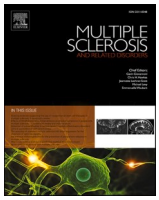
Multiple Sclerosis and Related Disorders 90 (2024) 105829

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Review article

Clinical practice guidelines for multiple sclerosis, neuromyelitis optica spectrum disorder, and myelin oligodendrocyte glycoprotein antibody-associated disease 2023 in Japan

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ARTICLE INFO

Key words:
Multiple sclerosis
Neuromyelitis optica spectrum disorder
Myelin oligodendrocyte glycoprotein antibody-associated disease
Guideline
Japan

ABSTRACT

Background: The previous Japanese clinical practice guidelines for multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) were published in 2017. Recently, for the first time in 6 years, the MS and NMOSD guideline development committee revised the Japanese guidelines for MS, NMOSD, and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD).

Methods: The committee utilized the Grading of Recommendations Assessment, Development, and Evaluation system based on the "Minds Handbook for Clinical Practice Guideline Development 2020 Ver. 3.0″ with a focus on clinical questions (CQs). The committee also discussed clinical issues other than CQs, categorizing them as a question-and-answer (Q&A) section, including "issues on which experts' opinions agree to a certain extent" and "issues that are important but not included in the CQ".

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https://doi.org/10.1016/j.msard.2024.105829
Received 3 February 2024; Received in revised form 14 August 2024; Accepted 16 August 2024
Available online 17 August 2024

Results: The committee identified 3, 1, and 1 key CQs related to MS, NMOSD, and MOGAD, respectively, and presented recommendations. A Q&A session regarding disease-modifying therapies and relapse prevention therapies for MS, NMOSD, and MOGAD was conducted. The revised guidelines were published in September 2023.

Conclusions: The Japanese guidelines for clinical practice on MS, NMOSD, and MOGAD were updated. Treatment strategies for MS, NMOSD, and MOGAD are changing, and these updated guidelines may assist with treatment decisions for these diseases in clinical practice.

1. Introduction

The Japanese guidelines for multiple sclerosis (MS) were originally published as "Treatment Guidelines for Multiple Sclerosis 2010″ (Multiple Sclerosis Treatment Guideline Development Committee, 2010). These guidelines were succeeded by the "Clinical Practice Guidelines for Multiple Sclerosis and Neuromyelitis Optica 2017″ (hereinafter referred to as the "2017 Guidelines") (Multiple Sclerosis and Neuromyelitis Optica Guideline Development Committee, 2017). Moreover, since the discovery in 2004 of neuromyelitis optica spectrum disorder-immunoglobulin G (NMO-IgG), also known as aquaporin 4 (AQP4) antibody, the distinct nature of NMO spectrum disorder (NMOSD) has been recognized. Consequently, numerous cases previously classified as "optic-spinal form MS" (Kikuchi et al., 2005) are now classified as NMOSD (Wingerchuk et al., 2015). Collectively, in the 2017 Guidelines, clinical question-and-answer (Q&A) sessions regarding MS and NMOSD were presented separately. After the publication of the 2017 Guidelines, the McDonald Criteria 2017 were published (Thompson et al., 2018). More recently, disease concepts and diagnostic criteria for myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) were published (Banwell et al., 2023).

Since the 2017 Guidelines release, advancements in the treatment of MS and NMOSD have emerged in Japan. Three disease-modifying drugs (DMDs) — dimethyl fumarate (DMF), siponimod, and ofatumumab — were approved and added to the 5 preapproved DMDs (interferon [IFN] β−1a intramuscular injection [im], IFNβ−1b subcutaneous injection [sc], glatiramer acetate [GA], fingolimod, and natalizumab) as alternatives for patients with MS. As for NMOSD, when the 2017 Guidelines were published, steroids and off-label oral immunosuppressants such as azathioprine (Imuran), tacrolimus, and mycophenolate mofetil (CellCept) were mainly used for the prevention of relapses in Japan. Following this development, 5 biological agents were approved for use in Japan. Consequently, treatment options for MS and NMOSD have advanced and become increasingly complex. Notably, there are currently no approved treatments in Japan to prevent relapses in MOGAD.

In contrast, the prevalence in Japan of MS, NMOSD, and MOGAD is not high. Specifically, MS, which exhibits the highest prevalence among the three diseases, affects approximately 10 to 20 per 100,000 individuals (Osoegawa et al., 2009; Houzen et al., 2023). This prevalence is much lower than those in European and North American countries. Collectively, patients with MS, NMOSD, and MOGAD are observed occasionally, especially in specific local areas in Japan.

A committee focused on "Guidelines for the Clinical Practice of Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders" discussed the diagnosis, treatments, and patient follow-up for individuals with MS, NMOSD, and MOGAD, taking into account the clinical landscape in Japan. Subsequently, they published the "Clinical Practice Guidelines for Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder 2023″ (hereinafter referred to as the "2023 Guidelines") in September 2023 (Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder Guideline Development Committee, 2023). The present study concentrates on and outlines disease-modifying therapies and relapse prevention strategies for patients with MS, NMOSD, and MOGAD based on the 2023 Guidelines.

