Current and future treatment approaches for neuromyelitis optica

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Nicolas Collongues and Jérôme de Seze

***Abstract*:** Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system (CNS) characterized by severe attacks of optic neuritis and myelitis, and which, unlike multiple sclerosis (MS), commonly spares the brain in the early stages. NMO used to be considered as a special form of MS. During the past 10 years, however, the two diseases have been shown to be clearly different. NMO is a B-cell-mediated disease associated with anti-aquaporin-4 antibodies in many cases and its pathophysiology seems to be near the acute lesion of necrotizing vasculitis. Assessment of prevalence shows that NMO is far less frequent than MS, which explains the absence of randomized clinical trials and NMO treatment strategies validated by evidence-based medicine. Recently, many data have been published that suggest that the therapeutic option in NMO should be immunosuppressive rather than immunomodulatory drugs. In the present study, after a brief overview of NMO, we review therapeutic studies and propose new therapeutic strategies in the relapse and disease-modifying fields.

***Keywords*:** CD20, complement, immunosuppressive drug, neuromyelitis optica

Introduction

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system (CNS) characterized by severe attacks of optic neuritis and myelitis, and which, unlike multiple sclerosis (MS), commonly spares the brain in the early stages. NMO was initially considered to be a monophasic disease associating paraplegia, due to severe myelitis, and blindness, due to severe optic neuritis. However, recent studies have shown that in more than 80% of cases NMO is a relapsing disease [Collongues *et al.* 2010; Wingerchuk *et al.* 1999]. In 2004, a specific pathogenic antibody called NMO-IgG was discovered in 50–70% of patients [Lennon *et al.* 2004]. This antibody is targeted against the aquaporin-4 (AQP4) water channel widely expressed in the optic nerves, the spinal cord and the periventricular regions [Pittock *et al.* 2006; Lennon *et al.* 2005]. This discovery clearly placed NMO in the B-cell disease category, which from a pathophysiological perspective mimics vasculitis rather than MS. In 2006, revised criteria for NMO were proposed including, in addition to the two major symptoms (myelitis and optic neuritis), any two [Bonnet *et al.* 1999] of the following three criteria: extended myelitis on spinal cord MRI, normal brain MRI at onset and positive anti-AQP4 antibodies [Wingerchuk *et al.* 2006]. The assessment of NMO/MS ratio differs from 1/7 in the Afro-Caribbean population of the French West Indies [Cabre *et al.* 2009] to 1/400 in the Caucasian population of France [Collongues *et al.* 2010]. The available data appear to show that the disease is more severe than MS [Collongues *et al.* 2010; Cabre *et al.* 2009; de Seze *et al.* 2003] and suggest that the most effective therapeutic option in NMO should be immunosuppressive (IS) rather than immunomodulatory (IM) drugs [Papeix *et al.* 2007]. Hereafter, we review therapeutic studies and propose some therapeutic strategies in both the relapse and disease-modifying fields. In order to stratify the importance of the previous studies we have classified the level of certainty from class I to class IV, following the American Academy of Neurology (AAN) recommendations [Gronseth and French, 2008]. Single case reports have not been classified.

How to treat relapses

Despite the absence of evidence-based medicine studies, administration of high-dose IV methylprednisolone (1 g daily for 3–6 days) is typically

Correspondence to:
Jérôme de Seze
Centre d'investigation Clinique, INSERM 002, Nouvel hopital civil, 1 place de l'hopital, BP 426, 67091 Strasbourg cedex, France; Department of Neurology, Hôpital Civil, 1 place de l'hôpital, BP 426, 67091 Strasbourg cedex, France
jerome.de.seze@chru-strasbourg.fr

Nicolas Collongues
Centre d'investigation Clinique, INSERM 002, Nouvel hopital civil, 1 place de l'hopital, BP 426, 67091 Strasbourg cedex, France; Department of Neurology, University Hospitals of Strasbourg, Strasbourg, France

the first treatment given to patients with NMO to reduce disease activity and further progression and restore neurologic function. However, in some cases this first-line treatment is not sufficient to reduce the inflammatory process and another strategy needs to be used, most notably plasma exchange (PE).

