World Journal of Clinical Cases

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DOI: 10.12998/wjcc.v3.i7.545

World J Clin Cases 2015 July 16; 3(7): 545-555
ISSN 2307-8960 (online)

REVIEW

Treatment strategies for multiple sclerosis: When to start, when to change, when to stop?

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Author contributions: Gajofatto A conceived and drafted the review; Benedetti MD revised the manuscript for important intellectual content.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

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Received: December 29, 2014
Peer-review started: December 30, 2014
First decision: February 7, 2015
Revised: May 1, 2015
Accepted: May 5, 2015
Article in press: May 6, 2015
Published online: July 16, 2015

Abstract

Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system determined by a presumed autoimmune process mainly directed against myelin components but also involving axons and neurons. Acute demyelination shows as clinical relapses that may fully or partially resolve, while chronic demyelination and neuroaxonal injury lead to persistent and irreversible neurological symptoms, often progressing over time. Currently approved disease-modifying therapies are immunomodulatory or immunosuppressive drugs that significantly although variably reduce the frequency of attacks of the relapsing forms of the disease. However, they have limited efficacy in preventing the transition to the progressive phase of MS and are of no benefit after it has started. It is therefore likely that the potential advantage of a given treatment is condensed in a relatively limited window of opportunity for each patient, depending on individual characteristics and disease stage, most frequently but not necessarily in the early phase of the disease. In addition, a sizable proportion of patients with MS may have a very mild clinical course not requiring a disease-modifying therapy. Finally, individual response to existing therapies for MS varies significantly across subjects and the risk of serious adverse events remains an issue, particularly for the newest agents. The present review is aimed at critically describing current treatment strategies for MS with a particular focus on the decision of starting, switching and stopping commercially available immunomodulatory and immunosuppressive therapies.

Key words: Multiple sclerosis; Disease-modifying therapy; Treatment start; Treatment switch; Treatment stop; Interferon beta; Glatiramer acetate; Azathioprine; Natalizumab; Fingolimod

Core tip: Disease-modifying therapies for multiple sclerosis (MS) modulate or suppress with different mechanisms the autoimmune process that underlies the

disease. Patients with relapsing MS may benefit from treatment but individual response to a given therapy and adverse events occurrence are largely unpredictable and many cases need to change several drugs to stabilize their disease. Nevertheless, a high proportion of patients evolve to a progressive phase, which is not responsive to any existing therapy. As opposed, some cases have a benign course without treatment. A critical review of strategies for starting, switching and stopping disease-modifying therapies for MS is here presented.

Gajofatto A, Benedetti MD. Treatment strategies for multiple sclerosis: When to start, when to change, when to stop? *World J Clin Cases* 2015; 3(7): 545-555 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i7/545.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i7.545

INTRODUCTION

Multiple sclerosis (MS) is a chronic neurological disease of unknown cause sustained by a widespread inflammatory process within the central nervous system (CNS) leading to multifocal demyelination and axonal loss mostly in the white matter but importantly also in the grey matter of both brain and spinal cord[1]. Clinical manifestations are heterogeneous depending on the anatomical location of inflammatory lesions, and are expression of acute demyelination which can fully or partially resolve, of chronic demyelination and neuroaxonal injury, that are generally irreversible, or both. Based on the predominance of episodic acute demyelinating events or of the chronic neurodegenerative process, the clinical course is defined either relapsing-remitting, which represents around 60% of prevalent cases, or progressive (primary if progression starts from onset or secondary if it begins after a preceding relapsing-remitting phase). About 10% of MS cases have a primary progressive (PP) course, while transition to the secondary progressive (SP) phase occurs in around half of RR MS patients, generally decades after clinical onset. An initial acute episode of neurological disturbance that is suggestive of MS but does not fulfill diagnostic criteria is defined clinically isolated syndrome (CIS), which is the typical presentation of relapsing forms of MS, although many patients may remain asymptomatic and free of disease-defining brain/spinal cord MRI activity for several years after a CIS has occurred[2,3].