2. Methods

2.1. Choosing outcomes

The 2023 Guidelines were developed with a focus primarily on MS, NMOSD, and MOGAD. The Grading of Recommendations Assessment, Development, and Evaluation system was used with reference to the "Minds Handbook for Clinical Practice Guideline Development 2020 ver. 3.0″ (Japan Council for Quality Health Care) (Minds, 2020) to assess clinical questions (CQs). First, the committee members (NI, MA, T. Ohashi, T. Okamoto, MO, TO, HO, IK, YS, KT, HT, MT, NC, IN, HF, TM, YM, KM, and MM), excluding the committee chair (MN), were asked to list issues they deemed important in clinical practice. Then, issues that were identified as eliciting conflicting opinions among experts were designated as CQs if they met two criteria: clinical issues for which there are multiple options with uncertain benefit−harm balances, leading to varying expert perspectives, and choices that could significantly impact crucial patient outcomes. Other clinical concerns, characterized as either harmonious expert opinions or vital matters not covered within the CQs, were categorized as Q&A.

After deliberating on the concerns raised by the committee members and narrowing down the list of topics, it was decided to address a total of 5 important clinical issues, with 3, 1, and 1 CQs on MS, NMOSD, and MOGAD, respectively. For these issues, PICO components (P: Patients, Problem, Population; I: Intervention; C: Comparison, Controls, Comparators; O: Outcomes) were extracted, and the relative importance of each extracted outcome was evaluated. Finally, the CQs were expressed using the extracted constructs. The findings of the systematic review (SR) on the 5 CQs, conducted by the SR members (MK, YT, CF, and MW), are described in Appendix A.

2.2. Outcome adoption process

Outcomes were decided based on the following scale:

Grade Scale of Importance as Outcome		
1–3	4–6	7–9
Not important	Important but not critical	Critical

Outcomes with a median score of 4 or higher were selected; however, an upper limit was set so that a maximum of 7 outcomes per CQ were selected. (If there were more than 7 outcomes with a median score of 4 or higher, 7 outcomes with the highest median score were selected from the top. In cases where the median scores were the same around the cutoff, the outcomes with the highest mean score were selected.) Consequently, no more than 7 outcomes were adopted for each CQ. The details of the discussion and voting results for the CQs are described in Appendix B.

2.3. Determining recommendation state and level

After the outcomes were determined, the SR team conducted an SR for each CQ, and reports were compiled. The SRs were performed using papers published between January 1, 1990 and July 31, 2021. Subsequently, using the SR findings, the chairperson and several other committee members drafted recommendations. A panel meeting ensued,

where panel members and 7 individuals affected by MS, NMOSD, or MOGAD were invited to participate in the discussion, and their comments were included.

For each CQ, the strength of recommendation and certainty of evidence were adopted as follows:

Strength of recommendation:

1. Strong: Recommendation "to implement" or "not to implement."
2. Weak: Proposal "to implement" or "not to implement."

If the recommendation was "weak," it was "proposed with conditions," and the conditions in such cases were described in the Notes.

Certainty of evidence:

A	B	C	D
Strong	Medium	Weak	Very weak

Recommendations were voted on based on the following agreed-upon levels.

1–3 points	4–6 points	7–9 points
Inadequate/Non-agreement	Indeterminate	Appropriate/Agreement

If the median score was 7 to 9, the recommendation was "adopted." If the median minus mean absolute deviation was more than 6, the recommendation was "strictly agreed to." If the median score was less than 6, the recommendation was classified as "disagreement (indeterminate)."

The modified Delphi method was applied to discuss and decide on the outcomes, recommendations, and strengths of the recommendations, and all decisions were made by a vote of 19 committee members excluding the chairperson (MN).

As for the answer to each Q&A item, a committee member performed a literature search and drafted a response. The committee then discussed and modified all the drafted answers.

After the completion of the CQs and Q&A, the committee discussed the algorithms of relapsing–remitting MS (RRMS) and NMOSD.

3. Results

3.1. Multiple sclerosis (MS)

- **CQ 1 for MS**

Is it recommended that patients in the early disease course of RRMS initiate treatment with natalizumab or ofatumumab?

- **Recommendation to CQ 1 for MS**

For patients experiencing RRMS in its initial stages, characterized by high relapse frequencies, magnetic resonance imaging (MRI) activity, as well as high Expanded Disability Status Scale (EDSS) scores and severe brain atrophy, the induction of natalizumab or ofatumumab is recommended (conditionally). (Strength of recommendation: 2 [weak]; Certainty of evidence: C [weak]).

- **Conditional to CQ 1 for MS**

Some conditions should be considered, such as poor prognostic indicators, the risk of developing progressive multifocal leukoencephalopathy (PML), or a patient's life background and values.

- **CQ 2 for MS**

Is it advisable for elderly patients with MS to discontinue a DMD?

- **Recommendation to CQ 2 for MS**

For elderly patients with MS experiencing prolonged inactivity and maintaining a stable condition, but who carry high mental, physical, and financial burdens due to continued IFNβ-1a im, IFNβ-1b sc, or GA, a recommendation is made to gradually taper or discontinue the administration of DMDs (conditionally) (Strength of recommendation: 2 [weak]; Certainty of evidence: D [very weak]).

