

Myositis

diagnosis and management

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INTRODUCTION

The inflammatory myopathies comprise a group of acquired myopathies in which muscle weakness and inflammatory infiltrates are the principal clinical and histological findings. Traditionally, a distinction is made between polymyositis, dermatomyositis and inclusion body myositis. This brief review will focus on polymyositis.

CLINICAL FEATURES

Diagnostic criteria

Polymyositis is characterized by symmetrical proximal muscle weakness. Respiratory, pharyngeal and neck muscles may also be involved during later stages of the disease (Dalakas & Sivakumar 1996; Mantegazza *et al.* 1997; Dalakas 1998a). Up to half the patients suffer from muscle pain or arthralgia. The history, clinical symptoms and signs, elevated serum levels of muscle enzymes, electrophysiological changes and histological findings together provide the basis for the diagnosis. The main diagnostic criteria

	Polymyositis	Dermatomyositis	Inclusion body myositis
Age at manifestation	> 18 years	any age or two peaks: 5–15 and 45–65 years	> 50 years
Female: male ratio	2 : 1	2 : 1	1 : 3
Muscle involvement	proximal symmetrical	proximal symmetrical	distal to proximal, asymmetrical
Atrophy	+	(+)	++
Muscle pain	(+)	+	(+)
Serum CK	up to 50 times elevated	normal to 50 times elevated	normal to 10 times elevated
EMG	myopathic	myopathic	myopathic + mixed large units
Muscle biopsy	peri- and endomysial infiltrate, invasion of MHC I + fibres	perifascicular atrophy ± infiltrate (perivascular and perifascicular)	prominent endomysial infiltrate atrophic fibres, 'rimmed vacuoles' eosinophilic inclusions
Immunohistochemistry	autoinvasive CD8+ T-cells, macrophages	B-cells, macrophages CD4+ T-cells	autoinvasive CD8+ T-cells, α -amyloid, prion-protein, others
Electronmicroscopy		Tubulovesicular inclusions in capillary endothelium	helical filaments, fibrils

Table 1 Clinical and diagnostic criteria of the inflammatory myopathies.

and features are summarized in Table 1 for polymyositis and for the two other forms of idiopathic inflammatory myopathies, dermatomyositis, and inclusion body myositis. Clinically, polymyositis and dermatomyositis are distinguished by the characteristic skin changes seen in the latter but not the former.

Extramuscular manifestations

Cardiac involvement with ECG changes, pericarditis, cardiomyopathy or heart failure can occur during all stages of the disease. Pulmonary complications, which occur in 50% of all three types of myositis, can be secondary to aspiration or reduced vital capacity (if the pharyngeal or respiratory muscles are affected). Furthermore, about 10% of patients with polymyositis develop interstitial lung disease and about 50% of these patients have autoantibodies directed against histidyl transfer RNA (tRNA) synthetase, so-called Jo-1 antibodies. Interstitial lung disease indicates a severe course and poor prognosis.

EPIDEMIOLOGICAL AND GENETIC FACTORS

Polymyositis, like dermatomyositis, affects women twice as often as men. In contrast, inclusion body myositis affects men three times more often than women and usually begins after

the age of 50 years. The incidence of polymyositis has been estimated to be around 5–10 per million per annum and the prevalence 6–7 per 100 000.

There are numerous reports on the association of certain HLA haplotypes with subgroups of myositis (Engel *et al.* 1994). For example, polymyositis is associated with HLA-B8 and HLA-DR3 in white people; juvenile dermatomyositis with HLA-B8, HLA-DR3, HLA-DQA1 (DQA1*0501); inclusion body myositis with DR3, DRw52, B8; and the antisynthetase syndrome with B8, DR3, DRw52, DQA1*0501.

OVERLAP SYNDROMES

The overlap syndromes are a group of disorders in which an inflammatory muscle disease with the clinical and histological features of polymyositis occurs in association with another connective tissue disorder, such as scleroderma, mixed connective tissue disease, Sjögren's syndrome, systemic lupus erythematosus, or rheumatoid arthritis.

