

MSIF Off-Label Treatments (MOLT) Panel

Guideline for the use of off-label azathioprine and rituximab for the treatment of multiple sclerosis in low-resource settings

Public comment

Before publication of our guidelines, the recommendations are opened for public comment. You can provide us with feedback **by 25th of April 2022** using the following survey link:

<https://www.surveymonkey.com/r/Q8WPMJR>.

Please note that due to the potential large number of comments, we are unable to provide individual replies. We will aim to consider all potential errors in the evidence reviews.

We are committed to providing these recommendations to the MS community as soon as possible. We want to ensure people with MS in low-resource settings, who do not have access to a range of available and affordable disease-modifying-therapies, can benefit from these recommendations on off-label azathioprine and rituximab.

Background

The need for these guidelines has been outlined in our recent publication:

“Ethical use of off-label disease-modifying therapies for multiple sclerosis”

<https://journals.sagepub.com/doi/full/10.1177/13524585211030207>

The Cochrane systematic review protocols can be found here:

Azathioprine: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD015005/full>

Rituximab: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013874/full>

Rapid systematic review protocol for acceptability, equity, feasibility, and values of rituximab and azathioprine for the treatment of multiple sclerosis:

https://osf.io/w9qs8/?view_only=313e9807b71847ea860c4c2471aae0fe

We are using the [GRADE Evidence-to-Decision \(EtD\) framework](#) which includes 12 criteria for making a recommendation. The EtD framework also defines the certainty of the evidence considered in relation to treatment outcomes and their level of importance. Certainty then forms part of the recommendations, in particular the strength of the recommendations that can be made. You can view the [GRADE evidence profile](#), [Summary of Findings table](#), [Evidence to Decision framework and Interactive Summary of Findings](#) using the link below each PICO question and navigating through the [pink](#) tabs on the middle of the webpage.

The [scope of the project](#) and [FAQs](#) are available on MSIF's website.

Should azathioprine vs. no disease-modifying therapy be used for relapsing forms of multiple sclerosis as first choice treatment?

Author(s) of the Evidence Profile: Francesco Nonino, Elisa Baldin, Silvia Minozzi

Presentation for Clinicians

RECOMMENDATION

WE SUGGEST THE INTERVENTION

The MOLT Panel suggests using azathioprine compared with no disease-modifying therapy for relapsing forms of multiple sclerosis as first choice treatment (conditional recommendation, very low certainty of the evidence).

Remark: This recommendation is conditional because of the very low certainty of the evidence and of the lack of availability and affordability of other treatment options for the person with multiple sclerosis.

Background **Subgroup considerations** **Justification** **Implementation considerations**

Background

[GRADE evidence profile](#)

[Summary of Findings table](#)

[Evidence to Decision framework](#)

[Interactive Summary of Findings](#)

[Open in new window](#)

Abstract: Francesco Nonino, Elisa Baldin, Silvia Minozzi
Question: Azathioprine compared to no disease-modifying therapy for relapsing forms of multiple sclerosis as first choice treatment.
Setting: outpatient.
Interventions: Azathioprine, 2 mg/kg/d (low-dose), 4 mg/kg/d (medium-dose), 6 mg/kg/d (high-dose) compared with no disease-modifying therapy.
Outcomes: Relapse rate, disability, quality of life, adverse events.
Results: The evidence is very low certainty. The risk of relapse was significantly lower in the azathioprine group compared with no disease-modifying therapy (RR 0.45, 95% CI 0.25 to 0.81). There was no significant difference in disability, quality of life, or adverse events between the groups.
Conclusion: The evidence is very low certainty. The risk of relapse was significantly lower in the azathioprine group compared with no disease-modifying therapy. There was no significant difference in disability, quality of life, or adverse events between the groups.