MS predominantly affects young adults of female sex (female to male ratio 2.5:1 or greater), although the disease may begin in children and subjects over the age of 60. Caucasians are more frequently affected and the prevalence of the condition varies profoundly across different areas of the world, roughly following an increasing gradient from the equatorial zone - where it is below 5 cases per 100000 inhabitants - to the poles, reaching rates over 130 cases/100000 in several regions of Northern America, Europe and Australia[4-6]. Epidemiological studies indicate that genetic susceptibility, infections (particularly Epstein-Barr virus), reduced sun light exposure/blood levels of vitamin D, cigarette smoking, obesity, and increased dietary salt intake are risk factors for developing the disease but have not yet a completely established causative role[7]. Although the etiology of MS remains unknown, there is strong biological evidence of an autoimmune pathogenesis sustained by migration of peripheral T and B cells - reactive against one or more unidentified myelin or neuronal antigens - into the CNS, in which lymphocytes induce and maintain inflammation also through persistent microglia activation among other mechanisms that cause demyelination, axonal loss, and ultimately neuronal death[8].

Currently disease-modifying therapies (DMTs) for MS approved by the European Medicine Agency (EMA) and Food and Drug Administration (FDA) include interferon beta (IFNB) 1-a and 1-b, glatiramer acetate (GA), mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, and alemtuzumab. In addition, azathioprine and cyclophosphamide are used off-label or approved in some countries for MS treatment as a consolidated indication not initially registered (Table 1). Also methotrexate and rituximab are used as an off-label option in some cases. All mentioned agents act by modulating and/or suppressing the immune system at various levels and with different mechanisms of action, the description of which is beyond the scope of this review[9]. As a general rule, available DMTs have a favorable impact on relapsing-remitting MS, while they have no significant benefit in progressive MS in which neurological disability continues to worsen over time[10]. Even in relapsing-remitting MS, the efficacy, tolerability and safety profile vary greatly across treatments, ranging from combinations of modest effect and excellent safety to options that are highly effective but at increased risk of serious adverse events, which may be fatal in rare cases[11]. These include but are not limited to: cardiomyopathy and acute leukemia after long-term treatment with mitoxantrone; natalizumab-associated progressive multifocal leukoencephalopathy (PML); bradyarrhythmias, macular edema, and varicella-zoster virus infections occurring with fingolimod therapy; autoimmune thyroiditis, thrombocytopenia, and glomerulonephritis induced by alemtuzumab. Ideally, optimal treatment responders should be free from relapses, disability worsening and adverse events, outcomes that are difficult to assess experimentally in the long term given the relatively short duration of clinical trials for a lifelong condition such as MS. As a consequence, surrogate outcomes - mainly represented by brain MRI measures - have been increasingly used in trials for the last 20 years to demonstrate the biological activity of MS therapies[12,13]. However, the precise correlation between short-term effect on MRI measures and long-term clinical changes remains to be fully elucidated[14-16]. In addition, MS may have an extremely

Table 1 Main characteristics of available disease-modifying therapies for multiple sclerosis

