Canadian Journal of Health Technologies

CADTH

February 2021 Volume 1 Issue 2

CADTH Health Technology Review

Rituximab for the Treatment of Neuromyelitis Optica Spectrum Disorder

Rapid Review With Expert Input

CADTH

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External reviewer: This document was externally reviewed by Colin Chalk, MDCM, FRCPC, a professor at McGill University, who has granted permission to be cited.

ISSN: 2563-6596

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Table of Contents

List of Tables

CADTH

List of Figures

Abbreviations

AE	adverse event
AQP4	aquaporin 4
ARR	annualized relapse rate
AZA	azathioprine
CI	confidence interval
CrI	credible interval
CyA	cyclosporin A
CYP	cyclophosphamide
EDSS	Expanded Disability Status Scale
HR	hazard ratio
HRR	hazard risk for relapse
ICER	incremental cost-effectiveness ratio
IVMP	intravenous methylprednisolone
MMF	mycophenolate mofetil
MS	multiple sclerosis
NMA	network meta-analysis
NMOSD	neuromyelitis optica spectrum disorder
PSA	probabilistic sensitivity analysis
PLEX	plasmapheresis
QALY	quality-adjusted life-year
QOSI	quantification of optic nerve and spinal cord impairment
RCT	randomized controlled trial
RR	risk ratio
RTX	rituximab
SMD	standardized mean difference
THB	Thai baht
WTP	willingness to pay

Key Messages

- Four systematic reviews, 1 randomized controlled trial (RCT), 1 economic evaluation, and 2 evidence-based guidelines were identified.
- Four systematic reviews (2 that included moderate- to high-quality evidence and 2 that did not report the quality of the evidence) and 1 RCT (that provided high-quality evidence) reported on the clinical effectiveness of rituximab (RTX) for the treatment of neuromyelitis optica spectrum disorder (NMOSD). Overall, RTX treatment appeared to reduce the relapse rate and disability level compared with pre-treatment or placebo. In terms of reduction in relapse rate and disability, RTX was either better or not different from azathioprine (AZA). For relapse rates, disability levels, and incidence of adverse events, network meta-analyses showed that no treatment was favoured for comparisons between RTX, mycophenolate mofetil (MMF), and cyclophosphamide (CYP).
- One economic evaluation (of moderate quality) showed that, for patients with NMOSD, in the context of the Thai health care system, RTX biosimilar with $CD27^+$ memory B cell monitoring regimen had the highest probability (48%) of being cost-effective, followed by AZA (30%), MMF (13%), RTX with $CD27^+$ memory B cell monitoring regimen (9%), RTX biosimilar (0%), and RTX (0%) at a willingness-to-pay threshold of 160,000 Thai bhat (equivalent to US$5,289 in 2019 values) per quality-adjusted life-year gained.
- The 2 guidelines recommended immunosuppressants (RTX, AZA, and MMF) for prevention of NMOSD attacks. In addition, 1 guideline mentioned that tocilizumab, eculizumab, inebilizumab, and satralizumab can be used in NMOSD leave it up to patients who have no response to other immunosuppressants. The quality of the evidence that informed the guidelines and the strength of the recommendations were not reported.
- Findings need to be interpreted with caution given the limited quantity of evidence on comparative efficacy and safety between various immunosuppressants, that many of the included primary studies were retrospective studies, the heterogeneity among the studies included in the systematic reviews, and the lack of clarity with respect to the strength of the recommendations.

Context and Policy Issues

Neuromyelitis optica spectrum disorder (NMOSD), also referred to as neuromyelitis optica and Devic disease,[1] is an autoimmune disease that can cause severe demyelination of the nerve fibres of the spinal cord and optic nerve. The main pathogenic autoantibody is an astrocytic water channel aquaporin 4 (AQP4) antibody which targets AQP4 on the membrane of astrocytes resulting in inflammation of the astrocytes and eventually leading to oligodendrocyte injury and demyelination.[2] For those who are diagnosed with NMOSD, the body's immune system reacts against its own cells in the central nervous system, primarily the optic nerve and spinal cord.[1] This may cause blindness in 1 or both eyes, weakness or paralysis in the limbs, painful spasms, loss of sensation, and bladder or bowel dysfunction.[1,3] Although NMOSD has some similar clinical features as multiple sclerosis (MS), it is distinct from MS.

One publication reported that the incidence and prevalence of NMOSD varied by geographic region and ethnicity.[4] The highest estimates of incidence (0.73 per 100,000 person-years) and prevalence (10 per 100,000 persons) were found in the Afro-Caribbean region. The

lowest estimates of incidence (0.037 per 100,000 person-years) and prevalence (0.7 per 100,000 persons) were found in Australia and New Zealand. Among the Asian population in British Columbia (Canada), the estimates of incidence of NMOSD ranged from 0.39 per 100,000 to 0.6 per 100,000 person-years.[4] Another publication reported that the prevalence of NMOSD ranged from 0.5 per 100,000 to 10 per 100,000 persons, depending on ethnicity (e.g., prevalence estimates were 1 per 100,000 persons among those who were White, 3.5 per 100,000 persons among those who were East Asian, and 10 per 100,000 persons among those who were Black).[5] NMOSD disproportionally affects females.[6]

Treatment options for NMOSD include corticosteroids, plasma exchange, and immunosuppressive drugs such as azathioprine (AZA), mycophenolate mofetil (MMF), rituximab (RTX), cyclophosphamide (CYP), tocilizumab, eculizumab, inebilizumab, and satralizumab.[2,7,8] Eculizumab was the first immunosuppressive drug with a Health Canada indication for the treatment of NMOSD in adult patients who are seropositive for AQP4 antibody.[9] Rituximab is a monoclonal antibody that binds to the CD20 surface marker expressed on B cells, which results in depletion of B cells (B cells are precursors of antibody-producing plasma cells).[10]

The purpose of this report is to review the comparative clinical effectiveness and cost-effectiveness of rituximab for the treatment of NMOSD and to review the evidence-based guidelines regarding the use of pharmacotherapy for the treatment of NMOSD.

Research Questions

1. What is the clinical effectiveness of rituximab for the treatment of individuals with NMOSD?
2. What is the cost-effectiveness of rituximab for the treatment of individuals with NMOSD?
3. What are the evidence-based guidelines regarding the use of pharmacotherapy for the treatment of individuals with NMOSD?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid MEDLINE, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were rituximab and neuromyelitis optica spectrum disorder. No filters were applied to limit the retrieval by study type for questions 1 or 2. A methodological filter was applied to limit retrieval to guidelines for question 3. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015, and November 25, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published before 2015. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included systematic reviews. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[11] for systematic reviews, the Questionnaire to Assess the Relevance and Credibility of a Network Meta-Analysis[12] for network meta-analyses (NMAs), the Downs and Black checklist[13] for randomized studies, the Drummond checklist[14] for economic evaluations, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[15] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Table 1: Selection Criteria

Criteria	Description
Population	Individuals (of any age) with neuromyelitis optica spectrum disorder
Intervention	Q1 and Q2: Rituximab Q3: Any pharmacotherapy (e.g., rituximab, alternative immunosuppressant therapies)
Comparator	Q1 and Q2: Alternative immunosuppressant therapies (e.g., azathioprine, mycophenolate mofetil, tocilizumab, methotrexate, cyclophosphamide, mitoxantrone, cyclosporine, prednisone, bortezomib, eculizumab); placebo; no treatment Q3: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., mortality, time to first relapse, relapse rate, disability, health-related quality of life, functionality, symptom severity [e.g., pain, fatigue, bladder and bowel function, sexual dysfunction, respiratory symptoms], safety [e.g., rate of adverse events]) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained) Q3: Recommendations regarding best practices (e.g., appropriate patient populations, guidance regarding treatment protocols and the place of rituximab and other drug therapies in the treatment pathway)
Study designs	Systematic reviews, randomized controlled trials, economic evaluations, and evidence-based guidelines

Summary of Evidence

Quantity of Research Available

A total of 242 citations were identified in the literature search. Following screening of titles and abstracts, 222 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 20 potentially relevant articles, 12 publications were excluded for various reasons, and 8 publications met the inclusion criteria and were included in this report. These comprised 4 systematic reviews,[2,16-18] 1 randomized controlled trial (RCT),[8] 1 economic evaluation,[8] and 2 evidence-based guidelines.[19,20] Appendix 1 presents the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[21] flow chart of the study selection.

Summary of Study Characteristics

Four systematic reviews,[2,16-18] 1 RCT,[8] 1 economic evaluation,[22] and 2 evidence-based guidelines[19,20] were included. In 3 systematic reviews,[2,17,18] all of the included studies were relevant for this report. In the fourth systematic review,[16] a subset of studies was relevant, and only the characteristics and results of this subset will be described in this report. The relevant primary studies in the included systematic reviews are listed in Appendix 5. There was some overlap in the studies included in the systematic reviews; hence, there is double-counting of studies and findings from the systematic reviews are not exclusive. Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Each of the 4 relevant systematic reviews[2,16-18] included meta-analyses, and 1 systematic review[2] also included NMAs. The number of primary studies involving RTX that were included in the systematic reviews ranged from 3 to 46 studies. These comprised mainly prospective and retrospective observational studies, and 1 RCT which was included in 3 systematic reviews.[2,16,17] Three systematic reviews[2,16,17] were published in 2019, and the fourth systematic review[18] was published in 2016.

The included RCT[8] was a multi-centre, double-blind study that was published in 2020.

The included economic evaluation[22] was a cost-utility analysis using a Markov model. A societal perspective and a lifetime horizon were used. It was assumed that all patient groups had the same probability of relapse and that RTX biosimilar had the same efficacy as RTX. Clinical data were obtained from the literature, utility data were from a publication related to the context in Thailand, and cost data were from the Reference Drug Price Ministry of Public Health. Sensitivity analyses were conducted.

Two evidence-based guidelines[19,20] were included. For both guidelines, the guideline development group comprised experts in the area of inflammatory demyelinating disorders in the central nervous system and a systematic literature search was conducted to identify evidence and the recommendations were formulated based on consensus and voting.

Country of Origin

Of the 4 systematic reviews,[2,16-18] 2 systematic reviews[2,17] were from China, the third systematic review[16] was from the Philippines, and the fourth systematic review[18] was from

Italy. None of the systematic reviews reported in which countries the included primary studies were conducted.

The included RCT[8] was a multi-centre study conducted in 8 hospitals in Japan. The included economic evaluation[22] was from Thailand. One guideline[19] was from Latin America, and another guideline[20] was from Iran.

Patient Population

All 4 systematic reviews[2,16-18] involved patients with NMOSD, and the number of included patients ranged from 205 to 577. Patient ages ranged from 14 years to 54 years in 1 systematic review[17]; median ages were 34 years, 42 years, and not reported in the studies included in the second systematic review[2]; mean age was 32 years in the third systematic review[18]; and age was not reported in the fourth systematic review.[16] The proportion of females ranged between 67% and 100% in 3 systematic reviews,[2,16,17] and was reported as a mean of 87% across primary studies in the fourth systematic review.[18] The proportion of patients with a AQP4-positive serotype ranged from 43% to 94% in the primary studies in 1 systematic review,[16] 36% to 82% in the second systematic review,[2] and was reported as a mean of 75%[17] and 83%[18] across primary studies in the remaining systematic reviews. The duration of disease ranged from 11 months to 11 years across primary studies in 1 systematic review[17] and 9 months to 75 months in the second systematic review.[2] It was reported as a mean of 50 months in the third systematic review,[18] and was not reported in the fourth systematic review.[16]

The RCT[8] included patients with NMOSD. The median age of patients was 53 years in the RTX group and 47 years in the placebo group. The proportion of females was 90% in the RTX group and 100% in the placebo group. All patients were AQP4-serotype positive. The median duration of disease was 119 months in the RTX group and 80 months in the placebo group.