ASSOCIATION WITH MALIGNANCIES

The association of myositis with malignancies ranges between 0 and 28% for polymyositis and 6–45% for dermatomyositis in older studies (Engel *et al.* 1994). A retrospective analysis

of 1078 myositis patients from four well-controlled studies revealed that in 153 patients cancer was discovered between 5 years before and 5 years after the diagnosis of myositis (Zantos *et al.* 1994). The relative risk of suffering from cancer was 2.1 for polymyositis and 4.4 for dermatomyositis patients. A more recent study provides evidence that the overall risk of malignant disease is only modestly increased among patients with polymyositis (1.3 relative risk), with excess for some cancers: non-Hodgkin lymphoma (3.7), lung (2.8) and bladder cancers (2.4) (Hill *et al.* 2001). The risk of an associated malignancy is greatest in older patients with dermatomyositis. In such patients, a thorough search for an underlying neoplasm is clearly warranted. There is no increased risk of malignancy in inclusion body myositis.

LABORATORY FINDINGS

Creatine kinase

Of the enzymes released as a consequence of muscle fibre injury, the serum concentration of creatine kinase (CK) provides the best estimate of the extent of muscle damage and clinical activity. Both BB and MM isoenzymes may be elevated. The serum enzyme levels are often normal in inclusion body myositis and in children with dermatomyositis. However, CK levels can be elevated by up to 50 times the normal level in active disease phases of polymyositis. In

Figure 1 Increased signal intensity (arrows) in several muscles caused by fatty replacement of muscle tissue in polymyositis (thigh, T1-weighted axial image).



contrast, the erythrocyte sedimentation rate is not a reliable parameter for disease activity and is normal in half the patients.

Myositis-specific autoantibodies

In a minority of patients, myositis-specific autoantibodies are detectable in the serum (Miller 1993). Although the pathogenetic relevance of these autoantibodies has yet to be defined, they are often associated with certain disease characteristics and HLA haplotypes (Miller 1993; Engel *et al.* 1994).

One group of myositis-related antibodies, including antinuclear antibodies and other serological markers of collagen-vascular disease, can be considered as markers for an overlap syndrome. Another group of antibodies, the so-called myositis-specific antibodies, include antibodies directed against different components of the translational apparatus (e.g. transfer RNA synthetase or signal-recognition particle). Whether these antibodies are merely markers of disease activity or have direct pathogenic importance is unknown. Clinically, the most significant antibodies are the antitransfer synthetase antibodies, especially the antibody against histidyl-tRNA synthetase, also called Jo-1. This antibody helps define the anti-synthetase syndrome (myositis overlapping with polyarthritis, Raynaud's phenomenon, and/or interstitial lung disease) and was found recently in 18% of a large group of European patients (Brouwe *et al.* 2001).

Neurophysiology

Electromyography typically shows fibrillations and positive sharp waves. Action potentials are of low amplitude. Spontaneous activity serves as an indicator for the extent of inflammation. Neuropathic, in addition to myopathic changes are often seen in inclusion body myositis. However, in any form of myositis the EMG can be normal.

Imaging

Magnetic resonance tomography (MRT) may help demonstrate areas of muscle involvement, characterize the abnormality, evaluate disease progression with follow-up scans, and allow more accurate localization for muscle biopsy (Fig. 1).

Muscle biopsy

The single most important investigation for es-

tablishing the diagnosis of myositis is the histological evaluation of a diagnostic muscle biopsy (Hall 2001). If possible, an open biopsy of an affected muscle should be performed under local anaesthesia. Muscles that have been subjected to electromyography within the previous two weeks should not be biopsied in order to avoid artifacts. The choice of an affected muscle may be aided by sonographic or magnetic resonance imaging.

PATHOGENESIS

Histological features

In polymyositis the endomysial inflammatory infiltrate is typically dominated by CD8⁺ T lymphocytes, which surround, invade and eventually destroy muscle fibres (Fig. 2). A strikingly limited T-cell receptor repertoire is expressed in polymyositis muscle associated with a dissociation between the T-cell receptor usage of autoinvasive and interstitial T cells (Fig. 3) (Bender *et al.* 1995). The autoinvasive T cells are clonally expanded in muscle and in blood (Bender *et al.* 1995; Benveniste *et al.* 2001). In a rare subtype of polymyositis the infiltrate consists of gamma-delta T-lymphocytes (Hohlfeld *et al.* 1991). In contrast to noninflamed muscle, the invaded muscle fibres express HLA class I molecules. This is a prerequisite for the immunological interaction with CD8⁺ T cells. The different stages of cytotoxic T lymphocyte-mediated myocytotoxicity have been analysed by immunoelectron microscopy (Arahata & Engel 1986). Initially, CD8⁺ cells and macrophages abut on and send spikelike processes into non-necrotic muscle fibers. Subsequently, an increasing number of CD8⁺ cells and macrophages traverse the basal lamina and focally replace the fibre.

