Multiple sclerosis: current treatment algorithms
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Introduction
In 1993, the US Food and Drug Administration (FDA) approved the first interferon-beta (IFNβ) for the treatment of multiple sclerosis (MS). Since then, new drugs have joined therapeutic guidelines in the setting of the current armamentarium for MS. Evidence-based medicine derived from clinical studies must be supplemented by expert criteria in order to decide the best therapeutic option available for an individual patient.

Individualized treatment in daily practice must conform to the clinical form of the disease. Clinical studies select patients based on a phenotype or profile of the disease. The evidences obtained in clinical studies being considered decisive and conclusive, and assessment of them by the regulatory authority, together with professional experience, are prerequisites for achieving clinical excellence. Combining personal experience and scientific evidence are the goals of these recommendations. Recommendations should be based on level A evidence (class I clinical trials).

The purpose of this document is to provide actual recommendations and algorithms on the strategy in the treatment of MS.

Evidence and indications of approved treatments in different clinical forms of multiple sclerosis
The first episode of neurological dysfunction is called clinically isolated syndrome (CIS). Its identification is important because most of these patients will develop MS in the ensuing years. Approximately 85–90% of MS patients begin with the relapsing–remitting form (RRMS), a significant proportion of whom will evolve to the secondary progressive form (SPMS) after 10–15 years from the onset. The remaining 10–15% of patients have the primary progressive form (PPMS), with sustained disability progression from onset. A small number of patients have a progressive–relapsing multiple sclerosis (PRMS).

It has been shown that certain drugs are able to modify the course of MS, reducing the number of relapses and lesion load on MRI [1–5]. Evidence exists that axonal damage is present in the early stages of the disease and is closely associated with inflammation [6]. This axonal damage would be the pathological substrate of residual disability. Therefore, it has been argued that early initiation of treatment may avoid residual disability.
First-line treatment
First-line treatment includes the disease-modifying agents (DMAs) authorized for use after diagnosis.

Clinically isolated syndrome
Criteria for using DMAs in CIS are based on the identification of those patients at high risk of developing MS. Four studies have demonstrated the efficacy of IFNB and glatiramer acetate in the treatment of CIS (Table 1) [7–10]. The three published studies [7–9] collected 1160 patients with CIS and MRI suggestive of MS, who were treated for at least 2 years with IFNB (n = 639) or placebo (n = 521) and then showed a difference of around 45% in the rate of conversion to clinically definite MS. A meta-analysis [11] of the three studies resulted in a combined odds ratio (OR) of 0.53, with a confidence interval of 95% from 0.41 to 0.71, which shows striking evidence (P < 0.0001) that IFNB significantly delayed conversion to clinically definite MS in patients with CIS. Additionally, these studies demonstrated that treatment with IFNB decreased the number of lesions detected on MRI. After evaluation of these results, the European Medicines Agency (EMA) and the FDA authorized the use of intramuscular IFNB-1a and subcutaneous IFNB-1b for the treatment of CIS. Recently, the EMA has approved glatiramer acetate in this setting.

Relapsing–remitting multiple sclerosis
As the vast majority of patients with MS present with RRMS, clinical research is predominant in this form of the disease. In pivotal studies, patients included (Table 2) had active disease with at least two relapses in the previous 2 or 3 years. The effectiveness of these drugs is mainly substantiated by a reduction in the frequency of relapses, along with a decrease in lesion load and active lesions on MRI.

The drugs approved to treat relapsing forms of MS are: IFNB-1b 250 μg subcutaneous (s.c.) every other day, IFNB-1a 22 or 44 mg s.c. three times per week, IFNB-1a 30 μg intramuscular (i.m.) once a week, and glatiramer acetate 20 mg s.c. every day.