One randomized, double-blind (class II), study considered a transition from corticosteroids to PE in patients with either acute transverse myelitis (first episode, $n = 4$; recurrent, $n = 1$) or myelitis in the context of NMO ($n = 2$) [Weinshenker *et al.* 1999]. Patients with inadequate treatment response to steroids were randomized to active or sham exchange. A crossover was made if no recovery or only a mild recovery was observed after a 2-week treatment period. Of the four PE-treated patients with acute transverse myelitis, one patient experienced dramatic improvement, two failed, and one died of a rare complication of heparin treatment during the first treatment period. The two patients with NMO experienced marked therapeutic benefit with PE whereas no effect was observed with sham exchange. Retrospective studies (both class IV) showed apparent benefits in different groups, including 18 Afro-Caribbean patients with transverse myelitis (six NMO-IgG positive) [Bonnan *et al.* 2009], two NMO-IgG-positive patients with severe transverse myelitis [Watanabe *et al.* 2007] and subgroups with inflammatory transverse myelitis, a feature very similar to NMO [Greenberg *et al.* 2007]. Despite the lack of any specific and controlled studies on PE in NMO, there are many short experience reports consistent with a positive effect of this treatment. This was also underlined in a recent European Federation of Neurological Societies (EFNS) Task Force paper [Sellner *et al.* 2010].

In contrast to evidence of a positive effect of PE, the efficacy of intravenous immunoglobulin (IVIg) has not been demonstrated in patients with severe demyelinating events such as optic neuritis with severe visual impairment. Surprisingly, IVIg has not been used in severe relapses of NMO, but only for relapse prevention. This is likely due to the lack of efficacy of IVIg in severe optic neuritis observed in a placebo-controlled, randomized study (Class II). This study evaluated in 55 patients the effect of IVIg 0.4 g/kg daily for 5 days followed by three single infusions per month for 3 months, or placebo, and did not demonstrate any positive effects in terms of visual recovery in the IVIg-treated group [Noseworthy *et al.* 2001]. However, it should be noted that this study evaluated the effect of IVIg in patients with a recent residual visual deficit rather than in patients at the very acute phase.

How to prevent relapses

Only a few therapeutic studies on preventing relapses in NMO are available. Since NMO was initially considered to be a restricted form of MS, IM and IS treatments used in MS were also tried in NMO. Studies with most specific IS drugs, targeting B cells for example, were used thereafter, as illustrated in Figure 1. Except for rare case reports, the data on the efficacy of preventive treatment are derived from several cohort studies, which are summarized in Table 1. The results of therapeutic studies in cohorts of NMO patients are now presented in two parts, the first on the results of IM treatments and the second on IS therapeutics, whether administered *per os* or intravenously.

Immunomodulatory therapy

IVIg consists of purified immunoglobulins from the pooled plasma of up to 100,000 healthy human donors. The beneficial effects of IVIg are multifaceted, but likely include modulation of the Fc receptor by enhancing expression of the inhibitory IgG Fc receptor IIB, interference with complement activation, modulation of pro-inflammatory cytokines, alteration of both T-and B-cell activation and proliferation, and a decrease in inflammatory cell adhesion and diapedesis. Its action in NMO was reported in two patients (Class IV), including a patient who was unresponsive to azathioprine and prednisolone [Bakker and Metz, 2004]. Both patients were relapse free for 5.5 years after 1 year of treatment with IVIg infused monthly. However, it is not possible to reach any definitive conclusions based on only two patients.

The plasmapheresis technique involves separation of plasma from the cellular elements of blood, either by centrifugation or through permeable filters. Filter pore diameters measure up to 0.2 μM, resulting in filtration of substances up to a molecular weight of approximately 3×10^6 Da, such as circulating immunoglobulins and immune complexes directed at components of the central and peripheral nervous system. Plasmapheresis has been shown to reduce IgG,

