**IMMUNOSUPPRESSANTS IN INFLAMMATORY MYOPATHIES**

**Renato Mantegazza**
*Fondazione Istituto Neurologico Carlo Besta, Milan, Italy*

The main concerns about treatment for Idiopathic Inflammatory Myopathies (IIM) are related to the following aspects: i) identification of homogeneous subgroup of patients based on consensus criteria shared by distinct specialists (neurologists, rheumatologists or dermatologists); ii) controlled trials are few; iii) there are no standardized outcome measures to reflect changes in clinical evaluation, functional disability, quality of life [Distad et al., 2011].
The ideal therapy for the treatment of IIMs should be tailored on the basis of the immunopathogenetic mechanisms, which are distinct in the three major forms: polymyositis (PM), dermatomyositis (DM) or inclusion body myositis (IBM). PM is considered a cell-mediated, mostly CD8+, myocytotoxic myositis, DM an antibody-mediated microangiopathic myositis and IBM a degenerative myopathy (either sporadic or genetic) associated with an inflammatory reaction very similar to that observed in PM.
*Conventional therapies.* The main treatments for PM and DM are drugs that suppress or modify the immune system [Distad et al., 2011]. Oral corticosteroids (in particular a high dose of prednisone) represent the first-line medications used to manage these conditions. When the treatment with these drugs is prolonged for a long period, or when the disease reveals refractory to therapy, a second-line agent, usually a chronic, steroid-sparing immunosuppressive drug, such as azathioprine, methotrexate and mycophenolate mofetil, is added. Third line medication includes tacrolimus, cyclosporine and cyclophosphamide, whose use is based on small case series. Second and third line medications often allow corticosteroid dosages to be reduced, but monitoring is required for their own side effects, such as bone marrow suppression, kidney dysfunction, and respiratory concerns.
Intravenous immunoglobulin has also been reported effective by some controlled studies [Basta & Dalakas, 1994; Saadeh et al., 1995; Cherin et al., 1994; Sansome & Dubowitz, 1995, as cited in Choy & Isenberg, 2002], producing clinical improvement together with reduction in complement deposition, membrane attack complex formation, inflammation, fibrosis, cytokines, chemokines and adhesion molecules, especially in DM patients [Dalakas, 2011a].
*Emerging therapies.* These treatments target specifically key immunopathogenetic mechanisms responsible of IIMs in order to provide a very selective intervention. They are mostly humanized monoclonal antibodies, which on one hand avoid the daily administrative schedules, but on the other the safety profile is still not fully ascertained.
The most relevant encompass: Rituximab, a monoclonal antibody that depletes B cells, has also shown efficacy in uncontrolled studies on DM patients and is a promising treatment for the disease [Noss et al., 2006; Levine, 2005]; Infliximab, a blockers of TNF-a, has been studied in a clinical trial but its use was hampered by the occurrence of significant side effects and a high dropout rate [Hengstman et al., 2008]; a pilot study was conducted by the US Muscle Study Group to assess in DM the safety/tolerability, the steroid sparing effect and the outcome using Etanercept: no major safety concern and a steroid sparing effect was noted, suggesting further investigation with this drug [Muscle Study Group, 2011]. Other treatments currently under study include new agents targeting intracellular T-cell signalling pathways (associated with antigen recognition and costimulation), B cells or B cell growth factors. Monoclonal antibodies against components of the complement pathway, inhibitors of IFN-$\alpha$, and antagonists of the IL-1 receptor are also under study.