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Review article

Review of approved NMO therapies based on mechanism of action, efficacy and long-term effects

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A B S T R A C T

Importance: Neuromyelitis optica (NMO - including NMO spectrum disorders [NMOSD]) is a devastating disease. Eighty-three percent of patients with transverse myelitic (TM) attacks and 67% of patients with optic neuritis (ON) attacks have no or a partial recovery.

Observations: Up until recently, there was no proven agent to treat to prevent relapses. The neuro-immunological community had a dearth of indicated agents for NMOSD. We now have three agents indicated for the treatment of NMO including (eculizumab [Soliris®]), an anti-C5 complement inhibitor, satralizumab (ENSRYNG®), a monoclonal antibody against the IL-6 receptor (IL-6R) that blocks B cell antibody production and inebilizumab (Uplinza®), a monoclonal antibody that binds to the B-cell surface antigen CD19 with subsequent B and plasmablast cell lymphocytolysis with decreasing antibody production. Autologous hematopoietic stem cell bone marrow transplantation (AHSCBMT) has also been used. How do we sequence NMO therapies with the understanding of the acuteness and severity of the disease, the individual mechanism of action (MOA) and rapidity of onset of action, onset of efficacy and long-term safety of each agent?

Conclusions and Relevance: We might suggest the following sequence – 1st line using eculizumab for rapid efficacy and stabilization without effect on the acquired immune system followed by satrilizumab (long term immunomodulation). Reserve inebilizumab (immunosuppressant) for breakthrough disease and salvage the severe with AHSCBMT. In NMO, control the complement, transition to modulation, and reserve suppression – and salvage the severe with AHSCBMT.

Neuromyelitis optica (NMO - including NMO spectrum disorders [NMOSD]) is a devastating disease (Jiao et al., 2013, Jarius et al., 2012). Forty-one percent of AQP4+ patients are legally blind in 5 years (Jiao et al., 2013), 22% require a walker in 5 years from disease onset (Jiao et al., 2013), and 22–54% require inpatient admission < 1 yr of index date (Ajmera et al., 2018). Median time to 1st relapse is 8.5–14 months with 55% of relapses within 1 year, 78% within 3 years, 90% within 5 years (Jarius et al., 2012, Kitley et al., 2012). Ninety-two percent of NMOSD AQP4+ patients ultimately relapse (Jiao et al., 2013, Jarius et al., 2012, Kitley et al., 2012). Ninety-three percent of AQP4+ patients have relapsed with an average of 1.3 times/year [4]. Eighty-three percent of patients with transverse myelitic (TM) attacks and 67% of patients with optic neuritis (ON) attacks have no or a partial recovery (Jarius et al., 2012). Progression occurs during attacks as opposed to intervals between attacks (Jarius et al., 2012) in contrast to MS. There is an especially high mortality in African-Americans (Kitley et al., 2012, Mealy et al., 2018). There are significant physical, emotional, social, and financial tolls imposed by NMOSD (Beekman et al., 2019).

NMOSD is a relapsing, inflammatory, autoimmune disorder (Papp et al., 2018) characterized in large part by attacks of optic neuritis (ON) and transverse myelitis (TM) causing blindness and paresis in many patients (Mealy et al., 2019, Wingerchuk et al., 1999, Wingerchuk et al., 2007). Attacks are unpredictable and tend to be severe (a 'neuro-immunological stroke') and recurrent (Kitley et al., 2012, Wingerchuk et al., 1999). The initial presentation is 50% with TM, 35% with ON, and ON & TM in 10% patients, and 4% of patients with other syndromes (Mealy et al., 2019, Wingerchuk et al., 2007, Hinson et al., 2016). The seropositive patients are overwhelmingly female (Jarius et al., 2012). Seronegative NMO-IgG tend to be male, younger with a milder clinical presentation (Hyun et al., 2015, Bernard-Valnet et al., 2015, Melamed et al., 2015) and in 42% of patients positive for MOG antibodies (Narayan et al., 2018).