The economic evaluation[22] involved adult patients with NMOSD.

Both of the included guidelines[19,20] were for the treatment of NMOSD patients. The intended users of the guidelines were clinicians involved in the care of patients with NMOSD.

Interventions and Comparators

Two systematic reviews[17,18] included primary studies that compared before and after treatment with RTX. The third systematic review[16] included primary studies that compared RTX with MMF, AZA, or CYP, and the fourth systematic review[2] included primary studies that compared RTX with MMF or CYP. This systematic review[2] also included an NMA that included RTX, MMF, AZA, CYP, and cyclosporin (CyA).

The included RCT[8] compared RTX with placebo, both administered by drip infusion.

The economic evaluation[22] compared RTX fixed dose, RTX with $CD27^+$ memory cell monitoring regimen, RTX (biosimilar) fixed dose, RTX (biosimilar) with $CD27^+$ memory cell monitoring regimen, and MMF with AZA as reference.

In both guidelines,[19,20] the interventions considered for the treatment of NMOSD were IV methylprednisolone (IVMP), plasmapheresis (PLEX), AZA, MMF, and RTX. In addition, 1 guideline[19] considered tocilizumab, eculizumab, inebilizumab, satralizumab, CYP, and mitoxantrone.

Outcomes

Outcomes reported in the systematic reviews[2,16-18] included annualized relapse rate (ARR),[2,16-18] Expanded Disability Status Scale (EDSS) score,[2,16-18] hazard risk for relapse (HRR),[16] relapse-free rate,[16] adverse events (AEs),[2,16-18] and death.[17,18] Follow-up duration ranged from 19 months to 67 months in 1 systematic review,[17] 12 months to 31 months in the second systematic review,[2] 3 months to 272 months in the third systematic review,[18] and was not reported in the fourth systematic review.[16]

Outcomes reported in the included RCT[8] were relapse rate, EDSS scores, quantification of optic nerve and spinal cord impairment (QOSI) scores, steroid reduction, AEs, and death. Follow-up duration was a median of 72 weeks.

Scales used for outcome measures in the systematic reviews and RCT included the EDSS and QOSI. The EDSS is a rating scale from 0 to 10, with higher scores indicating greater disability.[9] The QOSI is a rating scale with higher scores indicating greater disability.[24]

The economic evaluation[22] reported on incremental cost-effectiveness ratio (ICER) expressed as cost per quality-adjusted life-year (QALY). Cost-effectiveness acceptability curves were presented.

In both guidelines,[19,20] the outcomes considered included relapse rate, disability, and safety.

Summary of Critical Appraisal

An overview of the critical appraisal of the included publications is summarized below. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

In all 4 systematic reviews,[2,16-18] the objective was stated, multiple databases were searched, article selection was described and was conducted independently by 2 reviewers, data extraction was conducted, lists of included articles were presented, and study characteristics were described. In 2 systematic reviews,[2,18] article selection was done independently by 2 reviewers; in 2 systematic reviews,[16,17] it was unclear how article selection was conducted. In 1 systematic review,[2] data extraction was done by 2 reviewers, and in another systematic review[18] the data extraction was done by 1 reviewer and checked by another reviewer. In the remaining 2 systematic reviews,[16,17] it was unclear if data extraction was conducted in duplicate; hence, the possibility of errors cannot be ruled out. In 2 systematic reviews,[2,16] quality assessment of the included primary studies was conducted and the authors judged the quality to be good or moderate. In the remaining 2 systematic reviews,[17,18] a quality assessment did not appear to have been undertaken; hence, the quality of the included primary studies is not known. In all 4 systematic reviews,[16,17] conflicts of interest of the authors were declared; for 3 systematic reviews,[2,16,17] there appeared to be no issues. In the fourth systematic review,[18] 1 of the authors had an association with the pharmaceutical industry although the impact of this, if any, is unclear.

All 4 systematic reviews[2,16-18] included meta-analyses. In addition, 1 systematic review[2] included an NMA. Limitations in the NMA should be considered when interpreting results. First, the number of included studies and closed loops per comparison were few. Second, as some of the immunosuppressive therapies were not used as monotherapies, their definitive therapeutic effect could not be ascertained. Third, there was variability in the immunosuppressant doses. Fourth, some of the outcome measures in the individual studies

were not available so the authors had to use estimated values. These limitations could impact the validity of the NMA results.

The included RCT[8] was generally well-conducted. The objective was stated and inclusion and exclusion criteria, patient characteristics, interventions, and outcomes were described. The randomization procedure was appropriate, and allocation was concealed. The study was double-blinded (patients and study investigators were blinded). Sample size was calculated, and the appropriate number of patients were recruited. Intention-to-treat analysis was conducted. There was 16% withdrawal in the intervention (RTX) group and no withdrawal in the comparator (placebo) group. The reasons for withdrawals were provided and did not appear to be of major concern. All patients were included in the analysis, but it was unclear how the missing data were handled. The study authors declared their conflicts of interest. Several authors had association with pharmaceutical companies, some in relation to this study and some unrelated to this study. It was unclear how conflicts of interest were addressed; however, it was mentioned that the funders had no role in study design, data collection, analysis, and interpretation or writing of the report.

In the economic evaluation,[22] the objective, strategies compared, perspective taken, time horizon, and sources for clinical and cost data were reported. The sources of clinical and cost data used seemed appropriate. The model was described but it was unclear if convergence had been achieved. Assumptions used for the analysis were reported and generally appeared to be reasonable. However, the basis of the assumption that RTX (biosimilar) has the same efficacy as the original RTX, was unclear. Both 1-way and probabilistic sensitivity analyses were conducted. Incremental analyses results were reported. Conclusions were consistent with the results reported. Conflicts of interest of the authors were not presented, hence potential for bias (if any) is unclear.

In both guidelines,[19,20] the scope and purpose were described, the target users were specified, the guideline development groups comprised individuals with relevant expertise, a systematic literature search was undertaken to identify evidence, the recommendations were clearly described, and the guidelines were externally reviewed. In both guidelines, the recommendations were based on consensus and voting. In both guidelines, the quality of evidence and strength of the recommendations were not reported, and applicability of recommendations were not described. In 1 guideline,[19] conflicts of interest were declared but it was unclear how conflicts of interest were addressed. Several authors received grants or fees from pharmaceutical manufacturers; therefore, the potential for bias cannot be ruled out. In the other guideline[20] it was reported that no funding had been received for the research; however, conflicts of interest of the authors were not reported so it was unclear if there was any potential for bias.

Summary of Findings

The main findings are summarized below. Appendix 4 presents additional details of the study findings and authors' conclusions. There was some overlap in the studies included in the systematic reviews (Appendix 5); therefore, the pooled estimates from the systematic reviews contain some of the same data.

Clinical Effectiveness of Rituximab

Relapse Rates

Four systematic reviews[2,16-18] reported on relapse rates in terms of ARR or HRR. Two systematic reviews[17,18] showed that pooled estimates of ARR were statistically significantly reduced after RTX treatment compared with before RTX treatment. There was substantial statistical heterogeneity among the pooled studies: I^2 was 81%[17] and 53%.[18] The third systematic review[16] reported ARR values for the individual studies, and the findings were mixed. In this systematic review,[16] ARR was significantly lower with RTX compared with AZA (2 studies), not significantly different between RTX and AZA or MMF (1 study), and not compared statistically for the comparison of RTX and AZA (one study). One NMA[2] showed RTX was favoured for ARR reduction when compared with AZA, but no treatment was favoured for comparisons between RTX, MMF, CYP, and CyA.

The included RCT[8] reported no relapse in the RTX group, whereas 37% of patients had relapse in the placebo group; the between-group difference was statistically significant.

Disability

Four systematic reviews[2,16-18] reported on disability in terms of EDSS scores. Two systematic reviews[17,18] showed that pooled estimates of EDSS scores were statistically significantly reduced after RTX treatment compared with before RTX treatment; however, there was substantial statistical heterogeneity (I^2 = 62%) among the pooled studies in 1 systematic review.[18] The third systematic review[16] reported values for the individual studies and the results were mixed. In this systematic review,[16] 1 study reported significantly reduced EDSS scores with RTX compared with AZA, 2 studies reported there were no statistically significant differences in EDSS score reduction with RTX compared with AZA or MMF, and 1 study did not report on statistical significance for RTX compared with AZA (i.e., RTX appeared to be either better or not different compared to AZA). One NMA[2] showed that in terms of EDSS score reduction, no treatment was favoured for comparisons between RTX, AZA, MMF, CYP, and CyA.

The included RCT[8] reported disability based on EDSS and QOSI scores. No statistically significant difference between RTX and placebo groups was found with respect to change in EDSS scores. However, the change in QOSI scores was statistically significantly greater in the RTX group compared with the placebo group.

Steroid Reduction

In the included RCT[8] that compared RTX with placebo, no statistically significant between-group difference was found with respect to reduction in use of steroids.

Adverse Events

Four systematic reviews[2,16-18] reported on AEs. Two of the systematic reviews[17,18] reported on outcomes before and after treatment with RTX. One systematic review[17] reported 16.5% of patients had AEs with RTX. The second systematic review[18] reported infusion-related AEs (10.3%), infection (9.1%), persistent leukopenia (4.6%), and posterior reversible encephalopathy (0.5%) with RTX. The third systematic review[16] showed that the pooled estimate for AEs was not statistically significantly different for RTX compared with AZA. One NMA[2] showed that, in terms of AEs, no treatment was favoured for comparisons between RTX, MMF, AZA and CYP.

The included RCT[8] reported 1 or more AEs in 90% of patients in each group (RTX or placebo). Infusion reaction was observed in 37% of the RTX group but not in the placebo group. One or more serious AEs were reported in 16% of patients in the RTX group and in 11% of patients in the placebo group.

Mortality

Two systematic reviews[17,18] reported on outcomes before and after treatment with RTX. After RTX treatment, the occurrence of death was 0.8% in 1 systematic review[17] and 1.6% in another systematic review[18]; however, the cause of death was not specified.

In the included RCT,[8] no deaths were reported in the RTX group or the placebo group.

Cost-Effectiveness of Rituximab

One economic evaluation[22] presented relevant cost-effectiveness data. Aungsumart and Apiwattanakul[22] conducted a cost-utility analysis in the context of the health care system in Thailand. They compared 5 different treatment options with treatment with AZA. These options were RTX fixed dose, RTX with $CD27^+$ memory B cell monitoring regimen, biosimilar of RTX fixed dose, biosimilar of RTX with $CD27^+$ memory B cell monitoring regimen, and MMF.

The authors conducted a probabilistic sensitivity analysis (PSA) and 1-way sensitivity analyses. The PSA demonstrated that RTX biosimilar with $CD27^+$ memory B cell monitoring regimen had the highest probability (48%) of being cost-effective, followed by AZA (30%), MMF (13%), and RTX with $CD27^+$ memory B cell monitoring regimen (9%), at a willingness-to-pay (WTP) threshold of 160,000 Thai bhat (THB) (equivalent to US$5,289 in 2019 values) per QALY gained. Also, it appeared from the cost-effectiveness acceptability curves that the probabilities of being cost-effective at a WTP threshold of 160,000 THB were 0% for RTX and RTX biosimilar. One-way sensitivity analysis (tornado plot), demonstrated that the greatest impact on ICER was variations in cost due to severe relapse treatment, followed sequentially by the efficacy of RTX in preventing relapse, discount rate for outcome, discount rate for cost, price of biosimilar RTX, efficacy of RTX for preventing severe relapse, utility of patients with moderately severe disability, and utility of patients with no or mild disability.

