

New therapies for neuromyelitis optica spectrum disorder

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Summary

Background Neuromyelitis optica spectrum disorder is an autoimmune disease of the CNS that primarily affects the optic nerves and spinal cord. Most patients have serum antibodies targeting the aquaporin-4 water channel expressed on the end-feet of astrocytes. Although the prevalence of neuromyelitis optica spectrum disorder is limited to around 1–2 people per 100 000, severe immune-mediated attacks can quickly lead to blindness and paralysis if undiagnosed and untreated. However, diagnosis is straightforward when the highly specific serum aquaporin-4 antibodies are detected with cell-based assays.

Recent developments Four randomised controlled trials have tested the efficacy of three new therapies (eculizumab, satralizumab, and inebilizumab) for patients with neuromyelitis optica spectrum disorder that all showed a benefit in preventing future attacks. These therapies have different targets within the immune pathogenic process, and the four trials have similarities and differences that mean they might change the therapeutic landscape for people with neuromyelitis optica spectrum disorder in different ways. Efficacy, safety, tolerability, and practical considerations, including potential cost, differ for each drug and might affect the rate of use in real-world populations of patients with neuromyelitis optica spectrum disorder.

Where next? Despite the rarity of neuromyelitis optica spectrum disorder, a relative abundance of preventive treatment options now exists. In the future, trials should focus on areas of unmet need, including aquaporin-4 seronegative disease, and on development of treatments for acute relapses and for recovery from autoimmune attacks in the CNS.

Introduction

Neuromyelitis optica spectrum disorder is a rare autoimmune disease mediated by recurrent inflammatory attacks against the aquaporin-4 water channel on astrocytes primarily in the optic nerves and spinal cord, often leading to blindness and paralysis.¹ Among demyelinating diseases of the CNS, neuromyelitis optica spectrum disorder is less prevalent than multiple sclerosis, especially in white populations, and is distinguished by a highly specific serological biomarker, aquaporin-4 immunoglobulin G (IgG), in 70–80% of patients.^{2,3} Seropositivity for aquaporin-4 IgG in the context of an inflammatory attack on the CNS, especially within the optic nerve or spinal cord, is all that is required to confirm a diagnosis of neuromyelitis optica spectrum disorder, on the basis of the newest clinical criteria; seronegativity for aquaporin-4 IgG requires various additional criteria to be met.⁴ Because presence of aquaporin-4 IgG is so strongly predictive of a future relapse, treatment efforts have focused on preventive therapies that could help avoid severely disabling attacks in people with neuromyelitis optica spectrum disorder.^{5,6}

Conventional immunosuppressive therapies have been used for prevention of relapses out of license because of their effectiveness in other antibody-mediated conditions and because they appear to provide some benefit to people with neuromyelitis optica spectrum disorder; these include rituximab, mycophenolate mofetil, azathioprine, and prednisone.^{7,8} Consensus treatment recommendations⁹ have been based on a few observational clinical studies that lacked masking or control groups; yet these studies all suggested that immune suppression in general prevents relapses compared with no immunosuppressive

treatment. The discovery of aquaporin-4 IgG prompted research into how the immune system causes astrocyte damage and led to identification of crucial immunological targets, among which were the terminal complement system, the interleukin-6 (IL-6) receptor, and B cells.

This Rapid Review compares and contrasts four randomised controlled trials that have tested these three approaches, and the way their results might change the therapeutic landscape for patients with neuromyelitis optica spectrum disorder.

New immunosuppressive therapies and their mechanisms

Targeting the complement system with eculizumab

Terminal complement deposits are a notable pathological feature of lesions in patients with neuromyelitis optica spectrum disorder. Although not pathognomonic for neuromyelitis optica spectrum disorder, labelling of complement deposits with anti-C9neo antibody is frequently observed along with immunoglobulin deposits, particularly around blood vessels in affected spinal cord autopsy or biopsy tissue.¹⁰ An important role for the complement system in the immunopathogenesis of neuromyelitis optica spectrum disorder was supported by studies in which aquaporin-4 IgG could fix complement in cell culture conditions, ex-vivo slice cultures, and in-vivo rodent models.^{11,12} Human clinical trials of a C1-esterase inhibitor to mitigate complement-mediated damage in acute relapses in patients with neuromyelitis optica spectrum disorder showed a modest benefit, suggesting that complement-mediated activity is contributing to the active inflammatory lesion.¹³ The possibility that relapses might be prevented using a C5 inhibitor was initially shown in a

