

Commentary

Neuromyelitis Optica Spectrum Disorder: A Commentary on Current and Future Targeted Therapies

Chetan Gandhi^{1,2}, Derrick Robertson^{1,2*}, and Janice Maldonado²

¹Department of Neurology, James A. Haley VA Hospital, USA

²Department of Neurology, University of South Florida, College of Medicine, USA

***Corresponding author:** Chetan Gandhi, Department of Neurology, James A Haley Veterans' Hospital, 13000 Bruce B Downs Blvd, VAH 127, Tampa, FL, USA, Tel: 813-972-7633; Email: cgandhy@health.usf.edu

Received: May 16, 2017; **Accepted:** July 17, 2017; **Published:** July 24, 2017

Copyright: ©2017 Chetan Gandhi. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Citation: Gandhi C, Robertson D, Maldonado J (2017) Neuromyelitis Optica Spectrum Disorder: A Commentary on Current and Future Targeted Therapies. Front Neuroinflamm Neurodegener Dis 1(1): 100002.

Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disorder of the central nervous system (CNS) that typically targets the aquaporin-4 (AQP4) water channel found in astrocytes. The disease was found to target optic nerves and the spinal cord where high densities of AQP4 water channels are found. The identification of autoantibodies against aquaporin-4 and myelin oligodendrocyte glycoprotein (MOG) has led to the recognition of this disease in diverse spectrum of presentations. Treatment of this disease has long focused on broad immunosuppression due to its aggressive nature. In more recent years, treatment has focused on the adaptive part of the immune system, in particular B cells. Due to the very small cohort of patients, no completed randomized placebo-controlled disease-modifying therapy trial data exists for the initial therapies used for this condition as part of standard practice. Most of the treatment data has been collected through retrospective reviews and case reports. The focus of this commentary is to discuss the standard B cell therapies and the emerging more targeted therapies that are available but do not have the approval of the Food & Drug Administration (FDA) for the treatment of NMOSD. These therapies provide insight into the future of treatments against this disabling, life-threatening disease.

Keywords: neuromyelitis optica spectrum disorder, aquaporin-4 antibody, rituximab, tocilizumab, eclizumab, aquaporin-4

Abbreviations: AQP4: Aquaporin-4; CNS: Central Nervous System; CSF: Cerebral Spinal Fluid; EDSS: Expanded Disability Status Scale; FDA: Food & Drug Administration; IL-6: Interleukin – 6; MAC: Membrane Attack Complex; MOG: mAb: Monoclonal Antibody; MS: Multiple Sclerosis; Myelin Oligodendrocyte Glycoprotein; NMO: Neuromyelitis optica; NMOSD: Neuromyelitis Optica Spectrum Disorder; TM: Transverse Myelitis

Commentary

Neuromyelitis optica (NMO) is a rare inflammatory disorder of the central nervous system (CNS) that selectively damages specific areas, mainly the optic nerves, brainstem, and spinal cord [1]. The selectivity of the damaged sites is largely due to the autoantibodies that form against aquaporin-4 (AQP4) which is a water channel found on foot processes of astrocytes that are significantly expressed in those areas of the CNS [2]. The discovery of

these autoantibodies against AQP4 has allowed NMO to be distinguished from another more common CNS inflammatory disorder, multiple sclerosis (MS) [3]. Given the rapidly evolving understanding of NMO from a basic science research perspective, a revised diagnostic criteria has been proposed and is slowly being adopted in the medical community that calls for NMO to fall under a broader umbrella term called neuromyelitis optica spectrum disorder (NMOSD) [4]. The multifaceted immunological assault against AQP4 is orchestrated by T and B cells, the complement system, eosinophils, neutrophils, and various other pathogenic antibodies [4]. The identification of these different points of involvement has allowed for the clinical development of targeted therapies for NMOSD. Of particular interest has been the development of multiple monoclonal antibodies (mAbs), not to mention the use of rituximab for many years for NMOSD. Controversy exists around the how to approach NMOSD patients with these mAbs with respect to when to initiate them and sequencing, among many other issues. We will explore the currently used mAb for NMOSD, rituximab, along with those mAbs that are in late-stage development.