No of studies	Study design	Risk of bias	Grading assessment				No of patients		Effect		Certainty	Importance
			Inconsistency	Indirectness	Imprecision	Other considerations	azathioprine	no disease-modifying therapy	Relative (95% CI)	Absolute (95% CI)		
1	randomized	serious	serious	very serious ¹	very serious ²	none	207 (50%)	227 (20%)	RR 0.45 (0.25 to 0.81)	30 fewer relapses per 1000 patients treated for 1 year	⊕○○○ Very low	CRITICAL

Azathioprine Recommendations

5. Should azathioprine vs. no disease-modifying therapy be used for relapsing forms of multiple sclerosis as first choice treatment?

https://guidelines.gradepr.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_1119feab-f154-4c23-985c-11a17ad74109/1c2c4c97-2a69-4c19-ad59-c10a7af34ec3

The MOLT Panel suggests using azathioprine compared with no disease-modifying therapy for relapsing forms of multiple sclerosis as first choice treatment (conditional recommendation, very low certainty of the evidence). Remark: This recommendation is conditional because of the very low certainty of the evidence and of the lack of availability and affordability of other treatment options for the person with multiple sclerosis.

Justification: The Panel judged that the balance of desirable and undesirable health effects for the use of azathioprine over no DMT in this population does not favour either of the options. However, when the Panel considered the resources required, the feasibility of use and the impact on equity, for the final recommendation, the Panel judged that azathioprine should be suggested, but only in settings where no other DMT is available and affordable, and the alternative would be no treatment with a DMT. In this specific context, given the poor prognosis most people with MS face without treatment, azathioprine has more desirable than undesirable consequences but requires the patient to understand and accept the very low certainty of the evidence.

Voting commentary: The Panel reached consensus without voting.

6. Should azathioprine vs. other disease-modifying therapies (Interferon) be used for relapsing forms of multiple sclerosis as first choice treatment?

https://guidelines.gradepr.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_2e5398d9-0793-4af5-ba3f-73b01c4cf335/fa980640-fc7a-4b0c-87c3-422fc8957ab5

The MOLT Panel suggests using azathioprine or interferon for relapsing forms of multiple sclerosis as first choice treatment (conditional recommendation, very low certainty of the evidence). Remark: Azathioprine use is conditional on the lack of interferon or other treatment options that are available and affordable.

Justification: The Panel assessed evidence for azathioprine versus other DMTs, but only evidence for azathioprine versus interferon was identified. The direct evidence for health outcomes (head-to-head trials) of azathioprine versus interferon probably favoured azathioprine. However, the certainty of the evidence was very low and the effect of azathioprine in larger trials is unknown. Effects of older diagnostic criteria which may have included patients with NMOSD were also discussed.

Recommendations on the use of interferon was outside the scope of this guideline, and based on the existing and reviewed evidence, the Panel felt there was insufficient evidence to rank azathioprine and interferon. The Panel suggested azathioprine to be a suitable alternative to interferon where interferon and other DMTs are not available and affordable.

Note: Panel members conflicts of interests were re-assessed for interferon products after the formulation of this recommendation. The Panel agreed this recommendation was still appropriate after disclosure of conflicts.

7. Should azathioprine vs. no disease-modifying therapy be used for relapsing forms of multiple sclerosis when switching from another DMT?

https://guidelines.gradepro.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_b5af60b5-1bc6-4aff-97dd-3d2fdc9a1a61/b0c9862f-967e-4b2d-b0f1-9177278c8677

Due to lack of evidence the MOLT Panel decided not to make a specific recommendation.

Remark: The conditional recommendation for using azathioprine or interferon for relapsing forms of MS as first choice treatment may guide decision-making on whether to prescribe azathioprine if a switch was required due to adverse effects or continuous availability or affordability of another DMT, but the Panel felt uncomfortable to make a specific recommendation. The Panel noted this would not be appropriate if switching was due to lack of treatment response.

Justification: The systematic review did not identify any studies that specifically considered azathioprine vs. no DMT when switching. The Panel did not feel extrapolation from other evidence was appropriate.

8. Should azathioprine vs. other disease-modifying therapies be used for relapsing forms of multiple sclerosis when switching from another DMT?

https://guidelines.gradepro.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_5ddf727d-63b5-4ee8-b5e7-12cde4108c3d/196ef8e3-840b-4397-bc77-93522cd80ffc

Due to lack of evidence the MOLT Panel decided not to make a specific recommendation.

Remark: The conditional recommendation for using azathioprine or interferon for relapsing forms of MS as first choice treatment may guide decision-making on whether to prescribe azathioprine if a switch was required due to adverse effects or continuous availability or affordability of another DMT, but the Panel felt uncomfortable to make a specific recommendation. The Panel noted this would not be appropriate if switching was due to lack of treatment response.

