



## REVIEW ARTICLE

# Monoclonal antibodies in inflammatory disease of the muscle and peripheral nervous system<sup>☆</sup>

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### KEYWORDS

Autoimmune neuropathies;  
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Lambert-Eaton;  
Polymyositis;  
Dermatomyositis;  
Inclusion body myositis;  
Monoclonal antibodies;  
Rituximab;  
Alemtuzumab

### Abstract

**Introduction:** A significant group of neuromuscular diseases are of autoimmune origin, but the classic immunomodulatory drugs are not often effective. For this reason, there is a need to find new more effective treatments that will lead to better control of these conditions, particularly those that are usually more resistant. In the last few years, the use of monoclonal antibodies against specific antigens of lymphocyte populations or against pro-inflammatory molecules has seen a great expansion, and has been demonstrated to be a useful alternative in autoimmune diseases.

An intensive search was made in Medline using the key words: neuromuscular, myopathy, neuropathy, myasthenia, Lambert-Eaton, monoclonal antibody, rituximab, alemtuzumab, and anti-TNF- $\alpha$ .

**Development:** Clinical trials performed to evaluate the efficacy of monoclonal antibodies in neuromuscular disease are very limited and of reduced size. Thus, the experience in this field is basically limited to anecdotal cases or short series of patients on open-label treatment. The published data are encouraging, with favourable responses having been observed in patients resistant to classic treatments and in diseases that do not normally respond to the usual immunosuppressant drugs. On the other hand, it has been observed that anti-TNF- $\alpha$  antibodies may trigger the appearance of autoimmune neuromuscular diseases.

**Conclusions:** Monoclonal antibodies could be an effective alternative treatment in autoimmune neuromuscular diseases, but the favourable responses observed need to be confirmed by means of controlled clinical trials with a sufficient number of patients.

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**PALABRAS CLAVE**

Neuropatías autoinmunitaria; Guillain-Barré; Polineuropatía desmielinizante crónica; Multineuritis multifocal motora; Neuropatía anti-MAG; Miastenia; Lambert-Eaton; Polimiositis; Dermatomiositis; Miositis de cuerpos de inclusión; Anticuerpos monoclonales; Rituximab; Alemtuzumab

**Anticuerpos monoclonales en patología inflamatoria del sistema nervioso periférico y músculo****Resumen**

**Introducción:** Un importante grupo de enfermedades neuromusculares son de origen autoinmune, pero con relativa frecuencia los fármacos inmunomoduladores clásicos no son eficaces. Por este motivo, se hace necesario encontrar nuevos tratamientos más eficaces, que permitan mejorar el control de estas entidades, especialmente aquellas que habitualmente son más resistentes. En los últimos años, el uso de anticuerpos monoclonales contra antígenos específicos de poblaciones linfocitarias o contra moléculas proinflamatorias ha conocido una gran expansión, y se han revelado como una alternativa útil en las enfermedades autoinmunitarias. Se ha realizado una búsqueda intensiva en Medline usando como palabras clave: neuromuscular, miopatía, neuropatía, miastenia, Lambert-Eaton, anticuerpo monoclonal, rituximab, alemtuzumab, anti-TNF- $\alpha$ .

**Desarrollo:** Los ensayos clínicos realizados para valorar la eficacia de los anticuerpos monoclonales en patología neuromuscular son muy escasos y de tamaño muy reducido, de modo que la experiencia en este ámbito se limita fundamentalmente a casos anecdóticos o series cortas de pacientes tratados de forma abierta. Los datos publicados son esperanzadores, habiéndose observado respuestas favorables en pacientes resistentes a tratamientos clásicos y en patologías que habitualmente no responden a los fármacos inmunosupresores habituales. Por otro lado, se ha observado que los anticuerpos anti-TNF- $\alpha$  pueden provocar la aparición de enfermedades neuromusculares autoinmunitarias.

**Conclusiones:** Los anticuerpos monoclonales pueden ser una alternativa terapéutica eficaz en la patología neuromuscular autoinmune, pero es preciso confirmar las respuestas favorables observadas mediante ensayos clínicos controlados con un número suficiente de pacientes.