The first therapies to be used for NMOSD were oral broad-spectrum immunosuppressive medications, specifically azathioprine and mycophenolate mofetil. While they were the best choice at time, now they have begun to largely grow out of favor, mainly due to the broad effect on the immune system that has led to many difficulties with short and long-term management. The most common issues to arise are hepatotoxicity and frequent infections, along with tolerability issues such as gastrointestinal issues, hair thinning, rash, and fatigue [5,6]. In addition, the medications could take up to 6 months to take full effect which means there is often a need for concurrent use of oral corticosteroids which causes additional numerous potential side effects. In general, these approaches are being passed over for more targeted approaches despite the attractiveness of their low cost. The issues are lost time and worsening disability that can occur along with the previously mentioned side effects of these medications. These medications often should be bypassed for the mAbs, which can have efficacy in as little as two weeks. In addition, mAbs target the cell line or epitope on cells that are most broadly implicated as the main cause of damage in NMOSD, i.e. the B cell, interleukin-6 (IL-6), or AQP4 antibody.

The first mAb to emerge in the treatment of NMOSD was rituximab. It is a chimeric mAb against B cells expressing CD20 (absent from plasmablasts and plasma cells) leading to complement-mediated cytotoxicity or apoptosis of B cells and their peripheral depletion. The data of its efficacy in NMOSD comes from non-randomized, unblinded, retrospective or open-label studies that have included small numbers of patients [7-15]. All studies have demonstrated consistent reduction in annualized relapse rates with a high percentage of patients remaining relapse-free over a wide range of follow-up, from 12 to 60 months. In four studies, the mean annualized relapse rate was zero [8-10,13]. Improved neurological function and reduced disability has been demonstrated by change in the expanded disability status scale (EDSS) score in most studies [7]. Dosing variations of rituximab and practice differences in maintenance administration of treatments are evident in the current available data. In general, there is agreement that induction phase is 2 grams intravenously given in a divided dose two week apart. Many maintenance regimens repeat single-dosing at 6 months or guide administering the next dose by monitoring for re-emergence of CD19+ B cells. The main safety concerns arise from infusion-related reactions. The most common infusion reactions include chills, rigors, hypotension, headache, nausea, fatigue, rash or pruritus, with these side effects being mild to moderate in severity. Pre-treatment regimens usually manage these side effects along with slow titration of rituximab infusion. Concern exists for increased risk of worsening of the NMOSD itself with rituximab administration due it is inducing the tumor necrosis factor family cytokine B-cell activating factor [16]. There have not been any severe opportunistic infections or cases of progressive multifocal leukoencephalopathy reported to date in NMOSD patients treated with rituximab. Only 2 studies have recorded fatal outcomes in rituximab treated NMOSD patients; one patient died from septicemia and another by presumed cardiovascular failure 3 days post infusion, the latter case not having

ascertained association to the drug effect [7]. Overall, the safety profile of rituximab in NMOSD appears to be consistent with what is known from other diseases in which it has been used. Rituximab has largely become the true first line agent due to its efficacy and has led to the development of emerging therapies in the treatment in NMOSD.

Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor, working by decreasing plasmablast longevity that reduces the production of AQP4 antibody [17]. In 2013, tocilizumab emerged on the scene when Araki and his colleagues used it to treat one patient with NMO [18]. The data that has been presented has come from small case series and case reports. The first case to be treated was in Japan by Araki and his colleagues using 8 mg/kg per month of tocilizumab which resulted in a reduction in the patient's EDSS from 3.5 to 2 after four months [18]. After this experience, Araki and his colleagues conducted a small study in Japan involving 7 patients with incomplete responses to standard therapies for NMO who were then treated with tocilizumab 8 mg/kg per month for one year [19]. Response was measured using EDSS along with numerical rating scales for fatigue and pain. The study observed a decrease in annualized relapse rate from 2.9 to 0.4 ($p < 0.005$) [19]. In addition, there was a reduction in the EDSS, neuropathic pain, and fatigue. The pain reduction was an unexpected result. Since these initial reports, other studies and case reports have been documented in Europe and the United States that show similar efficacy [20,21]. This further supports the involvement of IL-6 in the immunopathogenesis of this disease. The information presented above makes tocilizumab a very attractive treatment option for patients who are unable to tolerate rituximab. However before using this treatment the patient should be evaluated for the following contraindications; history of tuberculosis, liver disease, severe elevations in cholesterol, neutropenia, and thrombocytopenia [17]. Main side effects are gastrointestinal disturbance, neutropenia, leukopenia, fatigue, urinary tract infections, transient elevation of transaminases, deep vein thrombosis, and tuberculosis reactivation [17]. Tocilizumab monitoring includes a complete metabolic panel, complete blood count, and lipid panel which need to be performed every 6 weeks initially and every 3 months after 6 months. Additionally, patients need to be screened for tuberculosis. In considering the results and risks of tocilizumab, it is quite feasible that this medication may replace rituximab as first line for the treatment of NMOSD. In addition, it is 3,000 dollars cheaper than rituximab at about 24,000 dollars per year [17]. This makes it quite attractive as a first line treatment for NMOSD. A major limitation is the same as rituximab, the cost compared to azathioprine and mycophenolate mofetil, which are both 2,000 dollars per year [17]. In addition, the lack of randomized control trials makes it even more difficult to get approval through insurance.