- **Conditional to CQ 2 for MS**

When tapering or discontinuing a DMD, medical practitioners and patients should consider the risk of heightened disease activity and the advancement of physical disabilities. There is not enough data on DMDs other than IFNβ-1a im, IFNβ-1b sc, and GA to make recommendations.

- **CQ 3 for MS**

Which is recommended for patients with secondary-progressive MS (SPMS), ofatumumab or siponimod?

- **Recommendation to CQ 3 for MS**

1 For patients with SPMS, ofatumumab (Certainty of evidence: B [medium]) and siponimod (Certainty of evidence: A [strong]) are recommended (Strength of recommendation: 1 [strong]).

2 For patients with SPMS with relapse and/or MRI activity (conditionally), ofatumumab is recommended (strength of recommendation: 2 [weak], certainty of evidence: D [very weak]).

- Conditional to CQ 3 for MS

Ofatumumab and siponimod would be expected to have therapeutic effects in SPMS; however, the certainty of evidence is stronger for siponimod. Despite the lack of evidence, ofatumumab may be more promising in cases with relapses and/or MRI activity, based on the efficacy of other CD20 antibodies used in other countries.

Q&A related to treatments for MS

Question 1 for MS:
When should patients with MS initiate a DMD?

Answer 1 for MS:
- Patients should initiate DMD treatment as soon as possible after being diagnosed with MS.
- Individuals with clinically isolated syndrome may be advised to initiate a DMD.

Question 2 for MS:
On what basis should a DMD be selected for use in patients with MS?

Answer 2 for MS:
The selection of a DMD should be guided by factors such as the frequency of recurrence, MRI activity, poor prognostic factors including EDSS and brain atrophy at diagnosis, and the patient's life background and values. Patients deemed to have a poor prognosis should be started on a DMD with high efficacy. If the prognosis is considered good, a safer DMD may be considered.

Question 3 for MS:
When should a switch in DMDs be considered?

Answer 3 for MS:
- Switching a DMD should be considered when the therapeutic effect of the DMD is inadequate, when the side effects necessitate discontinuation, or when the side effects are a cause for concern. An insufficient response is defined as recurrence or progression of disease after the start of a DMD, or the presence of new or enlarged lesions on MRI. However, the effect may not be apparent in the early stages of DMD administration. The degree of disability has been proposed to include not only physical abilities but also brain atrophy and cognitive functions.
- Each DMD has side effects that should be noted.
- Switching should also be considered when there is concern regarding the risk of infection (especially PML) or fetal effects with continued treatment.

Question 4 for MS:
How should patients with SPMS be treated?

Answer 4 for MS:
- DMDs should be introduced early in SPMS cases presenting with relapse or MRI activity.

- In Japan, 2 DMDs, ofatumumab and siponimod, are approved for the treatment of SPMS.

Question 5 for MS:

How should patients with primary progressive MS (PPMS) be treated?

Answer 5 for MS:

No DMDs have been approved for patients with PPMS in Japan. Management includes symptomatic treatments and rehabilitation aimed at addressing issues such as gait disturbance, spasticity, pain/numbness, and dysuria/defecation.

Based on the above CQs and Q&A, a treatment algorithm for RRMS was proposed (Fig. 1).

Commentary on treatment algorithm for RRMS

In patients with RRMS in the initial phases, the selection of a DMD should be based on several factors. These include the frequency of relapses, MRI evaluation of disease activity, and poor prognostic factors spanning demographic and environmental aspects (such as older age, male gender, low blood vitamin D levels, and smoking); clinical indicators such as multiple symptoms at the initial onset, onset in the brainstem, cerebellum, or spinal cord lesions, poor recovery post-onset, short duration to second relapse, high EDSS score at MS diagnosis, high relapse frequency, high degree of disability 5 years post-onset, and early-stage cognitive impairment; MRI findings concerning numerous/large T2-hyperintense lesions, contrast lesions, infratentorial and/or spinal cord lesions, and brain atrophy; and laboratory parameters such as the presence of cerebrospinal fluid-specific oligoclonal bands, high levels of neurofilament light chains in spinal fluid/blood, and thinning of the retinal nerve fiber layer in optical coherence tomography. Additional considerations include the risk of PML, as well as each patient's background and values. Natalizumab or ofatumumab should be selected if relapse frequency or disease activity evaluated by MRI is high, the EDSS is high, or brain atrophy is severe. Otherwise, commencing treatment with IFNβ, GA, or DMF could be considered, as these options have lower probabilities of causing serious side effects. However, given the potential impacts on QOL associated with these drugs (psychiatric symptoms and fever by IFNβ, skin reactions by IFNβ and GA, and skin and gastrointestinal symptoms by DMF), along with efficacy concerns, the decision to initiate treatment with natalizumab or ofatumumab should be made only after the patient and doctor reach a consensus on the risk–benefit balance. In the case of other diseases, including NMOSD, the use of DMD in MS may worsen the disease. Therefore, the diagnosis of MS should be made with caution, especially regarding the measurement of AQP4 antibodies; if necessary, CBA should be considered.