Lancet Neurol 2020

Published Online
November 10, 2020
[https://doi.org/10.1016/S1474-4422\(20\)30392-6](https://doi.org/10.1016/S1474-4422(20)30392-6)

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phase 2 open-label study of eculizumab in 14 participants with neuromyelitis optica spectrum disorder (eight of whom had a severe disease course marked by previous relapses despite use of other treatments); eculizumab reduced the median number of relapses from three per year (ranging between zero and four) to zero (ranging between zero and one) during treatment ($p < 0.0001$).¹⁴ Although this was a small study, the promising effect formed the basis for the PREVENT trial, an international phase 3 pivotal study with eculizumab.¹⁵

Targeting the IL-6 receptor with satralizumab

Two international phase 3 trials, known as SAKuraStar¹⁶ and SAKuraSky,¹⁷ tested whether relapses in patients with neuromyelitis optica spectrum disorder could be prevented by satralizumab, a monoclonal antibody that blocks the IL-6 receptor. IL-6 is a powerful proinflammatory cytokine that is capable of crossing the blood–brain barrier and is elevated in the blood and CSF of some patients with neuromyelitis optica spectrum disorder during a relapse,^{18–20} potentially due to secretion by astrocytes in response to binding by aquaporin-4 antibodies.²¹ IL-6 is used by the immune system in multiple ways that all contribute to the inflammatory process of neuromyelitis optica spectrum disorder, including (1) promoting the differentiation of naive T cells to proinflammatory T-helper-17 cells;²² (2) blocking activation of regulatory T cells;²³ (3) stimulating aquaporin-4-IgG-producing plasmablasts;²⁴ and (4) activating the innate immune response.²⁵ Case reports and series using tocilizumab, upon which satralizumab is based, had suggested benefit in preventing neuromyelitis optica spectrum disorder relapses by blocking the IL-6 receptor, including one unblinded randomised placebo-controlled study.^{26–29} Satralizumab was designed on the basis of tocilizumab with novel antibody-recycling technology, allowing for increased duration of antibody circulation.³⁰

Targeting B cells with inebilizumab

Among the historical off-label treatment options that appeared to work well in preventing relapses was rituximab, a monoclonal antibody to the B-lymphocyte antigen CD20 that depletes circulating B cells. In an early retrospective study in the USA and the UK using rituximab in people with neuromyelitis optica spectrum disorder, the median relapse rate decreased from 1.7 (0–3.2) per year to 0.0 (0.5–5.0; $p < 0.001$).³¹ A decrease in relapse rate has since been reproduced in over 20 retrospective and prospective international cohorts³² and two controlled clinical trials (although one was not blinded).^{33,34} Additionally, rituximab appeared to reduce risk of relapse by up to 96% from baseline in some patient populations, in contrast to other immunosuppressive agents such as azathioprine, which reduced risk by up to 54% from baseline.^{33–35} These results for rituximab suggested that patients might benefit from inebilizumab, a monoclonal antibody targeting the B-lymphocyte antigen

CD19 that, like rituximab, depletes B cells but also removes B-cell precursors and plasmablasts from circulation. In light of safety results from a phase 1 study in patients with multiple sclerosis³⁶ and an abundance of data on efficacy with rituximab in patients with neuromyelitis optica spectrum disorder, an international phase 2/3 trial of inebilizumab in patients with neuromyelitis optica spectrum disorder, N-Momentum,³⁷ started shortly after the start of the satralizumab trials.

Comparison

Trial design

All four trials were multicentre, international, double-masked, randomised, placebo-controlled trials but they differed in three important ways. First, there was a difference in whether additional immunotherapy was permitted. At the start of the eculizumab trial, there was near-unanimous agreement among neuromyelitis optica spectrum disorder specialists that a monotherapy placebo arm with no background immunosuppression was unethical because relapses can involve severe and permanent neurological deficits.³⁸ However, after the eculizumab trial began, the US Food and Drug Administration (FDA) changed their perspective and insisted that use of background immunotherapy in any future trial on neuromyelitis optica spectrum disorder would confound the interpretation of results. For satralizumab, the US-based SAKuraStar trial¹⁶ had a monotherapy placebo arm that met the FDA standard, whereas the SAKuraSky trial,¹⁷ based outside the USA, required background immunotherapy. For inebilizumab, a single international trial included strategies to mitigate the risk of placebo, such as limiting placebo exposure to 6 months per patient and reducing the chance of randomisation to the placebo arm to 25% by use of a 3:1 randomisation ratio. Because of concerns about the severe disability caused by attacks,⁹ all four trials permitted only a single relapse in the experimental period of the study, after which placebo exposure was not permitted. Thus, the primary outcome measure for all trials was the time to relapse after initiation of the investigational product. Following the experimental period of each trial, there was an open-label period during which all participants received the investigational drug, for which more relapses were permitted than during the experimental period, and the decision to stay in the trial following a relapse was deferred to the site investigator.