Most of the 16,000–17,000 US NMO patients (approximate 80%) (Jiao et al., 2013, Hamid et al., 2017, Flanagan et al., 2016) have a pathogenic antibody biomarker in contrast to multiple sclerosis (MS). The pathogenic antibodies bind to AQP4 receptors concentrated on astrocyte endfoot processes surrounding intraparenchymal vessels, ependymal cells and subependymal layers lining the ventricles (Badaut et al., 2000, Amiry-Moghaddam et al., 2000, Verkman et al., 2017) disrupting the BBB and causing an astrocytopathy followed by oligodendrogliopathy and neuronal death. NMO typical brain lesions

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are in AQP4 rich sites (Pittock et al., 2006).

Preceding the approval of eculizumab there were a number of agents that were used in the *acute* treatment of NMOSD including corticosteroids (Filippini et al., 2000), plasma exchange (Watanabe et al., 2007), apheresis therapy (Kleiter et al., 2018), IV IgG (Elsone et al., 2014) and even cyclophosphamide (Greenberg et al., 2007).

Up until recently, there was no proven agent to treat to *prevent relapses*. Treatment strategies to control the disease included azathioprine (Bichuetti et al., 2010, Mandler et al., 1998), prednisone, mycophenolate mofetil (Jacob et al., 2009) and rituximab (RTX) (Cree et al., 2005, Jacob et al., 2008) with a low risk for PML 1/25,000 (Clifford et al., 2011) even as a 1st line therapy with a 97% annualized relapse reduction (ARR) (Zephir et al., 2015)! RTX re-administration has been monitored by the re-appearance of CD27 memory B cells (Kim et al., 2013). NMO activity has been correlated with B cell levels but not AQP4 levels in RTX treated patients (Pellkofer et al., 2011). A meta-analysis of 25 studies using RTX in NMO suggested a mean reduction of 0.79 in relapses and 0.64 points in EDSS (Damato et al., 2016). Another meta-analysis suggested a 63% ARR (Gao et al., 2019). We on the other hand have had variable results using RTX (Lindsey et al., 2012). IV IgG, not useful in MS, has barely been studied (Magraner et al., 2013). Cyclophosphamide (Yaguchi et al., 2013) and mitoxantrone have been evaluated in small studies (Kim et al., 2011, Weinstock-Guttman et al., 2006) but the latter's long-term (leukemogenic) side effect profile makes it a poor choice.

MS therapies do not work - indeed they can make the disease worse including alemtuzumab (Gelfand et al., 2014), natalizumab (Kleiter et al., 2012), beta interferon (Shimizu et al., 2010, Papeix et al., 2007) and fingolimod (Min et al., 2012). Tocilizumab has also been used in NMOSD in small trials with modest efficacy (Ringelstein et al., 2015, Araki et al., 2014).

In contrast to the adaptive immune system and antigen-specific responses after antigen processing and generation of immune cells with memory in MS, NMO at its target is a disease of the innate immune system. The innate immune system is a nonspecific defense mechanism that comes into play immediately or within hours. These mechanisms include complement proteins in the blood (Dunkelberger and Song, 2010, Noris et al., 2012, Hill et al., 2013). NMO-IgG activates the complement system after IgG antibody molecules bind to the surface of the astrocyte. The self-amplifying, inflammatory, and destructive properties of the complement cascade make it essential that activated components be rapidly inactivated. Deactivation is achieved by specific inhibitor proteins in the blood or on the surface of host cells that terminate the cascade. These inhibitors are not present in the CNS. Therefore, complement fixation by NMO-IgG is unopposed once initiated. Anti-AQP4 antibodies fix compliment and begin a cascade of events to give rise to formation of the membrane attack complex (MAC) resulting in disruption of the astrocyte cell membranes (Mealy et al., 2019, Wingerchuk and Weinshenker, 2017). This damage can occur quite rapidly, perhaps within hours (Herwerth et al., 2016). Once the rapid effect of complement fixation occurs during an NMO attack, there is unopposed and continual destruction. Indeed, it is unclear why it stops! Halting the acute ongoing destruction is an important therapeutic goal. The most effective interventions should prevent relapses but also have rapid anti-complement activity.