Recently, fingolimod, an oral agent, has shown significant effects in reducing relapse rate, decreasing time to progression of disability and MRI-related measures in two phase III studies [12,13], against placebo and against an active agent: IFNB-1a i.m. Fingolimod is a sphingosine analog that, when phosphorylated, becomes a prototypical modulator of sphingosine 1-phosphate (S1P) receptors. It has documented effects on lymphocyte egress, selectively retaining lymphocytes within the lymph nodes. Because of the ubiquity of S1P receptors in the body, fingolimod can have several though nonserious adverse side-effects. Fingolimod treatment can produce bradycardia with the first dose and a mild decrease in the forced expiratory volume. Cases of macular edema have been observed, although most of these were subclinical and detected by optical coherence tomography. The total number of infections did not differ between cases and controls, but there were two fatal viral infections during the study: one was due to a primary infection and dissemination of varicella (chicken pox) while being treated with high doses of corticosteroid for MS relapse; another corresponded to a case of herpes encephalitis. The FDA

### Table 1 CIS studies with evidence level A

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment groups</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>E TOMS (2001)</td>
<td>308 CIS and suggestive MRI</td>
<td>154 IFNB-1a 22 mg s.c./week 154 placebo</td>
<td>Conversion risk at 2 years Placebo 45% IFNB-1a 34%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>193 IFNB-1a 30 μg i.m./week 190 placebo</td>
<td>Conversion risk at 2 years Placebo 39% IFNB-1a 21%</td>
</tr>
<tr>
<td>CHAMPS (2001)</td>
<td>383 CIS and ≥ 2 lesions MRI</td>
<td>292 IFNB-1b 250 μg s.c./2 days 176 placebo</td>
<td>Conversion risk at 2 years Placebo 45% IFNB-1b 28%</td>
</tr>
<tr>
<td>BENEFIT (2006)</td>
<td>468 CIS and ≥ 2 lesions MRI</td>
<td>243 GA 20 mg s.c./day 238 placebo</td>
<td>Conversion risk at 2 years Placebo 43% GA 25%</td>
</tr>
</tbody>
</table>

CIS, clinically isolated syndrome; GA, glatiramer acetate; IFNB, interferon-beta.
has approved this drug to treat patients with relapsing forms as a first-line agent. Also in Europe fingolimod has been approved as a second-line drug.

Another oral agent, cladribine, has also shown positive effects on relapse rate, progression and MRI measures in a phase III trial, the CLARITY study [14]. Cladribine is a deaminase-resistant deoxyadenosine analog that preferentially affects both resting and dividing lymphocytes, resulting in prolonged and profound lymphopenia. Such an effect is conferred by a higher deoxycytidine kinase (dCK) to 5’-nucleotidase (5-NT) ratio in these cells: dCK phosphorylates cladribine, whereas it is inactivated by 5-NT, and also by its adenosine deaminase inhibition, resulting in accumulation of 2-CdA nucleotides in lymphocytes. Four cases of cancer have been reported in the CLARITY study: one in-situ cervical carcinoma, one metastatic pancreatic carcinoma, one ovarian cancer, and one skin melanoma. Given the small number of cancer cases, it is not possible to establish a cladribine-related risk. So, the safety profile was remarkably good during the trial. But it has the potential for serious side-effects and its long-term effects remain to be seen. At the moment of writing these recommendations, cladribine approval has been rejected by the FDA and EMA and the drug is only available in Australia and Russia.

Secondary progressive multiple sclerosis
At present, two IFNβ preparations (IFNβ-1b and IFNβ-1a s.c.) have been approved for treatment of SPMS with relapses based on the results of pivotal trials [15,16] supporting evidence of level A (Table 3).

In patients without clinical evidence of relapses, but with MRI showing evidence of inflammatory activity, the indication could be evaluated individually.

Primary progressive multiple sclerosis
To date, no clinical study has shown efficacy in patients with PPMS.

Recommendations
Table 4 shows the current recommendations for the different approved first-line drugs in the treatment of MS.

Second-line treatment of multiple sclerosis
In MS, a second-line drug is used when a failure or intolerance of prior first-line treatments is observed (Table 5).

Mitoxantrone
As a result of the demonstration of efficacy against placebo of mitoxantrone (Novantrone) [17], this drug became the first to be approved as a second-line treatment for RRMS, in patients unresponsive to treatment with first-line drugs.

Mitoxantrone is cardiotoxic and should be administered with a left ventricular ejection fraction at least 50% and its
use requires ultrasound or isotope control of the left ventricular function before and during treatment [18]. The other major risk of mitoxantrone is the development of acute leukemia, which means that blood analysis should be carried during treatment and for several years after completion. In addition, the total cumulative dose should not exceed 140 mg/m$^2$.

