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Disease-modifying therapy for multiple sclerosis

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High-efficacy therapy from the time of diagnosis substantially improves the prognosis for multiple sclerosis. The national guidelines on MS nevertheless recommend less effective therapy for many patients, and must be updated in pace with medical advances. We consider in the following how multiple sclerosis should be treated.

In multiple sclerosis (MS), the immune system attacks the central nervous system through lymphocytes initiating local inflammation. Clinically this gives rise to fully or partly transient neurological deficits, known as relapsing-remitting multiple sclerosis (RRMS). If untreated, the relapses convert to gradually increasing functional deficits, termed secondary progressive disease, when the neurodegeneration is no longer driven by lymphocyte attacks.

Disease-modifying MS therapy suppresses lymphocyte attacks. The effect is pronounced early in the course of the disease, and abates with the development of progressive disease (1). Early, high-efficacy therapy for relapsing-remitting multiple sclerosis slows the advance of progressive functional impairment in the majority of patients (2). Conversely, a more defensive escalation strategy, with gradually increasing therapeutic intensity, leads to progressive functional decline in the majority (3). This therapeutic principle used to be the dominant one (4), and is partly supported by the national guidelines on MS, which several of the authors were involved in drawing up in 2017 (5).

Therapeutic effects

The effect of relevant drugs on relapse frequency is shown in Table 1 (6–9). Owing to variation in the comparator and disease activity prior to the start of the study, it is not clear which drug is the most effective. Network-based analyses, as in the Norwegian Institute of Public Health's method evaluation of 2019, may shed light on this (10), but are usually based on short studies of selected patients. Real-world registry-based studies with long follow-up times provide clinically relevant evidence of long-term therapeutic efficacy and risk (11).

Table 1

Key data on disease-modifying drugs for relapsing-remitting multiple sclerosis (RRMS)

	Reduction of relapses in phase III trials (6)	Administration (6)	Relevant comorbidity	Appropriate for those wanting children (7, 8)	Significant reduction in response to vaccine (9)	Approved indication	Approved by Decision Forum
Alemtuzumab[1]	50–54 % vs interferon beta	Intravenously annually for two years	Immunodeficiency Vascular disease Autoimmunity	Partial	Probably transient	Very active RRMS	Yes
Ocrelizumab	46–47 % vs interferon beta	Intravenously semi-annually	Immunodeficiency Latent hepatitis	Yes	Yes	RRMS and PPMS	No
Ofatumumab	50–60 % vs teriflunomide	Subcutaneously monthly	Immunodeficiency Latent hepatitis	No	Probably yes	RRMS	In process
Rituximab	Not conducted	Intravenously semi-annually	Immunodeficiency Latent hepatitis	Yes	Yes	Not applied for	Yes, to be registered in MS registry
Natalizumab	68 % vs placebo	Intravenously monthly	JCV carrier	Partial	No	Very active RRMS	Not for new patients
Cladribine	55 % vs placebo	By mouth annually for two years	Immunodeficiency	Yes	Unknown	Highly active RRMS	Yes
Fingolimod	42 % and 52 % vs placebo 52 % vs Interferon-beta	By mouth daily	Immunodeficiency Hypertension AV block Diabetes	No	Yes	Highly active RRMS, also children	Not for new patients
	Reduction of relapses in phase III trials (4, 17)	**Administration (4, 17)**	**Relevant comorbidity**	**Appropriate when wanting children (18, 19)**	**Significant reduction in response to vaccine (20)**	**Approved indication**	**Approved by decision-making forum**
Ozanimod	39 % and 49 % vs interferon beta	By mouth daily	Immunodeficiency Hypertension AV block	No	Probably yes	Active RRMS	Yes
Dimethyl fumarate	44–53 % vs placebo	By mouth daily	Immunodeficiency Effect on psoriasis	No	No	RRMS	Yes

	Reduction of relapses in phase III trials (6)	Administration (6)	Relevant comorbidity	Appropriate for those wanting children (7 , 8)	Significant reduction in response to vaccine (9)	Approved indication	Approved by Decision Forum
Teriflunomide	32 % vs placebo 18 % vs interferon beta	By mouth daily	Immunodeficiency Hypertension Liver disease	No	No	RRMS	Yes
Interferon-beta	19–32 % vs placebo	Self-injection every 2 to 14 days	Depression	Yes	No	RRMS, CIS, SPMS	Yes
Glatiramer acetate	29–34 % vs placebo	Self-injection from daily to 3 x weekly	No	Yes	No	RRMS	Yes

[1]Because of its adverse effects profile, the Pharmaceutical Purchasing Cooperation's specialist team does not class alemtuzumab on the same level as other MS therapy.