Several pathophysiologic mechanisms are involved in the permanent CNS damage associated with NMOSD. While NMOSD is often referenced as an astrocytopathy driven by AQP4 autoantibodies, direct damage to oligodendrocytes and neurons also occurs as a result of several inflammatory mechanisms resulting from T and B cell activation. CD19 + CD20- plasma cells produce AQP4 autoantibodies (Jasiak-Zatonska et al., 2016, Bradl et al., 2018, Bennett et al., 2015, Petersone et al., 2018) inducing IL-6 and breaking down the BBB and endothelial cell function (Takeshita et al., 2017).There is also a complement-independent cell-mediated cytotoxicity from NK and cytotoxic T cells (Ratelade and Verkman, 2012) and IFN I and Th17 cells (Agasing et al., 2020). B cell depletion in autoimmune settings may derive its therapeutic effect on T follicular helper cells (Tfh) that require B cells in tertiary lymphoid structures (Petersone et al., 2018). Both B and T cells produce inflammatory cytokines (Melamed et al., 2015, Kaneko et al., 2018) toxic to neurons and oligodendroglial cells (Bennett et al., 2015).

The neuro-immunological community will have gone from a dearth of indicated agents for NMOSD to multiple indicated agents over a relatively short period of time. As MS has been transformed from a diagnostic dilemma to a therapeutic dilemma (J. Dunn, Stanford), so NMO may well become a therapeutic dilemma too. The initial and subsequent interventions using indicated agents may depend on the mechanism of action (MOA), rapidity of the onset of action (OOA), duration of efficacy and long-term safety. Frequency of administration, route of administration and monitoring will also assuredly play a role for the patient and the clinician. Let's review the available clinical data on the present agents and potential future approaches.

The first agent indicated for the treatment of NMO is eculizumab (Soliris®), an anti-C5 complement inhibitor. It is the first and sole FDA approved treatment for adults with AQP4 antibody positive NMOSD. Eculizumab is a monoclonal antibody that specifically binds to the complement component C5, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-C9. Eculizumab inhibits AQP4 antibody induced terminal complement C5b-C9 deposition and the formation of the MAC. The PREVENT trial showed that eculizumab reduced the risk of relapse by 94% compared to placebo (3/96 in eculizumab group vs 20/47 in the placebo group) and the risk reduction persisted at 48 (98% in eculizumab vs 63% in placebo group) and 144 weeks (96% in eculizumab vs 45% in placebo group) (Pittock et al., 2019). In slight contrast, fig S3 (in the supplemental appendix to (Pittock et al., 2019)) based on the investigator's determination of relapses (time to first clinical relapse/non-adjudicated) shows a decline to 89% relapse free at 48 weeks for active treatment compared to 98% relapse free (adjudicated) (figure A in (Pittock et al., 2019)) at 48 weeks for active treatment. There was an 83% relapse free (clinical relapse) (fig S3 in the supplemental index to (Pittock et al., 2019)) for active treatment vs 96% at 144 weeks (adjudicated) for active treatment (figure A in (Pittock et al., 2019)). Eculizumab had a relatively rapid onset of action, its efficacy plateaued at 48 weeks (96% relapse free – adjudicated) and 96 weeks (85% relapse free – clinical relapse) and was maintained for 3 + years. Blocking the formation of the MAC (where the rubber meets the road) allows relatively rapid cessation of disease activity and decreases hospitalizations, corticosteroid treatments and PLEX frequency. Although indicated for the prevention of attacks, its immediate effect argues for its utility during acute attacks when it may have even greater efficacy. Disadvantages are the frequency and route of administration (q 2 weeks after weekly infusions for 5 weeks) along with significant cost. Eculizumab did not decrease the rate of progression – related to the trial design that precluded follow up beyond 6 weeks and terminated after a prespecified number of relapses. We might consider eculizumab an immunomodulator of the innate immune system without effect on acquired immunity notwithstanding precautionary prophylaxis vaccination for Neisseria sps. Ravulizumab, a second generation to eculizumab with a four aminoacid change, has a prolonged terminal half-life with eight week dosing intervals, is currently in clinical trials (Duchow et al., 2020).