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**Introduction**

A considerable group of neuromuscular diseases, including neuropathies and myopathies, or diseases of the neuromuscular junction, have an autoimmune pathogenesis. Among neuropathies these include Guillain-Barre syndrome, chronic demyelinating neuropathies, demyelinating multiple neuritis or Lewis-Sumner syndrome, multifocal motor neuropathy (MMN) with conduction blocks, neuropathies associated with gammopathies and paraneoplastic neuropathies. Among myopathies, there are polymyositis, dermatomyositis and, to some extent, inclusion body myositis. Finally, the two most common motor endplate diseases, myasthenia and Lambert-Eaton syndrome, also have an autoimmune pathogenesis. The current treatment of these entities is immunomodulating drugs such as corticosteroids, various immunosuppressants (particularly azathioprine), high-dose intravenous immunoglobulin and plasmapheresis. However, these drugs are not always effective, especially in some of these entities, and their side effects are sometimes severe. For this reason, it is necessary to find new, more effective treatments to improve the control of these entities, especially those that are generally more resistant.

In recent years, the use of monoclonal antibodies against specific antigens of lymphocyte populations or against pro-inflammatory molecules has undergone a great expansion, especially in rheumatic inflammatory diseases. The field of neuroscience has begun to use these drugs primarily in inflammatory diseases of the central nervous system, especially in multiple sclerosis. However, experience from other

fields, such as inflammatory pathology of the peripheral and muscular nervous system, has also accumulated gradually. In the latter field, B lymphocytes have been established as the primary therapeutic target and rituximab as the most commonly used drug.<sup>1</sup>

In this work we will review the published experience with monoclonal antibodies in various neuromuscular diseases with an inflammatory basis.

**Autoimmune neuropathies**

Chronic autoimmune neuropathies are a continuous spectrum ranging from the most polyneuropathic and predominantly sensitive forms, which would be those neuropathies with anti-myelin associated glycoprotein (MAG) antibodies, to the purely motor forms with a multineuritic pattern, which would be multifocal motor neuropathy, including intermediate, more polyneuropathic forms (chronic inflammatory demyelinating polyneuropathy or CIDP) or more multineuritic forms (Lewis-Sumner syndrome).

**Anti-MAG neuropathy**

Neuropathy with anti-MAG antibodies is a well-characterised clinical entity that appears with progressive sensory ataxia. The pathogenic relationship between anti-MAG antibodies and polyneuropathy has been clearly demonstrated, since deposits of antibodies capable of fixing complement in

areas of myelin damage have been found and the administration of these antibodies to animals reproduces the clinical symptoms. However, this neuropathy has so far proven resistant to standard immunomodulating therapies, both steroids and intravenous Ig or cyclophosphamide.<sup>2</sup> Following the publication of some isolated cases that did respond to rituximab and others that did not,<sup>3</sup> Renaud et al.<sup>4</sup> reported a first series of 9 patients with anti-MAG neuropathy resistant to various immunomodulatory therapies treated with rituximab. Of these, 6 improved in the functional scales of gait, 2 became stabilised and 1 suffered a worsening, although the latter suffered from concomitant intermittent vascular claudication that may have been the cause of gait deterioration. In parallel, a decrease in IgM and anti-MAG antibodies levels between 35% and 82% was observed, with a mean of 58%.

Encouraged by these results, Dalakas et al.<sup>5</sup> conducted a double-blind, placebo-controlled study including 13 patients treated with rituximab and 13 treated with placebo. Patients treated with rituximab improved significantly compared to those treated with placebo, both in the INCAT scale and in the time taken to travel 10 m. Out of those treated with rituximab, 7 patients experienced significant improvement in activities of daily living, 5 remained stable and 1 worsened. In contrast, out of those treated with placebo, 7 remained stable and 6 worsened. Improvement took between 2 and 6 months to start, generally peaked at 6 months and remained for a year or even longer in some patients. This improvement was accompanied by a 34% decrease in the levels of IgM and a 50% decrease in the levels of anti-MAG antibodies. The best response was achieved in the patients with a higher initial disability or higher levels of anti-MAG at baseline. However, the degree of response did not correlate with patient age, time of disease progression, amplitude of sensory potentials or levels of anti-SGPG antibodies. In fact, the response to rituximab has been very irregular in the few patients with neuropathy associated to IgM with anti-sulphatide antibodies (SGPG or SGLPG) in whom it has been tested.<sup>6</sup>

The effect of treatment persists over time. In an open series of 9 patients, Benedetti et al.<sup>7</sup> found that a single, month-long course consisting of a weekly administration of 375 mg/m<sup>2</sup> achieved an improvement lasting over 24 months in 80% of patients and over 36 months in 60%, despite the fact that a normalisation of the number of circulating B lymphocytes could be observed by then.

