

Treatment of the idiopathic inflammatory myopathies: A retrospective analysis of 63 Caucasian patients longitudinally followed at a single center

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Abstract

Objective

To analyze the therapies used over the past 20 years at a single center to treat patients with idiopathic inflammatory myopathies (IIM), and to compare their effectiveness.

Methods

Sixty-three Caucasian IIM patients were selected for this study based on the following parameters: (i) a definite diagnosis of IIM; (ii) a follow-up period of at least one year; and (iii) a complete record of clinical and serological data for the course of the follow-up. The following data were collected from the patients' records: the first choice and subsequent therapies, the patient's response to these treatments, the outcome at the end of the follow-up.

Results

Two therapeutic approaches were identified: steroids alone and the combination of steroids with immunosuppressive drugs. Of the 63 patients studied, 36 received steroids alone and 27 received steroids plus immunosuppressors. Sixteen patients did not respond to the initial therapy, 33 showed a stable response, and 14 experienced a relapse in disease activity during the follow-up. No statistically significant differences among these 3 groups of patients were observed with respect to sex, age at disease onset, diagnosis, CPK levels at disease onset, and therapeutic approach.

Conclusion

Corticosteroids represent the mainstay of IIM therapy, both as the first choice treatment and as maintenance therapy. The use of immunosuppressive agents should be restricted to those patients with severe contraindications to steroid treatment.

Keywords

Idiopathic inflammatory myopathies, therapy, corticosteroids, immunosuppressive drugs.

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Introduction

The idiopathic inflammatory myopathies (IIM) comprise a heterogeneous group of diseases of unknown etiology characterized by chronic inflammation of the skeletal muscles. The management of these conditions remains an unsolved issue for a number of reasons. First of all, the pathogenetic mechanisms underlying these diseases are still largely unknown and probably differ for the different variants of the diseases (1-3). Secondly, despite the fact that they may exhibit similar clinical and serological manifestations, some patients respond promptly to the first choice therapy, while others turn out to have resistant disease (2,4). In this regard, the role of social, racial, and environmental factors has only been partially evaluated (5,6). Therefore, the different studies that have been conducted in different geographical areas are difficult to compare. Thirdly, the rarity of these diseases makes it practically impossible to recruit a sufficient number of patients for controlled trials. For these reasons the therapeutic armamentarium used to treat IIM consists essentially of corticosteroids and immunosuppressive drugs such as those used to treat other systemic autoimmune disorders, i.e. cyclophosphamide, azathioprine, methotrexate and cyclosporine (7-10). Alternative treatment modalities, such as combinations of immunosuppressive drugs, plasma exchange, intravenous gammaglobulins and total body irradiation, have been attempted in resistant cases of IIM (11-16).

Over the past 20 years, 107 IIM patients have been seen at the Immunology Unit and Rheumatology Unit of the University of Pisa. The aim of this retrospective study was to analyze the different therapeutic approaches used to treat these patients and to compare their effectiveness.

Patients and methods

Between 1975 and 1998, 107 patients (40 males and 67 females) being followed at the Clinical Immunology Unit and the Rheumatology Unit of the University of Pisa were diagnosed as having IIM. The diagnosis was made based on previously described criteria (17), and the patients were further classified in the following

subgroups: polymyositis (PM), dermatomyositis (DM), juvenile polymyositis/dermatomyositis (J-PM/DM), IIM associated with malignancy (p-PM/DM), and IIM associated with connective tissue diseases (CTD-PM/DM).

Patients were selected for the study using the following criteria: (i) a diagnosis of IIM; (ii) a follow-up of at least one year; and (iii) the availability of complete clinical and serological data for the course of the follow-up. The following parameters were studied: the first choice and subsequent therapies used, the response to therapies, and the outcome at the end of the follow-up period.

Patients were defined as "responders" when they showed serological improvement (CK values decreased at least by 20%) within the first six weeks of treatment (10,11), based on the assumption that an improvement in muscle enzymes was indicative of a reduction in disease activity. A relapse was defined as the recurrence of serological abnormalities after an initial improvement. A positive outcome was defined as the remission of clinical manifestations and/or normal enzymes values at the last observation (by definition at least one year after the first observation) (8).