Justification: The systematic review did not identify any studies specifically considering azathioprine vs. other DMTs when switching. The Panel did not feel extrapolation from other evidence was appropriate.

9. Should azathioprine vs. no disease-modifying therapy be used for progressive forms of multiple sclerosis as first choice treatment?

https://guidelines.gradepro.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_ff361383-3f41-45b7-8804-e0a48fbd7581/e71a789f-7a3d-44bf-9149-491654ea8531

Due to lack of evidence the MOLT Panel decided not to make a recommendation.

Justification: The systematic review only identified one study (Ellison 1989) on azathioprine vs placebo, which included patients with progressive MS. However, the applicability of its results to the population of interest is poor, mainly because the definition of "progressive MS" referred to the classification of Schumacher et al (1965), which has been superseded by several diagnostic criteria updates. From the outcomes reported by the authors, "relapse rate" was the only one prioritised by the MOLT Panel, which is conflicting with the current definition of progressive forms of MS.

The Panel did not feel extrapolation from other evidence was appropriate.

10. Should azathioprine vs. other disease-modifying therapies be used for progressive forms of multiple sclerosis as first choice treatment?

https://guidelines.gradepro.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_7c8db06b-c2f1-40dd-ae8f-b5929e1b171b/6738b26e-e8f7-4809-a6f9-c1c5e7e35a3d

Due to lack of evidence the MOLT Panel decided not to make a recommendation.

Justification: The systematic review did not identify any studies specifically considering azathioprine vs. other DMTs for progressive forms of MS. The Panel did not feel extrapolation from other evidence was appropriate.

11. Should azathioprine vs. no disease-modifying therapy be used for progressive forms of multiple sclerosis when switching from another DMT?

https://guidelines.gradepro.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_114ca373-c358-48cf-89ca-7ea6253ef247/1f6f4df6-f939-48d2-93c0-4af903fb3ec2

Due to lack of evidence the MOLT Panel decided not to make a recommendation.

Justification: The systematic review did not identify any studies specifically considered azathioprine vs. no DMT for progressive forms of MS when switching. The Panel did not feel extrapolation of other evidence was appropriate.

12. Should azathioprine vs. other disease-modifying therapies be used for progressive forms of multiple sclerosis when switching from another DMT?

https://guidelines.gradepro.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_3154810b-3e2c-47fc-bbc7-db3390cb2937/4dedfcfb-caa0-4aa5-adbe-45cae2db67ad

Due to lack of evidence the MOLT Panel decided not to make a recommendation.

Justification: The systematic review did not identify any studies specifically considered azathioprine vs. other DMTs in progressive forms of MS when switching. The Panel did not feel extrapolation from other evidence was appropriate.

Rituximab Recommendations

13. Should rituximab vs. no disease-modifying therapy be used for relapsing forms of multiple sclerosis as first choice treatment?

https://guidelines.gradepro.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_f3d818af-5bc2-40c4-8141-1cd7395a4df3/b47006e6-6766-4994-9205-f7ba20df355f

The MOLT Panel suggests using rituximab compared with no disease-modifying therapy for relapsing forms of multiple sclerosis as first choice treatment (conditional recommendation, very low certainty of the evidence). Remark: The Panel used indirect evidence from the comparison of rituximab against other DMTs to make this recommendation.

Justification: The Panel judged the desirable health effects to be greater than the undesirable health effects. The Panel noted that additional data are emerging on the potential adverse effects of anti-CD20 therapies in patients with COVID-19 and possibly negative effects on vaccination efficacy. These data were not explicitly considered by the Panel because the relevant publications appeared after the systematic review was completed.

When considering the resources required, although moderate compared to no treatment, the Panel suggested the cost-effectiveness would favour treatment with rituximab and improve equity due to the relatively low cost. Rituximab would allow people in low-resource settings, where other DMTs may not be available and affordable, to have access to treatment for MS with a monoclonal antibody. Rituximab is off-patent and several biosimilars are already available. As rituximab is used to treat several different conditions, it has administrative and logistical advantages over drugs that are only used to treat MS. B cell enumeration and lymphocyte studies can be used if CD20/19 analysis is not available. Rituximab allows for drug free periods where no maintenance therapy is needed. In general, healthcare professionals are familiar with the infusion, pre-medication regimes and monitoring requirements.

