

Molecularly Targeted Therapies for Dysimmune Neuropathies

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Conventional treatment options, including corticosteroids, intravenous immunoglobulin, or plasma exchange, often fail to treat dysimmune neuropathies, such as chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and monoclonal gammopathy with its subtypes. Therefore, a significant percentage of patients require adjunctive immunosuppressive therapies. Considering that even immunosuppressive agents often are ineffective and/or associated with significant toxicities, the need for the development of safe and effective new treatment options is rising. Currently, several monoclonal antibodies (MAbs) have been tested in open-label small-sized studies or even in single cases so as to establish future directions in the therapy of diseases of the peripheral nervous system (PNS). Rituximab, an MAb targeting against the B cell surface membrane protein CD20, is the most widely used and promising MAb for the treatment of dysimmune neuropathies, especially for those in which immunoglobulin M (IgM) autoantibodies are pathogenetically involved. The efficacy of alemtuzumab, bevacizumab, and etanercept to treat various forms of dysimmune neuropathies is currently under investigation. This review looks critically at recent developments in molecularly targeted therapies for dysimmune neuropathies and also highlights areas of future research to pursue.

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INTRODUCTION

The armamentarium of conventional treatment options for diseases of the peripheral nervous system (PNS), especially for dysimmune neuropathies, include the administration of corticosteroids, plasmapheresis, long term intermittent intravenous immunoglobulin (IVIg) infusion, and immunosuppressive agents. However, the efficacy of these treatment approaches is usually short lasting or associated with adverse events, mainly because of the clinical heterogeneity and the huge variability of treatment responses (1). Furthermore, the economic burden most of these interventions bear is high.

Recent advances in the thorough understanding of the complex immunological pathogenesis of dysimmune neuropathies or nerve root syndromes have led to the arousal of rationale applications of new molecularly targeted treatment

options, especially for disorders that are resistant to conventional treatment options. In this review, recent developments in molecularly targeted therapies for dysimmune neuropathies are evaluated critically. Future research perspectives also are highlighted. To the best of my knowledge, this is the first review article in the topic.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

References for this review were identified by searches of PubMed from 2000 until December 2008 with the terms "dysimmune neuropathy," "treatment of dysimmune neuropathy," "monoclonal antibodies for diseases of the peripheral nervous system," "monoclonal antibodies and dysimmune neuropathy," "molecularly-targeted treatment for dysimmune neuropathy," "rituximab for

dysimmune neuropathy," "rituximab for CIDP," "rituximab for MMN," and "rituximab for anti-MAG neuropathy."

RITUXIMAB

Rituximab, a chimeric MAb against the protein CD20 targets both normal and malignant B lymphocytes, and is therefore used to treat diseases characterized by having a plethora of B cells, overactive B cells, or dysfunctional B cells. It is currently used in the treatment of B cell non-Hodgkin lymphoma, B-cell leukemias, and some autoimmune disorders. Over the last decade, rituximab has been used to treat dysimmune neuropathies with IgM antibodies to myelin-associated glycoprotein (MAG) or to GM1 ganglioside by depleting B lymphocytes as also by reducing titers of serum autoantibodies (2,3).

Chronic Idiopathic Demyelinating Polyradiculopathy (CIDP)

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated inflammatory disease of the PNS, in which elevated levels of antibodies against GM1 and M-proteins are involved pathogenetically (4). Cur-

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rent knowledge shows that the efficacy of rituximab in idiopathic CIDP is debatable, since conflicting results are reported from small case series (5).

In a prospective, open label study, two patients with CIDP were treated with rituximab (375 mg/m² intravenously [i.v.] each week for 4 weeks). This study revealed a lack of rituximab efficacy for CIDP patients, since the primary endpoint (reduction of IVIg dosage by at least 25% at 1 year after rituximab therapy compared with the previous year) was not reached. The dosage remained unchanged in one patient with CIDP and increased in the other (6). On the contrary, another small sized study proposed that rituximab may be effective in some CIDP patients. Following the administration of the standard rituximab dose, one patient with CIDP experienced improvement of strength that sustained for more than 5 years (7). In line with the latter study, there is another case report of rituximab-responsive CIDP (8).

In any case, the small sample size and the open label design of the latter studies clearly limit the interpretation of results and further studies obviously are warranted to elucidate the issue as to whether rituximab is effective in CIDP patients who do not respond to conventional therapies.