From an analysis of the clinical records the following therapeutic modalities were identified: steroids alone (S) or steroids in association with immunosuppressors (cyclophosphamide, azathioprine, methotrexate) (S-IS). Steroids were given as i.v. pulses followed by rapid dosage tapering, or as daily oral/i.m. doses. A low steroid dose (LDS) was defined as < 0.5 mg/Kg/die, a medium dose 0.5 - 1 mg/Kg/die (MDS), and a high dose > 1 mg/Kg/die (HDS). Cyclophosphamide was administered as monthly pulses (750 mg/m²), methotrexate was administered at a weekly dose of 0.15 mg/kg and azathioprine at a dose of 1.5-2 mg/kg/die.

Statistical analysis

The Mann-Whitney U-test was used to correlate the evolution of the disease with the clinical and serological variables for each patient. For the categorical variables the χ^2 test was used. In view of the large number of correlations studied, a significance level of 1% was adopted.

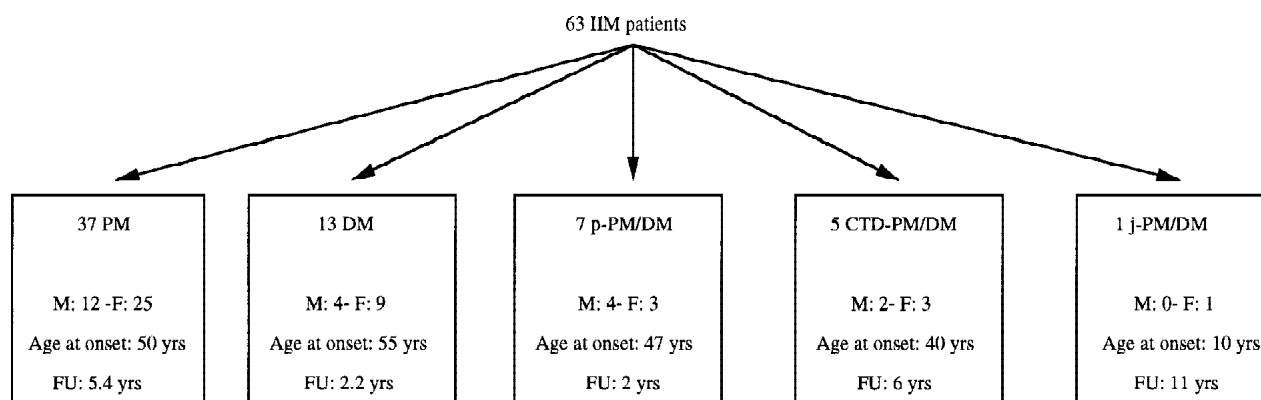


Fig. 1. Epidemiological data on 63 Caucasian IIM patients.

Results

Out of the 107 IIM patients seen at the Clinical Immunology Unit and the Rheumatology Unit of the University of Pisa in the period between 1975 and 1998, 63 (22 males and 41 females, all Caucasians) were selected for inclusion in this study. Fifteen patients were excluded because they had been seen only once for consultation, and the remaining 28 because they had a disease duration of less than one year. The relevant epidemiological and clinical data on the 63 patients studied are reported in Figure 1.

Sixty percent of the study cohort (38 patients) were still being followed by us at the time of the chart review, while 26% (16 patients) had been lost to follow-up and 14% (9 patients) had passed away. Death occurred after a mean disease duration of 47 months (range 12 - 216; median 21); 2 patients died from IIM-related causes, 3 due to neoplastic disease, and the remaining 4 from other causes.

Thirty-six patients (57%) received steroids (methylprednisolone) alone as the first choice therapy (S group); the remaining 27 (43%) received steroids and immunosuppressors (19 patients cyclophosphamide, 4 patients azathioprine, and 4 patients methotrexate) (S-IS group). Although the number of patients in each diagnostic subgroup was too small to draw definitive conclusions, no differences in the epidemiological and clinical profile or disease subgroup were observed between the two treatment groups (Table I).