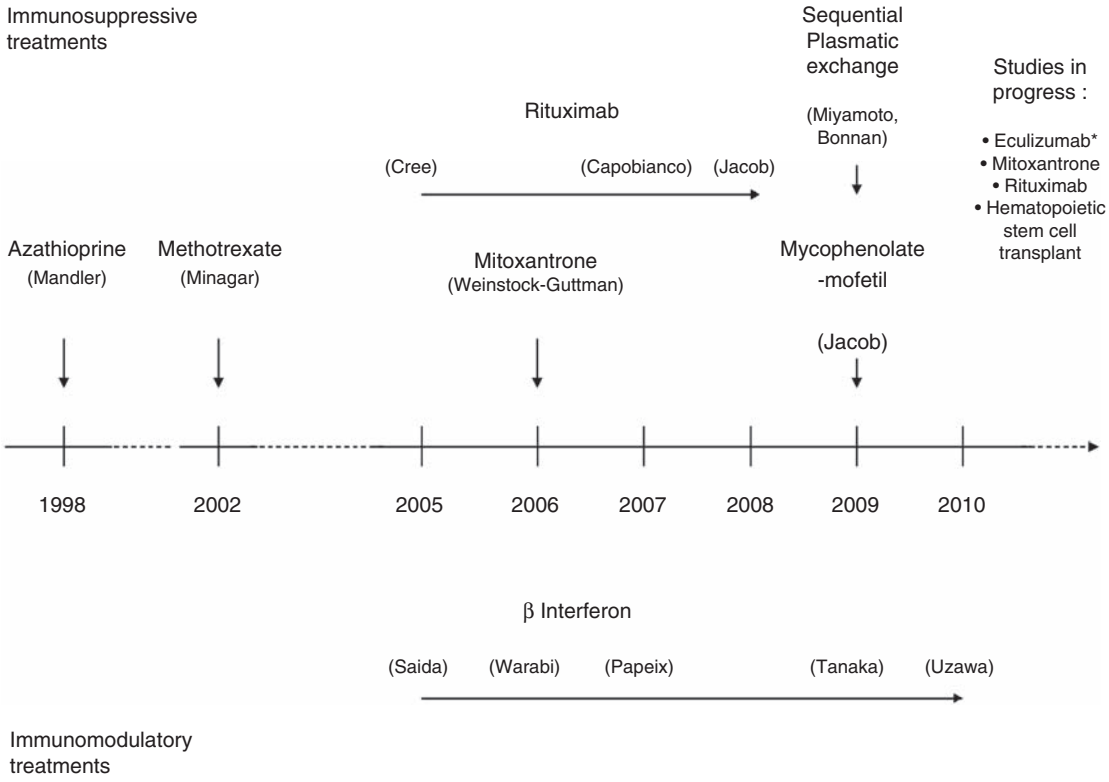

Figure 1. Therapeutic studies in cohorts of neuromyelitis optica patients.
The first author of each study is indicated in parentheses.
*Eculizumab is a monoclonal antibody directed against the complement protein C5 and halts the process of complement-mediated cell destruction.

IgM and total complement levels by 63.4%, 68.9% and 57.1%, respectively, after one exchange and 80.1%, 79.5% and 59.7%, respectively, after five exchanges [McDaneld *et al.* 2010]. In NMO, this technique was used for recurrence prevention in two patients with NMO and anti-AQP4 antibodies, and involved one to five exchanges over a period of 1 or 2 weeks, two or three times a year (Class IV) [Miyamoto and Kusunoki, 2009]. A reduction in relapse rate was observed but mainly in a patient receiving a combination of PE, azathioprine and prednisolone during a 3-year follow up. Once again, no definitive conclusions can be drawn from only two patients.

Interferon β (IFN β) induces an inhibitory effect on the proliferation of leukocytes, antigen presentation and T-cell migration across the blood-brain barrier and enhances anti-inflammatory cytokine production. IFN β treatment has been evaluated in several studies (Class III) and the results show that this form of therapy is not effective in NMO or opticospinal MS in terms of relapse rate and disability [Uzawa *et al.* 2010; Tanaka *et al.* 2009; Saida *et al.* 2005]. In the study by Saida and colleagues, both patients with NMO and patients with opticospinal demyelination were included, which may well account for the good responses observed in several patients with an MS phenotype. Furthermore, there have been reports of an exacerbation of the disease after IFN β treatment. One study (Class IV) reported two patients with NMO and anti-AQP4 antibodies who developed extensive brain lesions two months after IFN β initiation [Shimizu *et al.* 2008]. In a recent study, one patient presented a dramatic increase of anti-AQP4 antibodies during the IFN β treatment, followed by a marked decrease in relapse rate and level of anti-AQP4 antibodies after the introduction of an immunosuppressive therapy [Palace *et al.* 2010]. In another study, patients with severe opticospinal MS and a similar genetic background to NMO patients presented new relapses a few months after the introduction of IFN β [Warabi *et al.* 2007]. In a retrospective uncontrolled French study of 26 patients with

Table 1. Main results of immunosuppressive therapy studies in cohorts of NMO patients.