**Natalizumab**

Natalizumab (Tysabri) is the only monoclonal antibody approved for the treatment of MS. It works by blocking leukocyte integrin α4 and thus limits the migration of lymphocytes and monocytes through the blood–brain barrier into the central nervous system. Two large phase III studies have been conducted in RRMS, one with natalizumab in monotherapy [19] and the other in combination therapy with i.m. IFN-β-1a in nonresponders to IFN-β-1a i.m. [20].

Trials were stopped for safety reasons when isolated cases of progressive multifocal leukoencephalopathy (PML) began to arise. As a result of this circumstance, health authorities granted approval of natalizumab only as a treatment for patients not responding to first-line drugs or as a first choice in patients with aggressive RRMS [21]. Patients should be advised that the risk of PML (ranging from 1/1000 to 1/100) increases with duration of treatment, especially beyond 2 years, and that risk is greater if they have previously taken an immunosuppressant. Serological studies of JC virus should be used in the future to stratify patients at risk of having PML. Patients positive for JC virus, with more than 2 years of therapy and with previous treatment with immunosuppressant were those with higher risk of PML.

**Fingolimod**

As has been mentioned above, fingolimod has shown significant effects in reducing relapse rate, and decreasing time to progression of disability and MRI-related measures. It has recently been approved as the first oral treatment for relapsing forms of multiple sclerosis.

**Recommendations**

Mitoxantrone, natalizumab, and fingolimod are medications which have shown efficacy in reducing the progression of disability in patients with RRMS, the frequency of relapses and the number of brain lesions detected on MRI. As a result of different risk–benefit

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### Table 3 Studies of class I SPMS

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment groups</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eur Group (1998)</td>
<td>718 SPMS</td>
<td>360 IFNβ-1b 250 μg s.c./2 days</td>
<td>Probability of no progression: 1 year, 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>358 placebo</td>
<td>IFNβ-1b 250 μg: 0.71, 0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo: 0.53, 0.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relapses/year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>204 IFNβ-1a 44 μg s.c./3xw</td>
<td>Progression, hazard ratio (HR) in patients with relapses:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 IFNβ-1a 22 μg s.c./3xw</td>
<td>IFNβ-1a 44 vs. placebo: 0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>205 placebo</td>
<td>Relapses/year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFNβ-1a 44 and 22: 0.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo: 0.71</td>
</tr>
<tr>
<td>SPECTRIMS (2001)</td>
<td>618 SPMS</td>
<td>63 MTX 12 mg/m$^2$/3m</td>
<td>Mean difference 12 mg vs. placebo group</td>
</tr>
<tr>
<td></td>
<td>66 MTX 5 mg/m$^2$/3m</td>
<td>66 placebo</td>
<td>EDSS: 0.24 (CI 0.04–0.44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relapses: 0.39 (CI 0.18–0.59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time to first relapse: 13.7 months</td>
</tr>
</tbody>
</table>

CI, confidence interval; EDSS, Expanded Disability Status Scale; RRMS, relapsing–remitting multiple sclerosis; s.c., subcutaneous; SPMS, secondary progressive multiple sclerosis.

### Table 4 First-line drugs and approved indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ-1b (Betaferon, Extavia)</td>
<td>250 mg every other day</td>
<td>s.c.</td>
<td>CIS considered at high risk of developing MS RRMS SPMS with relapses</td>
</tr>
<tr>
<td>IFNβ-1a (Avonex)</td>
<td>30 mg once a week</td>
<td>i.m.</td>
<td>CIS considered at high risk of developing MS RRMS</td>
</tr>
<tr>
<td>IFNβ-1a (Rebif)</td>
<td>22 or 44 mg three a week</td>
<td>s.c.</td>
<td>RRMS according to McDonald criteria SPMS with relapses</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>20 mg daily</td>
<td>s.c.</td>
<td>CIS considered at high risk of developing MS RRMS</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>0.5 mg daily</td>
<td>Oral</td>
<td>Relapsing forms of MS</td>
</tr>
</tbody>
</table>

CIS, clinically isolated syndrome; i.m., intramuscular; MS, multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; s.c., subcutaneous; SPMS, secondary progressive multiple sclerosis.
Combination therapy concurrently is intended to cover more than one mechanism of action of MS to increase efficacy. However, there is no approved therapeutic combination or clinical studies that provide evidence of efficacy.

Recent reviews [22,23] of combination therapies in MS have identified a lot of different combinations, although the quality of the studies is debatable.