A second major difference in trial design was the definition of a relapse. The eculizumab trial initially used a definition that was based on the judgment of individual investigators. After the first 88 participants were enrolled, the sponsor implemented a new adjudication process to try to exclude pseudorelapses from true relapses. Pseudorelapses are transient exacerbations of neurological symptoms due to circumstances other than neuromyelitis optica spectrum disorder inflammatory attacks and would not be considered treatment failures. In the eculizumab trial, 21 relapses previously classified by a treating

	PREVENT (eculizumab) ¹⁵	SAkuraSky ³⁷ and SAkuraStar ⁴⁶ (satralizumab)	N-Momentum (inebilizumab) ³⁷
Immunological target	Complement component 5	Interleukin-6 receptor	CD19 B-cell marker
Trial design*	Phase 3 trial of eculizumab with immunosuppressive therapy vs placebo with immunosuppressive therapy	Phase 3 trials of satralizumab with immunosuppressive therapy vs placebo with immunosuppressive therapy (SAkuraSky) or satralizumab alone vs placebo alone (SAkuraStar)	Phase 2/3 trial of inebilizumab vs placebo
Background immunotherapy	Background immunotherapy was permitted	SAkuraSky: background therapy was necessary SAkuraStar: no background immunotherapy	No background immunotherapy
Aquaporin-4 serostatus	Aquaporin-4-IgG seropositive only	Aquaporin-4-IgG seropositive or seronegative	Aquaporin-4-IgG seropositive or seronegative
Relapse history	At least two relapses in previous year, or at least three relapses in previous 2 years with at least one in previous year	SAkuraSky: at least two relapses in previous 2 years and at least one relapse in previous year; SAkuraStar: at least one relapse in previous year	At least two relapses in previous 2 years and at least one relapse in previous year
Previous rituximab	Yes, but not within 3 months before baseline	Yes, but not within 6 months before baseline	Yes, but not within 6 months before baseline or B cells below lower limit of normal†
Primary endpoint	Time to event (relapse)	Time to event (relapse)	Time to event (relapse)
Event (relapse) definition	New or worsening symptoms persisting for 24 h not attributable to another cause; relapses were classified as minor or major using Opticospinal Impairment Score	New or worsening symptoms persisting for 24 h and meeting any one of four EDSS or Functional System Score thresholds	Report of neurological symptoms attributable to NMOSD, meeting a set of criteria specific for the area of involvement (eg, optic neuritis, transverse neuritis, brain)
Adjudication committee for assessment of primary outcome	Not in original design; protocol amended after enrollment of 88 patients; 21 relapses occurred before amendment	Yes	Yes
Secondary endpoints	ARR, EDSS, modified Rankin Scale, Hauser Ambulation Index, EQ-5D-3L	Pain (VAS), fatigue (FACIT), SF-36, EQ-5D, timed 25-foot walk, percentage of relapse-free patients, ARR, modified Rankin Scale, Zarit Burden Interview, EDSS, visual acuity	EDSS, incidence of new MRI lesions, disease-related admissions to hospital, visual acuity
EDSS at baseline	≤7·0	≤6·5	≤8·0
Maintenance	Intravenous every 2 weeks	Subcutaneous every 4 weeks	Intravenous every 6 months
Age	≥18 years	12–74 years	≥18 years

ARR=annualised relapse rate. EDSS=Expanded Disability Status Scale. EQ-5D(-3L)=(3-level) EuroQol-5-dimension questionnaire. FACIT=functional assessment of chronic illness therapy. NMOSD=neuromyelitis optica spectrum disorder. SF-36=36-item Short Form survey. VAS=visual analogue scale. *All four trials were double-masked studies. †Rituximab depletes B cells for an average of 6–8 months depending on the dose; when rituximab wears off, B-cell counts start to climb again.