Treatment	Patients (*n*)	Follow up (months)	Therapy		Major evaluation criteria	Results	
			Induction	Maintenance		Baseline	End of the study
MITO	5	24 (mean)	12 mg/m^2 and 1 g methyl-prednisolone per month during 3 months (3 patients) or 6 months (2 patients)	12 mg/m^2 each 3 months (4 patients) with a maximum dose of 100 mg/m^2	Mean EDSS ± SD	4.4 ± 1.8	2.25 ± 0.65
					Mean relapse rate/patient/year ± SD	2.4 ± 0.89	0.4 ± 0.55
					Spinal cord MRI	3 Gd+ myelitis and 3 LETM	No Gd+ myelitis, 1 LETM with worsening, 2 LETM and 1 myelitis with improvement
RTX	8	12 (mean)	375 mg/m^2 infused once per week for 4 weeks	2 infusions of 1000 mg, 2 weeks apart when B-cell became detectable	Median EDSS	7.5	5.5
					Median relapse rate/patient/year	2.6	0
	25	19 (median)	375 mg/m^2 infused once per week for 4 weeks ($n = 18$) and 2 infusions of 1000 mg, 2 weeks apart ($n = 4$). NA in 3 patients.	375 mg/m^2 infused once per week for 4 weeks ($n = 8$) and 2 infusions of 1000 mg, 2 weeks apart ($n = 7$). NA in 2 patients.	Median EDSS [range]	7 [3–9.5]	5 [3–10]
					Median relapse rate/patient/year [range]	1.7 [0.5–5]	0 [0–3.2]
AZA	7	18 (mean)	2 mg/kg/day during 18 months and prednisone (1 mg/kg/day) during 2 months	75–100 mg/day and decreased prednisone to 10 mg/day	Median EDSS [range]	8.2 [6–9]	4 [3–6]
					Median relapse rate/patient/year	NA	0
MMF	24	28 (median)	2 g/day	2 g/day	Median EDSS [range]	6 [0–8]	5.5 [0–10]
					Median relapse rate/patient/year [range]	1.3 [0.2–11.8]	0.1 [0–1.6]

MITO, mitoxantrone; RTX, rituximab; AZA, azathioprine; MMF, mycophenolate mofetil; LETM, longitudinally extensive transverse myelitis; NA, not available; SD, standard deviation; NMO, neuromyelitis optica; EDSS, Expanded Disability Status Scale.

NMO (Class III), patients treated with IM drugs showed a significantly shorter mean relapse-free period (9 months, $n = 7$) than patients treated with IS drugs (40.2 months, $n = 19$) [Papeix *et al.* 2007]. This observation may be explained by the increased effect of type 1 IFN on B-cell activation and differentiation [Fink *et al.* 2006].

Glatiramer acetate (GA) is a mixture of synthetic polypeptides composed of four amino acids resembling myelin basic protein. It induces antigen-presenting cells with anti-inflammatory properties and promotes the generation of immunoregulatory T cells that suppress pathogenic T cells. Its efficacy in NMO was only evaluated in two reported cases in the literature. One patient experienced a decrease in relapse rate from 0.9/year in the 15-year pretreatment period to 0.25/year after 9 years of GA therapy [Bergamaschi *et al.* 2003]. Another patient, unresponsive to cyclophosphamide, was treated with GA and steroid pulses monthly for 1 year. During this period, no relapses and no new spinal cord lesions occurred [Gartzen *et al.* 2007].

Immunosuppressive therapy

Oral immunosuppression. Azathioprine (AZA) is a prodrug form of 6-mercaptopurine (6-MP) that was first introduced in clinical practice in 1960s for kidney transplantation to prevent immunological rejection. AZA is converted non-enzymatically to 6-MP, which is metabolized in the liver to the active metabolite 6-thioinosinic acid and works as a purine antagonist that gives negative feedback on purine metabolism and inhibits DNA and RNA synthesis. Its action results in the inhibition of T-cell activation, a reduction in antibody production and a decrease in the level of circulating monocytes and granulocytes. 6-MP has a terminal half-life of between 0.5 and 2 hours [Nielsen *et al.* 2001]. AZA is widely used in humans to treat a variety of autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus (SLE).