Guidelines

Two relevant evidence-based guidelines[19,20] were identified. Recommendations are summarized below and additional details are presented in Appendix 4.

The guideline from Latin America[19] presented consensus recommendations on various treatment modalities for NMOSD patients. Recommendations for relapse and disease management included IVMP treatment in the early phase followed by a slow tapering course of oral steroids, depending on the severity of attack. PLEX or immunoadsorption could be beneficial if there is partial or no response in terms of NMOSD relapse onset, with or without previous treatment with IVMP. Recommendations for long-term prevention of relapse included the following. Treatments with immunosuppressants (e.g., AZA, MMF, and RTX) should be started early to reduce disease activity and thereby prevent NMOSD attacks. MMF can be used as first-line treatment. In patients who receive AZA or MMF, oral steroid with gradual tapering should be maintained for at least 4 to 6 months. RTX (induction and maintenance treatment) can be used for NMOSD patients. After starting RTX treatment, oral steroids should be maintained for at least 1 month to 2 months. Tocilizumab, eculizumab, inebilizumab, and satralizumab can be used in NMOSD patients who have no response to other immunosuppressants prescribed in clinical practice. Cyclophosphamide or

mitoxantrone can be used as induction and maintenance treatment if there no response with RTX or if RTX is unavailable. The strength of the recommendations was not presented.

Another guideline from Iran[20] presented consensus recommendations on various treatment modalities for NMOSD patients. The recommendations for acute attack were followed by recommendations for prevention of attacks. For acute attacks, the panel recommended IVMP as a first-line and conventional treatment for acute attacks and starting PLEX if there was no response with IVMP. If an appropriate response was not achieved with IVMP or PLEX, immunosuppressive treatment could be considered. The panel recommended the use of oral steroids with slow tapering. For prevention of attacks, AZA, MMF, or RTX should be considered, depending on patient characteristics, availability, cost, and side effects, as first-line therapy and monitored. The strength of the recommendations was not presented.

Limitations

In the systematic reviews, the RTX doses in the included primary studies were not always reported and when reported there was variability in the doses. This could have contributed to some of the variability in the results (heterogeneity in the pooled analyses, and favourable versus null effects across primary studies). There was variability in patient characteristics (e.g., proportion of females, disease duration, and AQP4 immunoglobulin G serotypes), which could have influenced the efficacy and safety results, although the impact, if any, is unclear.

The majority of the primary studies included in the systematic reviews were observational studies, with many being retrospective studies. Therefore, there is potential for biases such as selection bias, performance bias, and recall bias. There was limited evidence on the effectiveness and safety of RTX compared with other active treatments.

The generalizability of the findings to the Canadian context is unclear because the countries where the primary studies (in the selected systematic reviews) were conducted were not reported, the selected RCT was conducted in Japan, and the economic evaluation related to the Thai context. In addition, the evidence-based guidelines were developed in Latin America[19] and Iran,[20] and not all treatments recommended in these guidelines may be available or approved for use in Canada.

Conclusions and Implications for Decision- or Policy-Making

Four systematic reviews[2,16-18] and 1 RCT[8] regarding the clinical effectiveness of RTX for the treatment of individuals with NMOSD were included, and 1 economic evaluation[22] regarding the cost-effectiveness of RTX for this indication was included. There were 2 relevant evidence-based guidelines[19,20] regarding the use of pharmacotherapy for the treatment of individuals with NMOSD.

Four systematic reviews[2,16-18] reported on the clinical effectiveness of RTX. Of these, 2 systematic reviews[2,16] included moderate to high quality of evidence and 2 systematic reviews[17,18] did not report on the quality of the evidence. In 1 systematic review,[18] 1 of the authors had an association with the pharmaceutical industry, and the impact of this, if any, is unclear. The systematic reviews were of moderate to high quality. One RCT[8] (that provided

high-quality evidence) reported on the clinical effectiveness of RTX for the treatment of NMOSD. Overall, relapse rates were statistically significantly reduced after RTX treatment compared with before RTX treatment (2 systematic reviews[17,18]) or with placebo (1 RCT[8]). According to an NMA,[2] RTX was also favoured when compared with AZA, but no treatment was favoured for comparisons between RTX, MMF, CYP, and CyA. Disability (in terms of EDSS score) was statistically significantly reduced after RTX treatment compared with before RTX treatment (2 systematic reviews[17,18]), but no statistically significant difference was observed for RTX compared with placebo (1 RCT[8]). Relapse rates and disability for RTX compared with AZA were either statistically significantly better or not worse than AZA (1 systematic review[16]). In terms of EDSS score reduction, the NMA[2] showed that no treatment was favoured for comparisons between RTX, AZA, MMF, CYP, and CyA. For AEs, the NMA[2] showed that no treatment was favoured for comparisons between RTX, MMF, AZA, and CYP. However, the NMA findings need to be interpreted with caution considering the limitations (e.g., the immunosuppressive drugs were not used as monotherapies and there was variability in doses, and some of the outcome measures that were not available in the individual studies were estimated).

The economic evaluation[22] showed that, in the context of the health care system in Thailand, RTX biosimilar with $CD27^+$ memory B cell monitoring regimen had the highest probability (48%) of being cost-effective, followed by AZA (30%), MMF (13%), and original RTX with $CD27^+$ memory B cell monitoring regimen (9%) at a WTP threshold of 160,000 THB (US$5,289 in 2019 values) per QALY gained.

The 2 guidelines[19,20] (developed in Latin America and Iran) recommended immunosuppressants (RTX, AZA, and MMF) for prevention of NMOSD attacks. In addition, the guideline developed in Latin America mentioned that tocilizumab, eculizumab, inebilizumab, and satralizumab can be used in NMOSD patients who have had no response to other immunosuppressants. The quality of the evidence that informed the guidelines and the strength of the recommendations were not reported in either guideline.

Findings need to be interpreted with caution given the limitations, such as the limited quantity of evidence on comparative efficacy and safety between various immunosuppressants, that many of the included primary studies in the systematic reviews were retrospective, the RTX doses varied and were not always reported, the heterogeneity among the studies included in the systematic reviews, and the lack of clarity with respect to the strength of the recommendations.

Further studies are needed to investigate the efficacy and safety of RTX compared with other active drugs to have a better understanding of the role of RTX for management of NMOSD.

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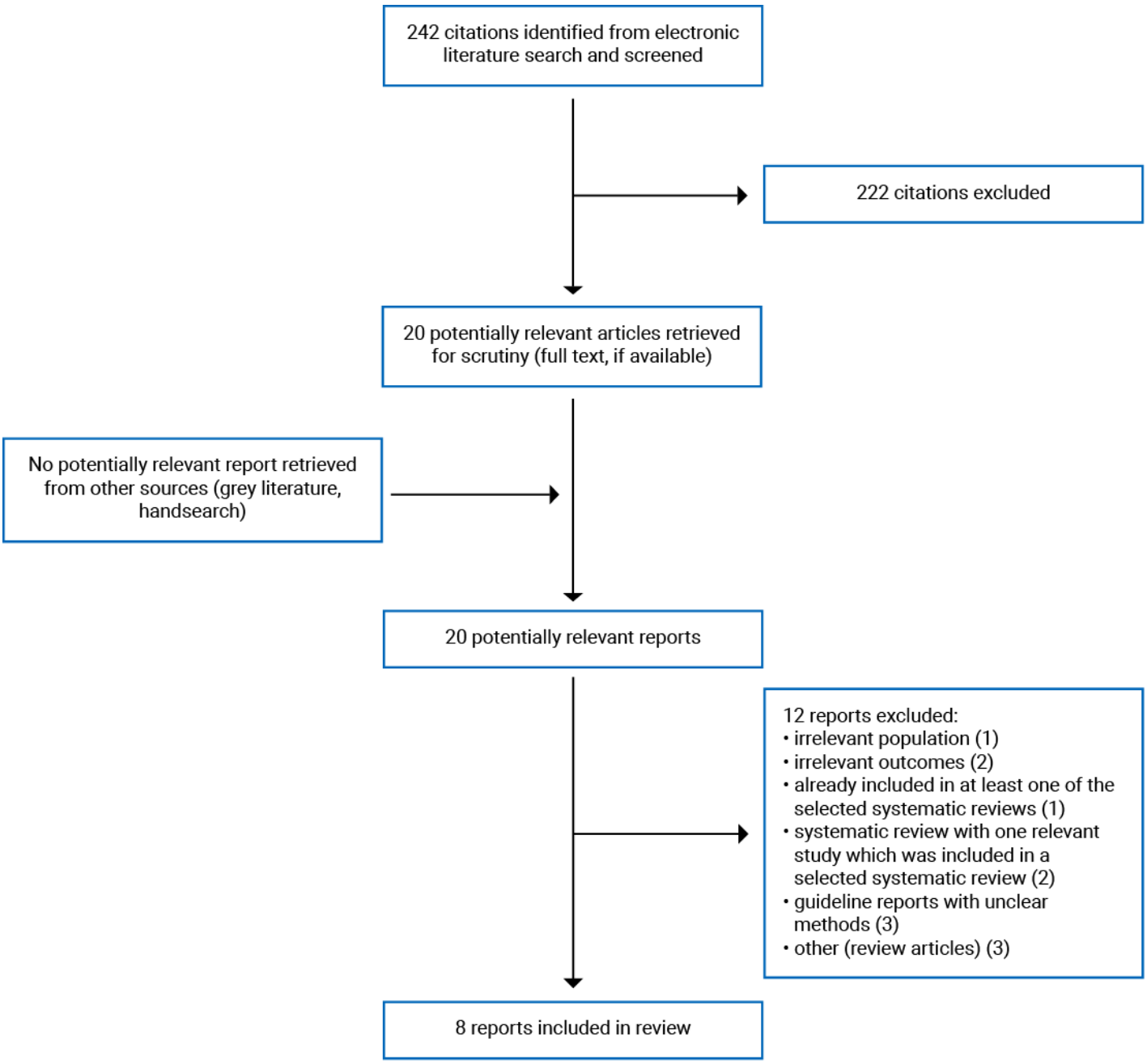
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Network Meta-Analyses

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Espiritu and Pasco (2019)[16] Country: Philippines Funding: Authors reported that no specific grant was received for the research from any public, commercial, or not-for-profit agencies	Systematic review with meta-analysis It included 9 primary studies, 6 of which were relevant to the present report (1 RCT, 5 cohort studies [prospective and retrospective]) published between 2014 and 2018. Countries where the studies were conducted were not reported Inclusion criteria: RCT or cohort studies on AZA treatment involving patients (adult or pediatric) with NMOSD Exclusion criteria: Studies without a comparator arm. Studies involving patients with other causes of demyelination Aim: To assess the efficacy and tolerability of AZA compared with other drugs for treating NMOSD	Patients with NMO or NMOSD diagnosed by IPND criteria N = 493 (number in the individual studies ranged from 62 to 138) Age: NR Female:male ratio range: 2.6:1 to 9.3:1 (% female: 72% to 90%) % of patients with positive AQP4 antibody: 43.1% to 93.5% Duration of disease before treatment: unclear (unclear as range was reported as 0.8 years to 6.0 years for all 9 studies considered together and not specifically for the 6 studies relevant for the current report)	RTX and AZA (3 studies) RTX, AZA, and MMF (2 studies) RTX, AZA, MMF, and CYP (1 study) RTX dosage: NR AZA: 2 mg/kg to 3 mg/kg per day for at least 6 months to 12 months MMF dose: NR CYP dose: NR Concomitant treatment if any: NR	ARR, HRR, relapse-free rate, EDSS, and AE Follow-up: NR

