NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINES

Disease Modifying Treatments (DMTS) In Relapsing Remitting Multiple Sclerosis (RRMS)

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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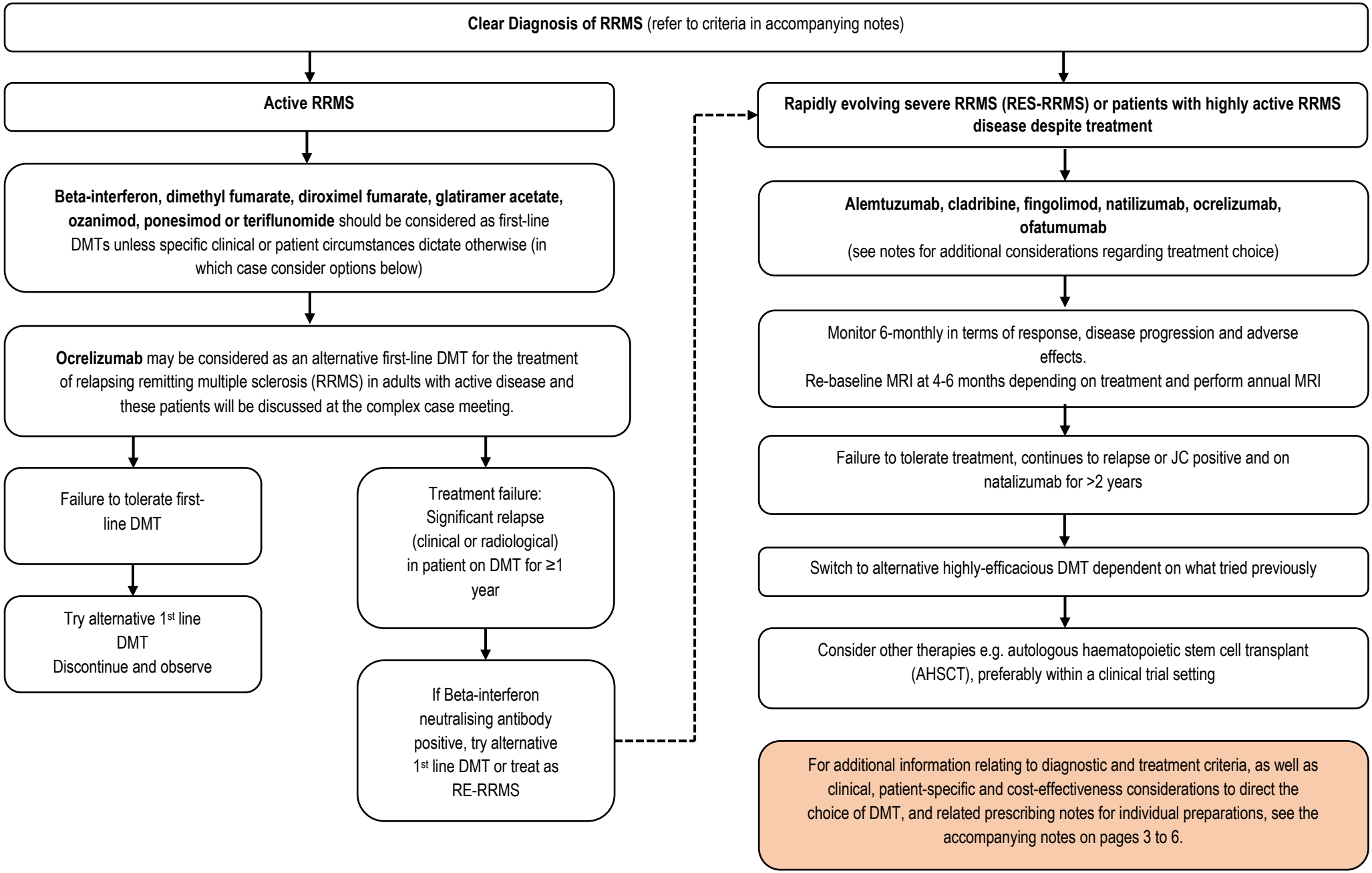
Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

West of Scotland Multiple Sclerosis Service

Clinical Management Algorithm for Disease Modifying Treatments (DMTs) in Relapsing-Remitting Multiple Sclerosis (RRMS)



Disease Modifying Treatments (DMTs) in Relapsing Remitting Multiple Sclerosis (RRMS)

These notes accompany the West of Scotland Multiple Sclerosis Service Clinical Management Algorithm for Disease Modifying Treatments (DMTs) in Relapsing Remitting Multiple Sclerosis (RRMS)

DIAGNOSIS CRITERIA FOR RRMS

Diagnosis of RRMS is based on the McDonald criteria from 2001 1 and the most recent revisions made in 2017 [1]

DEFINITIONS OF RRMS

Active relapsing-remitting multiple sclerosis (RRMS) is defined as ≥2 clinically significant relapses in the last 2 years and ambulant with maximum EDSS of 6.5 (ability to walk at least 10m with or without assistance). [2]

Rapidly evolving severe RRMS (RES-RRMS) is defined as ≥2 relapses in the prior year, whether on treatment or not, and at least one T1 gadolinium-enhancing lesion on MRI or a significant increase in T2-lesion load compared with a previous MRI.