In a prospective, open-label case series (Class IV) of seven NMO patients without autoimmune systemic disease, the efficacy of AZA at 2 mg/kg/day in association with oral corticotherapy was considerable, with an improvement in median Expanded Disability Status Scale (EDSS) score from 8 to 4 after an 18-month follow up [Mandler *et al.* 1998]. In another study, involving three patients treated with AZA and prednisone, a marked decline in relapse rate was observed in two patients and a mild decline in the other. Interestingly, the interruption of therapy in these patients was followed by a clinical relapse and an increase in anti-AQP4 values [Jarius *et al.* 2008]. However, whether or not the antibody level is correlated with disease activity in NMO remains a subject of debate.

Mycophenolate mofetil (MMF) has been used since the 1980s for its IS property for the prevention or treatment of acute rejection in organ transplantation. MMF is a semisynthetic derivative of mycophenolic acid (MPA), a selective noncompetitive inhibitor of inosine 5-monophosphate dehydrogenase, which is a rate-limiting enzyme in the *de novo* synthesis of guanine ribonucleotide and 2-deoxyribonucleotide. MMF indirectly depletes the guanosine pool in lymphocytes and inhibits T- and B-cell proliferation, dendritic cell function and immunoglobulin production, and inhibits B- and T-cell transendothelial migration and antibody response [Allison and Eugui, 2000]. MPA has a mean terminal half-life of 17 hours. MMF is used in human autoimmune disease to treat rheumatoid arthritis or psoriasis.

In a recent study (Class IV), 15 patients with NMO and nine patients with NMO spectrum disorders including relapsing idiopathic optic neuritis ($n = 1$) and longitudinal extensive transverse myelitis (monophasic, $n = 1$; or relapsing, $n = 7$), previously treated with IS ($n = 6$), IM ($n = 2$) or a combination ($n = 9$), were treated with MMF and analysed retrospectively [Jacob *et al.* 2009]. Efficacy was noted in patients in terms of relapse rate and disability independently of treatment duration and the addition of corticotherapy. Relapse rate improved in 19 (79%) patients and EDSS scores in seven (28%) patients, whereas EDSS scores remained unchanged in 15 (62.5%) patients. One patient died of cardiorespiratory failure related to NMO and one patient experienced a low white blood cell count that required discontinuation of MMF treatment.

Intravenous immunosuppression. Cyclophosphamide (CYC) was first developed in the 1960s as an antineoplastic alkylating drug, related to nitrogen mustards. This prodrug is converted in the liver to active alkylating

metabolites which bind to a guanine base of DNA and interfere with mitosis.

Treatment with CYC causes suppression of cell-mediated and humoral immunity through its effects on B and T cells. It decreases the secretion of IFN γ and interleukin (IL)-12 by monocytes and increases secretion of IL-4 and IL-10 from peripheral blood mononuclear cells. Furthermore, this drug selectively targets CD45/CD4/RA+T cells and increases the number of T helper 2 cells [Weiner and Cohen, 2002]. CYC has a terminal half-life of between 3 and 12 hours and the immune system returns to baseline 3–12 months after cessation [de Jonge *et al.* 2005]. CYC is commonly used in humans to treat several autoimmune disorders, including immune-mediated neuropathies, lupus nephritis and MS.

Studies relating experience in treating NMO with CYC are mainly case reports of patients who have an association of NMO and another autoimmune systemic disease, such as SLE [Birnbaum and Kerr, 2008; Mok *et al.* 2008; Bonnet *et al.* 1999] or Sjögren's syndrome (SS) [Arabshahi *et al.* 2006]. An illustrative case report shows that the use of CYC can be successful after a lack of response to high-dose corticotherapy, IVIg, MMF, tacrolimus, low-dose daily oral CYC and rituximab [Mok *et al.* 2008]. In a patient without any systemic disease, the oral long-term therapy (50 mg daily) was associated with a decrease in anti-AQP4 antibody level and a strong reduction in relapse rate (2.82/year to 0.23/year) during a 4.4-year follow-up [Jarius *et al.* 2008].