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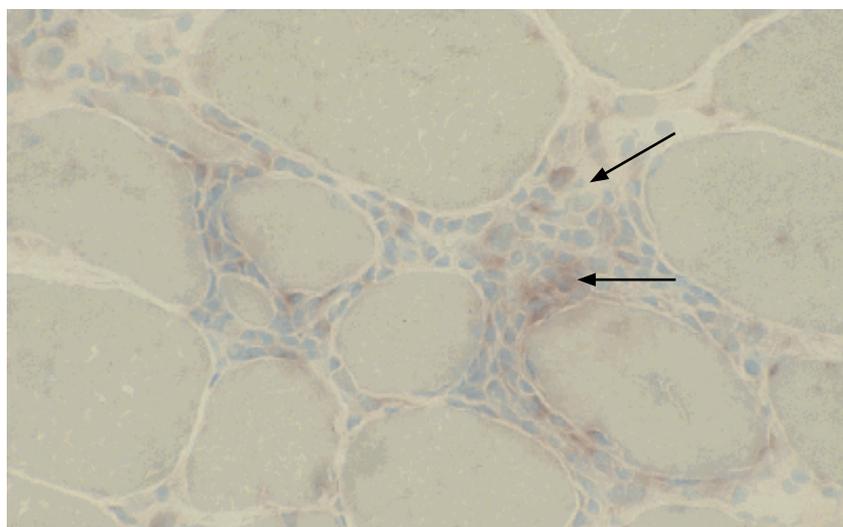


Figure 2 Inflammatory infiltrate in polymyositis muscle. Acid-phosphatase-positive (red) cells staining macrophages (arrows).

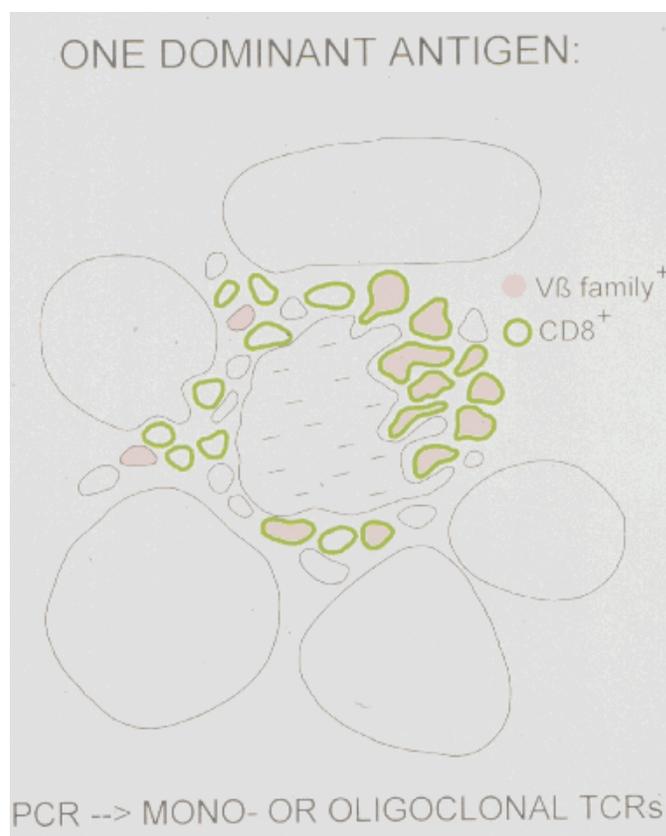


Figure 3 Scheme of the typical histological changes observed in polymyositis. T cells surround and invade a muscle fibre. A strikingly limited T-cell receptor repertoire is expressed in polymyositis muscle associated with dissociation between the T-cell receptor repertoire usage of autoinvasive and interstitial T cells. The autoinvasive T cells are clonally expanded as demonstrated by polymerase chain reaction.