Agent	Indication and line of therapy	Dosage, route and frequency	Clinical efficacy in placebo-controlled phase III trials	Tolerability issues	Safety issues
Interferon beta 1b	RR MS; SP MS with relapses; CIS First line	250 mcg *s.c.* every other day	34% reduction of ARR over two years (RR MS) 50% risk reduction of conversion to CD MS at two years (CIS) No statistically significant effect on disability progression	Flu-like syndrome; injection site reactions	Hepatotoxicity; myelotoxicity; autoimmune thyroiditis; microangiopathy; epileptic seizures (rare)
Interferon beta 1a	RR MS; CIS First line	30 mcg *i.m.* once a week	18% reduction of ARR over two years (RR MS) 44% risk reduction of conversion to CD MS at two years (CIS) No statistically significant effect on disability progression	Same as above	Same as above
Interferon beta 1a	RR MS; CIS First line	44 mcg *s.c.* three times a week	32% reduction of ARR over two years (RR MS) 45% risk reduction of conversion to CD MS at two years (CIS) 30% reduction of progression of disability at two years (RR MS)	Same as above	Same as above
Peginterferon beta 1a	RR MS First line	125 mcg *s.c.* every two weeks	36% reduction of ARR over one year	Same as above	Same as above
Glatiramer acetate	RR MS; CIS First line	20 mg *s.c.* every day	29% reduction of ARR over two years (RRMS) 45% risk reduction of conversion to CDMS at three years (CIS) No statistically significant effect on disability progression	Injection site reactions; post-injection reaction (chest pain, flushing and dyspnea)	Cutaneous necrosis; anaphylaxis (rare)
Mitoxantrone	RR MS; SP MS; PR MS Second or third line	12 mg/m^2 *i.v.* every three months or 8 mg/m^2 *i.v.* every month	65% reduction of relapse risk over two years (mostly in RR MS)[98] 66% reduction of risk of disability progression at two years (mostly in RR MS)[98]	Nausea/vomiting; amenorrhea/infertility; alopecia; blue discoloration of sclera and urine	Infusion site tissue necrosis; myelotoxicity; infections; cardiotoxicity; acute leukemia
Natalizumab	RR MS Second line	300 mg *i.v.* every four weeks	68% reduction of ARR over two years 42% reduction of progression of disability at two years	Headache	Infusion associated reactions; anaphylaxis; infections; hepatotoxicity; progressive multifocal leukoencephalopathy
Fingolimod	RR MS Second line (first line in the United States)	0.5 mg per *os* every day	48%-54% reduction of ARR over two years 30% reduction of progression of disability at two years	Fatigue; headache	Bradyarrhythmias after first dose; lymphopenia; viral infections (VZV); macular edema; hepatotoxicity; hypertension
Teriflunomide	RR MS First line	14 mg per *os* every day	31%-36% reduction of ARR over one year or more 26%-32% reduction of progression of disability at one year or more	Nausea; diarrhea; alopecia	Myelotoxicity; hepatotoxicity; infections; peripheral neuropathy; pancreatic fibrosis; teratogenicity (requires accelerated elimination procedure)
Dimethyl fumarate	RR MS First line	240 mg per *os* twice a day	44%-53% reduction of ARR over two years 38% reduction of progression of disability at two years	Flushing; gastrointestinal symptoms; pruritus	Lymphopenia; progressive multifocal leukoencephalopathy
Alemtuzumab	RR MS Second or third line	12 mg/d *i.v.* for five days followed by 12 mg/d *i.v.* for three days one year after the first course	49%-55% reduction of ARR over two years compared to *s.c.* interferon beta 1a 42% reduction of progression of disability at two years compared to *s.c.* interferon beta 1a	Infusion associated reactions; myalgia; arthralgia; irregular menstruation	Infusion associated reactions; cytokine release syndrome; lymphopenia; infections; autoimmune thyroiditis; thrombocytopenic purpura; glomerulonephritis
Azathioprine[1]	MS of all types First or second line	2.5 mg/kg per *os* every day	23% relative risk reduction of the frequency of relapses over two years No statistically significant effect on disability progression at two and three years[98]	Gastrointestinal symptoms; photosensitivity; irregular menstruation/reduced fertility	Myelotoxicity; hepatotoxicity; lymphopenia; infections; acute pancreatitis; increased toxicity in subjects with thiopurine methyltransferase deficiency; malignancies (cumulative dose > 600 g)
Cyclophosphamide[1]	SP MS; PP MS Third line	1 g *i.v.* over three days or 500 mg *i.v.* over five days	No statistically significant effect on disability progression at two and three years[98]	Nausea/vomiting; amenorrhea/infertility; alopecia	Myelotoxicity; hepatotoxicity; infections; hemorrhagic cystitis; bladder cancer

[1]The use of these drugs for the treatment of multiple sclerosis is off-label in most countries. ARR: Annualized relapse rate; CD: Clinically definite; CIS: Clinically isolated syndrome; PP: Primary progressive; PR: Progressive-relapsing; RR: Relapsing-remitting; SP: Secondary progressive.

Table 2 Critical factors affecting the decision of starting disease-modifying therapies for multiple sclerosis

Factors suggesting not to start a DMT	CIS with favourable prognostic factors
	RR MS with no relapses in previous two years, no disability, and no evidence of MRI activity (potential "benign" case)
	Progressive forms of MS with no relapses or evidence of MRI activity
	Pregnancy planning
	High risk of low adherence to treatment
Factors suggesting to start a first line DMT	CIS with unfavourable prognostic factors
	RR MS with at least one relapse in previous two years but less than two relapses in the last year, low residual disability, and/or active MRI
Factors suggesting to start a second line DMT	RR MS with at least 2 disabling relapses in the last year
	Progressive forms of MS with relapses and/or active MRI

DMT: Disease-modifying therapy; CIS: Clinically isolated syndrome; MS: Multiple sclerosis.

variable clinical course both within and between subjects, who may show extremely active and break-through disease despite treatment or, on the contrary, very mild forms or phases not necessarily requiring a potentially harmful and costly pharmacological therapy[17].