Tocilizumab (RoActemra®; Chugai/Roche), a precursor to an upcoming agent for NMOSD, is a first-in-class humanized monoclonal antibody that binds specifically to both sIL-6R and mIL-6R and inhibits IL-6R-mediated signaling and specifically blocks IL-6 activity (N Nishimoto et al., 2008). Tocilizumab was approved for patients with moderate to severe rheumatoid arthritis (RA) unresponsive to available disease modifying anti-rheumatic drugs (DMARD) (N Nishimoto et al., 2008, Yokota et al., 2005, Smolen et al., 2008, N Nishimoto et al., 2008,

Paul-Pletzer, 2006, Scheinecker et al., 2009). Parenteral tocilizumab, as a repurposed from RA DMARD, can also be effective in other inflammatory diseases including neuromyelitis optica (NMO) by reducing anti-AQP4 autoantibodies (Araki et al., 2013). Tocilizumab has also been used in NMOSD in small trials with modest efficacy (Ringelstein et al., 2015, Araki et al., 2014).

A recently approved agent in the US is satralizumab (ENSRYNG®), a newer version of tocilzumab (Actemra®), a monoclonal antibody against the IL-6 receptor (IL-6R). Satrilizumab blocks the IL-6R and B cell antibody production. The SakuraSky trial showed that satralizumab added to immunosuppressant treatment reduced relapse from 43% (18/42 patients receiving placebo) vs 20% (8/41 patients receiving satralizumab) in all patients regardless of AQP4-IgG-sero-positivity. For AQP4-IgG-sero-positive patients satralizumab significantly reduced relapses - 43% (6/14 patients receiving placebo) vs 11% (5/14 patients receiving satralizumab) (Yamamura et al., 2019). For AQP4-IgG-sero-negative patients satralizumab did not significantly reduce relapses - 43% (6/14 patients receiving placebo) vs 36% (5/14 patients receiving satralizumab). The trial designers use early censoring of patients who received rescue therapy, who had an increase or change in their baseline treatment, or who were continuing in the trial at the data-cutoff date in four separate post-hoc analyses using multiple imputations. Only 19/42 in the satrilizumab group and 7/41 patients in the placebo group were continuing in the trial at the cut-off date. The sensitivity analysis of time to any relapse, including both protocol-defined (adjudicated) relapses, was consistent with the analysis of protocol-defined relapse (fig 2 in (Yamamura et al., 2019)). However, fig S5 (in the supplemental appendix to (Yamamura et al., 2019)) based on investigator's determination of relapses (time to first clinical relapse/non-adjudicated) shows a precipitous decline to only 69% relapse free at 48 weeks for active treatment compared to 89% relapse free (adjudicated) (fig 2 in (Yamamura et al., 2019)) at 48 weeks for active treatment. There was only 51% relapse free (clinical relapse) (fig S5 in the supplemental appendix to (Yamamura et al., 2019)) for active treatment vs 74% at 144 weeks (adjudicated) for active treatment (fig 2 in (Yamamura et al., 2019)). Satrilizumab had a relatively slow onset of action, its efficacy plateaued at 48 weeks (74% relapse free – adjudicated) and 130 weeks (51% relapse free – clinical relapse) and was maintained for 3+ years. The SakuraStar satrilizumab monotherapy for relapse prevention trial showed a 25% relapse rate at 48 weeks for active treatment (Bennett et al., 2019). These latter data also suggest a delayed onset of action. The authors (SakuraSky) state that longer and larger trials are necessary to determine the efficacy and durability of satralizumab.