If the therapeutic response is inadequate with IFN, GA, or DMF, the clinician should promptly consider a switch to fingolimod, natalizumab, or ofatumumab. In the case of IFN or GA, DMF can also be considered. DMDs such as fingolimod, natalizumab, or ofatumumab are expected to be highly effective in curbing both relapses and disability progression in MS, potentially mitigating the shift to the secondary progressive phase of the condition.

If treatment using fingolimod, natalizumab, or ofatumumab proves ineffective, transitioning to natalizumab or ofatumumab should be contemplated if the patient is currently taking fingolimod, and vice versa. The decision should also account for the risk of PML and the patient's background and values.

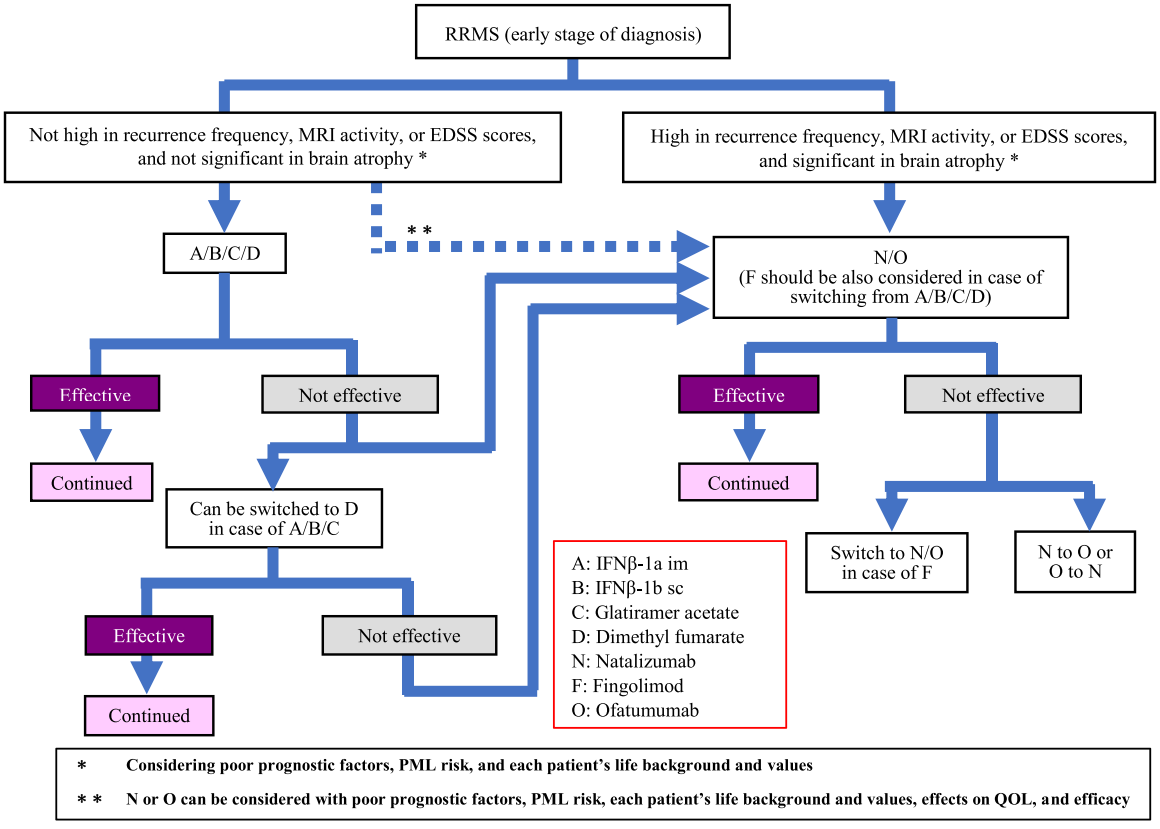

Fig. 1. Treatment algorithm for relapsing–remitting MS (originally in Japanese, permitted by Igaku-Shoin). MS, multiple sclerosis; RRMS, relapse-remitting multiple sclerosis; MRI, magnetic resonance imaging; EDSS, Expanded Disability Status Scale; PML, progressive multifocal leukoencephalopathy; QOL, quality of life.

3.2. Neuromyelitis optica spectrum disorder (NMOSD)

- **CQ 1 for NMOSD**

Is it advisable for NMOSD patients who are positive for AQP4 antibody to initiate treatment for attack prevention using biological agents?

- **Recommendation to CQ 1 for NMOSD**

Patients diagnosed with NMOSD who test positive for AQP4 antibody are advised to commence treatment with biological agents for attack prevention (conditionally) (Strength of recommendation: 2 [weak]; Certainty of evidence: C [weak]). However, a careful evaluation is necessary for patients requiring treatment initiation with biological agents.

Conditional to CQ 1 for NMOSD

- Commencing biological agents should be considered for patients experiencing life-threatening symptoms during the initial attack, showing unresponsiveness to treatment during an attack, or exhibiting reluctance to utilize oral immunosuppressive agents.
- Biological agents should be administered in hospitals/clinics that have implemented stringent infection control protocols, ensuring careful monitoring of infections. Close attention should also be given to comorbidities.
- Given that eculizumab, satralizumab, and inebilizumab are highly expensive, it is imperative to weigh the cost–benefit ratio with consideration for the escalation of national healthcare expenditures.