Table 1: Comparison of trial design features

physician as true relapses were ultimately excluded as pseudorelapses (11 from the treatment arm, ten from the placebo arm). In the satralizumab trials, a relapse adjudication committee used four criteria from the Functional System Scores, widely used for multiple sclerosis, whereas a relapse adjudication committee for the inebilizumab trial used a detailed relapse adjudication algorithm based on symptoms, clinical examination, and MRI.³⁹ The use of MRI in the inebilizumab and eculizumab trials was intended to improve the sensitivity of relapse adjudication.⁴⁰

The third major difference in trial design was the aquaporin-4-IgG serostatus of the participants. In the eculizumab trial, only aquaporin-4 IgG seropositive patients were permitted to enrol on the basis of the rationale that the antibody was necessary to fix complement. In the satralizumab and inebilizumab trials, aquaporin-4-IgG seronegative participants were not excluded, as historical data suggested they were likely to respond to these therapies.⁴¹ Neuromyelitis optica spectrum disorder in patients with antibodies to myelin oligodendrocyte glycoprotein

(MOG) is now thought to be due to a different immunopathogenic process to that in patients with aquaporin-4 antibodies but, when the three trials began, the MOG antibody test was not yet commercially available and MOG-antibody-positive patients were thus not excluded.

A comparison of other trial design features is provided in table 1. Of note, the eculizumab study had eligibility criteria that aimed to recruit patients with more active relapsing disease than the satralizumab and inebilizumab trials. The inebilizumab trial was unique in restricting the length of the double-blind placebo phase to reduce the risk to patients in the placebo arms. A comparison of participants at baseline is provided in table 2.

Efficacy

Of 96 participants in the eculizumab treatment arm, three (3%) relapsed over the course of the trial compared with 20 (43%) of 47 participants who relapsed in the control arm, resulting in a 94% reduction in adjudicated relapse risk over time (hazard ratio [HR] 0·06, 95% CI 0·02–0·20; $p<0·001$; number needed to treat 2·5).¹⁵ At 48 weeks,

	PREVENT (eculizumab) ³⁵		SAkuraSky (satralizumab) ³⁷		SAkuraStar (satralizumab) ³⁶		N-Momentum (inebilizumab) ³⁷	
	Placebo with or without IST (n=47)	Ecuzumab with or without IST (n=96)	Placebo with or without IST (n=42)	Satralizumab with or without IST (n=41)	Placebo (n=32)	Satralizumab (n=63)	Placebo (n=56)	Inebilizumab (n=174)
Aquaporin-4-IgG seropositive, n (%)	47 (100%)	96 (100%)	28 (67%)	27 (66%)	23 (72%)	41 (65%)	52 (91%)	161 (91%)
Female, n (%)	42 (89%)	88 (92%)	40 (95%)	37 (90%)	31 (97%)	46 (73%)	50 (89%)	159 (91%)
Age, mean years (SD)	45 (13)	44 (13)	43 (12)	41 (16)	41 (11)	45 (12)	43 (14)	43 (12)
Age at initial clinical presentation, mean years (SD)	39 (15)	36 (14)	39 (12)	35 (17)	39 (13)	36 (11)	Not reported	Not reported
Baseline EDSS	4.0 (1.0–7.0)*	4.0 (1.0–6.5)*	3.6 (1.3)†	3.8 (1.6)†	3.6 (1.6)†	3.9 (1.2)†	4.0*	3.5*
Discontinuation rate, n (%)	3 (6%)	16 (17%)	10 (24%)	3 (7%)	4 (12%)	7 (11%)	2 (4%)	6 (4%)
Baseline ARR in previous 2 years, mean (SD)	2.1 (1.0)	1.9 (0.9)	1.4 (0.5)	1.5 (0.5)	1.4 (0.6)	1.5 (0.7)	1.6 (1.5)	1.7 (1.5)
Background immunotherapy, n (%)	None: 13 (28%); Corticosteroids: 11 (23%); Azathioprine with or without corticosteroids: 13 (28%); Mycophenolate mofetil with or without corticosteroids: 8 (17%); Other with or without corticosteroids: 2 (4%)	None: 21 (22%); Corticosteroids: 16 (17%); Azathioprine with or without corticosteroids: 37 (39%); Mycophenolate mofetil with or without corticosteroids: 17 (18%); Other with or without corticosteroids: 5 (5%)	Corticosteroids: 20 (48%); Azathioprine: 13 (31%); Mycophenolate mofetil: 8 (19%); Mycophenolate mofetil with corticosteroids: 1 (2%)	Corticosteroids: 17 (41%); Azathioprine: 16 (39%); Mycophenolate mofetil: 4 (10%); Azathioprine with corticosteroids: 3 (7%); Mycophenolate mofetil with corticosteroids: 1 (2%)	None: 32 (100%)	None: 63 (100%)	None: 56 (100%)	None: 174 (100%)

ARR=annualised relapse rate. EDSS=Expanded Disability Status Scale. IST=immunosuppressive therapy. *Median. †Mean.