A recently approved agent in the US is inebilizumab (Uplinza®), a humanised, affinity-optimised, IgG1 monoclonal antibody that binds to the B-cell surface antigen CD19 with subsequent B and plasmablast cell lymphocytolysis with decreasing antibody production. Anti-CD19 mAb recognizes and depletes a wider range of lymphocytes from the B-cell lineage compared to anti-CD20 treatments. The N-MOmentum trial showed inebilizumab reduced relapse from 39% (22/56 patients receiving placebo) vs 12% (21/172 patients receiving inebilizumab) in all patients regardless of AQP4-IgG-sero-positivity (Cree et al., 2019). For AQP4-IgG-sero-positive patients inebilizumab significantly reduced relapses - 42% (22/52 patients receiving placebo) vs 11% (18/161 patients receiving inebilizumab). Among the 17 AQP4-IgG-seronegative patients who were randomly allocated to treatment (13 to inebilizumab), three attacks occurred, all in the inebilizumab group. Secondary outcomes showed a significant effect on EDSS worsening favoring inebilizumab (34% placebo vs 16% inebilizumab). The supplementary appendix table S5a describes breakdown of on-study adjudication attack decisions. Adjudication decisions on attacks agree with the investigators (non-adjudicated) 80% of the time ($n = 43$ attack vs $n = 21$ non-attack [adjudicated]; overall [non-adjudicated] $n = 64$) without reference to attacks in the placebo or active arms. There is a falloff at 6 months with attacks in 13% of patients and 15% at 12 months according to extension data (Cree et al., 2020). We might assume a plateau at 12 months with extension data. A concern with this agent is its similarity to ocrelizumab, the fully humanized anti-CD20 mAb derived from rituximab, devised initially to treat lymphoma, repurposed to treat autoimmune disorders including MS and used off-label for the treatment of NMOSD. As it stands, there are at least 7 PML (confounded) cases and 1 unconfounded PML case associated with its use. Ocrelizumab was also associated with an increased incidence of breast cancer (increased, but statistically insignificant) particularly in the PPMS clinical trial. Ocrelizumab is immunosuppressive because it causes a B cell lymphopenia along with a definable incidence of PML. Ocrelizumab requires continual administration to maintain its effectiveness and has had a 5.5% mortality from confirmed COVID-19 infections (www.ocrelizumabinfo.com 2020).

Interventional strategies that target pathogenic AQP4 auto-antibodies should consider their ability to leave previously established humoral immunity intact (Forsthuber et al., 2018). Protective antibodies to vaccine antigens (i.e., influenza, tetanus, measles, mumps, rubella, and polio) are produced by both CD19+ and CD19- subsets and long-lived antibody producing plasma cells. Differences in CD expression occur throughout B cell maturation and within tissue-localized late-stage B cells (Forsthuber et al., 2018, Alexopoulos et al., 2016, Wilson et al., 2018). Therefore, targeting CD19+ *B* cells may leave some established humoral immunity relatively unscathed.

There is a 4th potential therapeutic option in NMOSD. Autologous hematopoietic stem cell bone marrow transplantation (AHSCBMT) is an example of immune reconstitution therapy (IRT) within autoimmunity. AHSCBMT is associated with profound qualitative immunological changes and the resetting of the immune system (i.e., immunostat) in patients with MS (Atkins and Freedman, 2013, Mancardi and Saccardi, 2008). AHSCBMT has been utilized in the treatment of advanced MS over long periods and reviewed in recent meta-analyses (Sormani et al., 2017). AHSCBMT has been studied in NMO also albeit in smaller numbers. AHSCBMT in refractory NMO/NMOSD was associated with clinical and radiological remission, improved disability and resolution of AQP-4 antibodies which were still undetectable 12 months later (Aouad et al., 2015, Peng et al., 2010). The European Group for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP) reported after a median follow-up of 47 months with baseline EDSS = 6.5, three of 16 cases were progression and treatment free, while in the remaining 13 patients further treatments were administered for disability progression or relapse after AHSCBMT. Altogether, relapse-free survival at three and five years was 31% and 10%, respectively, while progression-free survival remained 48% at three and five years (Greco et al., 2015). I have treated 1 AQP4+ NMO patient who became plegic for 6 months who after AHSCBMT was able to walk 2 miles (data not shown). The patient did have a mild relapse at 1-year post-transplant but was effectively treated back to her baseline. Despite the possibility of eventual relapse, AHSCBMT can be effective treatment in refractory NMO and can be successful in reversing recent severe disability (Case Report - Carlisle N., Hari P., Brod S. Plegia to walking: AHSCBMT in severe NMOSD relapse – JNNP *in press*).