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Gao et al. (2019)[17] Country: China Funding: No funding was received from public, commercial, or non-profit sectors	Systematic review with meta-analysis 26 relevant studies (1 RCT, 23 cohort [prospective or retrospective] studies, 1 observational study, and 1 case-control study) published between 2008 and 2018. Countries where the studies were conducted were not reported Inclusion criteria: Studies involving patients with NMO and reporting on ARR and/or EDSS Exclusion criteria: Case reports that included less than 2 patients Aim: To evaluate the efficacy and safety of RTX for treating patients with NMO	Patients with NMO N = 577 (range: 3 to 100) Age (range) (years): 14 to 54 Female (range): 67% to 100% (25 studies), NR (1 study) % of patients with positive AQP4 antibody: 75% Duration of disease before treatment (range): 11 months to 11 years (24 studies); NR (4 studies)	Before and after RTX therapy Unclear if there were any comparator treatments RTX dose not specified Concomitant treatment if any: NR	ARR, EDSS, and AE Follow-up (months): 19 to 67

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Huang et al. (2019)[2] Country: China Funding: the work was supported by the National Natural Science Foundation of China	Systematic review with NMA 6 studies (1 RCT and 5 observational studies [prospective or retrospective]) published between 2013 and 2018. Of the 6 studies, 3 studies had an RTX treatment arm and 3 studies did not (but all were included in the NMA). Countries where the studies were conducted were not reported. Inclusion criteria: Studies (RCT, cohort [prospective or retrospective]) with at least 2 treatment arms Exclusion criteria: Case reports, reviews, and studies with a single treatment arm Aim: To compare and rank the clinical effectiveness and tolerability of immunotherapies for NMOSD	Patients with NMOSD The 3 studies including RTX (N = 205): • Age (years) (median): 34 and 42 (2 studies); NR (1 study) • % Female: 71% to 95% • % Patients with positive AQP4 antibody: 36% to 82% • Disease duration (months): 9 to 75 All 6 studies in the NMA (N = 631): • Age (years) (median): 32 to 55 (5 studies); NR (1 study) • % Female: 70% to 100% • % Patients with positive AQP4 antibody: 36% to 100% • Disease duration (months): 9 to 96	RTX and AZA (2 studies) RTX, AZA, and MMF (1 study) AZA, MMF, and CYP (1 study) AZA and CyA (1 study) AZA and MMF (1 study) Dosage: RTX: 100 mg weekly IV (2 studies), 1,000 mg every 2 weeks IV (1 study). AZA: 100 mg per day p.o. (2 studies), 2 mg/kg per day p.o. (3 studies), 2 to 3 mg/kg per day p.o. (1 study) CyA: 150 mg per day p.o. (1 study) CYP: 400 mg weekly IV (1 study) Concomitant treatment if any: NR	ARR, EDSS, and AE Follow-up (months): 12 to 31 for the 3 studies including RTX; 12 to 40 for all 6 studies used in the NMA

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Damato et al. (2016)[18] Country: Italy Funding: supported by institutional funds from Catholic University, Rome	Systematic review with meta-analysis 46 studies for qualitative analysis, of which 25 studies were included in the meta-analysis. All studies were considered when reporting safety data. Countries where the studies were conducted were not reported. Inclusion criteria: No study type was specified Exclusion criteria: Case reports, studies that included < 2 patients, or without relevant clinical data were excluded from the meta-analysis Aim: to assess the efficacy and safety of RTX for the treatment of NMOSD patients	Patients with NMOSD. Summary of patient characteristics for 46 studies N = 438 Age (years) (mean [range]): 32 (2 to 77) % female (mean): 87% % of patients with positive AQP4 antibody: 82.7% (based on data for 387 patients). Disease duration (months) (mean [range]): 50 (1.5 to 276)	Before and after RTX therapy RTX regimen was reported for 313 patients: • 375 mg/m^2 weekly for 4 weeks in 44.4% of patients • 1 g every 2 weeks for 2 times in 49.8% patients • 500 mg/m^2 weekly for 2 weeks in 2.9% of patients Other regimens in 2.9% of patients Concomitant treatment: NR (it was reported that not all immunosuppressants were used as monotherapies)	ARR, EDSS, and safety (AEs, death) Follow-up (months) (mean [range]): 27.5 (3 to 272)

AE = adverse effect; AQP4 = aquaporin-4; ARR = annualized relapse rate; AZA = azathioprine; CyA = cyclosporin; CYP = cyclophosphamide; EDSS = Expanded Disability Status Scale; HRR = hazard risk for relapse; IPND = International Panel for NMO Diagnosis; MMF = mycophenolate mofetil; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; NR = not reported; p.o. = orally; RTX = rituximab.

Table 3: Characteristics of Included Primary Clinical Study

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Tahara et al. (2020)[8] **Country:** Japan **Funding:** Research grants from government agencies and a pharmaceutical company (Japanese Ministry of Health, Labour and Welfare; Japan Agency for Medical Research and Development; and Zenyaku Kogyo)	RCT, double-blind, multi-centre Setting: 8 hospitals in Japan Inclusion criteria: Patients aged 16 years to 80 years who were AQP4 seropositive (including AQP4-seronegative persons who had previously been seropositive), with a history of optic neuritis or myelitis, were receiving oral steroids, EDSS score ≤ 7, and neurologically stable Exclusion criteria: Patients treated with corticosteroid drugs or oral immunosuppressive drugs other than steroids Aim: To assess the efficacy and safety of RTX for treating patients with NMOSD	Patients with NMOSD N = 38 (19 in RTX group, 19 in placebo group) Age (years) (mean [IQR]): 53 (42 to 58) in RTX group; 47 (37 to 65) in placebo group % Female: 90% in RTX group; 100% in placebo group % Patients with positive AQP4 antibody: 100% in both groups Disease duration (median [IQR]) (months): 119 (15 to 143) EDSS score (median [IQR]): 3.5 (2.5 to 6.0) in RTX group, and 4.0 (2.0 to 6.0) in placebo group	RTX compared with placebo After randomization at visit 2, patients received by drip infusion either RTX (375 mg/m^2) or placebo every week for 4 weeks. Patients also received nonsteroidal anti-inflammatory drugs or anti-histamines to minimize infusion-related reactions At visits 8 and 14, patients received 1,000 mg RTX or placebo every 2 weeks Oral prednisolone was administered for 8 weeks from visit 2 to visit 4 and then gradually reduced by 10% (according to the protocol) at every visit to 2 mg per day; administration of restricted drugs was not permitted during the study period	Relapse, EDSS, steroid reduction, and AE Follow-up (weeks) (median [IQR]): 72.1 (64.6 to 73.0)

AQP4 = aquaporin 4; IQR = interquartile range; NMOSD = neuromyelitis optica spectrum disorder; RTX = rituximab; SD = standard deviation.

Table 4: Characteristics of Included Economic Evaluation

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Aungsumart and Apiwattanakul (2020)[22] Country: Thailand Funding: Not reported	Cost-utility analysis Time horizon: Lifetime Perspective: Societal Discounting: 3%	Adults with NMO or NMOSD	RTX fixed dose, RTX with $CD27^+$ memory cell monitoring regimen, RTX (biosimilar) fixed dose, RTX (biosimilar) with $CD27^+$ memory cell monitoring regimen, and MMF compared to AZA as reference	Markov model One-way sensitivity analysis and PSA were conducted	Clinical data were obtained from the literature (1 RCT, 1 retrospective study, and 1 systematic review and meta-analysis based on 5 studies) Cost data were obtained from Prasat Neurological Institute (a tertiary neurologic referral centre) and the reference drug price database of Thailand Utility data were obtained from the literature	Higher costs associated with relapse of greater severity All patient groups had same probability of relapse Patients with: • Mild relapse, return to previous health state after treatment • Severe relapse die or progress to severe disability • Moderate or severe disability with severe relapse can return to the previous health state • Moderate or severe disability cannot return to no or mild disability

AZA = azathioprine; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; NMOSD = neuromyelitis optica spectrum disorder; PSA = probabilistic sensitivity analysis; RCT = randomized controlled trial; RTX = rituximab.

Table 5: Characteristics of Included Guidelines

Country, intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Carneno Contentti et al. (2020)[19]						
Country: Latin America Intended users: Clinical practice involved in the management of patients with NMOSD in Latin America Target population: Patients with NMOSD in Latin America	Disease diagnosis, prognosis, and management regarding NMOSD Interventions considered for NMOSD treatment included IVMP, oral steroids, PLEX, AZA, MMF, RTX, tocilizumab, eculizumab, inebilizumab, satralizumab, CYP, and mitoxantrone	Relapse rate, disability, and safety	Systematic literature search was undertaken using MEDLINE and Embase (from1990 to 2019) Relevant articles were distributed to the working group (comprising a steering group and a rating group) for review and summarization	Quality of the evidence was not reported	GDG comprised a steering group and a rating group with representative users and professionals in neurology who were involved in the diagnosis and care of NMOSD patients A list of proposed statements were developed by the steering group and submitted to the rating group. The RAND/UCLA[a] methodology of reaching formal consensus was used. For statements in which there was no consensus, 2 further rounds of voting were conducted. Consensus was defined as 70% agreement among the group. Recommendations were not graded	The guideline report was externally reviewed and, where applicable, public consultation was sought

Country, intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Sahraian et al. (2017)[20]						
Country: Iran Intended users: Clinicians involved in the management of patients with NMOSD in Iran Target population: Patients with NMOSD in Iran	Diagnosis and treatment of NMOSD Interventions considered for NMOSD treatment included IVMP, oral steroids, PLEX, AZA, MMF, and RTX	Relapse rate, disability, and safety	Systematic literature search to identify evidence was undertaken using PubMed and Embase (from 1980 to 2016)	Quality of the evidence was not reported	GDG comprised a group of expert clinicians with special interest and experience in the area of inflammatory demyelinating disorders in the CNS A draft was prepared based on the evidence identified which was discussed by the experts at a 2-day meeting and recommendations were made. In case of discordance, there was voting and the recommendation was based on greater than two-thirds agreement. Recommendations were not graded	Apparently externally reviewed because published in a journal

AZA = azathioprine; CNS = central nervous system; CYP = cyclophosphamide; GDG = guideline development group; IVMP = IV methylprednisolone; MMF = mycophenolate mofetil; NMOSD = neuromyelitis optica spectrum disorder, PLEX = plasmapheresis; RTX = rituximab.

[a]RAND/UCLA methodology is an appropriateness method developed by RAND corporation and the University of California Los Angeles.[23]

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews and Network Meta-Analyses Using AMSTAR 2[11] and the ISPOR Questionnaire[12]

Strengths	Limitations
Espiritu and Pasco (2019)[16]	
• The objective was clearly stated. • Multiple databases (Medline, Embase, Scopus, LILAC, CENTRAL, and HERDIN [database of Philippines]) were searched from May 2017 to November 2018. • Study selection was described, and a flow chart was presented. • A list of included studies was provided. • Quality assessment was conducted. For the relevant RCT, the Cochrane risk of bias tool was used. The RCT was judged by the authors to have low risk of selection bias and reporting bias, high risk of performance bias and attrition bias, and unclear risk of detection bias. For the cohort studies, the Newcastle-Ottawa scale was used, and the studies were judged by the authors to be of good quality (on a scale of 9, the scores for the individual included studies ranged between 8 and 9; higher scores indicate better quality). • Study characteristics were reported. • Meta-analysis was conducted when appropriate. • The authors reported that there were no conflicts of interest.	• A list of excluded studies was not provided. • Unclear if article selection was done by 2 reviewers. • Unclear if data extraction was done by 2 reviewers. • Unclear if quality assessment was done by 2 reviewers. • Publication bias does not appear to have been examined.
Gao et al. (2019)[17]	
• The objective was clearly stated. • Multiple databases (PubMed, Embase, Cochrane library) were searched up to August 2018. • Study selection was described, and a flow chart was presented. • A list of included studies was provided. • Study characteristics were reported. • Meta-analysis was conducted. • Publication bias was investigated using funnel plot and no concerns were apparent. • The authors reported that there were no conflicts of interest.	• A list of excluded studies was not provided. • Unclear if article selection was done by 2 reviewers. • Unclear if data extraction was done by 2 reviewers. • Unclear if quality assessment was conducted; no quality assessment results were presented.