Table 2: Comparison of participants at baseline

94 (98%) of 96 participants who started on eculizumab were relapse-free compared with 30 (63%) of 47 participants in the control group; at 96 weeks, 93 (96%) of 96 participants were relapse-free in the eculizumab group versus 24 (52%) of 47 participants in the control group. Among participants not on background immunotherapy, none (0%) of 21 in the eculizumab group had any relapses compared with 7 (54%) of 13 participants in the placebo group.

In the SAkuraSky study of satralizumab plus background immunotherapy, 8 (20%) of 41 participants in the treatment arm relapsed over the course of the trial compared with 18 (43%) of 42 controls, resulting in a 62% reduction in adjudicated relapse risk over time (HR 0.38, 95% CI 0.16–0.88; $p=0.02$; number needed to treat 4.3). The proportion of participants on satralizumab who were relapse-free was 36 (89%) of 41 at 48 weeks, versus 28 (66%) of 42 for the control group, and 31 (78%) of 41 at 96 weeks, versus 25 (59%) of 42 for the control group. Post-hoc analysis by aquaporin-4-IgG serostatus revealed a greater effect in the aquaporin-4-IgG seropositive subgroup, with a 79% reduction in relapse risk compared with seropositive participants in the control group; 3 (11%) of 27 aquaporin-4-IgG seropositive patients receiving satralizumab had a protocol-defined relapse, compared with 12 (43%) of 28 aquaporin-4-IgG seropositive patients receiving placebo (HR 0.21, 95% CI 0.06–0.75). Aquaporin-4-IgG seronegative participants (n=28; 14 in each arm) showed no reduction in risk of relapse with satralizumab compared with placebo, but

there is no information on the number who were MOG-antibody-positive within this group. In the SAkuraStar study of satralizumab, 19 (30%) of 63 participants in the treatment arm relapsed over the course of the trial compared with 16 (50%) of 32 controls, resulting in a 55% reduction in adjudicated relapse risk (HR 0.45, 95% CI 0.23–0.89; $p=0.018$; number needed to treat 5.0). The proportion of participants on satralizumab who were relapse-free was 48 (76%) of 63, versus 20 (62%) of 32 for the control group, at 48 weeks, and 45 (72%) of 63, versus 16 (50%) of 32 for the control group, at 96 weeks. Post-hoc analysis by aquaporin-4-IgG serostatus revealed a 74% reduction in relapse risk among seropositive participants compared with the placebo group. Aquaporin-4-IgG seronegative participants (n=31; 22 in the satralizumab arm and nine in the placebo arm) showed no significant difference in relapses between the treatment and placebo groups, with 10 (46%) participants on satralizumab and 3 (33%) participants on placebo relapsing (HR 1.19, 95% CI 0.30–4.78).

Of 174 participants in the inebilizumab treatment arm, 21 (12%) relapsed over the course of the trial compared with 22 (39%) of 56 in the control arm, resulting in a 73% reduction in adjudicated relapse risk over time (HR 0.27; 95% CI 0.15–0.50; $p<0.001$; number needed to treat 3.7).³⁷ Relapse-free data at 1 and 2 years are not available because patients in the placebo arm were limited to a maximum exposure of 6 months. Post-hoc analysis by aquaporin-4-IgG serostatus showed a reduction of

relapse risk by 77% among the seropositive people in the inebilizumab group compared with seropositive people in the control group. As the aquaporin-4-IgG seronegative group made up only a small proportion of the entire trial cohort, the absence of relapses in the four patients on placebo and the three relapses in the 13 patients on inebilizumab could not be interpreted.

Safety

All three medications were relatively safe, especially compared with the neurological consequences of a neuromyelitis optica spectrum disorder relapse. There were no serious events that were judged to be directly related to the drugs. The main risk with eculizumab is infection by encapsulated organisms such as *Neisseria meningitidis*: in the phase 2 trial of eculizumab in patients with neuromyelitis optica spectrum disorder, there was one event of *N meningitidis* bacteraemia,¹⁴ but mandatory *N meningitidis* vaccinations in the phase 3 trial appeared to prevent any additional events of bacteraemia or meningitis. Upper respiratory tract infections and headaches were more common with eculizumab than with placebo, and there was one death in the eculizumab arm caused by pulmonary empyema with non-encapsulated organisms in a participant with pre-existing pulmonary disease and a history of azathioprine treatment.