The recommendation is conditional due to the very low level of certainty. It is important to ensure that patients understand the limitations of the evidence in deciding whether to choose treatment with rituximab.

Voting commentary: The Panel reached consensus without voting.

14. Should rituximab vs. other disease-modifying therapies be used for relapsing forms of multiple sclerosis as first choice treatment?

https://guidelines.gradepro.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_53f32d32-245b-4a7f-b256-7ab8d10e7b45/739e5796-edc1-4678-9d92-d04cb5347abd

The MOLT Panel suggests using rituximab compared with other DMTs for relapsing forms of multiple sclerosis as first choice treatment (conditional recommendation, very low certainty of the evidence). Remark: This recommendation depends which other DMTs are available and affordable. The Panel suggests rituximab is an appropriate option when a range of DMTs are not available and affordable.

The desirable effects were judged as 'large' compared to interferon and glatiramer acetate and 'moderate' compared to natalizumab and dimethyl fumarate.

Justification: The Panel judged rituximab compared favourably against a number of other DMTs, both with desirable health effects and undesirable health effects. The Panel noted that additional data are emerging on the potential adverse effects of anti-CD20 therapies in patients with COVID-19 and possibly negative effects on vaccination efficacy. These data were not explicitly considered by the Panel because the relevant publications appeared after the systematic review was completed.

When considering the resources required, the Panel judged it would be likely to result in large cost savings. Equity would improve due to the relatively low cost, allowing people in low-resource settings, where other DMTs may not be available and affordable, to have access to treatment for MS with a monoclonal antibody. Rituximab is off-patent and several biosimilars are already available. As rituximab is used to treat several different conditions, it has administrative and logistical advantages over drugs that are only used to treat MS. B cell enumeration and lymphocyte studies can be used if CD20/19 analysis is not available. Rituximab allows for drug free periods where no maintenance therapy is needed. In general, healthcare professionals are familiar with the infusion, pre-medication regimes and monitoring requirements.

The recommendation is conditional due to the very low level of certainty. Although there is a reasonable body of evidence for rituximab, there is not a RCT equivalent to a phase 3 clinical trial. It is important to ensure that patients understand the limitations of the evidence in deciding whether to choose treatment with rituximab.

Voting commentary: The Panel reached consensus without voting.

15. Should rituximab vs. no disease-modifying therapy be used for relapsing forms of multiple sclerosis when switching from another DMT?

https://guidelines.gradepr.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_23639646-6a48-45c0-ac7e-c57c963abb5e/0afc1f9c-3a5a-41a8-b434-3f6835adcea7

The MOLT Panel suggests using rituximab compared with no disease-modifying therapy for relapsing forms of multiple sclerosis when switching from another DMT (conditional recommendation, very low certainty of the evidence). Remark: The Panel used indirect evidence from the comparison of rituximab against other DMTs for relapsing forms of multiple sclerosis when switching to make this recommendation.

Justification: The Panel judged the desirable health effects to be greater than the undesirable health effects. The Panel noted that additional data are emerging on the potential adverse effects of anti-CD20 therapies in patients with COVID-19 and possibly negative effects on vaccination efficacy. These data were not explicitly considered by the Panel because the relevant publications appeared after the systematic review was completed.

When considering the resources required, although moderate compared to no treatment, the Panel suggested the cost-effectiveness would favour treatment with rituximab and improve equity due to the relatively low cost. Rituximab would allow people in low-resource settings, where other DMTs may not be available and affordable, to have access to treatment for MS with a monoclonal

antibody. Rituximab is off-patent and several biosimilars are already available. As rituximab is used to treat several different conditions, it has administrative and logistical advantages over drugs that are only used to treat MS. B cell enumeration and lymphocyte studies can be used if CD20/19 analysis is not available. Rituximab allows for drug free periods where no maintenance therapy is needed. In general, healthcare professionals are familiar with the infusion, pre-medication regimes and monitoring requirements.

