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Intravenous immunoglobulin is a treatment option for refractory dermatomyositis in adult patients

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ABSTRACT A critical appraisal and clinical application of Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med*. 1993;329:1993-2000. doi: 10.1056/nejm199312303292704.

Keywords: *dermatomyositis, refractory, intravenous immunoglobulins*

Clinical Context

K.S is a 55-year old African American female with a past medical history of hypertension who presented to the emergency department with multiple skin rashes and upper extremity muscle weakness that began 4 weeks prior. The patient's rashes were suggestive of dermatomyositis including a heliotrope rash (purple rash surrounding the eyes), Gottron's sign (papules on the knuckles), shawl sign (rash on back), and v-neck sign (rash on chest). Labs showed an elevation in inflammatory markers (C- reactive protein (CRP) at 21.0 mg/L and erythrocyte sedimentation rate (ESR) of 54 mm/hr), an elevated lactate dehydrogenase (LDH) of 451 units/L, and an elevated creatine phosphokinase (CPK) of 1,314 units/L. An electromyogram (EMG) test showed evidence of dermatomyositis affecting the proximal muscles more than distal muscles of upper extremities. A muscle biopsy of the right deltoid muscle showed extensive myofiber damage, perimysial inflammation, and structural changes consistent with inflammatory myopathy. Initial treatment was 50 mg of oral prednisone daily that was delayed 6 days until the biopsy could be performed. When the patient's symptoms were not improving after a few days of treatment, the dose was increased to 80 mg of prednisone daily. During the stay in the hospital, the patient complained of swelling that continued to worsen in the face and upper extremities, which prompted evaluation for malignancies, as this is commonly associated with dermatomyositis. A CT scan of the abdomen, pelvis, and thorax was negative for malignancies therefore the swelling was determined to be a symptom of the dermatomyositis. Milisenda et al. (2014) reported that edematous dermatomyositis was rare but was found to be associated with a more aggressive form of the disease.[1] The patient was concerned that her disease might be unresponsive to prednisone and wanted to know what other treatments would be beneficial to add on in the future to improve her symptoms.

Clinical Question

What medical treatment is shown to be effective for refractory dermatomyositis in adult patients?

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Research Article

Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med*. 1993;329:1993-2000. doi: 10.1056/nejm199312303292704

Related Literature

It should be noted that dermatomyositis (DM) is a rare disorder and therefore has limited research regarding treatment options, especially with randomized controlled trials. A search in PubMed was conducted using the terms “dermatomyositis,” “adult,” “treatment,” and “randomized” which populated 43 articles. These were narrowed down to focus on refractory dermatomyositis and excluded juvenile dermatomyositis or article reviews. A search of Google Scholar yielded similar results to PubMed. From these sources, there were five relevant articles:

Dalakas et al. (1993) was a double-blind, placebo-controlled study using intravenous immunoglobulins (IVIG).[2] Patients continued to receive prednisone and were divided into a group receiving intravenous immune globulin (IVIG) monthly or placebo monthly for 3 months. There was a significant improvement of muscle strength and neuromuscular symptoms in the IVIG group.

Oddis et al. (2013) was a randomized phase-controlled trial using rituximab for adults and children with refractory dermatomyositis and adults with refractory polymyositis.[3] Patients were allowed glucocorticoids or immunosuppressive therapy at study entry and were divided into an early arm (beginning of trial to week 8) or late arm (week 8 to week 16) for receiving rituximab. Although there was no designated control group, the late arm was a control while the early arm was being treated and vice versa. There was no difference between the early or late arm but overall 83% of the patients met the study’s definition of improvement.

Tjärnlund et al. (2018) was a randomized trial using intravenous abatacept either as an immediate start or a 3-month delayed start for patients with refractory dermatomyositis or polymyositis.[4] After 6 months of treatment, 47% of patients overall had met the study’s definition of improvement. It was noted however, that four mild and four moderate adverse events were caused by the drug.

Aggarwal et al. (2017) was an open-label clinical trial using repository corticotropin gel injection for patients with refractory polymyositis and dermatomyositis.[5] There was no control group therefore all patients received the injection. It was shown to be effective in 70% of patients and noted to be safe, tolerable and led to a reduction in steroid dose.

Vencovský et al. (2002) was a study with patients already taking corticosteroids who were given an add-on of either methotrexate or cyclosporine A.[6] There was no significant difference between the two groups when comparing better treatment responses. Overall, both add-on options were associated with clinical and laboratory improvement.

Although the Cochrane review was not in the narrowed search likely due to having no distinction between refractory or non-refractory dermatomyositis, it provides an excellent summary of studied treatment options.[7] The Cochrane review identified 14 randomized controlled trials (RCT) or quasi-RCTs that involved participants with dermatomyositis or polymyositis. They reported six studies that compared immunosuppressant with placebo: one was the Dalakas et al. (1993) study showing the IVIG group had statistically significant improvement in scores of muscle strength over three months. They also reported a study investigating etanercept that showed no improvement in primary outcomes but did find a longer median time to relapse in the etanercept group, a secondary outcome. Four other randomized placebo-controlled trials that were assessed in the review involved plasma exchange and leukapheresis, eculizumab, infliximab or azathioprine against placebo and all produced negative results.[7]

UpToDate has a chapter titled “Treatment of recurrent and resistant dermatomyositis and polymositis in adults” stating that rituximab and IVIG have shown to have the greatest significant benefit clinically.[8] The main studies cited were the aforementioned Oddis et al. (2013) rituximab study3 and the Dalakas et al. (1993) IVIG study.[2] UpToDate also cited other rituximab studies including two open-label studies where all patients in the trial received the treatment.[8-10]

The Dalakas et al. (1993) study was chosen to critically appraise because it was the only double-blind randomized trial with a true placebo group that did not receive the therapy in question for statistical comparison. In addition, the participants were all taking prednisone at baseline like our patient. The article also demonstrated improvement in symptoms for patients defined as having

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refractory dermatomyositis, which is what our patient was looking for. This article is widely cited, including 66 other PubMed articles in various journals about rheumatology, neurotherapeutics, musculoskeletal and dermatology.