Both network-based analyses and longitudinal studies indicate that natalizumab, alemtuzumab, ocrelizumab and ofatumumab are among the most effective drugs. Phase II trials with frequent MRI scans also show them to have a rapid onset of action (11). Cladribine, fingolimod and ozanimod are also more effective than the first-line drugs interferon beta, glatiramer acetate and teriflunomide (11).

In the absence of phase III trials, longitudinal studies and phase II trials form the evidence base for the use of rituximab for multiple sclerosis (12). Like ocrelizumab and ofatumumab, rituximab is a monoclonal antibody that kills B-lymphocytes. Rituximab is more immunogenic, but except in rare cases of serum sickness, the significance of this is uncertain (13).

The long-term effect on the development of disability is more important than the relapse frequency, but more difficult to establish because the pivotal studies only last for two years. However, registry-based and follow-up studies show that the effect on relapses corresponds to the effect on the development of disability (2, 3). Studies of brain atrophy and biomarkers for neuronal injury support this (14). An overall assessment indicates that natalizumab, alemtuzumab, ocrelizumab, ofatumumab, rituximab, cladribine, fingolimod and ozanimod are highly effective for RRMS.

Risk stratification

High-efficacy drugs are generally tolerated better than less effective drugs, but may entail greater risk. Alemtuzumab stands out in that almost half of patients develop Grave's disease or another autoimmune disorder. Moreover, opportunistic infections and acute angiopathy have caused deaths a short time after treatment (15). The Norwegian Hospital Procurement Trust's specialist team therefore does not class alemtuzumab with other MS treatment. Natalizumab can cause progressive multifocal leukoencephalopathy (PML) in carriers of JC virus. Other high-efficacy MS drugs, not least rituximab and ocrelizumab, reduce response to vaccines and increase the risk of infections (16).

The possibility of risk stratification has now substantially reduced the risk associated with high-efficacy treatment

The risk of progressive multifocal leukoencephalopathy in connection with natalizumab can be almost eliminated by not treating carriers of JC virus, and is substantially reduced for others by increasing the intervals between infusions (17). The risk associated with the other drugs can be reduced by taking comorbidity into account when selecting drugs (Table 1).

None of the MS drugs appear to appreciably increase the risk of COVID-19 infection. In registry-based studies, rituximab and ocrelizumab are associated with an increased need for intensive care and ventilation, but not with increased mortality (18).

Treatment strategies

When the association between natalizumab and progressive multifocal leukoencephalopathy was revealed in 2006, at-risk patients could not be identified. The

escalation strategy was then justified on the basis of the precautionary principle. The possibility of risk stratification has now substantially reduced the risk associated with high-efficacy treatment. Clinical experience also indicates that less effective treatment is often halted because of adverse effects or lack of efficacy. It takes several months for a new treatment to become fully effective. Patients age and undergo more inflammatory episodes, and are at increased risk of complications and reduced efficacy by the time high-efficacy treatment is finally initiated.

An alternative strategy is to recommend high-efficacy treatment if prognostic factors such as relapse rate, number of lesions detected by MRI and involvement of the brainstem and spinal cord indicate a severe course. Such factors largely reflect previous disease activity. Even if they predict the prognosis at group level, it is uncertain whether they predict treatment benefit at the individual level. The long-term prognosis at the time of diagnosis is normally so uncertain that prognostic factors do not justify starting less effective treatment.

Pivotal studies, longitudinal studies and effect on biomarkers all indicate that early treatment with high-efficacy agents results in the greatest benefit and least risk over time (2, 3, 19, 20). As a general rule we therefore recommend immediate initiation of high-efficacy drugs in cases of RRMS (Figure 1). Potential exceptions are patients who for reasons of age or comorbidity are particularly vulnerable to harmful treatment effects (Table 1), or where many years of observation since symptom onset point to a benign disease course.