In the future several key immune mechanisms in NMOSD that might be amenable to therapeutic restoration of immune tolerance include DNA, dendritic or autoreactive T cells vaccinations, antigen coupling, and engineered TcRs (Steinman et al., 2016) along with enhancing regulatory T and B cell function (Bar-Or et al., 2016). These interventions may shine new light on potential cures for NMO/SD and other autoimmune diseases, while sparing normal host defense mechanisms.

Short course IRT agents have long term advantages over immunosuppressive agents. They provide potential long-term efficacy without retreatment with minimal risk for opportunistic infections and malignancy. In addition, IRT maneuvers or agents may have favorable pharmaco-economics. The estimated cost of AHSCBMT was less than $4700 per quality-adjusted life year (Tappenden et al., 2010) in MS. In terms of clinical safety, AHSCBMT is associated with a very low

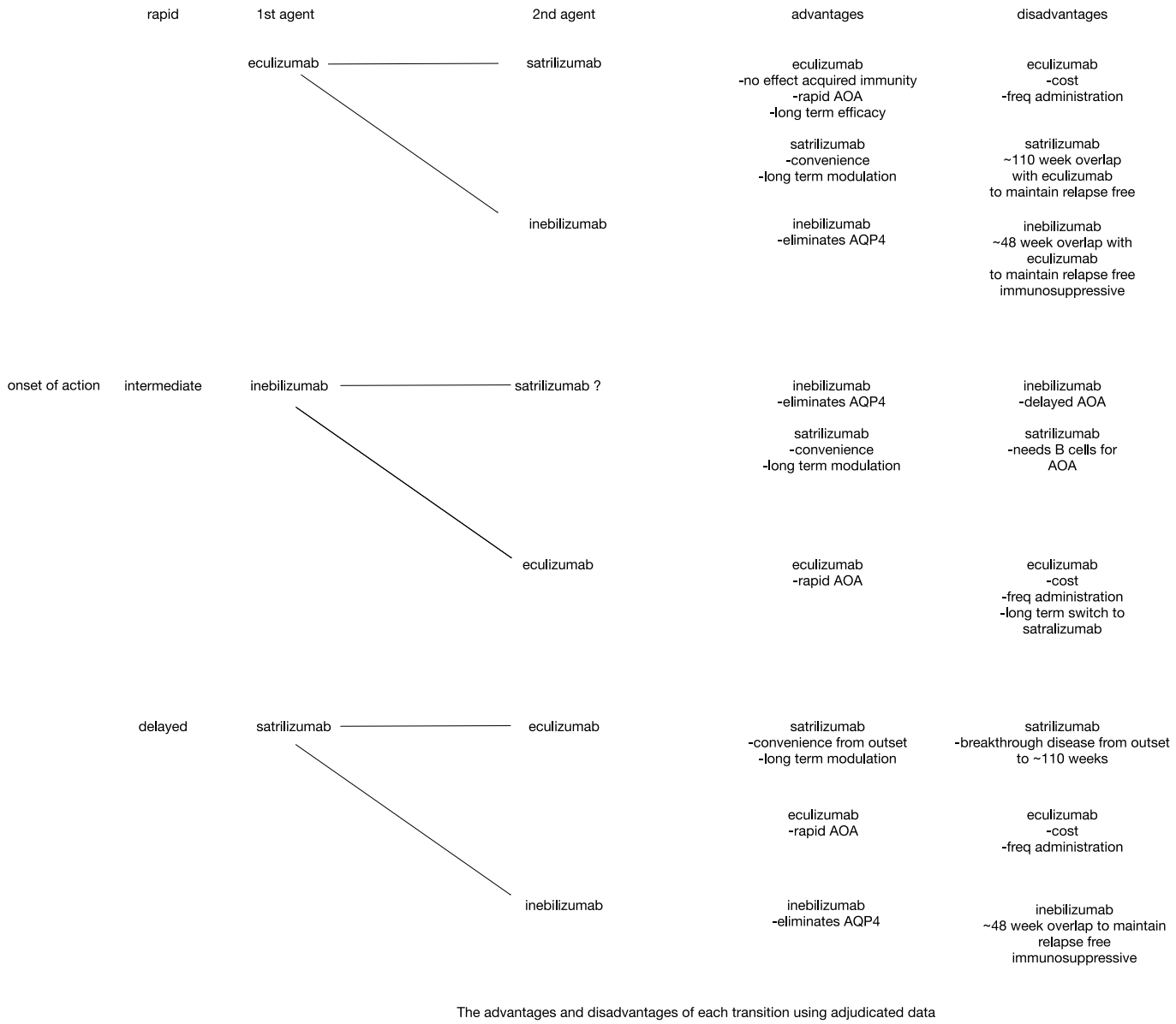

Fig. 1. The advantages and disadvantages of each of these transitions are outlined.

mortality (< 1%), time limited morbidity which resolves in a short time period in the order of 2 −3 months and improved long-term quality of life (Massey et al., 2018).

Then there is the issue of continual immunosuppression. I have previously opined on continual immunosuppression vs immunomodulation in MS (Brod, 2020). The preservation, reduction or elimination of immunosurveillance of the acquired immune system should be an important consideration in deciding on the optimal disease modifying treatments (DMT) for an individual NMOSD patient over time. *Eculizumab* has the advantage of not affecting the acquired immune system and would not