Critical Appraisal

The study by Dalakas et al. (1993) was a double-blind, placebo-controlled study of 15 patients ranging from the age of 18 to 55 who were proven to have dermatomyositis with a muscle biopsy. Inclusion criteria were patients with active disease characterized by a rash, progressive muscle weakness, impaired ability to perform activities of daily living, and were refractory to treatments.[2] Refractory was defined as patients who were unresponsive to high-dose prednisone or other immunosuppressant therapies given for a least 4 months.[2] Exclusion criteria were patients with coronary artery disease, IgA deficiency, kidney dysfunction, pregnancy or were bedridden.[2] The criteria in this trial fit our patient apart from fitting the refractory definition where at least 4 months must pass without improvement on her prednisone regimen.

Patients were randomly assigned to receive one infusion per month of immunoglobulin (2 g per kg of body weight) or placebo (dextrose in half normal saline) for three months. The patients had the option of crossing over to the alternative therapy for three months after a one-month washout period. Therapy response was assessed with the neuromuscular symptom scale, the activities of daily living scale, a modified Medical Research Council (MRC) scale and photographs of the rash.[2] Improvement were considered major when the total MRC and total neuromuscular-symptom scores increased by five or more grades each and considered mild when they increased by two to four grades each.[2]

The statistical analyses were conducted in the patient groups originally assigned which made it an intention-to-treat analysis. Another separate analysis was conducted after the crossover.

Of the 15 patients enrolled, 8 were randomly assigned IVIG and 7 received placebo.[2] Allocation concealment appeared successful as it was performed at the pharmacy where the vial of IVIG or placebo was wrapped in foil and brought to the patient's room and an opaque bag covered the intravenous set. The physicians, nurses, physical therapists, photographers and statisticians were unaware of which treatment was administered. It is difficult to assess if patient randomization was successful since patient demographics (age, gender etc.) were not reported for the two groups. They did however, report that the two patient groups were balanced regarding neuromuscular symptoms, duration of disease immunosuppressive therapy, and serum creatine kinase levels.[2] All patients were taking prednisone with a mean daily dose of 25 mg. Information on the recruitment of patients was limited and was based on "patients referred to us because of therapy-resistant dermatomyositis," which could lead to sampling bias if they were referred from the same small community with similar demographics. There were no dropouts in the study, which eliminated attrition bias.

After the 3-month trial, the IVIG group had a significant improvement in muscle strength ($P<0.018$) and neuromuscular strength ($P<0.035$) whereas the placebo group had no change. Using the assessment scales in the IVIG group, five patients had a major improvement, two had a mild improvement and one was unchanged. In the placebo group, three patients worsened, two patients had no change, and two had a mild improvement. Using improvement as the trial outcome, the number needed to treat is 1.7. These findings were further enhanced after the crossover where four patients moving from placebo to IVIG had a major improvement while four patients moving from IVIG to placebo had worsening conditions or remained unchanged.[2] It was also mentioned in the study that patients with severe muscle weakness who were treated with IVIG reported not feeling this strong since before their disease onset.[2]

This trial was important and clinically relevant for patients who suffer from refractory dermatomyositis. As this disease is rare, the sample size is an obvious challenge causing low statistical power. According to the Strength of Recommendation Taxonomy (SORT) criteria, this study could be classified as Level 2; although it is a double-blind, placebo-controlled randomized trial, it has a small sample size and poor reporting of pre-treatment demographics and other confounders which limit the quality of the study.[11]

Clinical Application

This study provides evidence that IVIG is an effective treatment option for refractory dermatomyositis from the statistically significant symptom improvements, the low number need to treat, and the positive patient anecdotes. While the results of this trial are at high risk of bias due to the small sample size, it is still the best available

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evidence of effective therapy for a rare disease and can be useful when making clinical decisions. The trial demonstrated clinically meaningful improvements in muscle strength and function with IVIG.

This trial is applicable to our patient who was concerned about being unresponsive to prednisone and wanted to be informed about additional medications that could be added to her regimen to effectively treat her symptoms. This trial also helped define refractory dermatomyositis with similar definitions from other sources. Glucocorticoids have a 4-6 week timeline to normalize creatine kinase levels and 3-4 months to regain muscle strength and thus dermatomyositis should not be classified as refractory without considering these time factors.[8]

We assured our patient that if she continues prednisone and finds that her symptoms do not improve after 4 months, IVIG would be a reasonable option as additional therapy to improve her quality of life. The patient was anxious for her treatment regimen to show dramatic improvements immediately so she was disappointed that it could take more time and that her prednisone regimen would likely not be changed or additional therapy added until she was deemed refractory. Overall, she was more hopeful when she learned that other options are available if prednisone alone was not sufficient for treating her dermatomyositis.

Learning points:

1. IVIG has been shown to be an effective treatment for refractory dermatomyositis.
2. Refractory dermatomyositis is typically defined when the disease is unresponsive to high-dose prednisone or other immunosuppressants given for at least 4 months.
3. Research is limited on dermatomyositis due to its rarity. Unfortunately, larger studies are difficult to conduct. Still, decisions must be made, so the best available evidence must be used to aid in decision making.

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