CIDP Associated with Other Medical Conditions

Literature contains few case reports of patients with CIDP and concurrent medical conditions who were unresponsive to intravenous immunoglobulin (IVIg) infusion and other conventional therapies. Rituximab effectively suppressed B lymphocyte levels and subsequently improved neurological function in a patient with CIDP associated with diabetes mellitus. Rituximab stabilized the course of the disease for over 10 months (9). In another case report, rituximab was given to a patient with CIDP and Evans syndrome (hemolytic anemia/thrombocytopenia), and was associated with substantial improvement of both neurological and hematological function. The benefi-

cial effect of rituximab lasted for more than 17 months after the completion of therapy (10). Finally, rituximab successfully put the course of CIDP associated with idiopathic thrombocytopenic purpura into remission for several months (11), thoroughly obviating the need for additional IVIg treatment.

With idiopathic CIDP, we cannot conclude definitely from single case reports on the efficacy of rituximab against CIDP associated with other diseases. One should also bear in mind that the remitting-relapsing course of CIDP might simply justify a spontaneous clinical improvement in these reports.

Multifocal Motor Neuropathy

Multifocal motor neuropathy (MMN) is defined as an asymmetric demyelinating autoimmune purely motor neuropathy that is clinically characterized by slowly progressive asymmetric weakness of the affected limb without sensory impairment. Elevated serum titers of IgM anti-GM1 antibodies are useful to support a diagnosis of MMN (12). Literature contains reports suggesting that rituximab may be beneficial for patients with MMN, by reducing circulating B cells and titers of IgM antibodies (13).

In a recently published study, 11 patients with motor conduction block, focal reduction in the area of the compound muscle action potential of more than 50% in at least one nerve, and elevated titers of IgM anti-GM1 antibodies, were treated with a single course of intravenous infusions of rituximab (375 mg/m²) for 4 weeks. Eight untreated patients with similar characteristics were used for comparison. Three months after the initial treatment, rituximab eliminated the levels of circulating B cells in all patients. One year after the administration of the initial course of rituximab, muscle strength improved significantly in the treated compared with untreated patients (14). Similarly, five yearly courses of rituximab reduced the dose of IVIg (42% reduction) in a patient with anti-GM1 antibody-negative MMN who was increasingly less responsive to IVIg (15).

Finally, in a prospective open label study, the results on the efficacy of rituximab for MMN were conflicting, since, from two patients with MMN, a total decrease of IVIg dosage by greater than 25% was observed in one of them, while the dosage was increased in the other. There was no improvement in muscle strength in either of them (6).

Overall, although data on the efficacy of rituximab in MMN are compelling and promising, the small number of patients enrolled in open label case series makes it difficult to generalize these results. However, the data are persuasive enough that larger double blind, placebo-controlled, randomized trials are indeed warranted.

Anti-MAG Neuropathies

Anti-myelin-associated glycoprotein (MAG) neuropathy is a well-defined autoimmune paraproteinaemic peripheral neuropathy caused by a complement-mediated mechanism. Peripheral neuropathies associated with IgM monoclonal gammopathies, with or without reactivity to myelin-associated glycoprotein (MAG), are the most difficult cases to treat as there is not enough evidence for any treatment to be recommended (16). Plasma exchange is considered as a first line treatment, while for cases with rapid progression or significant disability, monthly pulses with prednisone and cyclophosphamide are recommended (17). However, there are several cases that still remain unresponsive. Therefore, based on the idea that this neuropathy seems to be closely related to an antibody-mediated mechanism, rituximab has been tested in refractory cases of IgM-related anti-MAG neuropathies.

With few exceptions of cases experiencing a relapse after rituximab treatment in anti-MAG neuropathy (18), the results from small sized studies support the use of rituximab in refractory anti-MAG neuropathy. In an open label study, the efficacy of rituximab (375 mg/m²) was assessed in nine patients with anti-MAG-associated IgM polyneuropathy. After rituximab induced virtual elimina-

tion of the number of B-cells in the peripheral blood, six patients experienced a significant clinical improvement, two remained stable, and one worsened. The electrophysiological findings also favored the use of rituximab in the majority of patients (7/9) studied (19). The same group subsequently performed a study assessing the efficacy and safety of high dose rituximab (750 mg/m²) in patients with anti-MAG neuropathy. The analysis of results demonstrated that 4 of 8 patients were clinically and electrophysiologically improved, anti-MAG antibody titers were reduced, and the regimen was well tolerated (20).