Mitoxantrone (MITO) was developed in the 1970s and is an antineoplastic anthracenedione derivative related to the anthracyclines doxorubicin and daunorubicin. It interacts with the enzyme topoisomerase-2 and causes single- and double-strand breaks by intercalating the DNA through hydrogen bonding, thereby delaying cell-cycle progression by preventing ligation of DNA strands. MITO also inhibits B-cell functions, including antibody secretion, abates helper and cytotoxic T-cell activity, and decreases the secretion of Th1 cytokines, such as IFN γ, tumour necrosis factor α (TNF α) and IL-2 [Neuhaus *et al.* 2004]. MITO is released slowly from tissues and has a terminal half-life of between 9 hours and 9 days [Ehninger *et al.* 1990]. MITO can persist in the body for up to 272 days after treatment stops [Stewart *et al.* 1986]. In humans, the efficacy of monthly infusion of MITO (20 mg) and intravenous prednisone (1 g) was demonstrated in patients with aggressive MS and was characterized by a dramatic improvement of disability and a strong reduction in relapse rate during a 6-month follow up [Edan *et al.* 1997].

In NMO, a prospective, open-label 2-year study (Class IV) reported clinical and MRI improvement in 4/5 patients treated with MITO [Weinstock-Guttman *et al.* 2006]. The induction protocol was initially MITO monthly for 3 months (3QM) in three patients. This 3QM protocol had to be changed to a 6-month (6QM) protocol during the study, because the first two patients had relapses after 5 months. The results show a clinical (disability and relapse rate) and MRI improvement in all 6QM patients, whereas one patient died after the 3QM protocol with a worsening of the spinal cord MRI lesion. In a study that evaluated the quantitative modification of anti-AQP4 antibody blood level in patients treated with several IS therapies, three patients were treated with MITO. One of the three patients experienced a marked improvement in relapse rate and a decrease in anti-AQP4 antibody blood level, whereas the other two patients were unresponsive concerning these two evaluation criteria [Jarius *et al.* 2008]. However, the patients in this study were treated with several IS therapies and the dose and protocol of each treatment was not reported, making it difficult to interpret the results.

Rituximab (RTX) is a genetically engineered monoclonal antibody that binds with high affinity to the human CD20 antigen. This antigen is expressed in the membrane of pre-B and mature B lymphocytes but is not found on stem cells or plasmatic cells. Its mechanisms of action lead to B-cell apoptosis, complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). RTX has a terminal half-life of 120 hours and can persist in the body for up to 6–9 months after treatment stops [Boye *et al.* 2003]. Depth of B-cell depletion is variable among patients but restoration of the B-cell repertoire generally takes 9–12 months from the last perfusion of RTX [Dass *et al.* 2008].

RTX was originally used to treat B-cell malignancies but has recently proved effective in the

treatment of autoimmune diseases such as SLE and anti-MAG demyelinating neuropathies.

The first study (Class IV) was an open-label study that included eight patients with worsening NMO [Cree *et al.* 2005]. RTX was provided on an off-label, compassionate-use basis after IM therapies (six patients), AZA (three patients) and MITO (one patient). The relapse rate and EDSS score decreased and six patients were relapse free after 12 months of follow up. In another study, a retrospective open-label case series of 25 patients, EDSS score improved in 11 patients, stabilized in nine and worsened in five, two of whom died, after a median follow up of 19 months [Jacob *et al.* 2008]. These results must be interpreted with caution, especially since the EDSS score may have been determined immediately postrelapse at baseline and during a period of disease stability at the end of the follow up. An important point is that subsequent studies reported patients who experienced a severe relapse 3 months after the last RTX infusion [Nasir *et al.* 2009; Capobianco *et al.* 2007] or posterior reversible encephalopathy syndrome 24 hours after the first infusion [Sanchez-Carteyron *et al.* 2010]. These observations lead to the hypothesis that B cells could have an anti-inflammatory effect whereas the relapses were T-cell mediated. Another possibility is that RTX leads to anti-AQP4 release, and enhances transiently the pool of these pathogenic antibodies [Nakashima *et al.* 2010]. These data are offset by those of another study that showed a decrease in anti-AQP4 antibodies in three out of four patients treated with RTX; the fourth patient experienced a relapse 27 and 99 days after RTX and elevated anti-AQP4 antibodies [Jarius *et al.* 2008]. Lastly, recent studies have reported that nonresponse to RTX in patients with rheumatoid arthritis was correlated to higher circulating preplasma cell numbers at baseline and incomplete B-cell depletion [Vital *et al.* 2010; Dass *et al.* 2008].