In Figure 2 we show the steroid loading doses for the two therapeutic groups:

Table I. Epidemiological and clinical data on the two therapeutic groups.

	S group	S-IS group
Male: female	14: 22	8: 19
Age at onset (mean in yrs.)	49	49
CPK at onset (mean)	1450	2320
PM (37 pts.)	22 (60%)	15 (40%)
DM (13 pts.)	9 (69%)	4 (31%)
j-PM/DM (1 pt.)	1 (100%)	0
p-PM/DM (7 pts.)	2 (28%)	5 (72%)
CTD-PM/DM (5 pts.)*	2 (40%)	3 (60%)
Total (63 pts.)	36 (57%)	27 (43%)

* CTD-PM/DM: 2 cases associated with scleroderma, 2 cases associated with systemic lupus erythematosus, and 1 case associated with Sjogren's syndrome.

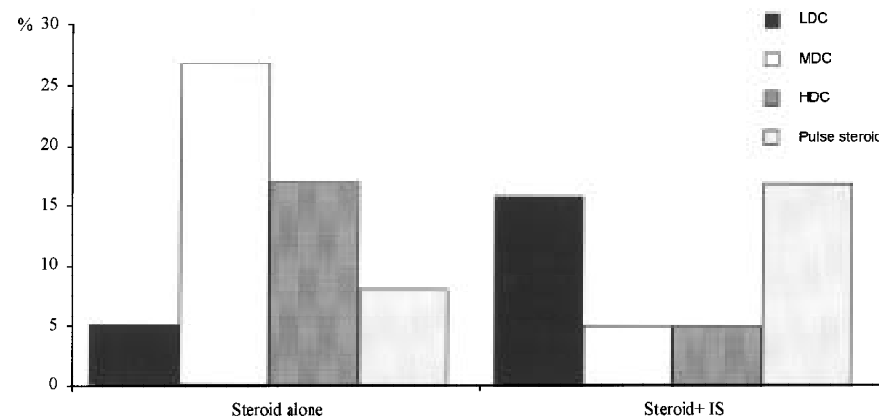


Fig. 2. Steroid loading dose in the two treatment groups.

most patients in the S group received medium or high dose steroids (27% and 17%, respectively), while most of the patients in the S-IS group received low dose or pulse steroids (16% and 17%, respectively) ($p < 0.002$). However, the mean cumulative steroid dose at the end of one year of treatment in the two groups was comparable (18 mg/day in

the S-group vs 24 mg/day in the S-IS group), even if the initial steroid dose (if administered in the form of a pulse) was not taken into consideration (17 mg/day in S-group vs 20 mg/day in S-IS group). Based on the immediate response to therapy, a total of 16 patients were classified by us as "non-responders" and 47 as "responders" (see Patients and Meth-