Satralizumab injections caused some skin reactions at the injection site in the SAKuraSky trial, but there were no other safety concerns in both satralizumab trials when compared with the placebo groups. There were no deaths.

The safety profile of inebilizumab mirrored those of observational studies of B-cell depleting agents in patients with neuromyelitis optica spectrum disorder.³² Potential concerns include opportunistic infections due to long-term impaired adaptive immunity and declining IgG concentrations, although no opportunistic infections occurred in the 6-month trial period. Urinary tract infections and arthralgias were slightly more common in the inebilizumab arm than in the placebo arm. Two deaths have occurred during treatment with inebilizumab in the ongoing extension phase, both probably due to neuromyelitis optica spectrum disorder attacks and one of which was linked to inebilizumab use. One of the deaths followed a high cervical myelitis that led to respiratory insufficiency; the second death involved extensive brain lesions that could not be attributed reliably to another cause such as progressive multifocal leukoencephalopathy and no autopsy could be done to confirm a final diagnosis. Additional data from participants with longer inebilizumab exposure are required for more accurate safety and efficacy comparisons.

Practical considerations

All three drugs have been approved by the FDA, but availability might be limited by cost (prices below are for the US market; the USA is the only country where prices are available, because these drugs are so new). Although

the efficacy of eculizumab was high in the phase 3 trial, compliance and cost are major challenges in a real-world setting. Infusions are required every 2 weeks and missing a single dose might result in recovery of C5 complement activity, increasing the risk of a neuromyelitis optica spectrum disorder relapse. Home-based infusions, rather than infusions provided at infusion centres or hospitals, might make the infusion schedule more convenient for patients. Vaccines against *N meningitidis* are required before initiation of therapy; when treatment initiation is urgent, concurrent antibiotic coverage is recommended until 2 weeks after immunisation. No routine monitoring is necessary while on eculizumab. The yearly cost of eculizumab is approximately US\$710 000 in the USA (four 300 mg vials every 2 weeks at \$6830 per vial⁴²), making access to this drug difficult for patients who are uninsured or underinsured and it remains to be seen what access other health-care systems will allow.

Satralizumab is dispensed in prefilled syringes, and monthly subcutaneous injections allow self-administration at home. No routine monitoring is necessary while on satralizumab. The cost of satralizumab in the USA is \$219 231 for the first year, accounting for additional loading doses, and \$190 000 per year thereafter.⁴³

Inebilizumab requires two infusions at induction two weeks apart, followed by two infusions per year. This schedule mirrors the dosing plan for rituximab, which has historically worked well for patients with neuromyelitis optica spectrum disorder, including in both cases B-cell counts twice a year to ensure depletion of these cells and of IgG concentrations to avoid hypogammaglobulinaemia, in addition to routine tuberculosis and hepatitis screening. The cost in the USA of inebilizumab for the first year of treatment has been set at \$393 000 for three infusions (two loading doses, followed by a single 300 mg dose 6 months later) and, in subsequent years, the cost will be \$262 000 for two yearly doses.⁴⁴ Compared with eculizumab, the long-term cost is less than half, but inebilizumab is approximately 25–40 times more expensive than rituximab.

Advantages and disadvantages of the new drugs

Despite the differences in design, comparison of the outcomes from the four trials is worth attempting. For example, despite the different eligibility criteria for baseline activity, the pretreatment relapse rates and disability levels were not so dissimilar. Additionally, the proportion of participants in the placebo groups who relapsed over time and the relapse-free rates in the eculizumab and satralizumab studies were within 4% points of each other. Although the efficacy, according to time to relapse, is greater for eculizumab than the other two drugs, the percentage of patients who remain relapse-free at 48 and 96 weeks is similar for eculizumab and satralizumab. Equivalent percentages were not available in the inebilizumab study because patients were in the experimental period for a maximum of 6 months. As might be expected, there are slightly fewer relapses in the add-on satralizumab

study versus the monotherapy trial, in both the placebo and active arms. However, in the eculizumab study, add-on therapy appeared beneficial only in the placebo arm and no additional benefit on relapse risk reduction was seen in participants on eculizumab plus background immunosuppression compared with those receiving eculizumab without background immunosuppression.