Criteria of therapeutic response
MRI and clinical measures have separately proven to be useful in the detection of disease activity in patients with RRMS treated with a DMA. Combination of both clinical and MRI measures could ease the way for assessment of response, although there is not sufficient data in the literature about the actual value of clinical and radiological measures to establish the quality of this response.

Guidelines based on expert opinion have been proposed on the grounds of different degrees of concern about clinical (i.e. relapses and increase of disability) and MRI activity in patients treated with a DMA [24,25–29].

A previous study demonstrated that considering the number of enhancing lesions on a baseline MRI and the number of relapses during the 2 previous years, investigators were able to estimate the short-term risk of relapses in patients with RRMS [30]. A recent study investigating the role of combined clinical and MRI measures applied early in the evaluation of response to a DMA has demonstrated that the combination of measures of disease activity (at least one relapse or the confirmed increase of one point on the Expanded Disability Status Scale) and the presence of new T2 lesions may have a prognostic value for identifying patients with a poor outcome during the ensuing years of therapy. The results of the study showed that the presence of at least two of the three clinical or MRI variables (relapses, increase of disability and new lesions on MRI) during the first year of therapy allows the identification of those patients with a significant risk (OR between 5.9 and 13.2) of clinical activity within the ensuing 2 years [31]. It is therefore recommended that a brain MRI scan is performed just before and after 1 year of treatment, which can then yield such data so as to predict further treatment response.

After all these observations about the clinical and MRI monitoring of the response to DMA, a tentative algorithm to disclose response is shown in Fig. 1. It is strongly recommended that an MRI scan is performed during the first 6–12 months of therapy to evaluate active lesions. In those patients with more than two active lesions and with clinical activity (relapses or increase of disability) during this period of time, a change in treatment needs to be considered. In the absence of clinical activity in spite of new MRI activity, close clinical monitoring is required, and in the case of the appearance of relapses or an increase of disability, a change of therapy needs also to be considered. In contrast, in those patients without MRI activity, a new clinical and MRI assessment should be performed in the following months.

Switching, escalation and induction treatment in multiple sclerosis
The current paradigm in the treatment of MS is to start with immunomodulatory agents as first-line therapy and then advance into the therapeutic pyramid if an inadequate response exists until the disease is effectively controlled. The first step of this strategy might be to first switch between therapeutic first-line drugs and then to second-line drugs such as monoclonal antibodies, fingolimod, or mitoxantrone. These second-line drugs can be more effective but also more toxic. The decision on therapeutic escalation should be done soon after treatment failure is detected in order to prevent irreversible neurological impairment. However, the use of more aggressive treatment in early stages can cause premature exhaustion of therapeutic options for chronic diseases such as MS. As described above, suboptimally controlled...
MS may be defined as unacceptably higher levels of MS disease activity despite current ongoing treatment, which may indicate a change in the management of therapy. It should be remembered that the definition of suboptimal response may change as the disease progresses and is influenced by other factors.

**First-line switching**

In the first group (IFNs), the reason of change for intolerance associated with the route of administration is clear. On the contrary, a common approach is to replace a low-dose IFN with another with a higher dose and/or frequency of administration in the presence of relapses or activity on MRI. There is level B evidence showing a benefit in increasing doses and/or frequency. Thus, the 44 mg dose of IFNB-1a was slightly more effective than the 22 mg dose [3]; in addition, s.c. IFNB-1b on alternate days showed greater clinical and MRI efficacies than single weekly i.m. administration of IFNB-1a [32], indicating a better response with increasing dose and/or frequency; however, doubling the dose of IFNB-1b to 500 mg did not improve the benefit of the standard dose of 250 mg [33].

In the second group (IFNs/glatiramer acetate), there is a theoretical basis for drug change, in the case of insufficient response or intolerance to treatment, based on a different mechanism of action. A recent study [34] with a level B of evidence did not show any difference in clinical response and tolerability between IFNB-1a and glatiramer acetate. There are several studies with a level C of evidence changing IFNB for glatiramer acetate in cases of intolerance or inefficacy, and vice versa. One of them [35] in patients with IFNB-1b showed that patients who switched to glatiramer acetate due to inefficacy had a significant reduction in the number of relapses. The methodological limitations reduce the level of evidence, but it seems that in patients with RRMS without high activity or accumulation of disability associated with relapses, the switch between these immunomodulatory agents is well tolerated and reasonable.