Another treatment currently being studied is eculizumab, which is a humanized monoclonal antibody directed against complement protein C5 leading to prevention of cleavage of C5 to C5a and C5b [22]. Inability to form C5a and C5b leads to prevention of cytolytic terminal membrane attack complex (MAC) of the complement cascade. Complement deposition has been found in NMO lesions around the aquaporin channel. This implicates complement in pathogenesis of NMOSD. As of 2017, the only ever conducted randomized placebo-controlled trial for NMO is currently enrolling patients along with a second open label trial [22]. To date only one trial has been completed and it was an open label study that enrolled 14 patients with results showing that 12 patients demonstrated no relapses while two patients were considered to have had one possible clinical relapse each [23]. The protocol was 600 mg of eculizumab intravenous weekly for four weeks then 900 mg of eculizumab intravenous every two weeks thereafter. Annualized relapse rate was reduced from 3.0 to 0 with improvement of the EDSS from 4.3 to 3.5. In the open label trial, one patient death occurred due to meningococcal sepsis and thus is contraindicated in patients with unresolved meningococcal infection. The reported side effects were headache and increased risk of infection with encapsulated bacteria [23]. This medication is an attractive option for patients who fail rituximab and tocilizumab. The major limitation for use of this medication first line, second line, or possibly even third line is the price tag of 400,000

dollars per year [17]. It is very difficult to justify the cost if there are alternative therapies that prove to be as effective as this medication with equal or less risk to the patient.

Currently there are other treatments in development for the treatment of NMOSD. One of the most interesting is aquaporin, a recombinant human monoclonal antibody that is non-pathogenic [17]. It is comprised of an Fc portion that tightly binds AQP4 and a mutated Fc portion that cannot activate the complement cascade that causes cellular damage. It has demonstrated the ability to prevent NMO lesions in ex vivo and in vivo experiments in mouse models [24]. It remains in preclinical development currently but if the mechanism of action proves reproducible in humans, there stands to be an improvement in the effectiveness of treatment while concurrently decreasing the risk to patients. This may prevent immunosuppression that occurs with other therapies thus potentially decreasing the risk of infection. This would reduce the concerns both physicians and patients have when deciding which treatment to pursue. What might we learn about the pathophysiology of this disease and about the duration of the production of AQP4 antibody from the use of aquaporin?

Anti-CD19 mAbs offer an attractive target for NMOSD as CD19 is found on the B cell lineage similar to CD20, which is the target for rituximab. To date there are anti-CD19 mAbs in development for the treatment of leukemias, lymphomas, and autoimmune disease such as rheumatoid arthritis and lupus [26]. There is one currently enrolling study for an anti-CD19 mAb for NMOSD [27]. Most recently, ocrelizumab was approved for the treatment of MS [28]. As it is the humanized form of an anti-CD20 mAb, similar to rituximab, it seems it would be effective in the treatment of NMOSD while reducing infusion reactions as was shown in OPERA I and OPERA II for relapsing MS patients [28]. To our knowledge, there are no current plans to study ocrelizumab for NMOSD.

In a similar direction as eculizumab, complement inhibitor CD59 is in development. It is a glycosphosphoinositol-anchored membrane protein on astrocytes which inhibits the terminal C5b-C9 MAC. There is current interest in treatments that upregulate CD59 because of a mouse model that demonstrated worsening disease with inhibition of CD59 thus increasing MAC formation [29,30]. In one study where CD59 knockout mice were used, demonstrated increased complement dependent cytotoxicity reinforcing the importance of CD59 in the prevention of complement dependent inhibition [29,30]. It is not currently being studied in humans but warrants further investigation.