Q&A related to treatments for NMOSD

Question 1 for NMOSD:
How can NMOSD attacks be prevented?

Answer 1 for NMOSD:
To prevent an attack, relapse prevention therapy should be initiated promptly after the completion of acute treatment in patients with NMOSD. Oral immunosuppressive agents (azathioprine (Imuran), tacrolimus, and mycophenolate mofetil) and biological agents (eculizumab, satralizumab, inebilizumab, and rituximab) are used for relapse prevention therapy. When oral corticosteroids are used concomitantly, the minimum necessary dose should be administered. The above biological agents should not be used in individuals diagnosed with NMOSD who test negative for AQP4 antibody.

Based on the above CQs and Q&A, a treatment algorithm for AQP4 antibody-positive patients with NMOSD was prepared (Fig. 2).

Commentary on treatment algorithm for AQP4 antibody-positive patients with NMOSD

In order to prevent NMSOD attacks, patients with AQP4 antibody-positive NMOSD who have completed the acute-phase treatment should be promptly treated with oral immunosuppressive agents or biological agents. Because oral immunosuppressive agents require several months to achieve a stable effect, these will generally be used in combination with faster-acting oral corticosteroids. If recurrence is not controlled using oral immunosuppressive agents with/without low-dose oral steroids, patients should be switched to a biological agent. Patients treated with biological agents must be monitored carefully.

3.3. MOG antibody-associated diseases (MOGAD)

- **CQ 1 for MOGAD**

Is recurrence prevention therapy recommended for patients with MOGAD?

- **Recommendation to CQ 1 for MOGAD**

Recurrence prevention therapy is recommended for patients with MOGAD (conditionally) (Strength of recommendation: 2 [weak], Certainty of evidence: D [very weak]).

- **Conditional to CQ 1 for MOGAD**

Since approximately half of all patients with MOGAD do not relapse, the course of the disease should be carefully monitored, and tapering or discontinuation should be considered in cases with no relapse.

Q&A related to treatments for MOGAD

Question 1 for MOGAD:
What should be done to prevent recurrence in patients with MOGAD?

Answer 1 for MOGAD:
Oral corticosteroids, azathioprine (Imuran), mycophenolate mofetil (CellCept), rituximab, intravenous immunoglobulin (IVIg), or tocilizumab may be effective for the treatment of recurrent MOGAD. After acute treatment, corticosteroids should be tapered to 10 mg per day or more over a period of 3–6 months. Subsequently, further tapering of corticosteroids in combination with mycophenolate mofetil (CellCept) and azathioprine (Imuran) should be considered. In highly active cases, rituximab, IVIg, or tocilizumab may be effective. MOGAD relapse rates decrease when MOG antibodies become negative after the initial onset. It is advisable to conduct MOG antibody testing during the phase of tapering and discontinuation of corticosteroids and other medications.

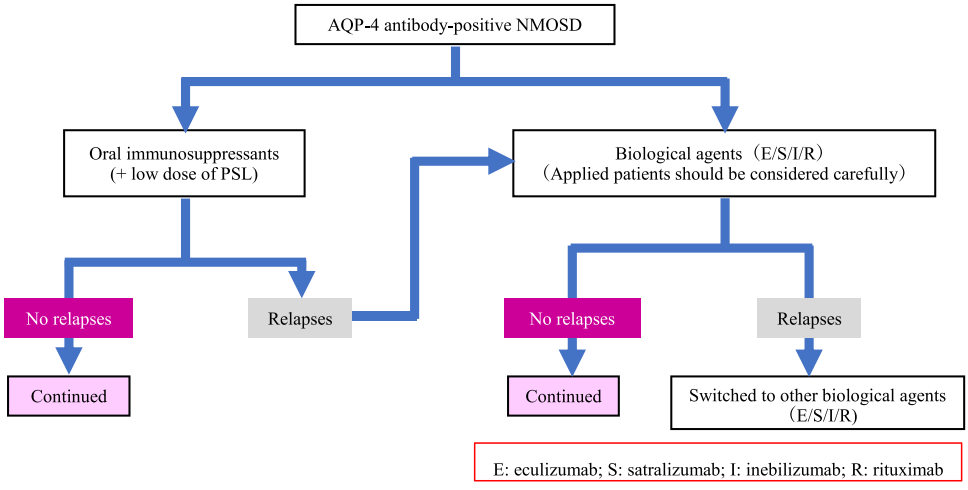

Fig. 2. Treatment algorithm for AQP4 antibody-positive neuromyelitis optica spectrum disorder (originally in Japanese; used with permission from Igaku-Shoin). PSL, prednisolone. NMOSD, neuromyelitis optica spectrum disorder.

4. Discussion

In Japan, the first guidelines for MS and NMOSD were published in 2010 (Multiple Sclerosis Treatment Guideline Development Committee, 2010) and included only treatments for MS. The 2nd guidelines were published in 2017 and included management as well as treatments for NMOSD and MS. In the 2017 Guidelines, MOGAD was also included (Multiple Sclerosis and Neuromyelitis Optica Guideline Development Committee, 2017). The clinical environments in these diseases have changed dramatically over the past 6 years, and updated guidelines are required in Japan.