The recommendation is conditional due to the very low level of certainty. It is important to ensure that patients understand the limitations of the evidence in deciding whether to choose treatment with rituximab.

Voting commentary: The Panel reached consensus without voting.

16. Should rituximab vs. other disease-modifying therapies be used for relapsing forms of multiple sclerosis when switching from another DMT?

https://guidelines.grade.pro.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_e31fb3b4-0dab-4d63-ac0a-5a3397e6e161/934dcffd-ebf6-4359-a465-d76047569068

The MOLT Panel suggests using rituximab compared with other disease-modifying therapies for relapsing forms of multiple sclerosis when switching from another DMT (conditional recommendation, very low certainty of the evidence). Remark: This recommendation depends on which other DMTs are available and affordable. The Panel suggests rituximab is an appropriate option when a range of DMTs are not available and affordable.

Justification: The Panel judged rituximab compared favourably against a number of other DMTs, both with desirable health effects and undesirable health effects. The Panel noted that additional data are emerging on the potential adverse effects of anti-CD20 therapies in patients with COVID-19 and possibly negative effects on vaccination efficacy. These data were not explicitly considered by the panel because the relevant publications appeared after the systematic review was completed.

When considering the resources required, the Panel judged it would be likely to result in large cost savings. Equity would improve due to the relatively low cost, allowing people in low-resource settings, where other DMTs may not be available and affordable, to have access to treatment for MS with a monoclonal antibody. Rituximab is off-patent and several biosimilars are already available. As rituximab is used to treat several different conditions, it has administrative and logistical advantages over drugs that are only used to treat MS. B cell enumeration and lymphocyte studies can be used if CD20/19 analysis is not available. Rituximab allows for drug free periods where no maintenance therapy is needed. In general, healthcare professionals are familiar with the infusion, pre-medication regimes and monitoring requirements.

The recommendation is conditional due to the very low level of certainty. Although there is a reasonable body of evidence for rituximab, there is not a RCT equivalent to a phase 3 clinical trial. It is important to ensure that patients understand the limitations of the evidence in deciding whether to choose treatment with rituximab.

Voting commentary: The Panel reached consensus without voting.

17. Should rituximab vs. no disease-modifying therapy be used for progressive forms of multiple sclerosis as first choice treatment?

https://guidelines.grade-pro.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_ad7f2376-926a-4931-9b39-34350d741dfb/d8859805-1395-4cb7-b391-b243bc8bd86c

The MOLT Panel suggests using rituximab compared with no disease-modifying therapy for **active** progressive forms of multiple sclerosis (conditional recommendation, very low certainty of the evidence). Remark: This recommendation is based on very low certainty of the evidence from a sub-population of active disease from primary progressive MS.

Justification: The Panel judged the desirable health effects to be greater than the undesirable health effects for the sub-population of active progressive forms of MS. There are few treatment options for this population in low resource settings.

The Panel noted that additional data are emerging on the potential adverse effects of anti-CD20 therapies in patients with COVID-19 and possibly negative effects on vaccination efficacy. These data were not explicitly considered by the Panel because the relevant publications appeared after the systematic review was completed.

When considering the resources required, although moderate compared to no treatment, the Panel suggested the cost-effectiveness would favour treatment with rituximab and improve equity due to the relatively low cost. Rituximab would allow people in low-resource settings, where other DMTs may not be available and affordable, to have access to treatment for MS with a monoclonal antibody. Rituximab is off-patent and several biosimilars are already available. As rituximab is used to treat several different conditions, it has administrative and logistical advantages over drugs that are only used to treat MS. B cell enumeration and lymphocyte studies can be used if CD20/19 analysis is not available. Rituximab allows for drug free periods where no maintenance therapy is needed. In general, healthcare professionals are familiar with the infusion, pre-medication regimes and monitoring requirements.

The recommendation is conditional due to the very low level of certainty and because only indirect evidence exists. It is important to ensure that patients understand the limitations of the evidence in deciding whether to choose treatment with rituximab.

Voting commentary: The Panel reached consensus without voting.

18. Should rituximab vs. other disease-modifying therapies be used for progressive forms of multiple sclerosis as first choice treatment?

https://guidelines.grade-pro.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_a8d277e3-fd4d-459e-b848-17b17bde5cb6/0f9f149c-d1b5-4333-b435-d535116f38b9

Due to lack of evidence the MOLT Panel decided not to make a recommendation.