The recent emergence of newer oral drugs such as fingolimod increases the possibilities of switching between first-line drugs.

**Therapeutic escalation: induction**

The rationale for therapeutic escalation is the sequential use of drugs which, although more effective, are also more toxic. The objective is to improve the risk–benefit balance, so that those drugs potentially more toxic are reserved for patients with more aggressive disease [36**].

After exhausting the first-line treatment options, if still no response, the second-line treatment as monotherapy should be initiated. The second line should begin with natalizumab or fingolimod when possible, leaving mitoxantrone as the second and last option due to its toxicity which limits the period of treatment.

An alternative to escalation schemes is induction therapy based on the theoretical basis of achieving a rapid control of inflammation to prevent parenchymal damage and the phenomenon of epitope spreading among others. This would be done by the initial use of a potent immunosuppressive drug for a short period, followed by the use of an immunomodulator as maintenance. There is limited experience with mitoxantrone followed by interferon or glatiramer acetate [37], but at present there is not enough evidence to recommend this option.

Finally, the lack of enough information on the efficacy of combination therapy makes it unlikely to be assigned a specific role within the framework of escalation treatment.

**Rescue therapy**

Rescue therapy is the use of unauthorized drugs in MS, such as those used in the treatment of other autoimmune diseases, or the establishment of therapeutic combinations of approved drugs as monotherapy for MS. The choice of rescue therapy depends on the experience and discretion of the neurologist. Monotherapy with a
drug not approved for MS is preferable to the combination of two approved drugs, because the probability of synergy is remote and an increase in toxicity is likely.

**Proposed algorithm on escalation in multiple sclerosis**

Current algorithms for MS treatment include the following approaches (Fig. 2):

1. **First-line treatment** (Table 4):
   - (a) IFNβ,
   - (b) glatiramer acetate,
   - (c) fingolimod (only in the USA),
   - (d) natalizumab and fingolimod in aggressive cases.

2. **Persistence of relapses and MRI activity** (Table 5):
   - (a) if IFNβ: increasing the frequency or dose,
   - (b) if high-dose IFNβ consider change to glatiramer acetate,
   - (c) if glatiramer acetate consider change to IFNβ or fingolimod,
   - (d) if fingolimod as first line consider change to IFNβ or glatiramer acetate,
   - (e) if natalizumab as first line consider change to IFNβ or glatiramer acetate,
   - (f) natalizumab,
   - (g) fingolimod;

3. **Patients with intolerance to natalizumab and fingolimod or unsatisfactory therapeutic response to these drugs** (Table 5):
   - (a) mitoxantrone;

4. **Patients with previous registered therapies and immunosuppressive treatments without control of the activity**:
   - (a) consider treatment through compassionate use:
     - (i) rituximab,
     - (ii) alemtuzumab,
     - (iii) daclizumab and
     - (iv) cyclophosphamide.

In the previous points, once remission of the disease or exhaustion of the dose of immunosuppressant is achieved, the return to immunomodulatory therapy with a different agent previously employed can be considered.

**Conclusion**

In the last two decades, we have had effective medications that alter the natural course of MS. There is a general sense that most of the medications, if taken consistently by patients, can effectively control disease. Nevertheless, these drugs are only partially effective, and it is unreasonable to expect complete disease control with current therapy.

First-line drugs for relapsing forms include interferons, glatiramer acetate, and recently fingolimod. Second-line drugs are natalizumab and mitoxantrone and fingolimod in Europe. These are indicated when a suboptimal response with first-line drugs is detected.

Combination of both clinical and MRI measures could ease the way for assessment of response. Therefore, every patient needs to be carefully monitored for an adequate response to therapy. If the response is not satisfactory, then a change in therapy is warranted. A change in therapy can be within class, escalation to a higher grade class, or to combination therapy.

The current paradigm in the treatment of MS is to start treatment with a first-line therapy and then advance into the therapeutic pyramid if an inadequate response exists, until the disease is effectively controlled. An alternative to escalation schemes is induction therapy.

As a result of advances in diagnostic techniques and the imminent arrival of new drugs, it is expected that the...
recommendations of this review will need to be assessed periodically.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 303).


32. Recent data about the response to therapy in MS.


38. Recommended reading about the management of patients with MS in daily clinical practice.