No curative treatment is available for MS, and the current therapeutic strategy aims to prevent relapses and disability progression. Initiation of treatment with DMDs as soon as possible after a diagnosis of MS is recommended in the 2023 Guidelines as well as in guidelines from other regions (Montalban et al., 2018). After the approval of IFNβ−1b sc injection as the first DMD in 2001, a total of 8 DMDs (IFNβ−1a im injection, IFNβ−1b sc injection, GA, fingolimod, DMF, natalizumab, siponimod, and ofatumumab) have been approved for use in Japan. However, the US Food and Drug Administration has thus far approved >2 dozen therapies for MS (Morgan et al., 2023).

The necessity to create accessible treatment frameworks from the abundance of treatment options has led to discussions about the initial use of DMDs in clinical practice (Morgan et al., 2023). Two main approaches have arisen: a strategy of escalation versus one of early highly effective treatment (Morgan et al., 2023). In Japan, 5 DMDs for MS (IFNβ−1a im, IFNβ−1b sc, GA, fingolimod, and natalizumab) were approved when the 2017 Guidelines were published. The 2017 Guidelines endorsed an escalation therapy strategy for RRMS, starting with IFN or GA (Multiple Sclerosis and Neuromyelitis Optica Guideline Development Committee, 2017). Following this, 3 DMDs (DMF, siponimod, and ofatumumab) for RRMS and/or SPMS were also approved. Recent studies have revealed the distinct effects of early intensive therapy (Kavaliunas et al., 2017; Iaffaldano et al., 2021). Furthermore, the concept of progression independent of relapse activity (PIRA) has been observed even in the early stages of MS (Portaccio et al., 2022), with DMDs potentially enhancing the prognosis associated with PIRA (Portaccio et al., 2022).

Fingolimod and natalizumab were launched in 2011 and 2014, respectively, in Japan. The risk for PML associated with fingolimod, the first oral DMD in Japan, had not been reported at the time fingolimod was approved. Following the approval, 9 confirmed cases and 1 suspected case of fingolimod-associated PML were reported in Japan (Fingolimod, 2023). Further, de-escalation or cessation of fingolimod was shown to cause a rebound (Sato et al., 2018). Accordingly, fingolimod does not hold a prominent position in the treatment algorithm for RRMS in the 2023 Guidelines. With respect to natalizumab, extended interval dosing (EID) has been shown to reduce the risk of PML (Ryerson et al., 2019). EID is recommended in the 2023 Guidelines, especially for patients who test positive for the JC virus antibody. Although the treatment of MS has radically improved the lives and mid- to long-term expectations of patients diagnosed with MS, better control and prevention of disease progression are needed (Kappos, 2021). Much of the current controversy stems from varying perspectives on the acceptable risk concerning the potential benefits achievable through treatment with the available DMDs (Kappos, 2021).

As for SPMS treatment, the guidelines of the European Committee for Treatment and Research in Multiple Sclerosis/European Academy of Neurology recommend that ocrelizumab or cladribine (Cladribine) be considered for patients with active SPMS (Montalban et al., 2018), although those guidelines were published before siponimod and ofatumumab were introduced. Ocrelizumab and cladribine (Cladribine) have not been approved for MS treatment in Japan, but siponimod and ofatumumab are covered under medical insurance for SPMS. The double-blind, randomized, phase III study of Siponimod targeted only SPMS patients (Kappos et al., 2018), but in the phase III ASCLEPIOS I and II trials for ofatumumab, SPMS patients accounted for only about 6 % of the total 1882 subjects (Gärtner et al., 2022). Thus, there are currently no large-scale SPMS-specific data on the safety and efficacy of ofatumumab. Nonetheless, the 2023 Guidelines recommend ofatumumab for SPMS patients displaying relapse and/or MRI activity (Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder Guideline Development Committee, 2023).While evidence for the use of ofatumumab in SPMS is weak, a similar B-cell targeted DMD, ocrelizumab, showed efficacy for PPMS and is recommended for active SPMS by the ECTRIMS/EMA guidelines (Montalban et al., 2018).

Ocrelizumab, a humanized antibody targeting CD20, has been approved for PPMS in other countries and is recommended in the ECTRIMS/EMA guidelines (Montalban et al., 2018). In Japan, however, neither ocrelizumab nor rituximab have been approved for MS. Overall, as stated in the 2023 Guidelines, “No DMDs have been approved for PPMS in Japan. Symptomatic treatment and rehabilitation are provided for gait disturbance, spasticity, pain/numbness, and dysuria/defecation.” While ofatumumab, another humanized CD20-targeting antibody, has been introduced in Japan, there is currently a lack of data concerning the drug’s effectiveness for PPMS.

