

Treatment of Recurrent & Resistant Dermatomyositis / Polymyositis

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INTRODUCTION

Dermatomyositis (DM) and polymyositis (PM) are two classic forms of inflammatory myopathy. Most patients respond to initial therapy, and some achieve sustained disease control either off all therapy or with low-dose maintenance therapy.

But many patients with DM or PM require intermittent or even continuous therapy:

- Recurrent disease is defined as the occurrence of a disease flare following the achievement of disease control with treatment.
- Resistant disease does not respond sufficiently to the conventional approaches of glucocorticoids plus either azathioprine or methotrexate. In such cases, alternative approaches to remission induction must be considered.

Recurrent Disease

Complete discontinuation of treatment is unsuccessful in the majority of patients.

For patients who experience disease flares after the achievement of disease control, there are four specific scenarios.

1. For disease flares at > 10 mg/day of prednisone, we suggest the addition of either azathioprine or methotrexate (if not already used) or treatment of the patient as a case of resistant disease (Grade 2C). With either action, a higher dose of prednisone, generally in the range of 1 mg/kg per day, will be required to reestablish disease control.
2. For disease flares at < 10 mg/day of prednisone, we suggest 2 options:
 - increasing the prednisone to the lowest dose required to reestablish disease control (according to disease severity 20 mg/day - 1 mg/kg per day)
 - and/or increasing the azathioprine or methotrexate dose, if this has not been maximized already (Grade 2C).

Once disease control is restored, we suggest slower tapering than that which was used during the initial course. Some patients are maintained on low-dose prednisone (e.g., 5 mg/day) for one year or more.

3. For disease flares off prednisone but on a glucocorticoid-sparing drug. There are two options:
 - reinstating prednisone at the lowest dose required to reestablish disease control
 - and/or changing the glucocorticoid-sparing medication from azathioprine to methotrexate or vice versa (Grade 2C).

If the patient has already failed both azathioprine and methotrexate, treatment as a case of resistant disease is appropriate.

4. For flare off all immunosuppressive medication, we suggest reinstating prednisone with an initial daily dose that varies according to relapse severity (Grade 2C). The minimum starting dose of prednisone is 20 mg/day. In addition, a glucocorticoid-sparing drug should be resumed or started.

Resistant Disease

Multiple options exist for treating patients who do not respond adequately to glucocorticoids plus either azathioprine or methotrexate; include:

- Rituximab
- Intravenous immune globulin (IVIG)
- Cyclosporine
- Tacrolimus
- Mycophenolate mofetil
- Cyclophosphamide
- Tumor necrosis factor inhibitors
- Combination therapy with azathioprine and methotrexate

Evidence of clinically significant benefit is greatest with rituximab and IVIG if rituximab fails.

Rituximab

Rituximab targets CD20-positive cells (i.e., B-cell precursors), leading in most patients to the depletion of B cells in the serum within several weeks

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of administration. The trend with the use of rituximab is to employ two 1 gram doses one week apart.

Other regimens for rituximab treatment include: 1 gram every other week for two treatments, and 375 mg/m² once weekly times four doses.

Controlled trials involving larger numbers of patients will be required before the full impact of this treatment can be accurately assessed.

The apparent success of rituximab in the PM patients suggests that B cells may be more important in the pathophysiology of PM than previously recognized.

Intravenous immune globulin

If rituximab is not effective, we suggest IVIG as the second-line agent for the treatment of resistant DM (Grade 2B).

The 2012 American Academy of Neurology guidelines support the use of IVIG for refractory DM but found evidence insufficient to support or refute its use in PM. The expense of this treatment is an important consideration in its long-term use.

Two studies, one in DM and one in PM, have provided evidence that IVIG is an effective short-term therapy for resistant myositis. The mechanism of action is not known.

Prednisone (mean dose 25 mg/day) and a monthly infusion of either IVIG (2 g/kg).

Plus one or more additional therapies, including methotrexate, azathioprine, cyclophosphamide, cyclosporine, chlorambucil, plasmapheresis, lymphapheresis, and total body irradiation.

Or patient was treated with IVIG (1 g/kg per day for two days per month for four to six months).

Data related to the use of rituximab and IVIG in interstitial lung disease are extremely limited.

Rituximab versus IVIG

The reasons for favoring rituximab over IVIG, the only treatment tested in a randomized trial, are the following:

- Rituximab appears to be effective in connective tissue disorders resembling DM and PM, such as systemic lupus erythematosus and rheumatoid arthritis.
- If effective, rituximab may be more likely to lead to a prolonged period of disease control. Many patients who respond to IVIG require continued treatments on a monthly basis.

Calcineurin inhibitors

Achieve their effects by interfering with T cell function. The limited evidence available presently suggests that tacrolimus offers some advantage over cyclosporine in efficacy, but larger studies are required before definitive conclusions are possible.

Cyclosporine

Efficacy for cyclosporine has been suggested for both primary therapy and resistant disease, including interstitial lung disease.

In one report, six patients previously resistant to methotrexate, azathioprine, cyclophosphamide, and/or IVIG underwent treatment with a mean daily cyclosporine dose of 3.5 mg/kg. Over the median six month course of treatment with cyclosporine, the mean daily prednisone dose was reduced by 75 percent. All six patients demonstrated improved strength in the shoulder girdle; four had stronger hip flexor muscles.

Tacrolimus

Tacrolimus has been used in a limited number of patients with inflammatory myopathy. The optimal dose for this indication is not certain.

In one report, tacrolimus (0.075 mg/kg per day in two divided doses) was effective in a series of eight patients with refractory PM complicated by ILD. Strength normalized in five of eight anti-Jo-1 antibody-positive patients and improved in the two anti-SRP positive patients. The mean CK declined from 3114 to 87 IU/mL. Three of five patients with ILD also showed improvement in pulmonary function.

Some data suggest that calcineurin inhibitors are particularly effective in the treatment of ILD complication of DM or PM. For ILD that is refractory to glucocorticoids plus either azathioprine or methotrexate, we use tacrolimus (0.2 mg/kg per day in divided doses) as the next agent (Grade 2C).

Mycophenolate mofetil

In patients with inflammatory myopathy, mycophenolate mofetil (1 to 1.5 g twice daily) is a reasonable alternative if rituximab and IVIG have failed.

Clinicians must be alert to the possibility of opportunistic infection.

Cyclophosphamide

The patients were treated with IV cyclophosphamide at doses ranging from 300 to 800 mg/m² every four weeks plus prednisone. All patients received at least six courses.

Because of their substantial side effect profiles, we suggest reserving alkylating agents (cyclophosphamide and chlorambucil) for patients whose disease has proven resistant to multiple other treatment options (Grade 1C).

Tumor necrosis factor inhibitors

Data related to the efficacy of tumor necrosis factor inhibition in DM and PM are mixed. Only small studies of etanercept and infliximab have been reported, and further studies will be required to further define their role. The following observations illustrate the range of findings:

- We suggest not using tumor necrosis factor inhibitors in DM or PM, unless all other treatment options have failed (Grade 2C).
- Combination therapy — with azathioprine (up to 200 mg/day) and methotrexate (up to 25 mg/week) hold some potential for efficacy in patients with resistant disease. However, the risk of treatment-related morbidity when using both of these medications together mandates the utmost care in monitoring patients for cytopenias and other adverse effects.

Refractory rash

In some cases of DM, the cutaneous manifestations are more refractory to treatment than the muscle disease.

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