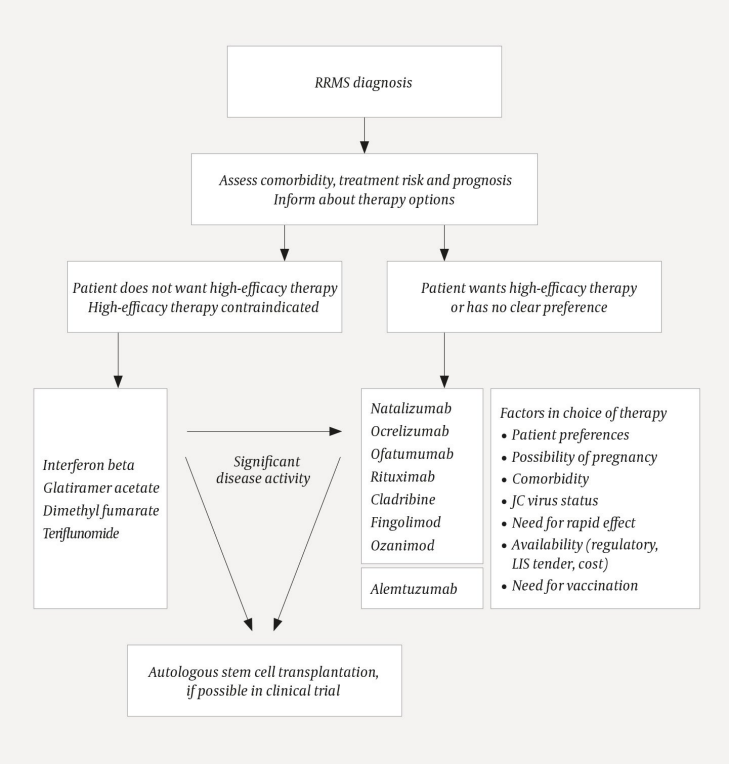

Figure 1 *Flow chart for choice of treatment of relapsing-remitting multiple sclerosis (RRMS). Decisions relating to therapy are taken in consultation with the patient according to individually tailored information. As a general rule, patients with recently diagnosed RRMS should be offered high-efficacy treatment with natalizumab, ocrelizumab, ofatumumab, rituximab, cladribine, fingolimod or ozanimod. Factors with a bearing on the choice of these drugs are shown in the box on the right. In the event of significant disease activity in the form of relapse or MRI activity, more effective therapy should be considered if possible. A change of medication will not necessarily improve disease control in patients who are already using a high-efficacy drug. On the contrary, switching from natalizumab, fingolimod or ozanimod to other therapy may trigger rebound disease activity. Changes in therapy must therefore be thoroughly considered and planned, and ongoing treatment must not be discontinued before the time of starting new treatment is known.*

Choice of high-efficacy drug

The differences in efficacy, risk and other treatment-related burden among most high-efficacy drugs are uncertain. The choice of drug therefore tends to depend on other factors (Table 1).

In cases of pronounced inflammatory activity, we recommend drugs with a fast onset effect, such as natalizumab, ocrelizumab and rituximab.

Multiple sclerosis often affects young women. Many pregnancies are not planned, and changes in treatment increase the risk of disease activity. Fertile women should therefore be offered treatment that makes pregnancy possible without a break in treatment.

The differences in efficacy, risk and other treatment-related stress among most high-efficacy drugs are uncertain. The choice of drug therefore tends to depend on other factors

The effects of cladribine, ocrelizumab and rituximab last long after they have been eliminated from the body, and they are therefore suitable for fertile women. Alemtuzumab has the same property, but the risk of Grave's disease means that close monitoring is required during pregnancy. Natalizumab can be used up to the last trimester. Breaks in treatment may cause severe disease breakthrough nonetheless. Fingolimod and ozanimod are probably teratogenic, and breaks in treatment may result in severe disease flare-ups. They are therefore less suitable for fertile women.