Another investigative direction for NMOSD is examining neutrophil elastase inhibitor, which has been studied in the treatment of acute respiratory distress syndrome in Japan [31]. It is involved in neutrophil migration and phagocytosis [31]. Two studies that examined markers in NMOSD showed elevated Th17 cytokines and neutrophil elastase [32,33]. In addition, one study showed in mice treated with neutrophil elastase, a reduction of inflammatory infiltrates in spinal cord and optic nerves [33]. This is yet another example where future treatments directed at the destructive end result could improve safety while improving treatment response. In these situations, by targeting the downstream effect, you could potentially treat most causative mechanisms in NMOSD without identification of exact antigen or antibody that is activating the cascade. This allows for treatment of a condition where the damage is occurring without disabling the ability of the immune system to defend the host.

Currently, NMOSD is being managed similarly to MS with corticosteroids, intravenous immunoglobulin, and plasmapheresis for acute attacks and immunosuppression for prevention of disease progression. The use of rituximab for the treatment of NMOSD has created opportunity for creative and innovative approaches for future treatments. The difficult part about future treatments is narrowing down the component of the immune system to target to modify this disease. It may create an opportunity to continue to decrease risk while increasing the efficacy of therapies. The medications described above create the possibility of treatments that not only halt disease progression but also reverse disability. Earlier diagnosis of NMOSD is occurring due to earlier testing thus presenting an

opportunity to manage this disease as a disease of chronic illness, similar to autoimmune thyroid disease, diabetes mellitus type 2, and hypertension. This creates the possibility of treating NMOSD in the model in which maintenance and monitoring is the mainstay of treatment with risk no different to that of taking an over the counter analgesic. It creates hope where patients whom once used to die from NMOSD and who now suffer terrible disability may have one attack in their lifetime and due to the treatment go on to lead normal lives. The sequela of blindness, tremendous pain, quadriplegia, incontinence of bowel and bladder, among many other signs and symptoms, may become ideas read about in textbooks and not experienced by patients. The emerging therapies have the potential to lead to more narrowly targeted therapies and to a better understanding of the pathophysiology of NMOSD. This will in turn reduce the risk and long-term sequela of this catastrophic disease.

References

1. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG (2006) Revised diagnostic criteria for neuromyelitis optica. *Neurology* 66: 1485-1489.
2. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR (2005) IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med* 202: 473-477.
3. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, et al. (2004) A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 364: 2106-2112.
4. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, et al. (2015) International Panel for NMOSD. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 85: 177-189.
5. Costanzi C, Matiello M, Lucchinetti CF, Weinshenker BG, Pittock SJ, et al. (2011) Azathioprine: Tolerability, efficacy, and predictors of benefit in neuromyelitis optica. *Neurology* 77: 659-666.
6. Huh SY, Kim SH, Hyun JW, Joung AR, Park MS, et al. (2014) Mycophenolate mofetil in the treatment of neuromyelitis optica spectrum disorder. *JAMA Neurol* 71: 1372-1378.
7. Collongues N, de Seze J (2016) An update on the evidence for the efficacy and safety of rituximab in the management of neuromyelitis optica. *Ther Adv Neurol Disord* 9: 180-188.
8. Cree BA, Lamb S, Morgan K, Chen A, Waubant E, et al. (2005) An open label study of the effects of rituximab in neuromyelitis optica. *Neurology* 64: 1270-1272.
9. Jacob A, Weinshenker BG, Violich I, McLinskey N, Krupp L, et al. (2008) Treatment of neuromyelitis optica with rituximab: retrospective analysis of 25 patients. *Arch Neurol* 65: 1443-1448.
10. Bedi GS, Brown AD, Delgado SR, Usmani N, Lam BL, et al. (2011) Impact of rituximab on relapse rate and disability in neuromyelitis optica. *Mult Scler* 17: 1225-1230.
11. Kim SH, Jeong IH, Hyun JW, Joung A, Jo HJ, et al. (2015) Treatment outcomes with rituximab in 100 patients with neuromyelitis optica: influence of FCGR3A polymorphisms on the therapeutic response to rituximab. *JAMA Neurol* 72: 989-995.
12. Pellkofer HL, Krumbholz M, Berthele A, Hemmer B, Gerdes LA, et al. (2011) Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. *Neurology* 76: 1310-1315.
13. Yang CS, Yang L, Li T, Zhang DQ, Jin WN, et al. (2013) Responsiveness to reduced dosage of rituximab in Chinese patients with neuromyelitis optica. *Neurology* 81: 710-713.
14. Collongues N, Brassat D, Maillart E, Labauge P, Ouallet JC, et al. (2016) Efficacy of rituximab in refractory neuromyelitis optica. *Mult Scler* 22: 955-959.