Future therapeutic directions

With the development of knowledge about the pathological mechanisms of NMO, numerous potential targets would appear to be of interest. The pathogenicity of NMO-IgG underlines the role of B cells in the autoimmune process in NMO and this provides an avenue for the development of new therapeutic approaches, including anti-CD20 antibodies and complement inhibitors or modulators. Some of the molecules listed in the following are already undergoing evaluation in NMO or MS, whereas others are potential new targets in NMO that will first require more development and validation in animal models. A better understanding of the various factors implicated in both MS and NMO should also help to identify specific therapeutic targets in NMO. For example, recent studies have indicated that IFN β potentially increases the induction of BAFF [Krumbholz *et al.* 2008]. It has also recently been suggested that lymphocyte T helper type 17 plays a key role in the response to IFN β in MS and this should now be explored in NMO [Axtell *et al.* 2010].

Targeting B cells by the CD20 antigen. Human antichimeric antibodies can be generated after treatment with RTX and provide resistance to anti-CD20 therapy. The second generation of humanized anti-CD20 antibodies may prevent therapy resistance in such patients. Among this new generation of treatments, two are under evaluation in phase I/II clinical trials in relapsing MS and could be selected for use in NMO in the future: ofatumumab and ocrelizumab [van Meerten and Hagenbeek, 2010]. Compared with RTX, different immunological activities and additional features are noted. Ofatumumab (Arzera; Genmab), an IgG1 antibody with a completely human CD receptor, particularly binds the small extracellular part of CD20 and has a slower off-rate than RTX. An enhanced CDC activity is observed, whereas ADCC and apoptosis are comparable to RTX. Ofatumumab also triggers a stronger natural killer (NK) cell-mediated ADCC. Ocrelizumab (Roche) is an IgG1 humanized antibody and binds a different but overlapping epitope on the large extracellular part of CD20 and shows a twofold to fivefold increased ADCC and threefold to fivefold decreased CDC compared with RTX. These therapeutics show very promising results in B-cell malignancies refractory to RTX and have a good safety profile. A third generation of an anti-CD20 monoclonal antibody is under development by the pharmaceutical industry to treat non-Hodgkin lymphoma (PRO131921, AME-133, GA101). In addition to a humanized IgG, they have an adjusted Fc region, modified in order to outperform RTX in inducing different effector functions.

Targeting the complement pathway. To date, only three agents that regulate or inhibit complement function are approved for clinical use

Table 2. Adverse effects of immunosuppressive treatments used in NMO.

MITO	Immunosuppression, myelosuppression, gastrointestinal disturbance, alopecia, cardiac toxicity, leukaemia, infertility
CYC	Immunosuppression, myelosuppression, allergy, alopecia, gastrointestinal disturbance, haemorrhagic cystitis, cystic cancer, leukaemia, infertility
RTX	Immunosuppression, myelosuppression, acute cytokinic release, nausea, headache, fatigue, flu-like syndrome, dyspnoea), opportunistic infections including progressive multifocal leukoencephalopathy
AZA	Immunosuppression, myelosuppression, allergy, gastrointestinal disturbance, hepatic toxicity, myalgia
MMF	Immunosuppression, myelosuppression, gastrointestinal disturbance, opportunistic infections

MITO, mitoxantrone; CYC, cyclophosphamide; RTX, rituximab; AZA, azathioprine; MMF, mycophenolate mofetil; NMO, neuromyelitis optica.

[Wagner and Frank, 2010]. Eculizumab (Soliris; Alexion) is the only one that targets specific complement protein. Eculizumab is a C5-specific humanized monoclonal antibody that inhibits C5a generation and membrane attack complex formation. Its use has been validated for the treatment of paroxysmal nocturnal hemoglobinuria, in which erythrocyte lysis results from improper complement regulation [Rother *et al.* 2007]. Despite an increased risk of neisserial and other infections, eculizumab is well tolerated and associated with a low rate of opportunistic infections. In neurology, efficacy has been reported in the prevention of the immune-mediated motor neuropathy in an animal model of Miller–Fisher syndrome [Halstead *et al.* 2008]. Phase I/II studies in NMO-IgG-seropositive patients are in progress at the Mayo clinic aimed at preventing relapses during a 12-month follow up [ClinicalTrials.gov identifier: NCT00904826]. Patients will receive eculizumab at a dose of 500 mg IV each week for 4 weeks, 900 mg IV the fifth week, and thereafter 900 mg every 2 weeks for 48 weeks. A single-chain version called pexelizumab (Procter & Gamble) is under development.

