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 the guidelines, the recommendations were opened for public comment on MSIF's website from the 4th of April until 25th of April 2022.

We received a total of 13 comments by email and through the provided survey. Feedback was received from Argentina, Australia, Canada, Czech Republic, Turkey, UK and the US.

Summary of public comment

Actions noted in green.

Question: Is there anything important that we have not included or any errors that you have noted?

No additional studies or errors in the analysis were highlighted through the feedback.

General comments were received highlighting the difference in clinical practice between rituximab and azathioprine. Rituximab is being currently used, or was used before ocrelizumab was approved in a number of countries (Europe, Turkey, US, Iran), but the use of azathioprine has been much more limited in recent years. Rituximab is often used an induction therapy when other alternatives are not available, especially in more active/aggressive forms of MS. Azathioprine's effectiveness is thought to be much more limited, especially long-term. Long-term adverse effects, especially the risk of cancer was highlighted.

The MOLT panel will consider these comments when drafting the manuscript(s) to provide a comprehensive view of these off-label DMTs.

An additional comment was received highlighting the limited quantity and low certainty of evidence for the use of azathioprine for MS.

This point has been extensively discussed in the EtDs, recommendations and FAQs already.

Question: Is there any context or background we should make sure to include in the final peer reviewed publication? Please include reasons why this particular point needs to be included or emphasized.

The following suggestions and comments were put forward for consideration:

- Simplify and remove duplication in recommendations to improve readability.

The MOLT panel will consider this feedback when drafting the manuscript(s).

- Note the importance of safe and effective follow-on products of azathioprine and rituximab. Many follow-on products exist and it is important that they have gone through appropriate assessment and regulatory approval processes to ensure high quality medicines. Suggestion that follow-on products must comply with the FDA, WHO or European Medicines Agency (EMA) standards for biosimilars or generic drugs.
  The MOLT panel will consider this feedback when drafting the manuscript(s) and we have amended Q5 in the FAQs.

- The comments around potential risks associated with COVID-19 and the possible lack of vaccination effects are easily misinterpreted due to the repetitive structure. It should be noted the panel did not assess this evidence systematically, and should therefore not make recommendations based on these studies. It is also important to highlight the difference between absolute and relative risks.
  The MOLT panel will consider this feedback when drafting the manuscript(s).

- The wording of 'first choice' can easily be misinterpreted to mean 'first line' rather than 'treatment naïve', despite the clarification in the FAQs. Suggest amending the wording to ensure clarity as this has substantial consequences in clinical practice.
  The MOLT panel will consider this feedback when drafting the manuscript(s) and we have further clarified this point in Q16 in the FAQs.

- Concern raised on the definition of 'affordable' where health systems would stop providing other DMTs based on price. Suggestion to remove affordability as a criterion and only recommend azathioprine when no DMT is available.
  The FAQs extensively discuss this question around affordability, and it would be a mis-interpretation of these guidelines to limit access on the premise of cost. Off-label use of DMTs to treat MS should be driven by the need to protect the person's health. Affordability is a major barrier for access to treatment. In many countries on-label DMTs are available in theory, but remain unaffordable for many people with MS.

- Question on whether there are situations where the use of azathioprine use can be justified, other than cost-saving to the healthcare system.
  Our Atlas of MS reported that 14% of countries globally do not have access to any on-label DMTs. We believe this is an underestimate, as a number of countries did not respond to the survey. In most low- and middle-income countries people with MS pay part or all of the costs of the DMTs themselves. Cost and affordability have been highlighted as a major barrier to access to treatment. We therefore believe that recommendations on the use of azathioprine is an important tool for clinicians and people with MS having to make difficult treatment decisions in low-resource settings.

- An introduction to the pathophysiology of MS and the mechanisms of disease control would be beneficial as pre-text to the MOLT recommendations.
  The MOLT panel will consider this feedback when drafting the manuscript(s).

- Other off-label DMTs are also used for MS, e.g. methotrexate, mycophenolate, cyclophosphamide.
  As discussed in the FAQs, other off-label DMTs are out of the scope of these recommendations.

Question: Do you have any suggestions on how these recommendations should be disseminated? Please share any relevant experience you may have from low-resource settings to help us consider implementation of these guidelines.

Dissemination suggestions included:

National level
MS organisations
MS centres
MS experts/specialists
Neurological societies
Medical associations
Ministries of health

Regional/global level
ECTRIMS
European Academy of Neurology
World Federation of Neurology

Channels
Webpages
Webinars
Discussion forums with with experts
Access to peer-support if needed