Here we will discuss current and potential strategies to start, change and stop disease-modifying MS therapies in the clinical practice.

WHEN TO START TREATMENT FOR MS?

Primum non nocere

To avoid overtreatment, it is important to start on a DMT MS patients who carry the highest probability of optimal therapy response, making decisions based on multiple factors, including evidence of efficacy and safety profile of drugs, disease course and activity, expected adherence and preferences of the individual case (Table 2)[18-20]. Placebo-controlled randomized trials of IFNB and GA in patients with CIS have shown that active treatment significantly delays conversion to definite MS and prevent accumulation of new brain lesions on MRI[21-25]. However, there is little or no significant benefit of early *vs* delayed therapy on worsening of neurological disability in the open-label extension phase of these trials up to 10 years after study initiation[26-28].

Randomized trials of DMTs for relapsing-remitting MS included patients who had experienced at least one or two relapses in the previous one or two years prior to randomization and showed that all therapies significantly reduce relapse rate over 2-3 years of treatment with largely different effect size depending on the specific drug considered (Table 1)[29-45]. Comparisons between old and new drugs or between pivotal and recent trials are limited by the changed profiles of MS subjects enrolled in clinical trials who are now generally in earlier phases of disease and with much lower clinical and MRI activity compared to patients included in studies between 1988 and 2000[46].

When taking the decision of treating a patient with MS for the first time, clinicians choose either an escalation or an induction approach[10]. The first consists of starting with a first-line medication - intended as a moderate-efficacy high-safety drug - and switching to a second-line treatment (more effective but also with more safety risks) in case of unsatisfactory response to the first line: this is reasonable in most patients seen in the clinical practice who present with mildly or moderately active disease. The induction approach is the initial use of a highly effective second-line treatment in order to obtain the rapid remission of a very active disease, which justifies the risk of serious adverse events. This strategy is intended for MS cases with frequent (*i.e.*, two or more per year) and severe relapses who are at increased risk of rapid accumulation of disability.

IFNBs, GA, teriflunomide, and dimethyl fumarate are considered first-line therapies, while natalizumab, alemtuzumab, are mitoxantrone are second-line or third-line drugs. Fingolimod is approved as a second-line treatment in the EU and as first-line in the United States, Canada and other countries[47]. Azathioprine and cyclophosphamide, which are not registered for MS treatment, are used by clinicians as first-line and second-line medications, respectively. Among first-line drugs, differences exist in terms of efficacy and tolerability, although direct comparison data are limited. Existing evidence indicates that high dose IFNB (particularly IFNB 1-a 44 mcg subcutaneously three times a week) is more effective than low dose IFNB, *i.e.,* IFNB 1-a 30 mcg intramuscular once a week[48,49]. However, high dose IFNB and GA have similar efficacy on clinical parameters, while they slightly differ in terms of impact on MRI measures, that is greater for IFNB than GA, and tolerability profile[50-53]. There is less experience worldwide with dimethyl fumarate given its recent introduction to the market. One of the pivotal studies included a group of GA-treated patients as reference arm: MS subjects receiving the experimental drug or GA had similar statistically significant reductions of relapse rate, while differences in disability progression at 2 years were not significant, compared to placebo[42]. Teriflunomide has shown a similar efficacy to high dose IFNB and, as dimethyl fumarate, has the advantage of being an oral medication[54]. Recently, an independent comparative study has shown that azathioprine is not inferior to IFNBs in relapsing-remitting MS in terms of relapse rate and disability progression reduction, confirming the utility of an old and safe drug as a low cost and oral administration treatment option for this

Table 3 Critical factors affecting the decision of changing current disease-modifying therapy for multiple sclerosis