Patients with highly active RRMS despite treatment with a disease modifying treatment. These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of disease modifying treatments. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion. A “non-responder” could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

GENERAL CONSIDERATIONS RELATING TO CHOICE OF DMT FOR RRMS

- There are a number of DMT treatment options available with variations in how they can be used in the treatment of RRMS and in terms of administration, monitoring and adverse effects.
- The following should be considered when choosing a DMT:
    - Clinical Factors (see below)
    - Patient-specific factors (see below)
    - Cost and cost-effectiveness, especially where there is no clear clinical imperative to select a particular agent. **If more than one preparation is clinically appropriate then the one with the lowest acquisition cost should be selected.**
- Patient and clinician engagement in the choice of therapy is important to ensure adherence to the treatment and monitoring schedules.

CLINICAL FACTORS TO CONSIDER RELATING TO CHOICE OF DMT FOR RRMS

Disease duration

Patients with a long history of MS may be expected to have less relapses in the future, and may already have a lot of disability and/or a lot of brain atrophy on MRI which might make you less aggressive in your treatment.

Disease activity pattern

RRMS activity varies between individuals but also within individuals. For example a patient with 2 relapses in 2 years followed by nothing for 10 years before relapsing again may not be started on disease modifying treatment. A patient with 1 relapse followed by nothing for 10 years and then two relapses in two years may be considered for DMTs.

Disability accrued from incomplete recovery from relapses
A patient who has two relapses with poor recovery and accumulating disability may be treated differently to a patient who has two relapses with good recovery and no disability.

JC virus status
Patients who are at high risk of developing progressive multifocal leukoencephalopathy (PML) as defined by:

- JC virus exposure indicated by anti-JCV antibody positive status
- High JC virus antibody titre (>0.9)
- Receiving an immunosuppressant prior to receiving natalizumab
- Natalizumab treatment duration of >2 years.

Alemtuzumab, cladribine, ocrelizumab or ofatumumab may be considered – by some patients and clinicians – a safer option than natalizumab when JC virus serology is high-titre positive.

MRI lesion load
Patients with large lesion loads may be offered more efficacious treatments.

MRI lesion distribution
Patient with brainstem or spinal lesions have a poorer prognosis and may be offered more efficacious treatments.

MRI activity
Patients with a lot of new disease activity may be offered more efficacious treatment.

Side effects of treatment
Some patients may prefer reduced risk even at the expense of having a less efficacious treatment. A patient's risk of PML may affect the decision about which treatment to use. Some patients like the older drugs because we have more long term experience with them and knowledge about their potential side effects.

Type of relapses (Sensory or motor)
Patients with sensory relapse only may be treated less aggressively than patients with motor relapses.

PATIENT-SPECIFIC FACTORS TO CONSIDER RELATING TO CHOICE OF DMT FOR RRMS

Age

- Older age group tend to have less relapses and more progressive disease
- Older patients may have completed their family or be post menopausalpost-menopausal
- Older patients tend to have more co-morbidity
- Younger patients have longer to live with their disease and with their disease modifying treatments

Sex

- Females may want to start a family now or in the future and might prefer DMTs like beta-interferon, glatiramer acetate, alemtuzumab or cladribine.

Lifestyle and Demographics

- Patients who are still working or have busy lifestyles may find it difficult to attend hospital for monthly infusions e.g. natalizumab. Alemtuzumab or cladribine which are only given for 2 weeks over two years may be more appealing, or ocrelizumab which is administered in hospital every 6 months.

Monitoring

- Monitoring of cladribine is minimal; with blood monitoring required at months 0, 3 and 7 each year (total 6 blood tests over 2 years) whereas alemtuzumab requires monthly blood tests for 4 years after the last infusion. There are no requirements to monitor bloods with ocrelizumab, other than prior to each 6 monthly infusion.

GUIDANCE NOTES RELATING TO SPECIFIC DMTS

For details of specific SMC and Formulary restrictions on use of DMTs see individual Formulary entries via www.ggcmedicines.org.uk

Alemtuzumab

- The European Medicines Agency safety has recommended restricting alemtuzumab for use in adults with relapsing remitting multiple sclerosis that is highly active despite adequate treatment with at least one disease-modifying therapy or if the disease is worsening rapidly with at least two disabling relapses in a year and brain-imaging showing new damage.
- Alemtuzumab must no longer be used in patients with certain heart, circulation or bleeding disorders or in patients who have auto-immune disorders other than multiple sclerosis.
- Treatment consists of a 5 day course of infusions in year 1, and a 3 day course of infusions in year 2. Some patients require a 3rd (and rarely 4th) course.
- Alemtuzumab (when used for MS) has not yet been associated with PML.
- Once alemtuzumab is given, the effects on the immune system are persistent and cannot be reversed.
- The most important adverse reactions for alemtuzumab are autoimmunity (36.8% risk of immune thyroid disorders, 2.8% risk of immune thrombocytopenic purpura, 0.4% risk of nephropathies and miscellaneous autoimmune conditions (0.2%).
- Because of the high risk of autoimmune disease this treatment needs monthly blood testing for 4 years after the last infusion, regardless of how well the patient feels.
- Unlike most other DMTs (that need to be discontinued before a patient tries to have children), alemtuzumab it is considered safe to conceive 4 months after the last infusion. The effects on the immune system are much longer lasting.