change (acquired) immunosurveillance, the constant process by which the immune system looks for and recognizes foreign pathogens such as bacteria and viruses or pre-cancerous or cancerous cells throughout the body. *Toclizumab* appears to be immunomodulatory (a decrease or increase in pitch or tone – in this case a decrease) and maintains immunosurveillance because no PML cases or fungal infections have been identified in the search of published medical literature for tocilizumab (Roche data on file) (https://www.sps.nhs.uk/wp-content/uploads/2019/07/Risk-of-PML-with-biologic-immunosuppressants-final.pdf) (Winthrop et al., 2015). Continual elimination of plasmablasts and B cells by *inebilizumab* causes immunosuppression (quashing, stamping out) and impedes immunosurveillance. Inebilizumab is similar to ocrelizumab but depletes an even wider range of lymphocytes from the B-cell lineage. Ocrelizumab was also associated with an increased incidence of breast cancer (increased, but statistically insignificant) particularly in the primary progressive MS OROTORIO clinical trial (Montalban et al., 2017). Inebilizumab targets a broader B cell community with potential greater effects on gamma globulins, B cell and plasmablast lymphocytotoxicity with a potential for decreased cancer surveillance similar to ocrelizumab (OCREVUS PI- 2020) with at least 7 PML (confounded) cases and 1 unconfounded PML case in MS. There is also a 6% incidence of hypo-gammaglobuliemia (Mikulska et al., 2018) with inebilizumab. Therefore, inebilizumab appears to be immunosuppressive because it causes a B cell lymphopenia along with a potential for PML and requires continual administration to maintain its effectiveness.