Justification: The Panel did not feel extrapolation from other evidence was appropriate.

19. Should rituximab vs. no disease-modifying therapy be used for progressive forms of multiple sclerosis when switching from another DMT?

https://guidelines.gradepr.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_6c6a75eb-1fba-419c-8460-0730de75cdd8/ae52d709-ca59-4cb3-9bfe-bdbb76216b46

The MOLT Panel suggests using rituximab compared with no disease-modifying therapy for **active** progressive forms of multiple sclerosis when switching from another DMT (conditional recommendation, very low certainty of the evidence). Remark: This recommendation is based on very low certainty of the evidence from a sub-population of active disease from secondary progressive MS when comparing rituximab versus other DMTs.

Justification: The Panel judged the desirable health effects to be greater than the undesirable health effects for the sub-population of active progressive forms of MS. There are few treatment options for this population in low resource settings.

The Panel noted that additional data are emerging on the potential adverse effects of anti-CD20 therapies in patients with COVID-19 and possibly negative effects on vaccination efficacy. These data were not explicitly considered by the Panel because the relevant publications appeared after the systematic review was completed.

When considering the resources required, although moderate compared to no treatment, the Panel suggested the cost-effectiveness would favour treatment with rituximab and improve equity due to the relatively low cost. Rituximab would allow people in low-resource settings, where other DMTs may not be available and affordable, to have access to treatment for progressive forms of MS. Rituximab is off-patent and several biosimilars are already available. As rituximab is used to treat several different conditions, it has administrative and logistical advantages over drugs that are only used to treat MS. B cell enumeration and lymphocyte studies can be used if CD20/19 analysis is not available. Rituximab allows for drug free periods where no maintenance therapy is needed. In general, healthcare professionals are familiar with the infusion, pre-medication regimes and monitoring requirements.

The recommendation is conditional due to the very low level of certainty and because only indirect evidence exists. It is important to ensure that patients understand the limitations of the evidence in deciding whether to choose treatment with rituximab.

Voting commentary: The Panel reached consensus without voting.

20. Should rituximab vs. other disease-modifying therapies be used for progressive forms of multiple sclerosis when switching from another DMT?

https://guidelines.gradepr.org/preview/p | justyna_litynska_admin_evidenceprime_com_0_7927_4784-253e-46ef-a7df-45c848b8582b_7ba88601-275a-40e8-a8c8-c8dacff35f08/1251940c-b4cb-4193-9d26-06ace66a102d

The MOLT panel suggests using rituximab compared with other disease-modifying therapies for **active** progressive forms of multiple sclerosis when switching from another DMT (conditional recommendation, very low certainty of the evidence). Remark: This recommendation is based on

very low certainty of the evidence on from a sub-population of active disease from secondary progressive MS. Following this recommendation should include consideration whether other DMTs are available and affordable. The Panel suggests rituximab is an appropriate option when a range of DMTs are not available and affordable.

Justification: The Panel judged the desirable health effects to be greater than the undesirable health effects for the sub-population of active progressive forms of MS. There are few treatment options for this population in low resource settings.

The Panel noted that additional data is emerging on the potential adverse effects of anti-CD20 therapies in patients with COVID-19 and possibly negative effect on vaccination efficacy. This data was not explicitly considered by the panel because the relevant publications appeared after the systematic review was complete.

When considering the resources required, although moderate compared to no treatment, the Panel suggested the cost-effectiveness would favour treatment with rituximab and improve equity due to the relatively low cost, allowing people in low-resource settings, where other DMTs may not be available and affordable, to have access to treatment for progressive forms of MS. Rituximab is off patent and several biosimilars are already available. As rituximab is used to treat several different conditions, it has administrative and logistical advantages over drugs that are only used to treat MS. B cell enumeration and lymphocyte studies can be used if CD20/19 analysis is not available. Rituximab allows for drug free periods where no maintenance therapy is needed. In general, healthcare professionals are familiar with the infusion, pre-medication regimes and monitoring requirements.

The recommendation is conditional due to the very low level of certainty and because only indirect evidence exists. It is important to ensure that patients understand the limitations of the evidence in deciding whether to choose treatment with rituximab.