Immunosuppression is the main therapeutic approach. Regular examination of muscle strength and serum CK is essential to assess the effect of treatment. However, a reduction of CK does not reliably reflect clinical improvement

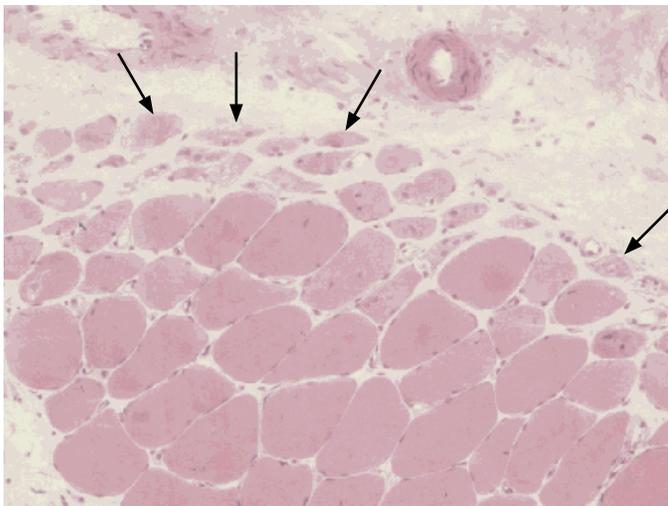


Figure 4 Perifascicular atrophy in dermatomyositis (H&E stain). Arrows point to atrophic muscle fibres at the periphery of the fascicle.

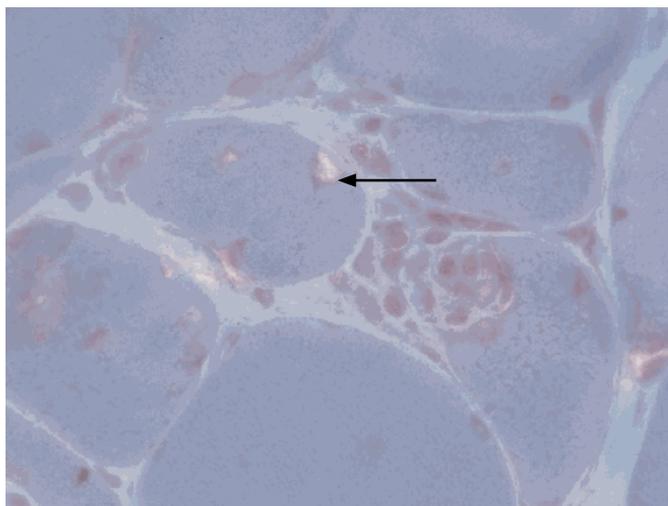


Figure 5 Trichrome stain of a muscle section of a patient with inclusion body myositis. Note rimmed vacuole (arrow) in one of the muscle fibres.

In dermatomyositis, capillary changes are an early and prominent finding (Fig. 4). Capillary depletion and deposition of complement point to a humoral effector mechanism. In inclusion body myositis, many otherwise normal-appearing muscle fibres express the small heat-shock protein alphaB crystalline (Fig. 5).

Cytotoxic effector mechanisms

The precise mechanism by which the invading CD8⁺ T cells kill muscle fibres in polymyositis is still unknown, but there is evidence of a contribution from a perforin- and secretion-dependent mechanism. Perforin has been detected in inflammatory T cells in polymyositis but not dermatomyositis (Goebels *et al.* 1996). The autoinvasive T cells orient their perforin-containing cytotoxic granules towards the target muscle fibre, providing suggestive evidence that secretion of this cytotoxic effector molecule contributes to muscle fibre injury.

In addition to perforin-dependent killing, cytotoxic T cells can kill by a nonsecretory, ligand-mediated mechanism. However, in several studies, different investigators have found no evidence that apoptosis is a mechanism of muscle fibre injury in human inflammatory myopathies (Schneider *et al.* 1996; Behrens *et al.* 1997).

Cytokine expression

The increased expression has been reported of both proinflammatory cytokines (possibly implicated in the muscle inflammation) such as interleukin-1 (IL-1) or tumour necrosis factor (TNF), and adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) in patients with polymyositis (Bartoccioni *et al.* 1994; Lundberg *et al.* 1997). This expression could be modulated by current standard treatment (Lundberg *et al.* 2000). The local production of cytokines is likely to induce several molecules that subserve cell interaction and adhesion. Cytokines should be the target of future therapy in polymyositis, as in rheumatoid arthritis or Crohn's disease (Feldman *et al.* 1998).