Factors suggesting to switch from a first line DMT to another	Tolerability/safety issues Suboptimal efficacy with disease activity not suitable for escalation to a second line DMT Persistent high-titre neutralizing antibodies in patients treated with interferon beta
Factors suggesting to switch from a first line to a second line DMT	RR MS patients experiencing at least one relapse and with an active MRI during the previous year on treatment RR MS patients transitioning to the secondary progressive phase with evidence of relapses or MRI activity
Factors suggesting to switch from a second line DMT to another or to a third line DMT	RR MS patients continuing to experience relapses Progressive forms of MS with relapses and/or active MRI despite treatment Safety issues (*e.g.*, patients on natalizumab at high risk of developing progressive multifocal leukoencephalopathy)
Factors suggesting to switch from a second line to a first line DMT	Tolerability/safety issues Risk perception of patient

DMT: Disease-modifying therapy; RR: Relapsing-remitting; MS: Multiple sclerosis.

condition[55].

Natalizumab, fingolimod, and mitoxantrone are consolidated second-line DMTs, which can be used as initial treatment in patients with aggressive MS requiring an induction approach. In addition, EMA and FDA recently approved alemtuzumab with the indication for "active" MS. In patients not previously treated with other medications, all the mentioned drugs strongly reduce the frequency of attacks compared to standard first-line therapy (around 50% relapse rate decrease *vs* IFNB) and have a profound effect on MRI activity measures[44,56-58]. However, the benefit on disability progression appears less robust and consistent across studies.

There are no approved DMTs for the PP form of MS[59-61], which carries the worst prognosis. For this reason, some patients - particularly in presence of rapid neurological worsening, superimposed relapses and evidence of inflammatory activity on brain/spine MRI - are treated off-label with immunosuppressants such as cyclophosphamide or mitoxantrone, based on the possible efficacy on disability progression suggested by some randomized trials[36,62].

WHEN TO CHANGE TREATMENT FOR MS?

Evidence-based data and guidelines on criteria and timing for DMT change in MS are limited and choices of clinicians on this matter are often based on observational reports and guided by good clinical practice (Table 3). In fact, MS patients who start a DMT discontinue it in a proportion ranging from 30% to 80% for various possible reasons[63]. One of the biggest challenges is the definition of treatment response/failure. An easy-to-apply and fairly validated tool is the Rio score, which combines clinical and MRI parameters to predict disability progression over five years[64,65]. In any case, MS patients receiving a first-line DMT who continue to have a similar relapse rate compared to the pre-treatment phase, have persistent MRI activity, and/or show irreversible neurological disability worsening, have a sub-optimal response and a therapy switch needs to be considered[66]. Second-line options for these cases are natalizumab, fingolimod and alemtuzumab, considering potential differences across drugs in efficacy and safety profiles[37-39,56,57,67,68].

For patients on first-line DMT with evidence of partial response but not fulfilling requirements for escalation to a second-line treatment (*e.g.*, isolated persistent MRI activity) or with adverse reactions/tolerability issues that affect patient safety or quality of life, a so called "lateral" switch to another first-line DMT is justified, *e.g.*, shifting from low-dose to high-dose IFNB (or the reverse in case of side effects), from GA to IFNB or *vice versa*[69,70]. In the near future switching from IFNB or GA to one of the newest oral agents such as teriflunomide and dimethyl fumarate will likely become very common. An additional option is switching from IFNB or GA to azathioprine.

Some authors suggest that patients treated with IFNB should be monitored for the serological status of neutralizing antibodies (NABs) both in cases in which suboptimal efficacy is suspected and with stable disease: persistent high-titer NABs positivity reflects IFNB biological activity loss, is associated with a higher risk of disease activity, and indicates the need of switching to a non-IFNB therapy[71]. Although NABs assay is not routinely performed in all IFNB-treated patients in all Centers, positivity is currently reported in less than 10% of cases on IFNB 1-a and over 30% of subjects receiving IFNB 1-b[72].

