side effects (lower limb paresthesia); and one with improvement of cutaneous activity, but persistent side effects (diarrhoea).

Twelve (66.6%) out of the 18 patients had good tolerance to leflunomide and total control of cutaneous activity. Among this group, mean age was 47.8±18.3 years, all Caucasian, and female gender predominated (91.7%). Mean disease duration was 4.3±3.6 years (Table I).

Previous and current IS/IM are also shown in Table I. Two patients had also used rituximab (case no. 2) or tocilizumab (case no. 4), but with persistent cutaneous activity.

All patients had cutaneous activity and two had concomitant muscle activity. There were no cases with joint, pulmonary and/or gastrointestinal involvement. During the six month of follow-up, median prednisone dose was tapered from 17.5 to 6.0 mg/day ($p=0.008$).

Two patients (cases no. 1 and 2) also fully recovered muscle strength (from IV to V degree in all four limbs) and had reduced serum creatinine phosphokinase level and prednisone dose.

There were no cases of serious infection or death.

Discussion

Leflunomide proved an effective and safe adjuvant drug in approximately two thirds of the refractory DM patients with primarily cutaneous activity.

Although DM is a rare disease and strict exclusion criteria were employed, the present study included a sample of 18 consecutive patients with defined DM (classical or clinically amyopathic). Moreover, in order to ensure reliable results, patient data were based on pre-

viously standardised and parameterised information. Finally, the protocol was performed at single center, adopting the same standardisation of reports, thereby reducing inter-examiner variability.

Due to the refractoriness and severity of the cutaneous activity found in our patients, as an internal protocol, leflunomide was associated with one previous IS/IM. Furthermore, studies analysing the efficacy and safety of leflunomide as monotherapy in this patient group are warranted.

There are no controlled studies investigating the treatment of DM with leflunomide. Currently, only five case or series reports on leflunomide use in patients with DM are available in the literature (15-19). In two of these studies (15, 19), leflunomide was not advantageous over other IS and was, therefore, replaced by immunobiological agents. In the other three studies, use of the drug was associated with successful outcomes (16-18).

Sangle *et al*. (17) showed the effectiveness of leflunomide in refractory DM, allowing glucocorticoid tapering. Boswell and Costner (17) described two case reports. In one of these cases, leflunomide was associated with methotrexate and hydroxychloroquine, promoting disease remission in refractory DM with cutaneous activity. In the other case, leflunomide was effective in the treatment of DM cutaneous lesions as an adjuvant drug with methotrexate and prednisone, allowing glucocorticoid tapering. Orden *et al*. (16) reported the first documented of leflunomide to treat a cytomegalovirus infection in a patient previously diagnosed with DM. Leflunomide seems to interfere with cytomegalovirus virion assembly, and its antiviral activity against cytomegalovirus was first described by Waldman *et al*. (28).

In the present study, four patients had persistence of disease activity and two patients had side effects (peripheral neuropathy and diarrhoea). Leflunomide side effects, such as paresthesia and diarrhoea, are reported in 0.01% and 10% of cases, respectively (29, 30). Two thirds of the patients had good tolerance and cutaneous activity control with leflunomide, allowing glucocorticoid tapering. Furthermore, two patients with muscular disease activity also showed improvements in muscle strength and serum creatinine phosphokinase levels. Notably, there were no cases of serious infection or death during leflunomide treatment in the patients assessed.

Limitations of this study included the relatively small sample of patients, due to the rarity of the disease, and short follow-up of six months. Also, the use of leflunomide as monotherapy was not investigated.

In summary, leflunomide proved safe and effective as an adjuvant drug in cases of refractory DM with primarily cutaneous activity. Further studies are needed to confirm the data found in the present study.

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