Strengths	Limitations
Huang et al. (2019)[2]	
• The objective was clearly stated. • Multiple databases (MEDLINE, Embase, CENTRAL, and ClinicalTrials.gov) were searched up to November 21, 2018. • Study selection was described, and a flow chart was presented. • A list of included studies was provided. • Article selection was done by 2 reviewers. • Data extraction was done by 2 reviewers. • Quality assessment was conducted. For the relevant RCT, the Cochrane risk of bias tool was used. The RCT was judged by the authors to be of moderate quality. For the cohort studies the Newcastle-Ottawa scale was used, and the studies were judged by the authors to be of good quality. • Study characteristics were reported. • Network meta-analysis was conducted using a Bayesian Markov chain Monte Carlo model. • The authors reported that there were no conflicts of interest.	• A list of excluded studies was not provided. • Unclear if quality assessment was done by 2 reviewers. • Publication bias was not examined as the number of studies were less than 10. • Limitations associated with the NMA are that the number of studies per comparison were few; not all immunotherapies were used as monotherapies, so concomitant medication could impact results; and some outcome data were not available for the individual studies, so the authors had to use estimates.
Damato et al. (2016)[18]	
• The objective was clearly stated. • Multiple databases (MEDLINE, CENTRAL, clinicaltriails.gov) were searched from January 1, 2000, to July 31, 2015. • Study selection was described, and a flow chart was presented. • A list of included studies was provided. • Article selection was done by 2 reviewers. • Data extraction was done by 1 reviewer and checked by another reviewer. • Study characteristics were reported. • Meta-analysis was conducted. • Of the 3 authors, 1 author was on the scientific advisory board of UCB Biosciences GmbH board; no other disclosures were reported.	• A list of excluded studies was not provided. • Quality assessment does not appear to have been done. • Publication bias does not appear to have been investigated.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NR = not reported.

Table 7: Strengths and Limitations of the Clinical Study Using the Downs and Black Checklist[13]

Strengths	Limitations
Tahara et al. (2020)[8]	
• The objective was clearly stated. • Patient characteristics, intervention, and outcomes were described. • Randomized study and the randomization method appeared appropriate (random allocation using a computer-aided system [VIEDOC], concealed allocation). • Study was double-blinded. • Sample size calculation was conducted (to achieve 80% power with a 5% significance level for a log-rank test), and the appropriate number of patients were recruited. • In the RTX group, 3 (15.7%) patients discontinued but were included in the analysis. Reasons for discontinuation were stated (1 withdrew consent, 1 used contraindicated drug, and 1 due to AE). In the placebo group, no patients discontinued. • ITT analysis was conducted. • The 95% confidence intervals were reported. • Authors declared their conflicts of interest. Several authors had association with pharmaceutical companies, some in relation to this study and some unrelated to this study. It was unclear how conflicts of interest were addressed. However, it was mentioned that the funders had no role in study design; data collection, analysis, and interpretation; or writing of the report.	• The patient characteristics in each group were stated, and there appeared to be numerical differences in some of the values reported. However, as statistical significance was not reported, it was unclear how well the 2 groups matched. • This study included Japanese patients with mild disease who were AQP4 seropositive. Hence, the findings may not be generalizable to other populations.

AE = adverse event; ITT = intention-to-treat; RTX = rituximab.

Table 8: Strengths and Limitations of the Economic Evaluation Using the Drummond Checklist[14]

Strengths	Limitations
Aungsumart and Apiwattanakul (2020)[22]	
• Objectives were stated. • The strategies compared were stated. • Time horizon (lifetime) and perspective (societal) were stated. • Clinical and utility data sources were stated. • Cost data sources were stated. • Discounting was reported. • Model description was presented but some details were lacking. • Incremental analysis was reported. • Sensitivity analyses were conducted. • Conclusions were consistent with the results reported.	• Indirect costs, such as productivity costs, do not appear to have been considered. • Although the model was described, it was unclear if the appropriate number of simulations had been conducted and convergence had been achieved. • Declaration of conflicts of interest was not presented.

Table 9: Strengths and Limitations of Guidelines Using AGREE II[15]

Item	Guideline	
	Carneno Contentti et al. (2020)[19]	Sahraian et al. (2017)[20]
Domain 1: Scope and Purpose		
• The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
• The health question(s) covered by the guideline is (are) specifically described.	Not explicit but implied	Not explicit but implied
• The population (e.g., patients, public) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: Stakeholder Involvement		
• The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
• The views and preferences of the target population (e.g., patients, public) have been sought.	Yes	No
• The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: Rigour of Development		
• Systematic methods were used to search for evidence.	Yes	Yes
• The criteria for selecting the evidence are clearly described.	No	No
• The strengths and limitations of the body of evidence are clearly described.	No	No
• The methods for formulating the recommendations are clearly described.	Yes	Yes
• The health benefits, side effects, and risks have been considered in formulating the recommendations.	To some extent, but lacked details	To some extent, but lacked details
• There is an explicit link between the recommendations and the supporting evidence.	Unclear	Unclear
• The guideline has been externally reviewed by experts before its publication.	Yes	Yes
• A procedure for updating the guideline is provided.	No	No
Domain 4: Clarity of Presentation		
• The recommendations are specific and unambiguous.	Yes	Yes
• The different options for management of the condition or health issue are clearly presented.	Yes	Yes
• Key recommendations are easily identifiable.	Yes	Yes
Domain 5: Applicability		
• The guideline describes facilitators and barriers to its application.	No	No

Item	Guideline	
	Carneno Contentti et al. (2020)[19]	Sahraian et al. (2017)[20]
• The guideline provides advice and/or tools on how the recommendations can be put into practice.	No	No
• The potential resource implications of applying the recommendations have been considered.	No	No
• The guideline presents monitoring and/or auditing criteria.	No	No
Domain 6: Editorial Independence		
• The views of the funding body have not influenced the content of the guideline.	No (the authors reported that they did not receive any specific grant for the research)	Unclear (the meeting and associated accommodation costs were supported by a grant from a biotechnology company)
• Competing interests of guideline development group members have been recorded and addressed.	Conflicts of interest were declared but it was unclear how they were addressed; several authors had received grants and/or consultation fees from pharmaceutical manufacturers	Not reported

AGREE II = Appraisal of Guidelines for Research and Evaluation II.

Appendix 4: Main Study Findings and Authors' Conclusions

Summary of Findings Included Systematic Reviews and Network Meta-Analyses

Espiritu and Pasco (2019)[16]

Main Study Findings

ARR

- Results from 1 RCT (68 patients) (1 RCT):
  - Pre-treatment – post-treatment ARR (mean [SD]) = 1.09 (0.72) for RTX
  - Pre-treatment – post-treatment ARR (mean [SD]) = 0.49 (0.59) for AZA
  - ARR was statistically significantly reduced RTX compared with AZA (P < 0.001)
- Results from 1 prospective cohort study (72 patients) (1 study): There was no statistically significant difference in post-treatment ARR between AZA, RTX, and MMF (P = 0.78)
- Results from 1 retrospective cohort study (54 patients) (1 study):
  - Pre-treatment and post-treatment ARR (median) = 1.17 and 0.25, respectively, for RTX
  - Pre-treatment and post-treatment ARR (median) = 0.92 and 0.56, respectively, for AZA
  - Statistically significantly reduced ARR with RTX compared with AZA (P = 0.021)
- Results from another retrospective cohort study (65 patients) (1 study):
  - Pre-treatment and post-treatment ARR (mean) = 1.39 and 0.05, respectively, for RTX
  - Pre-treatment and post-treatment ARR (mean) = 1.28 and 0.49, respectively, for AZA
  - Statistical significance was not reported

HRR

- Results from 1 retrospective cohort study (16 patients) (1 study):
  - For any relapse, HRR (95% confidence interval [CI]) for AZA compared to RTX was 1.82 (1.1 to 3.1); statistically significant higher risk with AZA compared with RTX
  - For severe relapse, HRR (95% CI) for AZA compared to RTX was 11.6 (2.6 to 52.3); statistically significant higher risk with AZA compared with RTX
- Results from another retrospective cohort study (62 patients) (1 study): For relapse, HRR (95% CI) for AZA compared with RTX is 2.12 (1.12 to 4.02); statistically significant higher risk with AZA compared with RTX

EDSS

- Results from 1 RCT (68 patients) (1 RCT):
  - Pre-treatment – post-treatment EDSS (mean [SD]) = 0.98 (1.14) for RTX
  - Pre-treatment – post-treatment EDSS (mean [SD]) = 0.44 (0.54) for AZA
  - Pre-treatment and post-treatment difference in EDSS between RTX and AZA was statistically significant (P < 0.001)
- Results from 1 prospective cohort study (72 patients) (1 study): There was no statistically significant difference in post-treatment EDSS between AZA, RTX, and MMF (P = 0.76)
- Results from 1 retrospective cohort study (54 patients) (1 study):

- Pre-treatment and post-treatment EDSS (median) = 7 and 5, respectively, for RTX
- Pre-treatment and post-treatment EDSS (median) = 7 and 6, respectively, for AZA
- Statistical significance was not reported

- Results from another retrospective cohort study (65 patients) (1 study):
  - Pre-treatment and post-treatment EDSS (mean) = 5.62 and 4.48, respectively, for RTX
  - Pre-treatment and post-treatment EDSS (mean) = 5.63 and 5.05, respectively, for AZA
  - Statistical significance was not reported.

Relapse-free rate

- Results from 1 RCT (68 patients) (1 RCT): Post-treatment relapse-free rate was 78.8% with RTX, 54.3% with AZA (P = 0.033)
- Results from 1 prospective cohort study (72 patients) (1 study): Post-treatment relapse-free rate was 65.0% with RTX, 54.5% with AZA, and 60.0% with MMF (P = 0.75)

AE, pooled estimates from meta-analyses

- Risk of any AE with AZA compared with RTX, risk ratio (RR) (95% CI) = 1.68 (0.88 to 3.19); (3 studies); risk of AE not significantly different between AZA and RTX
- Risk of elevated liver enzymes or hepatoxicity with raised transaminase levels with AZA compared with RTX, RR (95% CI) = 9.52 (2.28 to 39.79); (4 studies)
- Risk of leukopenia with AZA compared with RTX, RR (95% CI) = 4.10 (0.48 to 35.14); (2 studies)
- Risk of nausea, vomiting, or gastrointestinal disturbance, RR (95% CI) = 3.89 (0.44 to 34.61); (2 studies)
- Risk of allergic or anaphylactoid reactions, RR (95% CI) = 0.10 (0.01 to 0.76); (2 studies)
- Risk of treatment discontinuation due to drug related AE, RR (95% CI) = 2.48 (0.89 to 6.89); (3 studies)

Authors' Conclusion

"AZA, given at 2–3 mg/kg/day for at least 6–12 months, was inferior to RTX in terms of reduction and prevention of relapse and neurologic disability according to a single clinical trial and several observational studies in patients with NMOSD.…Based on current evidence, RTX may be used as first-line therapy in patients with NMOSD, and AZA may be given as second-line option for patients intolerant of RTX (p. 31)."[16]

Gao et al. (2019)[17]

Main Study Findings

ARR

Pre-treatment - post-treatment ARR, weighted mean difference (WMD) (95% CI) = −1.56 (−1.82 to −1.29); for RTX; statistically significant reduction in ARR after RTX treatment, (17 studies); heterogeneity, I^2 = 81.3%