Finally, one has to consider the possibility or necessity of changing a second-line or third-line treatment in a patient with MS. If a patient continues to experience relapses and - more importantly - shows disability progression, a DMT change is needed as well as in case safety concerns arise during treatment. MS patients on fingolimod with break through disease will typically switch to natalizumab if this is safe, or to "rescue-therapy" with cyclophosphamide, which is also a possible option for cases not responsive to natalizumab, although this rarely occurs and should raise the suspicion of NABs presence[73]. Anyway, this scenario will likely change in the next future as the use of alemtuzumab catches on as a third-line or earlier therapeutic strategy. A debated issue in the community of MS neurologists is changing therapy in patients treated with natalizumab and at risk of developing PML,

since treatment discontinuation is associated with a high risk of disease reactivation[74]. However, also switching to another DMT, including fingolimod, does not prevent relapse occurrence and MRI worsening in many cases, particularly if new therapy start is delayed[75-77]. Other strategies, such as continuing natalizumab with a strict surveillance of early PML signs[78], or shifting to a third-line option such as cyclophosphamide or alemtuzumab are being adopted in some Centers, although it is not excluded that PML risk could be carried over by prolonging immunosuppression after natalizumab[79].

WHEN TO STOP TREATMENT FOR MS?

Effective DMTs are essential to guarantee the highest possible well-being to people with MS. For the same reason there are circumstances in which ongoing DMT should or must be stopped to avoid that risks or costs overcome benefit. Given the nature of MS, DMT discontinuation is usually temporary but in some cases it can be permanent[19,80].

First, DMT must be stopped when a serious adverse event potentially correlated to treatment occurs or is suspected, in particular if it is life threatening since MS itself does not lead to a meaningful increase of mortality. Several MS therapies, especially among the newest, expose patients to the risk of infectious, hematologic, cardiac, and neoplastic complications that are potentially lethal and must be monitored carefully[81]. If a DMT is discontinued for this reason, a treatment change has to be considered with caution since other drugs with similar mechanism of action may interfere with recovery of the adverse event or even aggravate it. In some cases a precautionary interruption of treatment, which may be temporary or prolonged, is dictated by factors that are known to increase the risk of certain adverse events. This is the case of PML risk during natalizumab in patients with anti-JCV antibodies positivity, previous immunosuppressive exposure, and treatment duration of 2 years or more[68]. Other examples include: risk of opportunistic infections in patients treated with fingolimod or dimethyl fumarate and persistently low lymphocyte count in the peripheral blood[82,83]; risk of cardiotoxicity and leukemia for patients treated with mitoxantrone[84]; increased risk of cancer with immunosuppressive cytotoxic therapies prolonged for more than 3 years in the case of cyclophosphamide or more than 10 years for azathioprine[85,86]. Beside serious adverse events, DMTs may cause "minor" side effects and tolerability issues that disrupt patient quality of life[87]. Cases not obtaining a satisfactory management of such symptoms or not perceiving treatment benefit that justifies undesired effects generally have low adherence to the prescribed medication. This is known to be a risk factor for poor control of disease activity and progression: if lack of adherence to treatment cannot be improved DMT has to be discontinued[88].

Pregnancy is another event that requires immediate DMT interruption in women with MS who, however, must be carefully informed of the need of adequate contraception prior to and during treatment, of the possibility that some DMTs may reduce fertility, and of the importance of becoming pregnant when the disease is as stable as possible[89]. Treatment cannot be resumed during breast-feeding meaning that nursing mothers should be advised of stopping breast-feeding and (re)starting therapy only in presence of disease activity or in case of aggressive course prior to treatment interruption. Pregnancy planning requires DMT discontinuation with the appropriate timing according to the pharmacokinetic of the specific drug[90]. IFNB and GA may be continued until few weeks in advance or even up to conception; natalizumab, fingolimod and dimethyl fumarate should be stopped at least two months prior to planned conception; cytotoxic agents, such as mitoxantrone and azathioprine, need to be discontinued at least three months in advance. In addition to therapy interruption, patients on teriflunomide are required to undergo an accelerated elimination procedure with colestyramine or activated charcoal at least two months before conception (in case of unexpected pregnancy the procedure must be started immediately)[91]. For patients on alemtuzumab pregnancy program appears more complex as the effects of a single five-days course of the drug may last up to four years; however, based on pharmacokinetic data, maintaining contraception for at least four months after last alemtuzumab administration is currently recommended[92]. Data and guidelines regarding paternity planning for men with MS receiving DMT are lacking. Treatment interruption is generally not recommended for IFNB and GA, since the outcome of pregnancies fathered by patients receiving those drugs does not differ from general population[93]. However, male patients receiving therapies with mutagen potential that could lead to an increased risk of fetal malformations should be encouraged to avoid conception while on treatment.