PROGNOSIS

If there is no malignancy, five-year survival rates of between 70% and 90% have been reported (Engel *et al.* 1994). Indicators for a poor prognosis include increased age, extramuscular organ involvement (heart, lung, pharyngeal muscles), acute onset of the disease, malignancy and late

or insufficient treatment. Functional recovery is best if treatment is started within the first six months of the disease onset.

TREATMENT

Immunosuppression is the main therapeutic approach. Regular examination of muscle strength and serum CK is essential to assess the effect of treatment. However, a reduction of CK does not reliably reflect clinical improvement. Clinically, the patient's feeling of strength can increase even with placebo treatment and methods for objective quantification of muscle force are not widely used. Most clinicians use the British Medical Research Council scale but this gives only a relatively rough and partly subjective estimate of muscle strength. Magnetic resonance tomography with fat suppression sequences may also be helpful for follow-up in some cases.

Corticosteroids

A number of treatment studies have been performed to test the effect of corticosteroids in myositis. However, these often did not differentiate between dermatomyositis, polymyositis and treatment-resistant inclusion body myositis. Nevertheless, corticosteroids remain the treatment of first choice for both dermatomyositis and polymyositis (Dalakas 1991; Mastaglia *et al.* 1997; Rider & Miller 1997; Amato & Barohn 1999). For severe and acute disease, high dose (0.5–1 g/day) i.v. methylprednisolone for 3–5 days may be considered. Usually, however, adults are treated with 1 mg/kg body weight/day prednisolone as a single oral dose in the morning. After normalization of CK values, which can take 8–12 weeks, daily doses are tapered every week by 5–10 mg. Following this regimen, a daily dose of 5–10 mg prednisolone, or 10–20 mg on alternate days, is reached after 4–6 months (alternate day prednisolone is equally effective but seems to be associated with less adverse effects than daily doses). Changes of CK activity precede clinical improvement. In patients who deteriorate while on prednisolone, relapse of the myositis needs to be distinguished from steroid myopathy. Features indicating steroid myopathy rather than relapse of the myositis include a normal CK and a lack of abnormal spontaneous activity on EMG. With myositis relapse there may be gadolinium enhancement on MR tomography, but sometimes a repeat biopsy has to be performed to ascertain what is going on. Some of the well-known adverse affects of long-

term corticosteroids, such as gastric ulcers or osteoporosis, can be ameliorated by comedication of antacids or H₂-blockers, and oral supplementation with calcium and vitamin D. Patients may benefit from bisphosphonate treatment and postmenopausal women may also benefit from oestrogen supplements.

Treatment of myositis with immunosuppressants is empirical and may be required for years despite attempted slow withdrawal after the patient has been in remission for 2–3 years. The order of preference varies according to experience or on a case-by-case basis. Very few randomised trials are available for these agents (Lundberg & Chung 2000b).

Azathioprine

Most myositis patients require long-term immunosuppression (Dalakas 1991; Mastaglia *et al.* 1997; Rider & Miller 1997; Amato & Barohn 1999). Because of the adverse effects of prolonged corticosteroids, it is desirable to minimise the corticosteroid dose. Treatment with azathioprine, a 6-mercaptopurine derivative, allows the physician to reduce the dose of corticosteroids. Because it takes at least 2–3 months for azathioprine to become effective, therapy is often started with a combination of azathioprine and corticosteroids. The recommended dose of azathioprine is 2–3 mg/kg bodyweight/day.

The incidence of serious adverse effects of azathioprine is relatively low. The most frequently-observed during long-term treatment in patients with generalized myasthenia gravis, in decreasing order of frequency, were: reversible marrow suppression with leukopenia, gastrointestinal complications, infections and transient elevations of liver enzymes (Hohlfeld *et al.* 1988). Patients should be monitored carefully for adverse effects. Complete blood counts should be obtained at least weekly during the first two months, and then monthly thereafter. If the total white cell count is reduced to less than 3000/ μ L, the medication should be discontinued for a few days and treatment continued at a lower dose after the white count returns to more than 3500/ μ L. The long-term dose can be adjusted to maintain the white count around 4000/ μ L, and lymphocyte counts ranging between 800 and 1000/ μ L. However, it is not certain whether the immunosuppressive efficacy of azathioprine therapy in autoimmune disease is directly correlated with either the white blood cell or lymphocyte count.