In cases unresponsive to the usual dose, duplicating it may obtain an additional response without a significant increase in side effects. In an open series of 8 patients who did not improve with 375 mg/m<sup>2</sup>, Renaud et al.<sup>8</sup> achieved clinical improvement in 4 and neurophysiological improvement in another 2 when applying a cycle of 750 mg/m<sup>2</sup>.

### Multifocal motor neuropathy with conduction blocks

The autoimmune nature of this entity has been clearly established, since IgM deposits have been found in areas of demyelination and a high percentage present anti-ganglioside antibodies, usually anti-GM1 and sometimes anti-GalNAc-GD1a, which when transfused into an animal are capable of reproducing the clinical symptoms. About

70% of patients respond favourably to the administration of intravenous Ig, but the duration of this effect is short and repeated infusions, usually monthly, are required. Consequently, effective treatments for longer periods are being investigated. Monoclonal antibodies, particularly rituximab, would be good candidates to achieve this purpose, because their effect is usually prolonged. So far, the number of patients with this neuropathy treated with rituximab who have been included in publications is scarce and the response obtained very irregular. Rojas-García et al.<sup>9</sup> reported 2 intravenous Ig-resistant patients in whom rituximab did not produce any clinical improvement or modification of anti-ganglioside antibody levels. In another series of 6 patients with diverse neuropathies who responded to intravenous Ig 2 of them with multifocal motor neuropathy (MMN), concomitant administration of rituximab failed to reduce the need for intravenous Ig. However, given the heterogeneity of the series, it is difficult to draw significant conclusions.<sup>10</sup> In a separately published patient, the administration of rituximab did obtain a 42% reduction in the need for intravenous Ig, with stabilisation of clinical symptoms.<sup>11</sup> The largest series included 11 patients in whom it was possible to observe both clinical improvement and reduced levels of IgM, which persisted for a year.<sup>12</sup> Thus, although there are some encouraging data to support the belief that rituximab may be effective in some patients with MMN when they start to show a worse response to intravenous Ig, the available data are too scarce to draw any definitive conclusions.

### Chronic demyelinating polyneuropathy

So far, experience with monoclonal antibodies in this entity is only anecdotal. It is considered that its pathogenesis is mainly due to humoral immunity because numerous patients improve with plasmapheresis or intravenous Ig, some have high levels of IgM, IgM deposits have been found in areas of demyelination and the symptoms can be transmitted to experimental animals by infusion of patient serum. However, the experience with rituximab has been very irregular. Some patients have improved, others have become stable and others have worsened, coinciding with an increase in the levels of IgM.<sup>13,14</sup>

There have also been anecdotal case reports of improvement with alemtuzumab, which may indicate some involvement of cellular immunity in this pathology.<sup>15</sup>

### Neuropathy associated with cryoglobulinemia

Cryoglobulins are proteins that precipitate at 4 °C and redissolve at 37 °C. They can be monoclonal, both IgG and IgM, associated with blood dyscrasias, or polyclonal, such as those found associated with collagen diseases or infections such as hepatitis C. Cryoglobulins can cause demyelinating neuropathy through direct immune attack against myelin or be axonal, either by induction of vasculitis of the *vasa nervorum* or by precipitation and blockage of these vessels.

Two open series of patients with cryoglobulinemia secondary to hepatitis C with axonal neuropathy reported 1 case of stabilisation and 1 of improvement of symptoms with recovery of sensory potential amplitude.<sup>16,17</sup>

## POEMS

The acronym POEMS refers to an uncommon, multisystem disease associated with polyneuropathy, organomegaly, endocrine disruption, monoclonal gammopathy in the serum protein and skin changes. It is a serious disease with few therapeutic options. From a pathogenetic point of view, it is related to very high levels of vascular endothelial growth factor (VEGF). Bevacizumab is a monoclonal anti-VEGF antibody, so it was thought that it might be useful in treating this syndrome. However, experience so far is still very scarce and has been very uneven. Out of the 5 patients with POEMS resistant to other therapies who were treated with bevacizumab found in the literature, 2 underwent dramatic improvements, proportional to the decreases in plasma VEGF levels, whereas the course for the remaining 3 was grim, with death due to multi-organ failure, although there was also a decrease in VEGF levels.<sup>18–22</sup> The main difference between those who responded well and those who responded poorly was the time of evolution of the disease at the start of treatment, which was much longer among patients responding poorly. It is possible that once there has been a vascular proliferation induced by very high VEGF levels for a prolonged time, the abrupt reduction in the levels of this growth factor could cause a collapse of these neoformed vessels, leading to multi-organ failure.