Comorbidity such as immunodeficiency, chronic infections, liver disease, cardiovascular disease, hypertension and uveitis influence the choice of therapy (Table 1). Natalizumab results in limited immunosuppression and may be suitable for patients with immunodeficiency or chronic infections. Some MS drugs are also effective against other diseases; for instance, natalizumab and ozanimod are effective against inflammatory bowel disease and dimethyl fumarate is effective against psoriasis.

Discontinuing treatment

In the past it has been usual to discontinue immunomodulatory treatment after transition to secondary progressive disease. However, with high-efficacy treatment it is difficult to know whether patients with slow progressive functional decline still have latent RR disease.

Discontinuation of natalizumab, fingolimod and ozanimod is associated with a substantial risk of serious relapses, and great caution should therefore be exercised when discontinuing these drugs. On the other hand, the risks associated with immunosuppression increase with age, and approved dosage is based on studies of patients under the age of 60. Observational studies indicate that the effects of natalizumab and rituximab remain the same when inter-dose intervals are increased (13, 21) but there is a general lack of reliable evidence as to when and how immunomodulatory treatment should be tapered, and patients must always be monitored clinically and radiologically.

As alemtuzumab and cladribine are not usually redosed, the question of discontinuation of treatment is avoided.

Haematopoietic stem cell transplantation

In open-label studies, high-dose chemotherapy with autologous haematopoietic stem cell transplantation reduces disease activity in RRMM very effectively (22). The risk of serious complications is low in younger patients who are otherwise healthy. In Norway, the treatment is offered at Haukeland University Hospital on strict indication, mainly as part of a randomised trial. The treatment may be relevant for more patients in the future.

Progressive multiple sclerosis

Phase III trials show that ocrelizumab and siponimod are moderately effective for primary

and secondary progressive disease, primarily in patients with relapses or new MRI lesions (23). These drugs have not been approved by the Decision Forum. As their efficacy is probably due to suppression of lymphocyte attacks, we recommend attempting therapy with other high-efficacy drugs for younger patients with rapid clinical exacerbation, relapses or MRI activity.

Financial and regulatory aspects

Expenditure on MS drugs was almost a billion kroner in 2019 (Anne Helen Ognøy, Norwegian Hospital Procurement Trust, personal communication). The prices are negotiated by the Norwegian Hospital Procurement Trust and are exempt from public disclosure. Following a health economics assessment as part of the Norwegian Institute of Public Health's method evaluation, the Decision Forum decided in 2019 to halt the start-up of fingolimod and natalizumab, although the costs did not differ from those of drugs the specialist community judges to be equivalent.

Individually tailored high-efficacy treatment should be the general rule

The Decision Forum also declined to introduce siponimod and ocrelizumab. They have subsequently rejected all applications from the specialist community for exceptions for subgroups of patients, but have introduced rituximab, which costs about a twentieth as much as ocrelizumab. In 2019 rituximab was the drug most widely used in Norway for multiple sclerosis (8). Large regional differences may reflect different attitudes to providing treatment outside of the approved indications and without the support of phase III trials. Comparative studies are now being conducted with ocrelizumab and cladribine. The approved indication for other high-efficacy MS drugs is generally narrower than that applied in clinical practice (Table 1). Thus treatment outside of an approved indication is widespread and increasing.

Conclusion

Swift and effective treatment of relapsing-remitting multiple sclerosis substantially improves the prognosis. Individually adapted high-efficacy treatment should be the general rule. The national guidelines on MS must be revised continuously in pace with developments in the discipline.

REFERENCES:

1. Coles AJ, Cox A, Le Page E et al. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. J Neurol 2006; 253: 98–108. [PubMed][CrossRef]

2. He A, Merkel B, Brown JWL et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. Lancet Neurol 2020; 19: 307–16. [PubMed][CrossRef]

3. Brown JWL, Coles A, Horakova D et al. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. JAMA 2019; 321: 175–87. [PubMed][CrossRef]

4. Torkildsen Ø, Myhr KM, Bø L. Disease-modifying treatments for multiple sclerosis - a review of approved medications. Eur J Neurol 2016; 23 (suppl 1): 18–27. [PubMed][CrossRef]

5. Helsedirektoratet. Nasjonal faglig retningslinje for diagnostikk, attakk- og sykdomsmodifiserende behandling av multippel sklerose.
https://www.helsedirektoratet.no/retningslinjer/multippel-sklerose Accessed 24.3.2021.