Although it might be difficult to establish, MS patients who gradually accumulate irreversible disability without experiencing relapses and MRI inflammatory activity - *i.e.,* have transitioned to the SP phase of the disease - do not benefit significantly from any of currently available DMT, which should be therefore discontinued in this group of subjects[94]. On the other hand, for treated patients with prolonged stable disease and no apparent side effects DMT discontinuation is not recommended because the disease could reactivate. However, available data have been obtained from few patients treated for less than three years who had high pre-treatment MS activity and were not selected according to an a priori definition of stable disease[95]. In this context, patients treated with natalizumab represent an exception because it has been consistently reported that treatment interruption even in cases with no sign of MS activity for several years, frequently leads to disease reactivation - with a very severe clinical

picture in some cases - soon after stopping therapy[96].

CONCLUSION

General consensus and detailed guidelines on starting, changing and stopping DMTs for MS are lacking. Recently, an effort to guide the use of DMTs based on evidence from the literature with the aim of improving access to therapies for MS patients, led to a consensus paper by the MS coalition[97].

Based on current evidence and good clinical practice principles, we suggest the following.

When to start treatment for MS?

First-line DMT should be started in patients with a diagnosis of relapsing MS (according to 2010 McDonald's criteria) and at least one documented attack in the previous two years; as for the choice of the specific drug, high dose IFNB 1-a and GA are the preferred options among established injectable therapies, although oral therapies such as azathioprine, teriflunomide and dimethyl fumarate have at least comparable efficacy.

First-line DMT may be initiated in patients with a CIS or MS with a single attack and dissemination in space and time according to 2010 McDonald's criteria in presence of factors known to be associated with poor prognosis, such as male sex, incomplete recovery from attack, prominent neurological efferent systems involvement, and more than nine lesions on brain MRI (good clinical practice point - there is no evidence that subgroups of patients with such features are significantly protected by DMTs against long-term disability progression).

DMT-naïve MS patients experiencing at least two disabling relapses in the last year and with an active MRI scan should be treated with a second-line regimen, such as fingolimod or natalizumab; also alemtuzumab may be considered for patients with aggressive disease from onset.

Available DMTs are of no utility in PP MS, although cases with rapid progression, superimposed relapses and active MRI might benefit from immunosuppressants such as mitoxantrone, cyclophosphamide, or methotrexate.

When to change treatment for MS?

Given the current availability of multiple options, a DMT change needs to be considered in any MS patient with suboptimal response: in case of one or more relapses during the previous year on a first-line DMT, particularly in case of incomplete recovery, switching to a second-line medication is appropriate, while isolated MRI activity and/or increased relapse frequency not qualifying for second-line escalation are conditions for switching to another first-line DMT; patients relapsing while on fingolimod may be switched to natalizumab, or the reverse (although natalizumab is expected to reduce relapse rate more than fingolimod based on indirect comparison); alternatively, these cases may be shifted to a third line of treatment such as alemtuzumab or intravenous cytotoxic immunosuppressants.

Patients on IFNB who develop persistent high-titer NABs need to change treatment even if disease is stable.

Subjects with intolerable side effects from their current medication need to be switched to another DMT within the same line of treatment.

Patients receiving natalizumab for more than two years who are anti-JCV antibody positive and previously received cytotoxic immunosuppressants should be switched to another DMT due to the significantly increased risk of PML; possible options include fingolimod, alemtuzumab, cyclophosphamide, and less convincingly first-line DMTs; to minimize the risk of disease reactivation the wash-out interval should be shortened as much as possible.

When to stop treatment for MS?

DMT must be stopped in case a serious adverse event potentially related to the drug occur or is likely to occur, in patients becoming pregnant, and in subjects who are not adherent to treatment.

DMT should be also discontinued in patients with confirmed disability progression over one year in the absence of relapses and new/enhancing lesions on MRI; these subjects have progressive MS, which does not respond to any DMTs, and priority should be given to symptomatic treatment, physical therapy, and management of disability.

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P- Reviewer: Cepeda C, Rudroff T, Takahashi H **S- Editor**: Ji FF
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