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EVIDENCE 2 PRACTICE

Disease-modifying therapies in relapsing–remitting multiple sclerosis

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Clinical question: What is the best current disease-modifying therapy for relapsing–remitting multiple sclerosis?

Results: The evidence shows that the most effective disease-modifying therapy for delaying short- to medium-term disability progression, prevention of relapses, reducing the area and activity of lesions on magnetic resonance imaging, with the least side effects, is high-dose, high-frequency subcutaneous interferon-β1a 44 μg three times per week.

Implementation: The pitfalls in treatment of MS can be avoided by remembering the following points:

- The most effective therapy to prevent or delay the appearance of permanent neurological disability with the fewest side effects should be chosen, and treatment should not be delayed.
- Adherence to treatment should be monitored closely, and needs comprehensive patient information and education to establish long-term adherence, which is a critical determinant of long-term outcome.
- The correct approach to the disease includes disease management, symptom management, and patient management. A combination of tools is necessary to ease the various symptoms, which fall into three broad categories, i.e. rehabilitation, pharmacological, and procedural.
- It is important to understand that no treatment modality should be used alone, unless it is in itself sufficient to remedy the particular symptom/problem.

Keywords: relapsing–remitting multiple sclerosis, interferon, disease-modifying therapy, relapse prevention

Multiple sclerosis

Definition: Multiple sclerosis (MS) is a debilitating autoimmune disease, although some new studies have raised the possibility that there is more than one pathway to the final pathological changes, and that different pathways may predominate in different clinical forms of MS.[1] It has two major components, ie, axonal degeneration and inflammation, resulting in loss of the myelin-coated axons in the central nervous system (CNS).[2] MS is most commonly seen in the adult Caucasian population of Western European ethnic origin,[3] and most frequently affects women aged 20–40 years.[4] A definite diagnosis of MS requires the occurrence of at least two neurological events consistent with demyelination that are separated both anatomically in the CNS and temporally.[5]

There are three clinical forms of the disease, the most common being the relapsing–remitting form (RRMS), which is characterized by episodes of neurological

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impairment followed by complete or nearly complete recovery.[6] It has been shown that the systemic administration of interferon-beta-1a (IFNβ1a) decreases the frequency of exacerbations, slows the progression of physical disability, and reduces the development of brain lesions.[7] IFNβ1a is a 166-amino acid glycoprotein with a molecular weight of approximately 22,500 Da. It is produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human IFNβ gene has been introduced.[4,8]

Prevalence: Globally, the median estimated prevalence of MS is 30 per 100,000, with a range of 5–80. Regionally, the median estimated prevalence of MS is highest in Europe at 80 per 100,000, followed by the Eastern Mediterranean (14.9 per 100,000), and the US (8.3 per 100,000). The countries reporting the highest estimated prevalence of MS are Hungary (176 per 100,000), Slovenia (150), Germany (149), and the US (135).[9] The total estimated female:male ratio is around 2.0, and the prevalence rates reported are higher for women.[10] Other studies in the US have reported a prevalence of 58–95 per 100,00.[11] Moreover, in the past 25 years, prevalence studies of specific US regions have produced a range of estimates, up to 177 per 100,000 in Olmstead County, Minnesota.[12]

Incidence: Globally, the median incidence of MS is 2.5 per 100,000. Regionally, the median estimated incidence of MS is greatest in Europe (3.8 per 100,000), followed by the Eastern Mediterranean (2), and the US (1.5). The countries reporting the highest estimated incidence of MS include Croatia (29), Iceland (10), and Hungary (9.8).[9]

Economics: From the perspective of the US health care payer, and considering only the direct medical costs, the cost per relapse is close to 4700 USD, and the cost per disability progression step is nearly 1800 USD. Subcutaneous (SC) IFNβ1a injection, and glatiramer acetate had the most favorable costs per relapse avoided, and intramuscular (IM) IFNβ1a injection had the least favorable cost-effectiveness ratio (~ 142,000 USD per relapse avoided), in a two-year follow-up period, according to Goldberg et al.[13] In other study,[14] SC IFNβ1a was predicted to enable more patients to avoid relapse. Total mean costs per patient (discounted) were ~ 80,000 USD with SC IFNβ1a versus ~ 74,000 USD with IM IFNβ1a administration, representing a net increase of 5400 USD per patient.

Levels of evidence: Systematic reviews, randomized clinical trials (RCTs), and general reviews.

Search sources: Medline (PubMed), Cochrane Library, The Cochrane Multiple Sclerosis Review Group NHS evidence (UK), DARE, EMBASE.

Outcomes: The major outcomes seen in most reports were delayed disability progression, prevention of relapses, reduced magnetic resonance imaging (MRI) lesion activity and area, decreasing side effects, long-term effects, and tolerability.