Assuming the availability of all the agents mentioned above, how do we sequence NMO therapies with the understanding of the acuteness and severity of the disease, the MOA, rapidity of onset of action and long term safety of these four interventions? Eculizumab acts where the

rubber meets the road and has long term (4 year) data with continued high efficacy so it invites itself as initial therapy. Because eculizumab acts rapidly it could be used as an acute intervention during attacks. Its draw backs are frequency of administration and potential cost. Satralizumab may suffer from initial (SukuraSky 11% [adjudicated] - 31% [clinical]; SukuraStar 25%) relapse incidence at 48 weeks suggesting a delayed onset of action after intervention. Its advantages are relative ease of administration (sq) and its (in)frequency of dosing. Inebilizumab's advantage is its MOA directed at antibody producing cells (B cells and plasmablasts) but suffers a delay in onset of activity (13% incidence of time to first relapse at 24 weeks) and our present inability to forecast its plateau in relapse prevention beyond 24 weeks and continued efficacy and safety absent long term follow-up data.

We might suggest the following sequence – 1st line using eculizumab for rapid efficacy and stabilization followed by satrilizumab (see Fig. 1). How long do you keep patients on eculizumab understanding the dosing and cost before you segue to satrilizumab? That is unclear. The advantages of these two agents is that there is no effect on acquired immunity (by eculizumab) and immunomodulation without immunosuppression (by satrilizumab) of the acquired immune system. It would be ideal to overlap the 2 agents to allow for the attainment of effectiveness of satrilizumab. However, the disadvantage of this transition is that the patients' relapses did not plateau on satrilizumab monotherapy until ~ week 130. Of course, we have not mentioned the costs involved of concurrent treatments!

Alternatively, how long do you keep patients on eculizumab before you segue to inebilizumab? It would be ideal to overlap the 2 agents to allow for onset of effectiveness of inebilizumab. Since there is a modest delayed onset of activity with inebilizumab should there not be an overlapping of inebilizumab while still administering eculizumab? How long should that overlap last? Since the inebilizumab trial attacks apparently plateau at 48 weeks overlapping therapy may be required for 1 year. The ultimate disadvantage of this transition is the potential continual immunosuppression and decrease in immunosurveillance with continuous anti-CD19 mAb treatment.

Starting initially with inebilizumab and transitioning to satrilizumab would require concomitant therapy for extended periods of time as above. This transition may not be rational since satrilizumab requires B cells for its effectiveness despite the potential shift from an immunosuppressant to an immunomodulator more compatible for long term therapy.

Could we make a case for initial and continual satrilizumab treatment with convenient self- administration and immune modulation? Perhaps but any breakthrough disease would precipitate a retreat to potentially more efficacious agents so why start there and escalate?

How would we include AHSCBMT as a therapeutic option? AHSCBMT could be used as salvage therapy for severe breakthrough disease after sequencing of NMO-DMTs but that risks significant preceding disability. AHSCBMT could also be used as an induction therapy for severe initial presentations providing a safe segue for the initiation of long-term immunomodulation.

Is there a role for rituximab in NMO therapy despite the lack of class I evidence from randomized placebo controlled clinical trials [30,33]? If NMO patients are stable (relapse free) on off-label RTX, how long should they remain stable (relapse free) in order not to switch to agents proven to be effective in relapse prevention? If 90% of relapses occur within 5 years (Jarius et al., 2012, Kitley et al., 2012) perhaps 5 years relapse free on RTX or another off-label agent may suffice as evidence for disease control without the need for transition to an approved therapy.

Neuromyelitis optica (NMO - including NMO spectrum disorders [NMOSD]) is an interesting, devastating, and soon-to-be therapeutic challenging disease using approved (and off label) interventions. The expansion of the NMOSD pharmacopeia offers unique opportunities to prevent and control a neurological entity heretofore managed without solid clinical evidence. The MOA, onset of activity and long-term efficacy in clinical trials can help direct therapeutic sequencing. Transitioning from the most efficacious agent(s) without effects on acquired immunity to immunomodulators for long term treatment might be the best route. Immunosuppressive therapies could be used as a back-up as necessary. AHSCBMT could be used to reconstitute the immune system after severe attacks. In NMO, control the complement, transition to modulation, and reserve suppression – and salvage the severe with AHSCBMT.

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