Regarding NMOSD, no agents were sanctioned for relapse prevention in Japan before 2018. Oral prednisolone and/or oral immunosuppressants such as azathioprine (Imuran) and tacrolimus, which are still off-label, were predominantly employed in clinical settings. Then, between 2019 and 2022, eculizumab, satralizumab, inebilizumab, and rituximab were approved for the prevention of relapses in NMOSD in Japan (ravulizumab was approved in 2023). However, these agents were exclusively approved for patients with AQP4 antibody-positive NMOSD. The decision about which treatments should initially use oral immunosuppressants or biological agents is highly challenging but critical in clinical practice. Clinical trials demonstrated that these biological agents are significantly effective in preventing relapses (Yamamura et al., 2019; Pittock et al., 2019; Cree et al., 2019; Tahara et al., 2020). However, these phase III RCTs focused solely on patients with recent relapses, indicating a high disease activity level among the participants, with the majority not being treatment-naïve. On the other hand, CQ1 for NMOSD is: “Should patients diagnosed with NMOSD who test positive for AQP4 antibody be advised to commence treatment with biological agents to prevent attacks?”. In the phase III RCTs, the occurrences of patients experiencing monophasic attacks were very low (0 %, 0 %, 17.4 % in PREVENT, SAkuraSky, and N-Momentum, respectively) (Yamamura et al., 2019; Pittock et al., 2019; Cree et al., 2019). Therefore, the data from these phase III RCTs do not align with CQ1, which was one of the reasons for weakening the recommendation. The commencement of biological agents for patients should be approached with caution. Patients with NMOSD may encounter potentially life-threatening attacks even during their initial episode, necessitating vigilance to prevent further relapses, especially in cases with severe sequelae. In such cases, biological agents are an important treatment choice. In contrast, when using biological agents, it is vital to monitor infections and infusion reactions. Further, most of these biological agents are highly expensive in Japan. The panel recommended the initiation of biological agents for preventing relapses in patients with AQP4 antibody-positive NMOSD. The accessibility and affordability of recently approved treatments for NMOSD are likely to vary across countries and regions, significantly influencing decisions regarding the initiation or transition to these medications (Pittock et al., 2021). For example, the Neuromyelitis Optica Study Group in Germany recommended that conventional immunosuppressive therapies (such as azathioprine (Imuran), mycophenolate mofetil (CellCept), and oral glucocorticoids) could be employed but are deemed less effective than biologics. Long-term immunotherapy for AQP4-IgG-positive NMOSD should be initiated using one of the monoclonal antibodies eculizumab/ravulizumab, inebilizumab, rituximab, or satralizumab, whenever these options are available and accessible (Kümpfel et al., 2024). Further, the Group recommended that the selection of immunotherapy should consider

variables including attack severity, attack recovery, efficacy, speed of action, comorbidities, side effects, safety, drug-related mortality, age, family planning, patient preferences, adherence, clinical utility, and availability/costs (Kümpfel et al., 2024). The systematic review in the 2023 Guidelines was conducted using papers published between January 1, 1990 and July 31, 2021. Since the publication of the 2023 Guidelines, several real-world reports on biologics for NMOSD have appeared (Nakashima et al., 2024; Marignier et al., 2024). Nevertheless, extended treatment for attack prevention spanning probably several decades is necessary in NMOSD, and the current data on the long-term safety and effects of biological agents used over such durations remains inadequate. Subsequent research findings will fortify clinical guidelines and decision-making processes in the future. Biological agents are generally expensive, and their utilization may differ across regions and countries.

In contrast, no clear benefit was observed in any outcome measure for patients with AQP4 antibody-negative NMOSD in clinical studies involving biological agents (Pittock et al., 2021). As a result, biological agents have not been approved. Patients diagnosed with AQP4 antibody-negative NMOSD presently rely on oral prednisone and/or oral immunosuppressants for management.

A nationwide survey in Japan revealed that relapses affected 53.5 % of patients with MOGAD, with the median duration between onset and the initial relapse standing at 7 months (Nakamura et al., 2023). Overall, approximately 50 % of patients do not relapse, yet there remains a possibility that those who do not relapse may still require medication to prevent future occurrences. Patients with relapse could benefit from the prevention of recurrence; however, those without relapse may only face potential harm. In Japan, no drugs for the prevention of relapse for MOGAD have been approved. The nationwide survey in Japan mentioned above reported that oral prednisolone was administered in 86.5 % of patients with MOGAD, and immunosuppressants and immunomodulators such as azathioprine (Imuran), tacrolimus, cyclophosphamide, IVIg, and rituximab were also administered (Nakamura et al., 2023). Numerous reports have suggested that the relapse rate of MOGAD decreases when MOG antibodies become negative after the initial onset (Gastaldi et al., 2023; Huda et al., 2021; Wendel et al., 2022). The 2023 Guidelines recommend assessing MOG antibodies during the tapering and discontinuation of corticosteroids and other medications (Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder Guideline Development Committee, 2023). In the future, it will be crucial to address the issue of patients with MOGAD who tend to relapse and to identify effective medications.