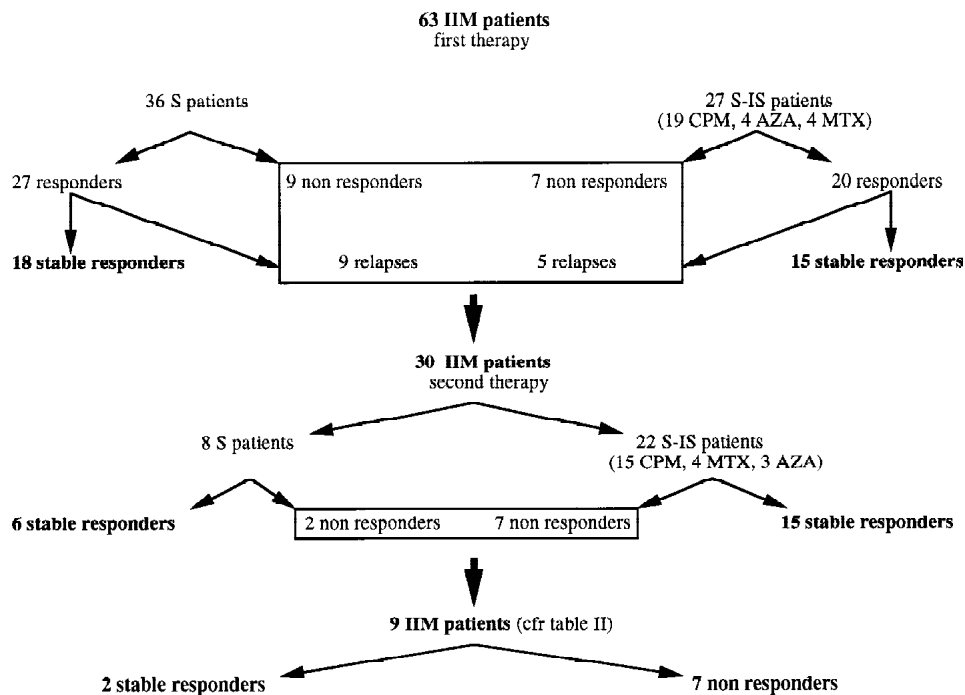


Fig. 3. Response to therapy in the two treatment groups.

ods). The proportion of responders and non-responders was similar between the S group [27 (75%) responders versus 9 (25%) non-responders] and the S-IS group (74% responders and 26% non-responders). In the responder group, during their follow-up 14 patients (9 PM, 2 DM, 2 p-PM/DM, 1 CTD-PM/DM) experienced a relapse in disease activity after a mean period of 25 months (range 6 - 72 months; median 15), while 33 remained in remission (stable responders) (Fig. 3). Therefore, we could identify 3 broad groups of patients based on their response to the initial therapy: stable responders, relapsed patients, and non-responders. No statistically significant differences among these 3 groups were observed with respect to sex, age at disease onset, diagnosis, disease duration, CPK levels at disease onset and, most significantly, therapy administered. Thirty patients (16 non-responders and 14 relapsed patients) received a second

Table II. Good response to first and second therapy.

	S group	S-IS group
First therapy	75% (27/36)	74% (20/27)
Second therapy	75% (6/8)	68% (15/22)

Table III. Treatments administered to the 9 patients who did not respond to therapy, and their final outcome.

Patient	Diagnosis	First therapy	Second therapy	Other therapies	Outcome
M.A.	p-PM/DM	S-IS	S-IS	S-IS	good
C.R.	PM	S-IS	S-IS	*	poor
C.A.	p-PM/DM	S-IS	S-IS	S, IVIG	good
C.N.	DM	S-IS	S-IS, IVIG	S-IS	poor
B.F.	p-PM/DM	S	S-IS	*	poor
P.M.	PM	S-IS	S-IS	S-IS	poor
F.F.	PM	S-IS	S, IVIG	S	poor
C.A.	DM	S	S-IS	S-IS	poor
Z.X.	PM	S	S-IS	S-IS	poor

* These patients died during the second phase of therapy due to myostis-related causes.
IVIG: intravenous immunoglobulins.

choice therapy; 8 were given steroids alone (S group) and 22 received steroids plus immunosuppressors (15 CPM, 4 MTZ, 3 AZA) (S-IS group). Twenty-one patients responded to this therapy, while 9 patients did not. Among the non-responders 6 (4 PM, 1 DM, 1 p-PM/DM) had been unresponsive to the first choice therapy and 3 (2 p-PM/DM, 1 DM) were relapsed patients (Fig. 3). In Table II we report the percentages of positive responses to the first and second therapies. In Table III we summarise the treatment modalities followed by these 9 non-responder patients and their final outcome. No differences were noted be-

tween responders and non-responders to the second choice therapy with respect to sex, age, diagnosis and the therapy given.

At the last observation, of the 63 IIM patients studied 55 presented a good outcome and the remaining 7 (4 PM, 2 DM, 1 p-PM/DM) a poor outcome. With respect to the final outcome, no differences in sex, age at disease onset, diagnosis, CPK levels at disease onset or treatment were observed.

Discussion

This retrospective evaluation of 63 Caucasian IIM patients treated at our units

over the past 20 years allowed us to identify two main therapeutic approaches to the treatment of IIM: one based on the administration of steroids alone and the other based on a combination of steroids and immunosuppressive drugs, mainly cyclophosphamide.