In patients taking azathioprine and corticosteroids, the total white blood cell count is usually elevated because of steroid-induced neutrophilia. Therefore, the preceding suggestions for monitoring therapy do not apply. A white cell count of 6000–8000/ μL as the lower limit during combined treatment should be used. The lymphocyte count is less markedly altered by corticosteroids and can also be used for monitoring.

Another measure of drug effect is the mean corpuscular volume of the red cells, which is usually but not invariably elevated (up to 15%) during long-term treatment. This may be useful in situations when there is doubt about the compliance of patients taking their medication.

An important drug interaction occurs with allopurinol. Inhibition of xanthine oxidase by allopurinol impairs the conversion of azathioprine to 6-thiouric acid, which accumulates and eventually leads to myelosuppression. If allopurinol has to be administered concurrently, the dose of azathioprine must be reduced to 25% of the regular dose, and the white blood count should be closely monitored.

Methotrexate

An alternative to azathioprine is the folic acid antagonist methotrexate, given in a starting oral dose of 7.5 mg/week. After three weeks the dose may be increased, according to clinical symptoms, in 2.5 mg steps per week up to a total dose of 10–25 mg/week. Methotrexate can cause interstitial lung disease, so it should be avoided in patients with myositis who already have the associated interstitial lung disease. Baseline and periodic pulmonary function tests should be obtained in patients treated with methotrexate. Complete blood counts and liver function tests should also be monitored regularly.

Other immunosuppressive agents

Cyclosporine inhibits T-cell activation and is routinely used to prevent transplant rejection. In myositis, daily doses between 2.5 and 5 mg/kg body weight have been used. Cyclosporin requires regular monitoring of the blood level and kidney function because of the variable absorption and dose-dependent nephrotoxicity, which usually occurs only with doses above 5–6 mg/kg body weight. Pre-existing kidney disease and elevated blood pressure increase the risk of kidney damage.

Treatment with cytotoxic drugs such as cyclophosphamide, may be required for patients re-

fractory to other agents and in cases of severe extramuscular organ manifestations such as interstitial lung disease.

Intravenous immunoglobulin (IVIg)

Immunoglobulin preparations consist mostly of IgG and are derived from the pooled immunoglobulins of several thousand donors. The mechanism of action is not completely understood (for review see Voltz & Hohlfeld 1996; Dalakas 1998b; Pritchard & Huges 2001). High-dose IVIg has been tried in randomised controlled trials in all three major subsets of the inflammatory myopathies (for review, see Dalakas 1998c). The most convincing effect was observed in a double-blind crossover study in patients with dermatomyositis (Dalakas *et al.* 1993). In polymyositis, uncontrolled trials have shown improvements in muscle strength, but efficacy has not yet been established with controlled trials.

The IVIg dose used in most studies was between 1.6 and 2 g/kg body weight per treatment cycle. Because of the effect on blood viscosity of the large protein load, a fractionated infusion distributed over five days is recommended for the initial (empirical) treatment protocol. Depending on the clinical symptoms, treatment cycles may be required every 6–8 weeks.

Frequent (up to 15%) but harmless adverse effects include fever, headache, nausea and myalgias. Rarely, anaphylactic reactions (mostly in patients with Ig A deficiency), haemolytic anaemia and acute disturbances of kidney and liver function can occur. An increased risk for ischaemic events has been described in patients with previous heart or brain infarcts, or migraine. Most IVIg preparations contain different types of sugar additives, so for patients with diabetes mellitus or fructose intolerance, suitable preparations need to be chosen. Major disadvantages of IVIg therapy are the high cost and the need for repeated treatment cycles. During treatment, serum electrolytes, kidney and liver function, and the direct Coombs test should be monitored (Voltz & Hohlfeld 1996).

Plasmapheresis

Although beneficial effects of plasmapheresis in myositis have been reported in case reports and open studies, a randomized, placebo-controlled trial failed to demonstrate a significant effect of either plasmapheresis or leukapheresis over placebo (Miller *et al.* 1992).

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