EDSS

Pre-treatment - post-treatment EDSS, WMD (95% CI) = −1.16 (−1.36 to −0.96); for RTX; statistically significant reduction in EDSS score after RTX treatment, (22 studies); heterogeneity, I^2 = 15.5%

Safety

- An AE was reported in 16.46% (95 of 577) of patients
- Number of patients experiencing severe AEs = 12
- Number of deaths = 5

Authors' Conclusion

"RTX has acceptable tolerance, reduces the relapse frequency, and improves disability in most patients with NMO. Future studies should focus on reducing the health-care costs, improving the functional outcomes, and reducing the adverse effects associated with RTX treatment (p. 6)."[17]

Huang et al. (2019)[2]

Main Study Findings

ARR

- Results from traditional pairwise meta-analyses
  - RTX compared with AZA, standardized mean difference (SMD) (95% credible interval [CrI]) = −0.91 (−1.78 to −0.038); RTX favoured with lower ARR compared with AZA
  - RTX compared with MMF, SMD (95% CrI) = 0 (−0.57 to 0.57)
  - CyA compared with AZA, SMD (95% CrI) = −0.57 (−1.65 to 0.52)
  - MMF compared with AZA, SMD (95% CrI) = −0.0070 (−0.20 to 0.21)
  - MMF compared with CYP, SMD (95% CrI) = −0.27 (−0.71 to 0.17)
  - AZA compared with CYP, SMD (95% CrI) = −0.15 (−0.50 to 0.21)
  - (With respect to ARR, the comparisons in which the 95% CrI encompasses zero, the drug is not favoured in comparison to the comparator drug)
- Results from NMA
  - RTX compared with AZA, SMD (95% CrI) = −0.86 (−1.60 to −0.11). RTX favoured with lower ARR compared with AZA
  - RTX compared with CyA, SMD (95% CrI) = −0.18 (−1.97 to 1.63)
  - RTX compared with MMF, SMD (95% CrI) = −0.70 (−1.62 to 0.26)
  - RTX compared with CYP, SMD (95% CrI) = −0.98 (−2.31 to 0.40)
  - CyA compared with MMF, SMD (95% CrI) = −0.53 (−2.05 to 0.99)
  - CyA compared with AZA, SMD (95% CrI) = −0.69 (−2.39 to 1.01)
  - CyA compared with CYP, SMD (95% CrI) = −0.79 (−2.71 to 1.12)
  - MMF compared with AZA, SMD (95% CrI) = −0.15 (−0.89 to 0.57)
  - MMF compared with CYP, SMD (95% CrI) = −0.27 (−1.45 to 0.91)
  - AZA compared with CYP, SMD (95% CrI) = −0.12 (−1.29 to 1.08)
  - (With respect to ARR, the comparisons in which the 95% CrI encompasses zero, the drug is not favoured in comparison to the comparator drug)

EDSS

- Results from traditional pairwise meta-analyses
  - RTX compared with AZA, SMD (95% CI) = −0.67 (−0.97 to −0.36); RTX favoured with lower EDSS score compared with AZA

- RTX compared with MMF, SMD (95% CI) = 0 (−0.57 to 0.57)
- CyA compared with AZA, SMD (95% CI) = 0.20 (−0.73 to 1.13)
- MMF compared with AZA, SMD (95% CI) = −0.04 (−1.20 to 1.11)
- MMF compared with CYP, SMD (95% CI) = −1.05 (−1.53 to −0.58); MMF favoured with lower EDSS score compared with CYP
- AZA compared with CYP, SMD (95% CI) = −0.56 (−0.92, −0.20); statistically significant reduction in EDSS score with AZA compared to CYP
- (With respect to EDSS score, the comparisons in which the 95% CrI encompasses zero, the drug is not favoured in comparison to the comparator drug)

- Results from NMA
  - RTX compared with AZA, SMD (95% CrI) = −0.55 (−1.37 to 0.29)
  - RTX compared with CyA, SMD (95% CrI) = −0.35 (−2.18 to 1.47)
  - RTX compared with MMF, SMD (95% CrI) = −0.50 (−1.50, 0.57)
  - RTX compared with CYP, SMD (95% CrI) = −1.32 (−2.83 to 0.19)
  - CyA compared with MMF, SMD (95% CrI) = −0.14 (−1.94 to 1.69)
  - CyA compared with AZA, SMD (95% CrI) = −0.20 (−1.83 to 1.44)
  - CyA compared with CYP, SMD (95% CrI) = −0.96 (−3.08 to 1.12)
  - MMF compared with AZA, SMD (95% CrI) = −0.06 (−0.88 to 0.75)
  - MMF compared with CYP, SMD (95% CrI) = −0.82 (−2.18 to 0.49)
  - AZA compared with CYP, SMD (95% CrI) = −0.77 (−2.11 to 0.54)
  - (With respect to EDSS score, the comparisons in which the 95% CrI encompasses zero, the drug is not favoured in comparison to the comparator drug)

AE

- Results from traditional pairwise meta-analyses
  - RTX compared with AZA, hazard ratio (HR) (95% CI) = 0.34 (0.08 to 1.41)
  - MMF compared with RTX, HR (95% CrI) = 2.00 (0.21 to 19.23)
  - MMF compared with AZA, HR (95% CrI) = 0.22 (0.11 to 0.44); MMF favoured compared to AZA
  - MMF compared with CYP, HR (95% CrI) = 0.11 (0.03 to 0.50); MMF favoured compared to CYP
  - AZA compared with CYP, HR (95% CrI) = 0.59 (0.33 to 1.07)
  - (With respect to AE, the comparisons in which the 95% CrI encompasses 1, the drug is not favoured in comparison to the comparator drug)
- Results from NMA
  - RTX compared with AZA, HR (95% CrI) = 3.48 (0.71 to 18.71)
  - RTX compared with CYP, HR (95% CrI) = 6.09 (0.42 to 10.50)
  - MMF compared with RTX, HR (95% CrI) = 1.31 (0.15 to 9.67)
  - MMF compared with AZA, HR (95% CrI) = 4.47 (0.94 to 20.33)
  - AZA compared with CYP, HR (95% CrI) = 1.73 (0.18 to 20.85)
  - (With respect to AE, the comparisons in which the 95% CrI encompasses 1, the drug is not favoured in comparison to the comparator drug)

- Although the authors had conducted a meta-analysis and NMA using a Bayesian approach, they expressed results using the terminology CI and not CrI, the appropriate terminology. Here we have used the terminology CrI and not CI as used by the authors.

Authors' Conclusion

"In conclusion, this NMA provided a comprehensive summary of effectiveness and tolerability of preventive treatment for NMOSD, which might provide a reference for the optimal treatment. The results suggested RTX and MMF are superior to AZA, low-dose CyA may be alternative treatment for refractory NMOSD patients, CTX [CYP] should not be a common preventive treatment for NMOSD (p. 251)."

Damato et al. (2016)[18]

Main Study Findings

ARR

- Pre-treatment - post-treatment ARR, SMD (95% CI) = −0.79 (−1.09 to −0.50); for RTX; statistically significant reduction in ARR after RTX treatment (25 studies); heterogeneity, I^2 = 53%
- Meta-regression analysis showed that there was no significant correlation between ARR ratio reduction and the following variables: RTX reinfusion (P = 0.96), immunomodulatory drug treatment before RTX (P = 0.23), IV immunoglobulin (P = 0.42), plasma exchange (P = 0.69), different RTX regimens (P = 0.30 and 0.68), disease duration (P = 0.71), and AQP4 immunoglobulin G serostatus (P = 0.40); and the 95% CIs varied between negative and positive values (i.e., encompassed zero, indicating statistically non-significant)

EDSS

- Pre-treatment - post-treatment EDSS, SMD (95% CI) = −0.64 (−1.18 to −0.10); for RTX; statistically significant reduction in EDSS scores after RTX treatment (18 studies); heterogeneity, I^2 = 62%.
- A meta-regression analysis was conducted. A significant correlation was found between EDSS score change and disease duration (P = 0.04; 95% CI, −0.02 to 0.10). No significant correlation was found between change in EDSS score and the following variables: RTX reinfusion (P = 0.67), immunomodulatory drug treatment before RTX (P = 0.59), IV immunoglobulin (P = 0.73), plasma exchange (P = 0.76), different RTX regimens (P = 0.64 and 0.56), and AQP4-immunoglobulin G serostatus (P = 0.27); and the 95% CIs varied between negative and positive values (i.e., encompassed zero, indicating statistically non-significant).

Safety

- AE (% of patients): infusion-related AE (10.3%), infection (9.1%), persistent leukopenia (4.6%), and posterior reversible encephalopathy (0.5%)
- None of the patients developed progressive, multifocal leukoencephalopathy
- Death: 1.6%

Authors' Conclusion

"In summary, this systematic review and meta-analysis provides evidence that rituximab therapy reduces the frequency of disease relapses and neurologic disability in patients with NMOSDs. It also suggests caution in prescribing rituximab as a first-line therapy until randomized trials determine the safety of the drug in this patient population (p. 1347)."[18]

Summary of Findings of Included Primary Clinical Study

Tahara et al. (2020)[8]

Main Study Findings

- Relapse
  - Relapse in the RTX group: none
  - Relapse in the placebo group: 7 (36.8%) patients
  - Group difference: 36.8% (95% CI, 12.3% to 65.5%); log-rank P = 0.0058
- EDSS (score change from visit 2 to last study visit)
  - In the RTX group, change in EDSS score was −0.32; 95% CI, −0.62 to −0.01
  - In the placebo group, change in EDSS score was −0.26; 95% CI, −0.77 to 0.25
  - Between-group difference in EDSS score change was −0.053; 95% CI, −0.626 to 0.520; difference not statistically significant
  - (Note: for the 7 patients in the placebo group who experienced relapse, the EDSS scores worsened)
- QOSI
  - In the RTX group, change in QOSI score was −1.16; 95% CI, −2.31 to −0.01
  - In the placebo group, change in QOSI score was 0.63; 95% CI, −0.62 to 1.88
  - Between-group difference in QOSI score change was −1.79; 95% CI, −3.43 to −0.0.15; difference statistically significant, favouring RTX
- Oral steroid reduction
  - In the RTX group, steroid reduction rate (%) was 75.1; 955 CI, 62.4 to 87.9
  - In the placebo group, steroid reduction rate (%) was 65.3; 95% CI, 51.1 to 79.5
  - Between-group difference in steroid reduction rate (%) was 9.84, 95% CI, −8.58 to 28.3; difference not statistically significant
- Adverse events
  - Total number of AEs was 134 in the RTX group and 82 in the placebo group
  - One or more AEs occurred in 90% of patients in each group
    - Infusion reaction: 37% of patients in the RTX group and 0% of patients in the placebo group
    - Nasopharyngitis: 37% of patients in the RTX group and 47% of patients in the placebo group
    - Headache: 21% of patients in the RTX group and 16% of patients in the placebo group
      - Upper respiratory tract infection: 21% of patients in the RTX group and 5% of patients in the placebo group
      - Diarrhea: 5% of patients in the RTX group and 21% of patients in the placebo group
      - No progressive multifocal leukoencephalopathy occurred in any group
      - One or more serious AEs occurred in 16% of patients in the RTX group and 11% of patients in the placebo group
- Death
  - There were no deaths in any group

Authors' Conclusion

"Rituximab has been used as an off-label drug in patients with neuromyelitis optica for more than a decade. The findings of our trial suggest that rituximab is effective at preventing relapses in patients with NMOSD who are seropositive for the AQP4 antibody. In addition to other available drugs, rituximab could have an important role in maintenance treatment of patients with NMOSD, particularly those who are AQP4 antibody-positive (p. 305)."[8]

Summary of Findings of Included Economic Evaluation

Aungsumart and Apiwattanakul (2020)[22]

Main Study Findings

Results from cost-utility analysis in the context of the Thailand health care system

The authors reported costs in THB (Thai bhat) and also reported the equivalent cost in US$. The exchange rate used was 30.3 THB for 1 US dollar. The results in US dollars are reported in this report. WTP was reported as 160,000 THB (US$5,289 in 2019 values).