15. Radaelli M, Moiola L, Sangalli F, Esposito F, Barcella V, et al. (2016) Neuromyelitis optica spectrum disorders: long-term safety and efficacy of rituximab in Caucasian patients. *Mult Scler* 22: 511-519.
16. Katz Sand I (2016) Neuromyelitis Optica Spectrum Disorders. *Continuum (Minneapolis)* 22: 864-896.
17. Sherman E, Han MH (2015) Acute and Chronic Management of Neuromyelitis Optica Spectrum Disorder. *Curr Treat Options Neurol* 17: 48.
18. Araki M, Aranami T, Matsuoka T, Nakamura, Miyake S, et al. (2013) Clinical improvement in a patient with neuromyelitis optica following therapy with anti IL-6 receptor monoclonal antibody tocilizumab. *Mod Rheumatol* 23: 827-831.
19. Araki M, Matsuoka T, Miyamoto K, Kusunoki S, Okamoto T, et al. (2014) Efficacy of the anti-IL6 receptor antibody tocilizumab in neuromyelitis optica: A pilot study. *82*: 1302-1306.
20. Ringelstein M, Ayzenberg I, Harmel J, Lauenstein AS, Lensch E, et al. (2015) Long-term Therapy With Interleukin 6 Receptor Blockade in Highly Active Neuromyelitis Optica Spectrum Disorder. *JAMA Neurol* 72: 756-763.
21. Kieseier BC, Stüve O, Dehmel T, Goebels N, Leussink VI, et al. (2013) Disease amelioration with tocilizumab in a treatment-resistant patient with neuromyelitis optica: implication for cellular immune responses. *JAMA Neurol* 70: 390-393.
22. <https://clinicaltrials.gov/ct2/results?term=eculizumab&Search=Search> (accessed April 25, 2017).
23. Pittock SJ, Lennon VA, McKeon A, Mandrekar J, Weinshenker BG, et al. (2013) Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. *Lancet Neurol* 12: 554-562.
24. Tradtrantip L, Zhang H, Saadoun S, Phuan PW, Lam C, et al. (2012) Anti-aquaporin-4 monoclonal antibody blocker therapy for neuromyelitis optica. *Ann Neurol* 71: 314-322.
25. Jarius S, Aboul-Enien F, Waters P, Kuenz B, Hauser A, et al. (2008) Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. *Brain* 131: 3072-3080.
26. Hammer O (2012) CD19 as an attractive target for antibody-based therapy. *MAbs* 4: 571-577.
27. A Double-masked, Placebo-controlled Study With Open Label Period to Evaluate MEDI-551 in Neuromyelitis Optica and Neuromyelitis Optica Spectrum Disorders, A Double-Masked, Placebo-Controlled Study With Open Label Period to Evaluate MEDI-551 in Neuromyelitis Optica and Neuromyelitis Optica Spectrum Disorders. (accessed April 24, 2017).
28. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, et al. (2017) Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med* 376: 221-234.
29. Davies A, Lachmann PJ (1993) Membrane defence against complement lysis: the structure and biological properties of CD59. *Immunol Res* 12: 258-275.
30. Zhang H, Bennett JL, Verkman AS (2011) Ex vivo spinal cord slice model of neuromyelitis optica reveals novel immunopathogenic mechanisms. *Ann Neurol* 70: 943-954.
31. Iwata K, Doi A, Ohji G, Oka H, Oba Y, et al. (2010) Effect of neutrophil elastase inhibitor in the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. *Intern Med* 49: 2423-2432.
32. Herges K, De Jong BA, Kolkowitz I, Dunn C, Mandelbaum G, et al. (2012) Protective effect of an elastase inhibitor in a neuromyelitis optica – like disease driven by a peptide of myelin oligodendroglial glycoprotein. *Mult Scler* 18: 398-408.

33. Saadoun S, Waters P, MacDonald C, Bell BA, Vincent A, et al. (2012) Neutrophil protease inhibition reduces neuromyelitis optica – immunoglobulin G induced damage in mouse brain. *Ann Neurol* 71: 323-333.