Voting commentary: The Panel reached consensus without voting.

Multi-comparison recommendation

https://gdt.gradepr.org/presentations/#/multi-comparisons/mc_presentation_mc_d44a6cdf-2533-461f-9ddf-903ace0ec2ee

The MOLT Panel suggests using rituximab or azathioprine over no treatment for relapsing forms of multiple sclerosis as first choice treatment. Where both treatments are available and affordable, rituximab is suggested over azathioprine (conditional recommendation, very low certainty of the evidence). Remark: This recommendation is based on very low certainty of evidence. Azathioprine use is conditional on the lack of other treatment options that are available and affordable. Rituximab may be used when other appropriate DMTs for the specific clinical circumstances of the patient are not available and affordable. On the basis of the multiple intervention comparison, rituximab is suggested over azathioprine (ranking rituximab > azathioprine).

Justification:

The Panel judged that the balance of desirable and undesirable health effects for the use of azathioprine over no DMT in this population does not favour either of the options. However, when the Panel considered the resources required, the feasibility of use and the impact on equity, for the final recommendation, the Panel judged that azathioprine should be suggested, but only in settings where no other DMT is available and affordable, and the alternative would be no treatment with a DMT. In this specific context, given the poor prognosis most people with MS face without treatment, azathioprine has more desirable than undesirable consequences but requires the patient to understand and accept the very low certainty of the evidence.

The Panel assessed evidence for azathioprine versus other DMTs, but only evidence for azathioprine versus interferon was identified. The direct evidence for health outcomes (head-to-head trials) of azathioprine versus interferon probably favoured azathioprine. However, the certainty of the evidence was very low and the effect of azathioprine in larger trials is unknown. Effects of older diagnostic criteria which may have included patients with NMOSD were also discussed. Recommendations on the use of interferon was outside the scope of this guideline, and based on the existing and reviewed evidence, the Panel felt there was insufficient evidence to rank azathioprine and interferon. The panel suggested azathioprine to be a suitable alternative to interferon where interferon and other DMTs are not available and affordable. Azathioprine has some advantages due to the low cost, and potentially better acceptability and feasibility (cold-chain, mode of administration), but these are all context-specific criteria.

The panel judged the desirable health effects to be greater than the undesirable health effects for rituximab over no DMT and noted that it compared favourably against a number of other DMTs for health outcomes. The Panel noted that additional data is emerging on the potential adverse effects of CD20 therapies in patients with COVID-19 and possibly negative effect on vaccination efficacy. This data was not explicitly considered by the panel because the relevant publications appeared after the systematic review was complete. When considering the resources required, the Panel judged rituximab to have a considerably lower cost than other DMTs, only azathioprine would have a lower cost. Rituximab would improve equity due to the relatively low cost, allowing people in low-resource settings, where other DMTs may not be available and affordable, to have access to treatment for MS with a monoclonal antibody. Rituximab is off patent and several biosimilars are already available. As rituximab is used to treat several different conditions, it has administrative and logistical advantages over drugs that are only used to treat MS. It is important to ensure that patients understand the limitations of the evidence in deciding whether to choose treatment with rituximab.

In the multi-comparison rituximab ranks before azathioprine due to the judgement of larger net desirable health effects.

Note: This recommendation was amended for clarification after stakeholder feedback raised concerns over mis-interpretation of the multi-comparison ranking of interferon over azathioprine based on EtD criteria other than health effects. The pairwise recommendation suggested using azathioprine or interferon as it was judged there was insufficient clinical evidence to rank azathioprine and interferon. Azathioprine has some advantages due to the low cost, and potentially better acceptability and feasibility (cold-chain, mode of administration). However, including interferon in this multi-comparison ranking was interpreted to refer to health effects only, which is an incorrect interpretation. Due to concern over health systems reducing access to interferon based on

an inaccurate interpretation, and remaining with the scope of these guidelines, the Panel decided to remove interferon from the multi-comparison recommendation.

Panel members conflicts of interests were re-assessed for interferon products and only non-conflicted members voted whether to amend the recommendation.

Panel members with no conflicts of interests: 8

Voting results:

6 for amendment

2 against amendment