- Total cost (US$)
  - AZA: 120,969
  - RTX fixed dose: 137,163
  - RTX $CD27^+$ memory cell regimen: 113,962
  - MMF (2,000 mg per day): 123,661
  - Biosimilar of RTX fixed dose: 118,720
  - Biosimilar of RTX $CD27^+$ memory cell regimen: 102,239
- QALY
  - AZA: 8.40
  - RTX fixed dose: 12.31
  - RTX $CD27^+$ memory cell regimen: 12.31
  - MMF (2,000 mg per day): 11.52
  - Biosimilar of RTX fixed dose: 12.31
  - Biosimilar of RTX $CD27^+$ memory cell regimen: 12.31
  - (Note: It was assumed that the biosimilar RTX and its administration strategy had the same efficacy as that of the original RTX.)
- Life-year
  - AZA: 24.29
  - RTX fixed dose: 25.49
  - RTX $CD27^+$ memory cell regimen: 25.49
  - MMF (2,000 mg per day): 25.34
  - Biosimilar of RTX fixed dose: 25.49
  - Biosimilar of RTX $CD27^+$ memory cell regimen: 25.49
  - (Note: It was assumed that the biosimilar RTX and its administration strategy had the same efficacy as that of the original RTX.)
- ICER (incremental cost per QALY) using AZA as reference
  - RTX fixed dose: 4,143

- RTX CD27+ memory cell regimen: dominant
- MMF (2,000 mg per day): 863
- Biosimilar of RTX fixed dose: dominant
- Biosimilar of RTX CD27+ memory cell regimen: dominant

- ICER (incremental cost [US$] per life-year) using AZA as reference
  - RTX fixed dose: 13,480
  - RTX CD27+ memory cell regimen: dominant
  - MMF (2000 mg/d): 2,566
  - Biosimilar of RTX fixed dose: dominant
  - Biosimilar of RTX CD27+ memory cell regimen: dominant
  - Note: sequential ICERs were not reported
- Sensitivity analysis
  - The PSA demonstrated that RTX biosimilar with CD27+ memory B cell monitoring regimen had the highest probability (48%) of being cost-effective, followed by AZA (30%), MMF (13%), and RTX with CD27+ memory B cell monitoring regimen (9%) at the WTP threshold (160,000 THB = US$5,829 in 2019 values). Also, it appeared from the cost-effectiveness acceptability curves that the probabilities of being cost-effective at a WTP threshold of 160,000 THB were 0% for RTX and RTX biosimilar.
  - One-way sensitivity analysis (tornado plot) for treatment with RTX biosimilar with CD27+ B cells monitoring regimen compared to treatment with AZA was conducted. It demonstrated that the greatest impact on ICER was variations in cost due to severe relapse treatment, followed sequentially by the efficacy of RTX in preventing relapse, discount rate for outcome, discount rate for cost, price of biosimilar RTX, efficacy RTX for preventing severe relapse, utility of patients with moderately severe disability, and utility of patients with no or mild disability.

Authors' Conclusion

"In conclusion, this study demonstrated that, in the context of the Thailand healthcare system, treatment with a rituximab biosimilar combined with disease activity monitoring of the CD27+memory B cell count or treatment with a generic MMF were cost efficient and exhibited a high probability of being cost-effective when compared with the current practice (p. 12)."[22]

Summary of Recommendations in Included Guidelines

Carneno Contentti et al. (2020)[19]

Recommendations and Supporting Evidence

Consensus recommendations were formulated based of the available evidence and/or information. It was not always clear if the recommendations were based on direct evidence from studies conducted or from what is generally used in clinical practice.

Quality of Evidence and Strength of Recommendations

Quality of the evidence and strength of the recommendations were not reported. However, the recommendations were categorized as appropriate, inappropriate, or uncertain, and the extent of agreement was reported.

- Recommendations for relapse and disease management
  - "Early IVMP treatment (1 g daily for 3–5 days) in acute relapse is recommended (p. 8)."[19]

        - Typically, NMOSD patients are treated with 1 g of IVMP for 3 to 5 days consecutively (6 citations).
        - Appropriate, 90% agreement
    - "After IVMP treatment, a slow tapering course of oral steroids for 2–8 weeks depending on the severity of the attack, is recommended (p. 8)."[19]
        - After IVMP treatment, oral steroids may be started to ensure prolonged effect on inflammation and to avoid early relapse (2 citations).
        - Appropriate, 73% agreement
    - "PLEX or immunoadsorption can be beneficial if there is partial or no response within 5 days from NMOSD relapse onset with or without previously IVMP (p. 8)."[19]
        - Patients with severe relapse and those not responding to treatment with IVMP may benefit from 5 days to 7 days of PLEX (6 citations).
        - Appropriate, 90% agreement
    - "The clinical benefit of PLEX diminishes after day 20 whether or not IVMP has been administered; therefore, an early start of PLEX is recommended (p. 8)."[19]
        - Maximum improvement is found when PLEX is started within 5 days; the clinical benefit gradually diminishes with delay in starting (8 citations).
        - Appropriate, 80% agreement
    - "PLEX should be considered for NMOSD patients with persistent neurologic deficit, even beyond day 20 (acute phase) and particularly within 90 days after the attack onset (p. 8)."[19]
        - One study showed relapse rates were not significantly different between NMOSD patients treated within 20 days and those treated after 20 days.
        - Appropriate, 80% agreement
- Recommendations for long-term relapse prevention:
    - "Early start of IST [immunosuppressant treatment] treatments to reduce disease activity and therefore to prevent NMOSD attacks is recommended (p. 8)."[19]
        - For all AQP4 antibody-positive and antibody-negative patients who have been diagnosed with relapsing NMOSD, long-term relapse prevention should be considered (6 citations).
        - Appropriate, 100% agreement
    - "Azathioprine (AZA, 2-3 mg/kg/day divided into 2-3 doses per day) has shown to be effective and safe in preventing relapse of NMOSD as well as decreasing disability and therefore it can be used as first line treatment for NMOSD (p. 9)."[19]
        - Studies have shown that AZA is effective and safe for treating patients with NMOSD (5 citations).
        - Uncertain, 55% agreement
    - "NMOSD patients under treatment with AZA with a target dose of 2.5-3.0 mg/kg/day adjusted to the total lymphocyte count (< 600-1,000/μL) and a mean corpuscular volume increase of at least 5 points from baseline, who present a relapse after 6 months of therapy within 5 years of starting are classified as having "suboptimal treatment response (p. 9)."[19]
        - The recommendation was based on 3 citations.
        - Appropriate, 73% agreement

- "Mofetil mycophenolate (MMF, at a target dose of 2-3 g/day divided into two doses per day) has shown to be effective and safe for preventing relapse of NMOSD and for decreasing disability, and therefore it can be used as first-line treatment for NMOSD patients (p. 9)."[19]
  - Retrospective studies have shown that MMF is effective and safe for treating patients with NMOSD, and compared with AZA, MMF demonstrated greater efficacy and fewer side effects (7 citations).
  - Appropriate, 90% agreement
- "NMOSD patients under treatment with MMF with a dose between 1,500–3,000 mg/day adjusted based on the total lymphocyte count (> 1,000 µL) who present a relapse after six months of drug therapy within five years of treatment start are classified as having a "suboptimal treatment response (p. 9)."[19]
  - Retrospective studies have shown that MMF is effective and safe for treating patients with NMOSD, and compared with AZA, MMF demonstrated greater efficacy and fewer side effects (7 citations).
  - Appropriate, 80% agreement
- "In NMOSD patients who receive AZA or MMF, oral steroids tapering should be maintained for at least 4-6 months (p. 9)."[19]
  - The recommendation was based on 7 citations.
  - Appropriate, 73% agreement
- "Low-dose of oral steroids (5–10 mg prednisolone or its equivalent) should be administered for a prolonged period in combination with MMF/AZA in NMOSD patients who have "suboptimal treatment response (p. 9)."[19]
  - One prospective study showed that the combination of AZA and oral steroids prevented relapse and improved disability.
  - Appropriate, 73% agreement
- "Induction protocol with RTX should be based on the infusion of doses of 375 mg/m^2 body surface area, administered as an i.v. infusion a week for four weeks, or 1,000 mg i.v. with a re-treatment at 14 days (p. 12)."[19]
  - Prospective and retrospective studies have shown RTX to be effective and safe (17 citations) and comparative studies have shown that RTX is more effective than AZA and MMF in reducing relapse severity and preventing relapse (17 citations).
  - Appropriate, 100% agreement
- "Maintenance protocol with 1,000 mg of RTX with a re-treatment at 14 days or one infusion of 1,000 mg or one infusion of 375 mg/m^2 repeated every six months has shown to be safe and effective to prevent NMOSD relapses and can therefore be used as the standard protocol to treat NMOSD patients (p. 12)."[19]
  - Prospective and retrospective studies have shown RTX to be effective and safe (17 citations) and comparative studies have shown that RTX is more effective than AZA and MMF in reducing relapse severity and preventing relapse (17 citations).
  - Appropriate, 90% agreement
- "In NMOSD patients who receive RTX, oral steroids should be maintained for at least 1-2 months after starting RTX (p. 12)."[19]
  - Oral steroids need to be used because RTX treatment could be followed by relapse in the first month (1 citation).

    - Appropriate, 73% agreement
- "Regardless of the number and severity, relapse among NMOSD patients after the treatment starts occurrences of relapses after at least six months of correct use of the specific treatment indicates that disease activity still persists and justifies modifying the therapeutic scheme to balance risk and benefit (p. 12)."[19]
    - Based on experience in clinical practice (1 citation).
    - Appropriate, 100% agreement
- "NMOSD patients under treatment with RTX who present a relapse after 1 to 5 months are considered as suboptimal treatment response (p. 12)."[19]
    - Appropriate, 73% agreement
- "Tocilizumab can be used in NMOSD patients showing no response to other immunosuppressants in clinical practice (p. 13)."[19]
    - Compared with AZA, tocilizumab significantly reduced the risk of new relapses (1 citation).
    - Appropriate, 90% agreement
- "Eculizumab can be used in NMOSD patients showing no response to other immunosuppressants in clinical practice (p. 13)."[19]
    - Compared to placebo, eculizumab significantly reduced the risk of new relapses (1 citation) and it had a good safety and tolerability profile.
    - Appropriate, 80% agreement
- "Inebilizumab can be used in NMOSD patients showing no response to other immunosuppressants in clinical practice (p. 13)."[19]
    - Compared to placebo, inebilizumab significantly reduced the risk of new relapses (1 citation) and it had a good safety and tolerability profile.
    - Appropriate, 73% agreement
- "Satralizumab can be used in NMOSD patients showing no response to other immunosuppressants in clinical practice (p. 13)."[19]
    - Compared to placebo, satralizumab significantly reduced the risk of new relapses (2 citations) and it had a good safety and tolerability profile.
    - Appropriate, 73% agreement
- "For severely disabling clinical symptoms or life-threatening relapses (highly active disease), cyclophosphamide or mitoxantrone could be used as induction therapy followed by a maintenance protocol after failure of RTX or when RTX is unavailable (p. 13)."[19]
    - Mitoxantrone was found to significantly reduce relapse rates in NMOSD patients (1 citation); panels of experts on NMOSD have recommended that CYT should only be used when other immunosuppressant treatment have failed or are not available (5 citations).
    - Appropriate, 90% agreement
- "For NMOSD patients whose phenotype is indeterminate between MS and NMOSD (overlapping syndrome), Rituximab is recommended (p. 13)."[19]
    - Published expert recommendations have stated that an NMOSD-suitable immunosuppressant treatment strategy will be effective for both MS and NMOSD (2 citations); RTX has been found to be reduce relapse rates in both MS and NMOSD over various follow-up durations (citation not presented).