Our analysis of the response to treatment showed that steroids alone induced a disease remission in about two-thirds of the patients receiving this therapy, and that remission was stable in about one half of them. Although some patients showed a good response to immunosuppressive drugs, on the whole there was no statistically significant difference between the efficacy of steroids alone or steroids plus IS in terms of disease control or the maintenance of disease remission, and IS showed no steroid-sparing effect. This response to treatment was found when analyzing the patients both as a whole group and as single disease subsets.

A correlation between the autoantibody profile of patients with IIM and the response to treatment has been described (3). Due to the retrospective nature of this study, the serological data were not available for all of our patients and consequently this type of analysis was not possible.

In only 14% (9/63) of the patients was it found necessary to attempt an alternative treatment (intravenous immunoglobulins or combinations of immunosuppressive drugs) for refractory disease, and only 2 of these 9 patients improved. Overall 89% of the IIM patients showed a good final outcome. It was impossible to identify the predictive factors for a poor response to treatment.

Ours was a retrospective uncontrolled study and therefore presents all of the limitations of this type of study. Nevertheless, it is pertinent to note that the majority of the patients in this series were followed longitudinally by the same physician. Although relatively little data on large series of IIM patients studied for extended periods of time are available, our results are in broad agreement with those of other studies carried out on patient series in other geographic areas.

For example, in 1985 Tymms *et al.* (4) reviewed 105 Australian IIM patients followed over a period of 12 years. In this study most of the patients were

treated with high dose corticosteroids, and nearly half also received cytotoxic drugs (mainly methotrexate and azathioprine) as a second line therapy; improvement was seen in 69% of the patients. However, this was a descriptive study and no statistical comparisons were performed among the different groups of patients.

In 1993 Joffe *et al.* (9) retrospectively examined the response to therapy in a group of 113 IIM patients: 73 whites, 31 blacks and 9 of other races. They observed a complete clinical response in 25%, a partial clinical response in 61%, and no clinical response in 14% of the patients to a first prednisone trial. As a second trial therapy, patients received either prednisone, methotrexate or azathioprine. The authors found that methotrexate tended to be superior to azathioprine and to further steroid treatment alone in patients who did not respond completely to an initial course of prednisone.

In 1993 Koh *et al.* (6) described a cohort of 75 Oriental IIM patients (66 Chinese, 5 Malay, 2 Indian, and 2 of other ethnic origin) who were being treated for a first episode of PM/DM. Sixty-two patients received prednisolone alone, while 11 were also given immunosuppressive agents because of either a poor response or an adverse reaction to corticosteroids. Among the patients treated with prednisone alone, 56% remitted.

Considerable disagreement exists regarding the use of immunosuppressive drugs to treat IIM. In fact, while some authors use them only as a second line therapy for selected cases (7, 10), others recommend immunosuppressive drugs in association with corticosteroids as the first choice therapy in order to bring the disease under control and restore the patient's parameters to their baseline values as quickly as possible (11, 18). Disagreement also exists regarding the optimal immunosuppressive drug to be used for IIM. So far, good results have been obtained with azathioprine, methotrexate, cyclosporine, and chlorambucil, while conflicting results have been reported in a retrospective analysis of CFX for the treatment of myositis (7).

In this respect, it is interesting to note that in our patients the use of immuno-

suppressive drugs in association with steroids, was followed in some patients by a prompt response. Since we started to treat IIM patients with MTX or AZA in 1996, only a small number of the patients included in this study were treated with these drugs. For this reason, our analysis does not provide sufficient data for any firm conclusions to be drawn regarding the most effective immunosuppressive drug regimen for IIM.

In conclusion, the results of this analysis of a cohort of 63 Caucasian IIM patients confirm that corticosteroids represent the treatment of choice for IIM, both to bring the symptoms under control and as long-term maintenance therapy. The use of immunosuppressive agents should be restricted to certain patients with severe contraindications for steroid treatment. Other drugs such as intravenous immunoglobulins, immunosuppressive drug combinations, and plasma exchange should only be considered as rescue therapy in refractory cases.

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