5. Conclusion

The Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder Guideline Development Committee discussed the diagnosis, treatment, and follow-up care for patients with MS, NMOSD, and MOGAD while taking into account the clinical landscape in Japan, culminating in the publication of the 2023 Guidelines (Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder Guideline Development Committee, 2023). The present review focuses on and introduces disease-modifying and relapse prevention therapies for patients with MS, NMOSD, and MOGAD from the 2023 Guidelines. Information regarding the current benefits and harms of medications will be continuously revised, with additional DMDs and relapse prevention therapies anticipated to emerge in the future. It is crucial to remain abreast of the latest developments in understanding and treating these conditions, with these guidelines serving as a valuable point of reference.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

Disclosures

Masaaki Niino has received funding for travel and/or speaker honoraria from Biogen, Mitsubishi Tanabe, Chugai, Alexion, Takeda, and Novartis.

Noriko Isobe has received research grants from Biogen, Mitsubishi Tanabe, Chugai, Teijin, and Eisai, and speaker honoraria from Biogen, Mitsubishi Tanabe, Chugai, Alexion, Takeda, Novartis, UCB, Eisai, Japan Blood Product Organization, and Argenx.

Manabu Araki has received speaker honoraria from Biogen, Novartis, Takeda, Chugai, Alexion, and Mitsubishi Tanabe.

Takashi Ohashi has received funding for travel and/or speaker honoraria from Alexion, Biogen, Chugai, Novartis, Takeda, Tanabe, and Teijin.

Tomoko Okamoto has received speaker honoraria from Chugai, and research grants from Biogen, Chugai, PPD-Shin Nippon Biomedical Laboratories, Argenx, and Sanofi.

Mieko Ogino has received funding for travel and/or speaker honoraria from Takeda, Fujimoto, Kyowa Kirin, Otsuka, Sumitomo, Mitsubishi Tanabe, Eisai, Chugai, Novartis, UCB, Alexion, Biogen, Ono, Nobelpharma, Abbott, and Koninklijke Philips.

Tatsusada Okuno has received speaker honoraria from Biogen, Mitsubishi Tanabe, Chugai, Alexion, Takeda, and Novartis, and a research grant from Biogen and Mitsubishi Tanabe.

Hirofumi Ochi has received funding for travel and/or speaker honoraria from Biogen, Novartis, Mitsubishi Tanabe, Alexion, Chugai,

Nihon Pharmaceutical, Takeda, and Daiichi Sankyo.

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Hideyuki Takeuchi has served on scientific advisory boards for Alexion and Takeda and has received funding for travel and/or speaker honoraria from Alexion, Argenx, Alnylam, Biogen, Cosmic Corporation, Chugai, Eisai, Mitsubishi Tanabe, Novartis, and Sumitomo.

Masayuki Tahara has received speaker honoraria and consultation from Mitsubishi Tanabe, Chugai, Zenyaku Kogyo, Alexion, Biogen, and Novartis.

Norio Chihara has received funding for travel and/or speaker honoraria from Biogen, Mitsubishi Tanabe, Chugai, Alexion, AbbVie, and Novartis.

Ichiro Nakashima has served on scientific advisory boards for Biogen, Novartis, Chugai, and Alexion, and has received speaker honoraria from Biogen, Mitsubishi Tanabe, Novartis, Chugai, Alexion, and Eisai, and has received research support from LSI Medience.

Hikoaki Fukaura has received funding for travel and/or speaker honorarium from Alexion, Biogen, Chugai, Novartis, Takeda, Tanabe Mitsubishi, Otsuka, Asahi Kasei Medical, FP, Daichi Sankyo, UCB, Eisai and Teijin.

Tatsuro Misu has received speaker honoraria from Tanabe Mitsubishi, Novartis., Alexion., Teijin, Viela Bio, and Biogen, and research support from Cosmic Corporation, and Medical and Biological Laboratories.

Yusei Miyazaki has received funding for travel and speaker honoraria from Alexion, Biogen, Chugai, Mitsubishi Tanabe, and Novartis.

Katsuichi Miyamoto has received speaker honoraria from Alexion, Biogen, Chugai, Eisai, Mitsubishi Tanabe, Novartis, and Teijin.

Masahiro Mori has received speaker honoraria from Novartis and Biogen and has participated in trials with Alexion and Novartis.

Makoto Kinoshita has received speaker honoraria from Alexion, Biogen, Chugai, CSL Behring, Daiichi Sankyo, Mitsubishi Tanabe, and Novartis.

Mitsuru Watanabe has received honoraria for lectures and/or advisory boards from Novartis, Biogen, Alexion, Chugai, Mitsubishi Tanabe, Argenx, UCB, and Viatris.

Kazuo Fujihara has received consulting fees from Merck Biopharma, Japan Tobacco, and AbbVie; and payment or honoraria for lectures, presentations, manuscript writing, or educational events from Viela Bio/MedImmune, Biogen, Mitsubishi Tanabe, Novartis Pharma, Chugai, Eisai, Asahi Kasei Medical, Merck, and Takeda; has participated in a data safety monitoring board or advisory board of VielaBio/Horizon Therapeutics, Mitsubishi Tanabe, Novartis, Chugai, Alexion, Biogen, and UCB.

Kazuya Takahashi, Yoshiki Takai, and Chihiro Fujii have no disclosures.

Funding

This work was supported in part by the Health and Labor Sciences Research Grant on Intractable Diseases (Neuroimmunological Diseases) from the Ministry of Health, Labor, and Welfare of Japan (20FC1030). No payments were made to the authors for the writing of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.105829.

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