        - Appropriate, 80% agreement
    - "Early IVMP treatment (1 g daily for 3–5 days) in an acute relapse during pregnancy (depending on relapse severity) is recommended (p. 13)."[19]
        - Studies have shown that during pregnancy, with short-term use of IVMP, there were no apparent complications affecting the fetus, except for low birth weight (11 citations).
        - Appropriate, 100% agreement
    - "Early PLEX treatment in situations of acute relapse during pregnancy (depending on relapse severity) should be considered (p. 14)."[19]
        - During pregnancy, PLEX may be used to treat relapse in NMOSD, especially in women who do not respond to corticosteroids (7 citations).
        - Appropriate, 80% agreement
    - "Immunosuppressive therapy with AZA or RTX during pregnancy should be continued if the patient has had attacks of NMOSD within the past 3 years (p. 14)."[19]
        - Based on expert opinion, AZA and RTX should be continued in NMOSD patients (experiencing frequent and disabling relapses) during pregnancy and the postpartum period, after assessment of the risks and benefits (3 citations).
        - Appropriate, 73% agreement

Sahraian et al. (2017)[20]

Recommendations and Supporting Evidence

Consensus recommendations were formulated based of the available evidence and/or information. It was not always clear if the recommendations were based on direct evidence from studies conducted or from what is generally used in clinical practice.

- Recommendations for acute attacks:
    - "The panel recommended IVMP 1 g daily for 3–7 days depending on attack severity and initial response, as the first and conventional treatment for acute relapses (p. 147-148)."[20]
    - "Most experts agreed on starting IVMP even in mild attacks within 24 hour of symptom onset since patients may develop deep paraplegia or blindness after initially presenting with mild symptoms (p. 147-148)."[20]
    - "In the setting of an acute attack, the panel recommended to start PLEX if no response was noted to IVMP within 5 days of therapy (p. 147-148)."[20]
    - "PLEX should be considered for IV steroid refractory relapses or the patients that have not responded at all to steroids in previous exacerbations (p. 147-148)."[20]
    - "Currently there is insufficient evidence to advise administration of IVMP and PLEX simultaneously for NMO relapses and the panel does not suggest it for routine clinical practice except in few severely disabling or life-threatening relapses (p. 147-148)."[20]
    - "In refractory exacerbations, without proper responsive to IVMP and PLEX, treatment with IVIg [IV immunoglobulin] may be considered (p. 147-148)."[20]
    - "The panel strongly recommended oral usage of steroids with a dose of 1 mg/kg following IV pulse therapy and then a slow taper off (p. 147-148)."[20]
    - "A prolonged taper of prednisone is advised according to the conventional therapy that will be started for the patient. In cases who receive azathioprine a taper off to 6 months

is advised but in patients who will receive rituximab a taper off over 4–8 weeks is recommended (p. 147-148)."[20]

- Related evidence:
  - IVMP is the typical and well-accepted treatment for NMOSD exacerbations (no citation reported). According to experts, it is advisable to continue and slowly taper oral steroids after IV infusion (no citation reported).
  - PLEX may be considered in patients expected to have poor response to steroids or when steroids are contraindicated (1 citation).
  - Although there is lack of evidence for IV immunoglobulin use, it can be used when PLEX is not available (1 citation).

- Recommendations for attack prevention:
  - "Azathioprine, Mycophenolate Mofetil and Rituximab are the most investigated agents among the available options for prevention of attacks in NMO and should be considered as first-line therapy (p. 147-148)."[20]
  - "Selecting among the above 3 options depends on patient characteristics and preference, severity of previous attacks, present confirmed disability, availability, cost, and potential side effects (p. 147-148)."[20]
  - "The panel recommended to start 1 of the above options following diagnosis especially in seropositive patients as soon as possible and careful monitoring for drug safety and efficacy should be continued regularly according to the protocols (p. 147-148)."[20]
  - "Azathioprine is a well-tolerated drug with acceptable risk-benefit profile ratio. Azathioprine is preferred to be used in milder cases without significant disability and low attack rate. The panel reach to conclusion than as there is no study on the prevalence of TPMT [thiopurine methyltransferase] in Iranian population and they have not seen any case of proved TPMT toxicity with azathioprine, its routine check is not necessary and should be evaluated in those who have history of adverse event (especially severe type) with azathioprine (p. 147-148)."[20]
  - "The recommended dose of azathioprine is 2.5–3 mg/kg/day adequate suppression of the lymphocyte count or a rise in the MCV of at least 5 point from baseline are the clues for optimal dosing (p. 147-148)."[20]
  - "Exacerbations following a treatment with enough period of time need a careful and precise re-evaluation. Drug dosage, patient compliance and adherence may influence therapeutic response and should be considered before a decision to change or escalate the drug. In patients receiving monoclonal antibodies such as rituximab anti-chimeric antibodies or B cell repopulation should be considered as well (p. 147-148)."[20]
  - "Rituximab is an effective anti-CD20 drug and is considered as the first-line therapy for NMOSD. There are several dosing regimens but the panel preferred the most straightforward 1 which is to administer 2 doses of 1 g intravenously 2 weeks apart and to repeat this 6 monthly (p. 147-148)."[20]
  - "Checking CD19, CD20 and CD27 is an individualized approach and this has to be done differently in various centres without any standard level I evidence recommendation. The panel suggested to check CD19 on exacerbation and exactly before the next dose of rituximab to see if the previous infusion has proper effect in B cell depletion and clarify the quantity of the next dose (p. 147-148)."[20]
  - "As Rituximab may induce a relapse in a small number of patients, some expert suggests to start oral prednisolone during and at least 2 weeks following infusion (p. 147-148)."[20]

- "The panel recommended escalation to Rituximab following treatment failure with azathioprine and mycophenolate (p. 147-148)."[20]
- Related evidence:
  - AZA was found to prevent relapses in 37% to 57% of patient in 3 cohorts of NMOSD patients, 1 cohort each from US, UK, and China (no citation reported)
  - MMF was found to decrease ARR in 24 patients; 6 of these patients experienced AEs (1 citation)
  - Several studies compared RTX with other first-line treatments (AZA, MMF) and found a significantly greater reduction in ARR and fewer AEs in the RTX group (3 citations)

Quality of Evidence and Strength of Recommendations

Quality of the evidence and strength of the recommendations were not reported.

Appendix 5: Overlap Between Included Systematic Reviews

Table 10: Overlap in Relevant Primary Studies Between Included Systematic Reviews

Primary study citation	Systematic review citation			
	Espiritu and Pasco (2019)[16]	Gao et al. (2019)[17]	Huang et al. (2019)[2]	Damato et al. (2016)[18]
Alsharoqi et al. *Mult Scler Relat Disord*. 2014;3(6):761. doi:10.1016/j.msard.2014.09.206	No	No	No	Yes
Annovazzi et al. *J Neurol.* 2016;263(9):1727-1735.	No	Yes	No	No
Ayzenberg et al. *JAMA Neurol.* 2013;70(3):394-397.	No	No	No	Yes
Bedi et al. *Mult Scler.* 2011;17(10):1225-1230.	No	Yes	No	Yes
Beres et al. *Pediatr Neurol.* 2014;51(1):114-118.	No	No	No	Yes
Bourre et al. *Acta Neurol Belg.* 2013;113(3):335-336.	No	No	No	Yes
Cabre et al. *J Neurol.* 2018;265(4):917-925.	No	Yes	No	No
Capobianco et al. *Neurol Sci.* 2007;28(4):209-211.	No	No	No	Yes
Chay et al. *Intern Med J.* 2013;43(8):871-882.	No	Yes	No	No
Chen et al. *Eur J Neurol.* 24:219-226.	No	No	Yes	No
Cree et al. *Neurology.* 2005;64(7):1270-1272.	No	No	No	Yes
Cohen et al. *Neurol Sci.* 2017;373:335-338.	No	Yes	No	No
Collongues et al. *Mult Scler.* 2016;22(7):955-959.	No	Yes	No	No
Evangelopoulos et al. *Neurol Sci.* 2017;372:92-96.	No	Yes	No	No
Gredler et al. *Neurol Sci.* 2013;328(1-2):77-82.	No	Yes	No	Yes
Ip et al. *Neurol Sci.* 2013;324(1–2):38-39.	No	Yes	No	Yes
Jacob et al. *Arch Neurol.* 2008;65(11):1443-1448.	No	Yes	No	Yes
Jarius et al. *Brain.* 2008;131(Pt 11):3072-3080.	No	Yes	No	Yes

Primary study citation	Systematic review citation			
	Espiritu and Pasco (2019)[16]	Gao et al. (2019)[17]	Huang et al. (2019)[2]	Damato et al. (2016)[18]
Jeong et al. *Mult Scler.* 2015;22(3):329-339.	Yes	Yes	No	No
Kageyama et al. *J. Neurol.* 2013;260:627-634.	No	No	Yes	No
Kim et al. *JAMA Neurol.* 2015;72(9):989-995.	No	Yes	No	Yes
Li et al. *J Neuroimmunol.* 2018;316:107-111.	No	Yes	No	No
Lindsey et al. *J Neurol Sci.* 2012;317(1–2):103-105.	No	Yes	No	Yes
Longoni et al. *Neurol Neuroimmunol Neuroinflamm.* 2014;1(4):e46.	No	Yes	No	Yes
Mahmood et al. *J Child Neurol.* 2011;26(2): 244-247.	No	No	No	Yes
Mealy et al. *JAMA Neurol.* 2014;71(3):324-330.	Yes	No	No	Yes
Musafir et al. *Mult Scler Relat Disord.* 2014;3(6):741-742.	No	No	No	Yes
Nikoo et al. *Neurol.* 2017;264(9):2003-2009.	Yes	Yes	Yes	No
Pellkofer et al. *Neurology.* 2011;76(15):1310-1315.	No	Yes	No	Yes
Perumal et al. *Neurol Neuroimmunol Neuroinflamm.* 2015;2(1):e61.	No	No	No	Yes
Radaellli et al. *Mult Scler.* 2016;22(4):511-519.	No	No	No	Yes
Tallantyre et al. *Neurol.* 2018;265(5):1115-1122.	No	Yes	No	No
Torres et al. optica. *J Neurol Sci.* 2015;351(1-2):31-35.	Yes	No	No	Yes
Tosello et al. *Arch Pediatr.* 2012;19(8):827-831.	No	No	No	Yes
Valentino et al. *Neurol Neuroimmunol Neuroinflamm.* 2016;4(2):e317.	No	Yes	No	No
Xu et al. *J Neurol Sci.* 2016;370:224-228.	No	No	Yes	No
Weinfurtner et al. *J Child Neurol.* 2015;30(10):1366-1370.	No	Yes	No	Yes
Yang et al. *Neurology.* 2013;81(8):710-713.	No	Yes	No	Yes

Primary study citation	Systematic review citation			
	Espiritu and Pasco (2019)[16]	Gao et al. (2019)[17]	Huang et al. (2019)[2]	Damato et al. (2016)[18]
Yang et al. *J Neurol Sci.* 2018;385:192-197.	Yes	Yes	Yes	No
Zéphir et al. *J Neurol.* 2015;262(10):2329-2335.	No	Yes	No	Yes
Zhang et al. *Acta Neurol Belg.* 2017;117(3):695-702.	Yes	Yes	Yes	No