In countries where all three of these new treatments are approved for clinical use, clinicians are now faced with a changing landscape of options to offer their patients with neuromyelitis optica spectrum disorder, who might have different priorities among efficacy, safety, cost, monitoring burden, and logistics. With this in mind, we provide a summary of these features for the recently tested drugs (appendix pp 1–2), all of which can be considered as first-line, second-line, and third-line options; the reimbursement arrangements might define the order of preference in some countries. As these medications are fairly new and most patients with neuromyelitis optica spectrum disorder are still using off-label medications, the most common off-label medications have also been included in our summary, but these treatments do not all have unbiased randomised trials to support their use. To make informed decisions, pros and cons of each option should be taken into account.

With eculizumab, the obvious advantage is the high efficacy in preventing relapses and, from the wider experience in patients with myasthenia gravis, a fairly benign safety profile.^{45,46} Additionally, the evidence suggests there might be no advantage to using eculizumab in combination with other immunosuppressive therapies compared with eculizumab alone. The challenge is that the formulation requires infusions twice per month with minimal flexibility, as complement component 5 activity begins to rise within a few days of a missed dose.⁴⁷ The tight scheduling, along with the high cost, are being addressed with the development of a longer-lasting inhibitory drug for component 5 infused every 8 weeks (ravulizumab) instead of every 2 weeks, and which, if approved, would cost less per year than eculizumab (NCT04201262).⁴⁸

In terms of efficacy in aquaporin-4-IgG seropositive patients, satralizumab and inebilizumab appear to have a lower reduction in relapse risk than eculizumab, albeit with similar relapse-free proportions over time. Satralizumab might be more effective when given with an add-on immunosuppressive treatment than when given alone, as shown by the difference in efficacy between the SAKuraSky and SAKuraStar trials. Combination therapy has its disadvantages: for the patient, in the extra burden of taking more treatment than with monotherapy, and for the physician, in deciding which therapy has caused which side-effects. The obvious advantage of satralizumab is its subcutaneous formulation; it is the only one of the recently tested drugs that allows patients to avoid intravenous infusions. Patients should be able to access pre-filled syringes locally, with no monitoring requirements and no previous vaccinations required. Satralizumab is

priced at around 25% less than inebilizumab and more than 70% less than eculizumab. However, the widespread availability of subcutaneous tocilizumab (the parent compound of satralizumab that is dosed subcutaneously twice per month) and monthly intravenous tocilizumab might offer more affordable off-label options.

Inebilizumab will probably be used by people who have similar needs to those who have used rituximab for the past 15 years. Many patients with neuromyelitis optica spectrum disorder are already familiar and comfortable with B-cell depletion induced by infusions twice per year but, in contrast to rituximab, inebilizumab has been thoroughly tested in the largest neuromyelitis optica spectrum disorder trial to date with a pure placebo control, to provide the most reliable data about the magnitude of the effect of B-cell depletion on preventing relapses. Its advantage over the other two new drugs and rituximab is its less frequent administration. However, because of the high price of inebilizumab, patients with neuromyelitis optica spectrum disorder might fall back on rituximab. Additionally, inebilizumab is unlikely to be the treatment of choice for patients who have relapsed while using rituximab.

Newly diagnosed patients with neuromyelitis optica spectrum disorder have an abundance of preventive treatment options, in countries where these new drugs are available. For the many patients with neuromyelitis optica spectrum disorder who are currently using off-label treatments, the decision to recommend switching to an approved therapy depends on whether patients feel comfortable switching and whether they have access to and can afford the newer agents. For patients who have been in stable remission on their current off-label therapy, switching might impose unnecessary risks. If they choose to stay on their current treatment, they know that they have newer therapeutic options if their disease breaks through.

Conclusions and future directions

2019 saw the publication of results for three new therapies for a rare disease for which previously the only preventive treatment options were off label. The reason for this turnaround is the careful scientific investigation into the pathogenesis of neuromyelitis optica spectrum disorder that identified therapeutic targets spread across multiple mechanisms of action. Eculizumab yielded phase 3 trial results first and set a high bar for efficacy with a 94% reduction in relapse risk compared with the control group. Satralizumab followed with a 62% reduction in risk of relapse compared with placebo but among aquaporin-4-IgG seropositive patients, the risk reduction was 79% compared with placebo. With inebilizumab, risk reduction was 73% (77% among aquaporin-4-IgG seropositive patients) compared with placebo, mirroring the efficacy of rituximab, which has been a mainstay, albeit off-label, treatment option for many patients with neuromyelitis optica spectrum disorder. Each of the new drugs

