Use of methotrexate in inflammatory myopathies

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ABSTRACT
The inflammatory myopathies are a heterogeneous group of diseases including dermatomyositis, polymyositis, and inclusion body myositis. Few clinical trials have been reported in myositis, it is difficult to make definitive recommendations for the treatment of these potentially life threatening diseases. In addition to treatment with corticosteroids, immunosuppressive agents and immunomodulatory therapy are used to improve disease control and reduce the long-term side effects of corticosteroids. While these treatments are commonly used in routine clinical practice, the optimal therapeutic regimen remains unclear. However, most patients with dermatomyositis or polymyositis are treated with oral high-dose prednisone combined with azathioprine or methotrexate to facilitate tapering of prednisone.

Introduction
The inflammatory myopathies are a heterogeneous group of rheumatic diseases including dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM).

In 1975, Bohan and Peter first suggested a set of criteria to aid in the diagnosis and classification of dermatomyositis and polymyositis (1, 2). Four of the 5 criteria are related to the muscle disease: progressive proximal symmetrical weakness, elevated levels of muscle enzymes, an abnormal finding on electromyography, and an abnormal finding on muscle biopsy; the 5th criterion relates to cutaneous disease (1, 2). The association between DM and possibly PM and malignancy has been recognised for a long time. DM is a systemic disorder that frequently affects the esophagus and lungs and, less commonly, the heart (3, 4). Calcinosclerosis is a complication of DM that is observed most often in children and adolescents. Rather characteristic clinical signs are Gottron papules consisting of slightly elevated violaceous papules and plaques that are found over bony prominences, particularly the metacarpophalangeal and the interphalangeal joints (3, 4).

Autoantibodies are frequently present; some are more specific for myositis. The most frequent of these are the anti-aminoacyl tRNA synthetase antibodies of which the histidyl-tRNA synthetase antibody (anti-Jo-1) is the most common, present in >20% of poly- or dermatomyositis patients (5, 6). The anti-synthetase autoantibodies are associated with a distinct clinical phenotype, the anti-synthetase syndrome, which is characterised by myositis, ILD, arthritis, Raynaud’s phenomenon and skin changes on the hands, named mechanic’s hands (3-6). Other so-called myositis specific auto-antibodies, anti-Mi-2 and anti-signal recognition peptide (SRP) auto-antibodies, are less common (3-6). Presence of autoantibodies together with cellular infiltrates of T cells in muscle tissue suggests that polymyositis and dermatomyositis are auto-immune diseases (3, 4).

PM and DM are both characterised by chronic inflammation of skeletal muscle (3, 4, 7). The inflammatory cellular infiltrates are typically composed of T cells and macrophages, although infiltrates with B cells have been observed in occasional patients, often with DM. There seem to be two patterns of the localisation and cellular composition of the inflammatory infiltrates in the skeletal muscle. In patients with typical skin rash of DM, the inflammatory cellular infiltrates are predominantly localised to areas surrounding blood vessels, perivascularly and mainly observed in the perimysium surrounding the muscle fascicles. These perivascular infiltrates are predominated by CD4+T cells and by macrophages and dendritic cells. B cells are detected. Occasionally, in PM patients with no skin rash, the inflammatory infiltrates are typically localised within the muscle fascicles, in the endomysium, surrounding muscle fibres.
These endomysial infiltrates are composed predominated of CD8+ T cells and macrophages. Other characteristic histopathological features are muscle fibres changes, such as fiber degeneration or necrosis and regenerating fibres. These observations suggest that there may be two different pathways that are involved in the chronic muscle inflammation in skeletal muscle. However, this sharp distinction between DM and PM has recently been challenged (8). Methotrexate (MTX) is an antimetabolite and antifolate agent with antineoplastic, immunosuppressant, and anti-inflammatory activities. MTX binds to and inhibits the enzyme dihydrofolate reductase, resulting in inhibition of purine nucleotide and thymidylate synthesis and, subsequently, inhibition of DNA and RNA syntheses (9, 10). In rheumatoid arthritis, and possibly other rheumatic diseases, the primary mechanism of action involves anti-inflammatory activity, as discussed elsewhere in this supplement (11).

Treatment of polymyositis and dermatomyositis

The prevalence of the inflammatory rheumatic myopathies is in the range of 11/100,000 – thus, these diseases are relatively rare (12). Therefore, very few studies with large patient numbers and only a few randomised controlled trials have been performed. On the basis of clinical experience, there is no reasonable clinical doubt that prednisolone is efficient, generally initially in rather high doses which may be tapered in the course of disease to lower doses. Various retrospective studies showed some efficacy of the combination of prednisolone and MTX in the treatment of the myositides (13-17). Due to the low prevalence of the myositides, there are mainly studies combining both, DM and PM, although there is some evidence for differences in the pathogenesis (3, 8).