Serping 1 is a serine protease inhibitor that controls bradykinin generation and prevents the initiation of classical and lectine pathway activation. Concentrate serping 1 is approved for prevention (Cinryze; Viro Pharma) or acute treatment (Berinert; CSL Behring) of hereditary angioedema [Agostoni *et al.* 2004]. Recent findings show that the carbohydrate moieties of serping 1 can interact with E- and P-selectin on leukocyte and endothelial cells and in future should prove interesting for use in inflammatory diseases [Davis *et al.* 2008]. In hereditary angioedema, current IV infusion of serping 1 needs to be repeated every 3–4 days, and is unlikely to prove useful in chronic conditions.

IVIg is most likely an underestimated therapeutic option at the acute phase of NMO. Its action is large, including complement deposition inhibition, particularly when activation is triggered by antibodies. Because IVIg is an excellent acceptor of activated complement proteins, it may also act to intercept the activated complement proteins (C3b and C4b) before they have the opportunity to bind to targets and act as a scavenger for anaphylatoxins C3a and C5a. Its therapeutic effect in rapidly reducing the inflammatory reaction induced by complement activation could represent an interesting perspective to treat an attack of NMO.

Whatever the case, we have to keep in mind that complement also plays a role in prevention of infection and tissue injury and may have neuroprotective functions [Rus *et al.* 2006].

Other possible targets in NMO. New approaches with apheresis could be an interesting way to specifically deplete the blood of antibodies such as NMO-IgG1 in NMO patients. Specific immunoadsorption of ABO antibodies was used successfully in ABO-mismatched kidney transplanted patients [Kumlien *et al.* 2006]. In seronegative patients, lymphocytapheresis could be of interest, as described in an NMO patient who was resistant to high-dose IV methylprednisolone and PE [Moreh *et al.* 2008].

Glutamate excitotoxicity was recently proposed as a potential pathogenic mechanism in NMO. Indeed, the EAAT2 (astrocytic Na^+-dependent excitatory amino acid transporter) is downregulated after AQP4-IgG membrane fixation and gives a lower capability of glutamate uptake [Hinson *et al.* 2008]. To decrease the glutamate level in the environment of astrocytes could be protective for astrocyte apoptosis.

Lastly, as an induction therapy, complete immune ablation and subsequent reconstitution with autologous stem cells is in progress in a phase I study in NMO-IgG-seropositive patients [ClinicalTrials.gov identifier: NCT00787722]. It should be noted that, before stem cell infusion, intense chemotherapy consisted in high-dose CYC together with rAGT/RTX, which can by itself modify the course of the disease. Long-term follow up will be needed for these patients.

Conclusion

Although the frequency of NMO was probably underestimated for a long time, this pathology remains rare and randomized trials are difficult to manage. However, an expert consensus has recently developed on two important points relating to the therapeutic strategy: the first is the need for plasma exchange in the event of a severe relapse resistant to a high dose of corticosteroids; the second is the need for IS rather than IM drugs in the disease-modifying part of the treatment. However, the choice of drug (oral or IV immunosuppressive, B-cell specific or broader spectrum treatment) remains debated, and depends on the risk/benefit balance regarding the potential side effects of each drug (Table 2) and should be tested at least as comparative controlled studies. Currently, numerous interesting new therapeutic strategies are being proposed for the treatment of this rare disease, including new monoclonal antibodies targeting CD20 B lymphocytes and complement, two of the main factors implicated in NMO. T cells can be specifically targeted by lymphocytapheresis but, to date, the development of T-cell specific therapies is lacking in the literature. Owing to the low frequency of the disease, collaborative efforts will be needed for therapeutic trials in NMO.

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Dr Collongues report no disclosures. Dr de Seze serves on scientific advisory boards for and has received honoraria from Biogen Idec, LFB, Merck Serono, Sanofi-aventis, and Bayer Schering Pharma; and serves on the editorial board of *Revue Neurologique*.

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