6. Piehl F. Current and emerging disease-modulatory therapies and treatment targets for multiple sclerosis. J Intern Med 2020; joim.13215. [PubMed][CrossRef]

7. Holmøy T, Torkildsen Ø. Familieplanlegging, graviditet og amming ved multippel sklerose. Tidsskr Nor Legeforen 2016; 136: 1726–9. [PubMed][CrossRef]

8. Dobson R, Hellwig K. Use of disease-modifying drugs during pregnancy and breastfeeding. Curr

Opin Neurol 2021; Publish Ahead of Print. doi: 10.1097/WCO.0000000000000922. [PubMed][CrossRef]

9. Ciotti JR, Valtcheva MV, Cross AH. Effects of MS disease-modifying therapies on responses to vaccinations: A review. Mult Scler Relat Disord 2020; 45: 102439. [PubMed][CrossRef]

10. Sykdomsbegrensende legemidler for behandling av attakkpreget multippel sklerose, inkludert rituximab. En metodevurdering. Oslo: Folkehelseinstituttet, 2019. https://www.fhi.no/publ/2019/sykdomsbegrensende-legemidler-for-behandling-av-attakkpreget-multip-pel-skl/ Accessed 8.2.2021.

11. Comi G, Dalla Costa G, Moiola L. Newly approved agents for relapsing remitting multiple sclerosis: how real-world evidence compares with randomized clinical trials? Expert Rev Neurother 2021; 21: 21–34. [PubMed][CrossRef]

12. Myhr KM, Torkildsen Ø, Lossius A et al. B cell depletion in the treatment of multiple sclerosis. Expert Opin Biol Ther 2019; 19: 261–71. [PubMed][CrossRef]

13. Dunn N, Juto A, Ryner M et al. Rituximab in multiple sclerosis: Frequency and clinical relevance of anti-drug antibodies. Mult Scler 2018; 24: 1224–33. [PubMed][CrossRef]

14. Berger T, Adamczyk-Sowa M, Csépány T et al. Factors influencing daily treatment choices in multiple sclerosis: practice guidelines, biomarkers and burden of disease. Ther Adv Neurol Disorder 2020; 13: 1756286420975223. [PubMed][CrossRef]

15. Holmøy T, Fevang B, Olsen DB et al. Adverse events with fatal outcome associated with alemtuzumab treatment in multiple sclerosis. BMC Res Notes 2019; 12: 497. [PubMed][CrossRef]

16. Luna G, Alping P, Burman J et al. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. JAMA Neurol 2020; 77: 184–91. [PubMed][CrossRef]

17. Ryerson LZ, Foley J, Chang I et al. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. Neurology 2019; 93: e1452–62. [PubMed][CrossRef]

18. Peeters LM, Parciak T, Walton C et al. COVID-19 in people with multiple sclerosis: A global data sharing initiative. Mult Scler 2020; 26: 1157–62. [PubMed][CrossRef]

19. Harding K, Williams O, Willis M et al. Clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with multiple sclerosis. JAMA Neurol 2019; 76: 536–41. [PubMed][CrossRef]

20. Hauser SL, Cree BAC. Treatment of multiple sclerosis: A review. Am J Med 2020; 133: 1380–1390.e2. [PubMed][CrossRef]

21. Boremalm M, Sundström P, Salzer J. Discontinuation and dose reduction of rituximab in relapsing-remitting multiple sclerosis. J Neurol 2021 doi: 10.1007/s00415-021-10399-8. [PubMed][CrossRef]

22. Kvistad SAS, Lehmann AK, Trovik LH et al. Safety and efficacy of autologous hematopoietic stem cell transplantation for multiple sclerosis in Norway. Mult Scler 2020; 26: 1889–97. [PubMed][CrossRef]

23. Årsrapport. 2019. Bergen: Norsk multippel sklerose register og biobank, 2020. https://www.kvalitetsregistre.no/sites/default/files/21_arsrapport_2019_norsk_ms_register.pdf Accessed 8.2.2021.

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