Another open label study demonstrated that rituximab significantly improved strength in seven patients having anti-MAG neuropathy (14). Furthermore, preliminary results of a placebo-controlled trial enrolling 26 patients with anti-MAG antibody-demyelinating polyneuropathy suggested that rituximab is an effective treatment in 75% of patients with disability > 1 INCAT scores (21). The final results of this study, on equal sample size (n = 26; 13 patients randomized to rituximab and 13 to placebo), also favored rituximab treatment (four weekly infusions of 375 mg/m²) for anti-MAG polyneuropathy. After 8 months, 4/13 rituximab-treated patients improved by ≥ 1 disability inflammatory neuropathy cause and treatment (INCAT) score, compared with none of the patients allocated to placebo. Walking ability improved in 7/13 rituximab-treated patients. Patients with high anti-MAG titers and severe sensory deficits at baseline experienced the most marked improvement (22). Other placebo-controlled, double-blind studies in the early stages of anti-MAG neuropathy, with clinical and electrophysiological long-term follow-up are currently ongoing.

To identify the features of potential responders to rituximab, Benedetti *et al.* (23) performed a multicenter, open label study, in which 13 patients with anti-MAG neuropathy were included. This interesting study demonstrated that an overwhelming antibody reduction may

be warranted to achieve clinical improvement, particularly in patients with sensory impairment (23). The same group also reported on the long term effect of rituximab in anti-MAG polyneuropathy (24). In this recently reported study, 10 patients with anti-MAG polyneuropathy initially responding to rituximab were prospectively followed up for 36 months. Interpretation of results showed that the regimen, consisting of four weekly infusions of rituximab (375 mg/m²), may induce a long lasting benefit on both clinical and quality of life measures in patients with anti-MAG polyneuropathy, despite the reappearance of circulating B cells (24).

Overall, summarized data advocate in favor of the use of rituximab for treatment of refractory IgM-related anti-MAG peripheral neuropathies. Rituximab seems to be less effective in reducing levels of IgG and, therefore, its use in IgG antibody-mediated disorders may not be suitable.

Cryoglobulinemic Vasculitis

Cryoglobulins are cold-precipitable immunoglobulins from serum and their accumulation can lead to immune complex tissue deposition, causing cryoglobulinaemic vasculitis. Its cardinal neurological manifestation is the affection of the peripheral nerves, presenting as chronic axonal sensory polyneuropathy or an acute mononeuropathy in the form of vasculitic mononeuritis multiplex (25). The optimal approach of treating vasculitic neuropathy includes the administration of regimens consisting of corticosteroids, plasma exchange, and cyclophosphamide (26). The significance of rituximab in treating systemic manifestations and peripheral neuropathy in the context of cryoglobulinaemic vasculitis has been assessed in several uncontrolled open label studies and report of single cases.

In an open label study, 15 patients with type II mixed cryoglobulinemia (MC) were treated with rituximab (375mg/m²). This treatment approach was effective on skin vasculitis manifes-

tations, low-grade B-cell lymphoma, arthralgias, and fever, and also provided significant relief from subjective symptoms of peripheral neuropathy (27). In another controlled study, rituximab was given to 20 patients with MC and hepatitis C virus (HCV)-positive liver disease, resistant to interferon- α therapy. Improvement of peripheral neuropathy and decline of cryocrit was observed in 16/20 (80%) patients (28). Remission with rituximab was observed in other patients with refractory hepatitis C virus-related cryoglobulinemic vasculitis (29,30). Rituximab also was effective in a patient with chronic ataxic neuropathy with cold agglutinins (31) and in another patient with severe polyneuropathy secondary to cryoglobulinemia type III (32). Based on the results of a small case series, treatment with rituximab can be considered for other forms of vasculitic neuropathy, such as anti-neutrophil cytoplasmic antibody-positive vasculitis (33).

ALEMTUZUMAB

Alemtuzumab, a recombinant DNA-derived humanized MAb directed against the 21–28 kDa cell surface glycoprotein, CD52, currently is used in the management of B cell chronic lymphocytic leukemia and multiple sclerosis through mechanisms involving immune modulation.

CIDP

Considering that increased levels of circulating activated peripheral T lymphocytes are implicated in the pathogenesis of CIDP, and data also shows that MAbs directed against CD52 cause complement mediated lysis and reduce the numbers of circulating lymphocytes (34), alemtuzumab has been administered in a young female patient with CIDP, refractory to conventional treatment options. In this case report, remission was observed following the infusion of two courses of alemtuzumab (30 mg/day for 5 days) (35). However, based on a single case report, one cannot conclude on the efficacy of alemtuzumab to treat CIDP or any other dysimmune neuropathy.