## Motor endplate diseases

### Myasthenia

Myasthenia is an autoimmune disease mediated in more than 80% of cases by antibodies against muscular acetylcholine receptors. In most of the remaining cases, it is mediated by antibodies against a muscle-specific tyrosine kinase (MuSK) involved in the clustering of these receptors during the formation of synapses. In general, it is adequately controlled by an initial combination of corticosteroids and intravenous Ig and, in the long term, by using classical immunosuppressants, mainly azathioprine. However, some cases, especially those related to anti-MuSK antibodies, are resistant to conventional therapies. Rituximab, as a highly effective modulator of humoral immunity with excellent tolerability, is emerging as an attractive alternative in these cases, in which the use of any other immunosuppressive agents, often with greater toxic potential, would also need to be performed without indication.

So far, the number of patients with refractory myasthenia treated with rituximab whose cases have been reported in the literature is less than 30.<sup>23–28</sup> These are generally isolated case reports or communications for congresses and the largest published series consists of 6 patients. In virtually all cases, the clinical response has been excellent, accompanied by a significant reduction in the levels of pathogenic antibodies and showing a greater reduction in levels of anti-MuSK antibodies than in those of anti-acetylcholine receptor. This could indicate that rituximab may be particularly effective in anti-MuSK myasthenias, which are also the most resistant to conventional treatments. Experience is clearly scarce and probably biased, because it is

possible that cases that have not responded to the drug have not been published. Nevertheless, it remains an interesting alternative for resistant cases or those with poor tolerance to first-line immunosuppressants and its efficiency should be confirmed in controlled clinical trials.

### Lambert-Eaton syndrome

Lambert-Eaton syndrome is an autoimmune disease mediated by antibodies against voltage-gated calcium channels (VGCC), which leads to a presynaptic alteration in the neuromuscular junction. In approximately 60% of cases, it is a paraneoplastic disease, usually associated with small cell lung cancer, and it is sometimes associated with other paraneoplastic syndromes, including cerebellar degeneration. Given that it is a rare syndrome, it is treated empirically with immunomodulators, following a scheme similar to that used in myasthenia, but with no clinical trials that confirm the efficacy of these treatments.

So far, only 1 case has been published that associated Lambert-Eaton syndrome with elevated levels of anti-VGCC antibodies and cerebellar degeneration, not associated with cancer, refractory to standard treatment but with a good response to rituximab.<sup>29</sup>

## Inflammatory myopathies

There are basically 3 primary inflammatory myopathies, 1 (dermatomyositis) related to humoral immunity, and the other 2 (polymyositis and inclusion body myositis) associated with cellular immunity.

### Dermatomyositis

Dermatomyositis is a microangiopathy mediated by complement-fixing antibodies whose antigen is located in the endomysial endothelium and which affects the skin and muscle. In general, its response to classical drugs, corticosteroids and/or initial intravenous Ig and long-term azathioprine or methotrexate treatment is good, but there are some refractory cases. In the latter, there have been reports of a favourable response to rituximab in small series, of up to 8 patients, or in isolated cases, both with the adult and the juvenile forms, the latter of which is generally more refractory. The improvement encompasses both cutaneous and muscular involvement, both skeletal and cardiac. The latter is especially important, because although it is uncommon, when it does appear it can be very serious, even life-threatening, and often responds poorly to conventional therapy.<sup>30–32</sup> So far the experience with rituximab in this field is promising, but it is unfortunately only anecdotal.

Another avenue being explored in patients with refractory dermatomyositis has been that of monoclonal anti-TNF- $\alpha$  antibodies (etanercept, infliximab). Although the number of treated patients is still small, the response has been more irregular, negative in many cases and with frequent side effects, so it does not seem that this will be a useful path for the disease.<sup>33</sup>



## Polymyositis

Unlike dermatomyositis, polymyositis is mediated by cytotoxic T cells that directly attack muscle fibres overexpressing type I histocompatibility antigens. Rituximab acts primarily by decreasing the population of B cells and, therefore, also acts indirectly on cellular immunity, since it reduces presentation of antigen to T cells and lymphokine production, which leads to reduced activation of cellular immunity. For this reason, some patients with refractory polymyositis have been treated with this drug with good results, both in terms of gains in muscle strength and decreased levels of CK.<sup>34</sup> Unfortunately, once again, the published experience is limited to open and short series, between 1 and 4 patients, so this option must be considered as a promising, yet unconfirmed, therapeutic modality.