The question whether the addition of MTX to prednisone is superior to prednisone alone cannot be answered on the basis of randomised controlled trials. All three randomised controlled studies on MTX compare its efficacy with other immunosuppressants or with a combination of MTX with azathioprine (AZA, 18-20). In one study, patients with DM or PM (n=28) were treated with MTX or AZA in dosage of 15mg/week and 2.5mg/kg/day, respectively, in addition to prednisolone, over one year (18). In a second study (n=36) oral MTX 7.5–15mg/week (mostly 10mg/week) was compared to ciclosporine (CYA) in a dosage of 3–3.5mg/kg/day over at least 6 months (19). In the third study, MTX was given intravenously (i.v.) in a dosage of 500mg/m² every 2 weeks for 24 weeks – with every application being followed by leucovorin, and compared to a combination of oral MTX dosed up to 25mg/week and AZA 150mg/day for 6 months (20). No significant differences in efficacy were seen between the groups. However, the tolerability of MTX alone was better than with the combination. There were also no differences between DM and PM patients.

A Cochrane based review by Choy et al. has been published in 2005 (21). A recent update with some changes will soon be published. However, no major changes in therapy have been introduced over the last 5 years.

One open-label trial with a rather small number of early untreated PM or DM compared MTX and the TNF blocker infliximab (22). The results reported were inconsistent, as some patients improved, and others did not. The trial was discontinued because of legal problems. No firm conclusions can be drawn from this study.

In a small study with the B cell depleting antibody rituximab, all 6 evaluable patients with DM exhibited major clinical improvement, with muscle strength increasing over baseline by 36–113%. Maximal improvements in muscle strength occurred as early as 12 weeks after the initial infusion (23). In contrast, in another study with 8 patients, the results were much less convincing, as muscle enzyme levels and skin scores at week 24 were not significantly different from those at baseline. However, 3 patients had improved muscle strength and achieved partial remission at week 24 (24).

Juvenile dermatomyositis

Juvenile inflammatory myopathies also are rare diseases, the incidence of DM is in the range of 2–3/1,000,000 children per year (25) – and DM is much more frequent than PM in children (26). The symptoms of juvenile DM vary according to the localisation of the affected muscles and the skin, in addition to the potential involvement of inner organs – as in adult disease (3, 27). In spite of improved therapeutic possibilities DM is associated with increased mortality rates (28), as seen in all inflammatory rheumatic diseases.

There are no controlled studies of treatment in juvenile DM. Because of the rather favourable experiences with MTX therapy in juvenile arthritis (29, 30) MTX is frequently used in juvenile DM – as well of course in addition to corticosteroids that are always necessary, AZA is also given (26).

Several small, uncontrolled retrospective studies showed that the addition of MTX to prednisolone was beneficial in juvenile DM (27, 31, 32). In a study published in 2002, children with juvenile DM (n=35) were treated with MTX after 6 weeks of therapy with prednisolone. This increased the improvement rates significantly, with fewer cases of calcinosis (33). In a recent study (n=49), MTX was started very early in combination with prednisolone. This was very successful, since drug-free remission within 3 years was observed in 28 cases (57%) – again with fewer cases of calcinosis (34). However, in cases of insufficient response after 3 months, some patients had received CyA, intravenous (i.v.) immunoglobulins, tacrolimus and plasmapheresis in addition. Of interest, unfavourable outcomes were observed primarily in patients who received therapy at a later timepoint (34). In another study with 31 patients, additional therapy with MTX led to significant reductions of the prednisolone dose (35); again, many patients were also treated with i.v. immunoglobulins.

Inclusion body myositis (IBM)

IBM is primarily a disease of older people who report a slow course of worsening of muscle functions and weakness. In comparison to DM and PM, the serum values of creatinine kinase (CK)
are rather low. Histologically, endomyositis, cell infiltrates and basophil rimmed vacuoles are seen in affected muscle cells (36). The diagnosis is usually made by electron microscopy (36). However, the pathophysiology of IBM has remained largely obscure. It is unclear whether IBM is a primary inflammatory disorder or a degenerative disease with secondary inflammation.

No therapy has convincingly proven effective to date but positive results of therapeutic trials with prednisolone, CyA or tacrolimus have been reported (37, 38). One randomised double-blind, placebo-controlled study in 44 patients with IBM compared treatment for a total of 48 weeks with MTX or placebo. Although CK levels fell significantly in the ATLG group after one year (39), power was reported to have occurred in (ATLG). Significantly improved muscle biopsy infiltrates and basophil rimmed vacuoles of European patients with myositis. Ann Rheum Dis 2001; 60: 116-23.


