The current status of treatment for inclusion-body myositis

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Abstract—There is no established treatment that improves, arrests, or slows the progression of inclusion-body myositis (IBM). Many anti-inflammatory, immunosuppressant, or immunomodulating agents have been administered to patients with IBM but the design of clinical trials was such that it can only be concluded that none produced rapid improvement. The natural history of the disease is for stabilization or improvement in a third of patients for 6 months or more. Thus some agents that did not produce dramatic benefit may have been prematurely abandoned. However, because high-dose prednisone worsens strength while decreasing inflammation but increases amyloid accumulation, alternative targets for intervention and novel treatment strategies are needed.

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There is no established treatment for inclusion-body myositis (IBM).[1] Despite the evident inflammation characteristic of the histopathology of IBM, no anti-inflammatory agent has had consistent benefit. In fact, the most frequent presentation of IBM in many referral centers is a patient who had been diagnosed as "polymyositis" but failed to respond to corticosteroids and other immunosuppressant treatments. This paper will review the agents that have been used for treatment of IBM, summarize the data for those agents that may have shown a possible beneficial effect, and consider the implications of the natural history of IBM for future therapeutic trials. It will also note possible reasons for apparent benefit of treatment in anecdotal reports. Specific treatments tried are listed in table 1.

Corticosteroids. In the majority of cases, corticosteroids do not appear to be of any benefit. There are occasional cases reported of "stabilization" for a period of months but this probably reflects the natural history of the disease.[1-3] In the rare instances where improvement has been claimed, the studies have been uncontrolled trials and an additional, coexisting steroid-responsive disease was not excluded. Many "responsive" cases have been published in abstract form and subsequent enquiry has established that the improvements have not been maintained.[1]

One open but prospective prednisone treatment trial in IBM deserves specific comment.[4] Eight patients with IBM (four men and four women) were treated with prednisone 100 mg/day for four weeks followed by alternate day prednisone for a minimum of six months and as long as 12 months. All eight patients worsened in average muscle strength despite a fall in creatine kinase (CK). Importantly, although biopsies taken before and after treatment showed a marked reduction in T-cells coincident with prednisone use, the number of amyloid-containing fibers actually increased. This study suggests that prednisone worsened IBM (because the natural history stabilizes or improves in one-third of patients). It also suggests that a fall in CK is not a useful marker for a favorable response to treatment. Most importantly it suggests that anti-inflammatory treatment, even when successful at reducing inflammation, may not be effective.

Cytotoxic drugs. Cytotoxic drugs have usually been added to corticosteroids following failure to respond to corticosteroids alone. The response to cyclophosphamide, chlorambucil, azathioprine, and cyclosporin is unimpressive in the small numbers reported.[1] Methotrexate has been studied in larger numbers with a few showing apparent stabilization or improvement but the study period has been too short to consider the benefit greater than the fluctuation seen in untreated patients.[5-7]

Immune-modulating therapy. Total body radiation, leukopheresis, and plasma exchange have not shown convincing benefit.[8-11] Initial prospective trials of immunoglobulin were interpreted as resulting in improvement, but subsequent randomized controlled trials have not substantiated worthwhile benefit.[12-14]

Beneficial responses to treatment in individual cases? There continue to be single cases or small case series reporting dramatic benefit of treatments in a population of patients with IBM. There are a

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Table 1 *Immunosuppressive agents and other therapeutic approaches used for inclusion-body myositis*

Corticosteroids
Oxandrolone
Cyclophosphamide, other alkylating agents
Azathioprine
Methotrexate
Cyclosporin
Total-body irradiation
Anti-T-lymphocyte globulin
Leukapheresis
Plasma exchange
Intravenous immunoglobulin
Myophenolate

number of reasons for discounting such "treatment responses." IBM is associated with other diseases, notably autoimmune disorders, many of them responsive to immune modulating or suppressive treatment. Pain, in particular, is not usual in IBM and its response to treatment can not be considered a response of the myopathy of IBM. Moreover, because IBM diagnosis depends on both clinical and biopsy criteria,[15] treatment-responsive cases must be carefully categorized by these criteria.

A study of the natural history of IBM noted that one-third of cases appear stable or show improvement for periods of 6 months or more. Clearly if such cases were given an agent, patient and physician would be tempted to conclude that there was a benefit from treatment.

The lack of a defined pathogenesis and a highly specific diagnostic test for IBM makes it likely that the disorder is heterogeneous and could have differing responses to treatment. Such differences might be obscured by even the best designed randomized, controlled treatment trials. Such a possibility can be dealt with by performing randomized, placebo-controlled trials in individual patients. Such trials have not been carried out.