BEVACIZUMAB

Bevacizumab, a humanized MAb, inhibits the biological activities of vascular endothelial growth factor (VEGF) and blocks binding of VEGF to its receptor on vascular endothelium.

POEMS

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) is a rare hematological disorder in which increased serum levels of VEGF are closely involved in its progression by increasing microvascular permeability, by increasing endoneural pressure, and by exposure of myelin to serum cytokines and compliments, leading to demyelination (36).

To our knowledge, targeting VEGF with bevacizumab in the context of POEMS syndrome has been assessed only in single case reports. Literature contains two case reports of POEMS patients with increased VEGF levels in which the administration of bevacizumab resulted in a rapid decrease of VEGF levels and significant improvement of peripheral nerve function (37,38). However, a dramatic decline was subsequently observed following the initial positive response in the case of Straume *et al.* (38). In line with this observation is another report in which bevacizumab was administered in a POEMS patient and, after an initial improvement, the subsequent course was complicated by severe adverse events leading to death (39).

Increased apoptosis of motor neurons and endothelial cells secondary to a decrease of VEGF levels might hold response for the unfavorable outcome seen in these case reports (38,39). Furthermore, failure of treatment with bevacizumab in a case with long-standing (7 years) POEMS syndrome also has been reported. In this report, and despite a decrease in serum VEGF levels, no clinical improvement was observed (40). Overall, the outcome of these reports bolsters the argument that bevacizumab should be used with great caution in selected patients. Further studies are war-

ranted to explore the interactive role of VEGF in POEMS syndrome before indication of bevacizumab for POEMS syndrome is justified.

ETANERCEPT

Etanercept, a dimeric, recombinant soluble tumor necrosis factor (TNF) receptor blocker has a different mechanism of action than infliximab and is used currently to treat autoimmune and hematological disorders. However, preliminary clinical observations suggest that treatment with etanercept may also be considered in patients with dysimmune neuropathies. This assumption is based on the ability of etanercept to mediate inhibition of TNF- α , which is produced by activated macrophages, T and Schwann cells (41).

CIDP

Considering that elevated serum levels of TNF- α have been observed in a significant percentage (25%) of CIDP patients (42), the use of etanercept (25 mg twice per week) was retrospectively assessed in 10 CIDP patients refractory or intolerant to standard therapies. Etanercept significantly improved the peripheral nerve function in three patients, three had possible improvement, one had mixed results, one remained stable, and the remaining two patients experienced worsening of peripheral nerve function (43). However, the uncontrolled, retrospective study design and the small sample size clearly limit the generalization of results from this report. In any case, the efficacy of etanercept in CIDP warrants further examination in well-designed clinical trials.

SIDE EFFECTS

The safety profile of rituximab is generally good. Common side effects include mucocutaneous reactions and cytokine release syndrome (44). However, there may be concern about reactivation of HCV infection (45), and this is especially relevant when considering a possible treatment of HCV-related cryoglobulinemic neuropathy with rituximab.

Alemtuzumab infusion-related side effects are common, while serious toxicities, including progressive multifocal leucoencephalopathy may occur in patients with lymphoproliferative disorders (46). Therapy with etanercept should be avoided in patients with congestive heart failure and CNS demyelination (47).

CONCLUSIONS AND FUTURE RESEARCH PERSPECTIVES

Currently, there is not enough evidence to definitely recommend the use of new molecularly targeted agents as first line options for the treatment of dysimmune neuropathies. Administration of MAbs may be used as second line therapies, especially for refractory neuropathies in which IgM autoantibodies are pathogenetically involved. Rituximab currently appears to be the most promising agent, but other MAbs also are under investigation for the treatment of dysimmune neuropathies. Larger double blind, placebo-controlled, randomized trials are indeed warranted before one can conclude promise with confidence, and if positive, this will have an impact on the quality of life of many patients with dysimmune neuropathies or nerve root syndromes.

Outcome measures, such as changes in muscle strength, muscle wasting, functional ability, and quality of life should be included in future studies. The need to compare responsiveness studies between equally valid and reliable measures and to standardize their use is definitely needed in dysimmune neuropathies. Modern clinimetric approaches, such as the Rasch analysis, may be the most suitable methodology, and, therefore, should be further employed in measuring the outcome of dysimmune neuropathies so as to promote comparability of results obtained from different studies (48).

Changes in levels of autoantibodies should also be monitored closely and predictors of response to molecularly targeted agents should be identified. Finally, the interactive role of molecularly targeted agents within any specific syn-

drome should be explored so as to elucidate their safety.

DISCLOSURE

I declare that I have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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