Cladribine

- Cladribine is a treatment option for RES-RRMS and those patients with RRMS who have had one or more relapses in the previous year whilst on a DMT and have at least one T1 gadolinium-enhancing lesion or nine T2 lesions.
- Treatment consists of a course of tablets over two years. Each treatment course consists of two treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year.
- The most important side effect with cladribine is lymphopenia. As a result, baseline lymphocyte counts should be determined prior to each treatment year and 2 and 6 months after the start of treatment in each treatment year.
- This is a very effective drug with a good side effect profile and limited monitoring requirements.
- Immune system effect is persistent and irreversible.
- Not associated with PML during use for MS to date (though cases have occurred in its use in hairy cell leukaemia).
- Pregnancy – safe to conceive 6 months after the last treatment course, although the effects on the immune system are much longer lasting.

Diroximel Fumarate

- Bioequivalent to dimethyl fumarate, but with improved gastrointestinal tolerability.
- Suitable for use in patients unable to tolerate dimethyl fumarate or with co-morbid gastrointestinal conditions.

Fingolimod

- Oral treatment, although less effective than other second-line agents.
- Good side effect profile, with very low risk of PML and can be stopped if not tolerated, although severe rebound of disease activity after discontinuation of fingolimod has been reported.
- Contra-indicated in patients with pre-existing cardiac disorders.
- It may cause maculopathy (approx 1%), particularly if there is a history of diabetes or previous uveitis, and because of this patients are screened after 3 months and treatment is discontinued if there is any evidence of maculopathy. It has an immunosuppressive effect and can increase the risk of skin cancers and lymphoma and serious opportunistic infections.

Natalizumab

- Natalizumab is accepted for restricted use as a single disease modifying therapy in patients with rapidly evolving severe RRMS.
- Natalizumab can be considered in patients who are JCV positive but have a low titre (<0.9) or in patients with a high titre, where there is an imperative to establish disease control quickly with a highly effective DMT. These patients will usually switch to an alternative second line DMT after two years.
- Given as monthly intravenous infusion.
- Evidence suggests that treatment interval can be extended to 6 weeks with sustained efficacy.
- Annual MRI brain scan if JC virus negative, or 3-6 monthly if JC virus positive

Ocrelizumab

- Initial dose given as two intravenous infusions separated by two weeks, followed by infusions every 6 months
- Apart from screening and baseline investigations, there is no requirement for routine blood monitoring with ocrelizumab.
- Ocrelizumab is considered a favourable option for patients with rapidly evolving severe RRMS (RES-RRMS) or patients with highly active RRMS despite treatment with a disease modifying treatment.
- Ocrelizumab will be considered as a first-line treatment in some adult patients with relapsing remitting MS who have had a significant clinical relapse and radiological evidence of disease progression. These patients will be discussed at the MS team complex case meeting.

Ofatumumab

- Initiated with 20 mg dose subcutaneously at week 0, 2 and 4. Subsequently maintained at 20 mg S/C at 4 weekly intervals.
- First dose monitoring required, provided by Kesimpta Connect service.
- High efficacy treatment for RRMS, considered for treatment naïve patients with highly active/disabling/rapidly evolving MS. Also considered for treatment failures with other drugs.
- Apart from initial screening no ongoing monitoring of bloods mandatory.
- Female patients required to practice contraception, if relevant as not known to be safe during pregnancy.
- Considered as low risk for PML

Ozanimod

- Oral therapy (S1P class targeting receptor 1 and 5) to be offered as first line moderately effective treatment to treatment naïve patients and patients who cannot tolerate other moderately effective first line agents.
- Generally well tolerated, low risk profile, not known to be associated with PML.
- Contraindicated in immunodeficient states, severe active infections, cardiac conditions (review further information), and pregnancy.
- First dose monitoring for 6 hours and further may be required for some patients.
- Rebound may occur similar to S1P class drugs.
- BP monitoring, Skin monitoring for BCC, macular screening in patients with uveitis, pre-existing macular disease.

Ponesimod

- Ponesimod offers an additional treatment choice in the therapeutic class of sphingosine-1-phosphate receptor modulators (see ozanimod above for more information).

COST AND COST EFFECTIVENESS

All of the DMT options accepted for use by the SMC within restrictions (where applicable) are considered to be cost- effective treatments. However, the relative cost-effectiveness is unknown. There is insufficient information or direct comparative clinical evidence currently available to determine the most cost-effective sequencing. Clinicians are therefore asked to be mindful of prescribing costs when selecting a DMT where there is no clear clinical imperative to select a particular agent.

REFERENCES

1. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Annals of Neurology 2001;50(1):121-7.
2. Thompson AJ, Banwell BL, Barkhof F et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurology 2018:17(2); 162-173