A special form of polymyositis that is usually refractory to standard immunomodulatory therapies is that of syndromes with specific antibodies, such as antisynthetase syndrome, associated with anti-Jo-1 antibodies, or syndromes with anti-SRP antibodies. There have been reports of isolated cases of these syndromes with a good response to rituximab,<sup>35,36</sup> but others have not responded to the treatment.<sup>37</sup>

## Inclusion body myositis

Inclusion body myositis is the most common myopathy with onset after 50 years of age. Its pathogenesis combines autoimmune mechanisms, with endomysial T cell infiltrates and muscular overexpression of type I histocompatibility antigens, as well as degenerative disorders, such as coated vesicles and amyloid deposits in muscle fibres. Although immune mechanisms seem to be the trigger, the symptoms do not usually respond to immunomodulators and may even worsen with corticosteroids.

A clinical trial was conducted with etanercept, a monoclonal anti-TNF- $\alpha$  antibody, but the results were scarcely significant.<sup>38</sup>

Given that the disease is associated with cellular immunity, there have been attempts to act on T cell populations. Alemtuzumab is a monoclonal antibody directed against CD52, which is expressed on the membrane of mature T lymphocytes and monocytes. A recently published clinical trial compared the natural history of 13 patients for 12 months with their clinical course after the administration of alemtuzumab.<sup>39</sup> Prior to treatment, patients presented a progressive course, with a linear decrease of strength. After administration of this drug, 5 patients experienced a significant improvement with an impact on the activities of daily living, 3 experienced a moderate improvement and 5 did not appreciate any difference. Evaluation of strength measured with the Medical Research Council clinical scale and the QMT computerised procedure showed a significant improvement after administration of alemtuzumab. Patients regained their strength and returned to the level they were at 12–18 months earlier. The muscles that recovered the most were the quadriceps and wrist and finger flexors, which are also the most affected by the disease. Improvement started approximately 2 months after

starting the treatment and was maintained for 5–8 months. After this period, a progressive decrease of the effect was observed.

Clinical improvement was accompanied by a significant decrease in the number of T lymphocytes, both in blood levels and in muscle biopsies. These lymphocyte populations began to recover in the sixth month after treatment, thus following a parallel course to the clinical evolution. In addition, a decrease was observed in the expression of alpha-beta-crystallin, a protein associated with the degeneration of myofibrils, and an increase was observed in the expression of desmin, which is related to muscle regeneration. Drug tolerance was excellent, with no notable side effects in the short or long term. Although this was a small series and the benefit obtained was modest, it is the first time that a drug has demonstrated the ability to modify the clinical course of this disease. Consequently, the relevance of this trial is notable.

## Autoimmune neuromuscular pathology induced or aggravated by monoclonal antibodies

Immunomodulatory drugs are sometimes capable of producing a paradoxical effect and inducing the onset of autoimmune diseases. With regard to monoclonal antibodies, the appearance of neuromuscular inflammatory diseases has been described in association with anti-TNF- $\alpha$  antibodies, both etanercept and infliximab or adalimumab. In general, the pathologies consist of demyelinating polyneuropathies, both acute and chronic, which evolve satisfactorily after removal of the causal drug and administration of corticosteroids or intravenous Ig.<sup>40–43</sup>

## Conclusions

Several diseases of the peripheral and muscular nervous systems have an autoimmune origin. Some tend to respond favourably to standard immunomodulating therapies; however, there are some refractory cases and others are systematically resistant to these treatments. The possibility of developing new therapeutic modalities for refractory cases and resistant entities is always well received and, in this respect, monoclonal antibodies are regarded as an exciting alternative. The data available so far are very encouraging, but clearly not definitive and it is necessary to conduct controlled trials to confirm this hope. The first steps have already been taken in two entities, polyneuropathy with anti-MAG antibodies and inclusion body myositis, both of which have been elusive to the drugs tested. Undoubtedly, scientifically testing the effectiveness of these drugs before embarking on their widespread use must be the way forward. This becomes even more important when we consider that they may occasionally cause a paradoxical effect and induce or exacerbate the very same diseases that they are supposed to improve, as has been observed with drugs directed against TNF- $\alpha$ .

## Conflict of interests

The author has no conflict of interests to declare.

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