Treatments of possible benefit. Interferon-β,[16,17] oxandrolone (table 2),[18] and anti-T-lymphocyte globulin treatment[19] have each shown a small and possibly important benefit. Grip strength improved with high dose interferon-β.[17] "Oxandrolone had a borderline significant effect in improving whole-body strength and a significant effect in improving upper-extremity strength as measured by MVICT."[18] Anti-T-lymphocyte globulin treatment for 12 months induced improvement: "Myometry showed that patients in the ATG group (n = 6) increased in mean muscle strength by 1.4% compared with the MTX group (n = 5), whose muscle strength decreased by 11.1% ($p = 0.021$)."[19]

Table 2 *Treatments of possible benefit*

• Oxandrolone
• Anti-T-lymphocyte globulin
• High-dose beta interferon 1a

Responders vs non-responders: Possible subcategories of IBM. The short-term (<6 months) "stabilization" or even improvement of individual patients with IBM can be dismissed as simply a coincidental reflection of the variable natural history of the disorder. Nonetheless, there are reasons to consider the possibility that IBM includes two or more distinct disorders differing in pathogenesis and possibly therapeutic target/strategy. In thinking about pathogenesis, it is probably wise to find one cause before looking for another. However, for treatment one can argue for an approach to individual cases that might identify a subset of patients responsive to treatment. Patients with autoimmune, inflammatory, or collagen-vascular disease often respond to corticosteroids and to other immune suppressant medications. Because up to 4% of elderly subjects have polymyalgia rheumatica/giant cell arteritis and a similar percent have rheumatoid arthritis, pain, stiffness, and major functional limitations may respond dramatically. It will be problematic to know whether IBM or only the coincidental disease responds to treatment. Initiating treatment with analgesics as opposed to corticosteroids is one approach to limiting confusion.

Natural history of IBM and the design of randomized, controlled trials. Three studies of carefully defined patients with IBM have followed the natural history prospectively in untreated subjects.[3,16,17] The first, conducted without administration of placebo, followed 11 subjects for six months.[3] Prospective measurements of muscle strength, muscle mass, and lean body mass were performed. All subjects were ambulatory; none had been treated with corticosteroids for at least six months or cytotoxic drugs for at least one year. Strength was determined as maximum voluntary isometric contraction (MVIC) by a clinical evaluator trained to a standard of high test-retest reliability. There was an overall 4% decrease of strength from baseline in the six-month period. Importantly, over one-third of patients (4/11) stabilized or improved (figure).

In two recent randomized, controlled treatment trials,[16,17] a total of 29 placebo-treated IBM patients were followed for 24 weeks. Such placebo-treated patients are potentially more informative concerning the expected response of patients with IBM who are entered into any treatment trial. The placebo data from these two trials suggest that detecting a desired treatment effect of arrest of the progression of the disease may require over 200 subjects per group for a 6-month trial and over 100 subjects per group for a 12-month trial.

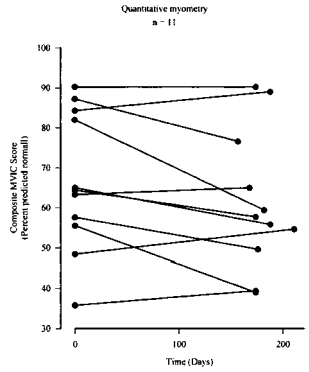

Figure. Six-month natural history study. Quantitative myometry in 11 subjects with IBM. (Reprinted with permission from Rose et al.[3])

Implications of the natural history for past and future clinical trials. Previous short-term trials demonstrating arrest or even slight improvement of IBM cannot be interpreted as indicative of a response to treatment. On the other hand, because diagnosis of IBM has become relatively straightforward and early recognition is possible, arrest of the disease is an acceptable goal for treatment. No clinical trials powered for arrest of the disease have been conducted. Thus agents that have not actually worsened the course have never had an adequate trial.

Supportive care strategies. The lack of specific treatment can lead to a nihilistic approach to patient follow-up. However, there are sensible treatment strategies that may prevent disability in IBM (table 3). Many patients with IBM are initially misdiagnosed as "polymyositis" and prescribed corticosteroids. Such patients frequent have arthritis, chronic obstructive lung disease, or other coincidental disease. Corticosteroid reduction and discontinuation is usually indicated but may require alternative treatment for pain, or other symptoms from coincidental disease.

Patients on long-term corticosteroids who have been permitted to become inactive can regain function, even at times ambulation, with corticosteroid withdrawal and exercise. Patients with dysphagia and weight loss can have swallowing function restored by cricopharyngeal myotomy. Patients with osteroarthritis and other arthropathies derive major benefit from appropriate treatment. Most bracing/orthoses are not helpful. However, ankle-foot orthoses (AFO) for foot drop are the major exception; AFOs are well-tolerated and of major benefit in appropriate cases. Virtually all patients who require AFOs require preventive treatment for dependent leg edema.

Table 3 *Supportive and rehabilitative strategies*

- Corticosteroid dose reduction/discontinuation: may require alternative treatment for COPD/arthropathy
- Exercise: may require analgesics
- Swallowing dysfunction—cricopharyngeal myotomy
- Ankle-foot orthoses for foot drop
- Prevent ankle edema

Prospects for the future. The failure of corticosteroids and many other immune active agents in IBM has not dampened enthusiasm for trying new classes of agents that have immune modulating effects. TNF-alpha receptor blockers, calcineurin inhibitors, and anti-integrins are each under active discussion as possible treatments. There has been progress in understanding the importance of amyloid-B, misfolded proteins and genetic predisposition,[20] all in the context of aging. These will form the basis for considering new strategies for treatment.

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