See Online for appendix

Search strategy and selection criteria

PubMed was searched for treatments of neuromyelitis optica spectrum disorder, from Jan 1, 2000, until May 31, 2020. A combination of search terms related to neuromyelitis spectrum optica disorder and related treatments were used: "neuromyelitis optica", "NMO", "NMOSD", "treatment", "therapy", "eculizumab", "satralizumab", "tocilizumab", "inebilizumab", "rituximab", "aquaporin 4", "AQP4", "AQP4-IgG", "myelin oligodendrocyte glycoprotein", "MOG", "MOGAD", and "MOG-IgG". The reference lists in published articles on neuromyelitis optica spectrum disorder were also queried to identify further studies. Studies with information on the treatment of neuromyelitis optica spectrum disorder in English, including the four randomised controlled trials of three monoclonal antibodies (eculizumab, satralizumab, and inebilizumab), were reviewed. The final list of publications was selected on the basis of relevance to the topic.

has proven efficacious, and all showed acceptable safety profiles, at least for the short durations for which they were studied. None of these drugs has shown efficacy in patients without aquaporin-4 IgG.

Increasingly, autoantibodies targeting alternative neural proteins, such as MOG, are being identified in patients with aquaporin-4-IgG seronegative disease. These autoantibodies have been found in up to 50% of aquaporin-4-IgG seronegative patients who otherwise meet neuromyelitis optica spectrum disorder criteria.⁴⁹ The results of the satralizumab and inebilizumab trials suggest a difference in the treatment responses between aquaporin-4-IgG seropositive and seronegative patients (albeit with low numbers in the seronegative group), suggesting their immunopathogenic mechanisms might be different. MOG antibody disease is emerging as a unique autoimmune condition requiring different treatments^{50–53} and, as yet, the number of people with MOG-IgG seropositivity within the aquaporin-4-IgG seronegative subgroups in the clinical trials has not been published. Thus, it is difficult to broadly apply the results of these trials to patients who are seronegative for aquaporin-4. This subgroup of patients with neuromyelitis optica spectrum disorder might have to continue to rely on off-label medications, which have been shown to be effective in observational studies.⁵⁴

Future studies should focus on several areas of unmet need. First, acute treatment trials to improve outcomes from relapses in neuromyelitis optica spectrum disorder are needed. Second, new therapies are needed to improve healing, regeneration, and restoration of neurological function in patients with chronic neurological injury. Third, patients who are aquaporin-4-IgG seronegative and MOG-IgG seropositive might not respond well to these three preventive drugs and should be a special focus for future trials. Additionally, because neuromyelitis optica spectrum disorder is a worldwide disease and, in the case

of aquaporin-4 antibody disease, is particularly common in non-white patients who are often in low-income countries,⁵⁵ affordable drugs and easy administration are crucial.

Contributors

ML, KF, and JP contributed equally to the writing, literature inclusion, interpretation, and supervision of the manuscript.

Declaration of interests

ML received consulting fees from all three manufacturers involved in the trials discussed in this Rapid Review: Alexion, VielaBio, and Genentech/Roche/Chugai. In addition, ML has received consulting fees from Quest Diagnostics and UCB Pharmaceuticals. KF serves on scientific advisory boards for Biogen, Mitsubishi Tanabe, Novartis, Chugai, Alexion, VielaBio, and UCB; has received funding for travel and speaker honoraria from Biogen, Eisai, Mitsubishi Tanabe, Novartis, Chugai, Roche, Alexion, VielaBio, Teijin, Asahi Kasei Medical, Merck, and Takeda; and has received the Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Grants-in-Aid for Scientific Research from the Ministry of Health, Welfare and Labor of Japan. JP received consulting fees and is partly funded by highly specialised National Health Services to run a national congenital myasthenia service and a neuromyelitis service, has received support for scientific meetings and honoraria for advisory work from Merck Serono, Biogen Idec, Novartis, Teva, Chugai Pharma and Bayer Schering, Alexion, Roche, Genzyme, MedImmune, EuroImmun, MedDay, Abide ARGENX, UCB, and VielaBio, and grants from Merck Serono, Novartis, Biogen Idec, Teva, Abide, MedImmune, Bayer Schering, Genzyme, Chugai, and Alexion, UK MS society, Guthy Jackson Foundation, National Institute of Health Research, Oxford Health Services Research Committee, Medical Research Council, Grant for MS Innovation, John Fell Fund, and Myaware for research studies.

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