Consumer summary: MS may be related to the immune system. IFNs have several effects on the immune system, and act against viruses. IFN can help to reduce disability and exacerbations for people with MS in the medium term. IFNβ1a administered IM or SC can lead to a moderate reduction in recurrences and disability in MS patients with remissions. The most common side effects are influenza-like symptoms, injection site reactions, pain in the joints and muscles, fatigue, and headache.

The evidence

Systematic reviews: 10

RCTs: 12

Systematic reviews

First-line treatment of RRMS is currently based on immunomodulatory drugs, including recombinant IFNβ1a and IFNβ1b or glatiramer acetate, although the latter has been shown to be only modestly effective. Recently it has been suggested that nerve damage and inflammation are early events in MS evolution which immunomodulatory drugs can only partially prevent. This paper makes a critical comparison between the main treatments[15–29] used in MS, to determine if IFNβ1a is the best treatment.

Interferon-β1a

It has been hypothesized that the efficacy of IFN could be higher if it is used at the first appearance of symptoms, in Clinically Isolated Syndromes suggestive of demyelinating events, a pathology which carries a high risk of conversion to clinically definite MS. The efficacy of IFNβ1a for exacerbations and disease progression in patients with RRMS was modest after one and two years of treatment. IFN administered by the oral route was not effective for prevention of relapses. Longer follow-up and more uniform reporting of clinical and MRI outcomes in these trials might have allowed for more convincing conclusions.[15] Other research confirmed the efficacy of IFNβ1a in preventing the conversion from a

Clinically Isolated Syndrome to clinically definite MS over two years of follow-up. It could be useful for clinical practice if future analyses of the efficacy of IFNβ1a treatment were undertaken in different patient subgroups, because patients in the studies reported to date have been clinically heterogeneous in terms of length of follow-up and clinical findings at the time of initial presentation.[16]

Glatiramer acetate

A Cochrane systematic review performed in 2003 concluded that glatiramer acetate did not show any beneficial effect on the main outcome measures in MS, and did not substantially affect the risk of clinical relapses. Therefore, its routine use in clinical practice was not supported.[17] Nevertheless, the ongoing US glatiramer acetate trial is the longest evaluation of continuous sole disease-modifying therapy in RRMS. It has been concluded[18] that MS patients with a mean disease duration of 22 years who were treated with glatiramer acetate for up to 15 years had reduced relapse rates, and decreased disability progression and transition to secondary progressive MS. There were no long-term safety issues. Patients with MS who have an unsatisfactory response to IFNβ should be considered for glatiramer acetate therapy.[18]

Natalizumab

An immunosuppressive drug, natalizumab was previously available for a short period of time for treatment of MS in the US. It was consistently more effective than placebo for both relapse-related outcomes and disease progression in two trials.[19] One of those trials included IM IFNβ1a used concomitantly with natalizumab and placebo arms; however, this did not appear to impact the findings of that trial in terms of efficacy outcomes. Natalizumab was initially suspended as a result of several confirmed cases of progressive multifocal leukoencephalopathy.[19] The exact relationship between multifocal leukoencephalopathy and natalizumab is unknown. However, in 2005, the manufacturers suspended the supply of this drug from commercial distribution.[20] After lengthy deliberation by an FDA advisory panel, natalizumab was reapproved in 2009, but with stringent restrictions including patient, provider, and site registration.[21] It is now considered as second-line therapy for patients who had failed first-line agents, i.e. IFN or glatiramer acetate.

Intravenous immunoglobulins

There is evidence to support the use of intravenous immunoglobulins (IVIG) as a preventative treatment for relapses in RRMS. There was no evidence of delay in progression of disease in secondary progressive MS,[22] but this needs to be evaluated carefully in relapsing–remitting disease.

Mitoxantrone

This agent has partial efficacy, but due to its unclear long-term safety profile, it should be reserved for patients with worsening RRMS and evidence of worsening disability.[23] Limited evidence from one small trial showed that mitoxantrone was more effective than placebo for both disease progression and relapse rates.[23]

Azathioprine

Azathioprine is a reasonable alternative to IFNβ1a for treating MS. A logical next step for future trials would seem to be a direct comparison of azathioprine and IFNβ1a, which has yet to be done.[24] Better evidence of the effects of this drug is needed.

Aminopyridines

These agents are possibly useful for treating MS symptoms, although the available information does not allow any objective statement about their safety or efficacy. Publication bias remains a pervasive problem in this area, and until the results of as yet unpublished studies are available to the scientific community, no confident estimate of the effectiveness of the aminopyridines in the management of MS symptoms is possible.[25]

Cyclophosphamide

Cyclophosphamide is an immunosuppressive drug used for various autoimmune diseases, although its use for MS has not been well studied. In the pertinent literature, there are scant data available to show that cyclophosphamide slows MS progression in the medium term. It has been noted that side effects, including alopecia, nausea, vomiting, and amenorrhea occur at high frequency, and there is also evidence to suggest adverse effects appearing after two years of treatment.[26]

Methotrexate

The only study of methotrexate in progressive MS revealed a nonsignificant trend in sustained reduction of disease progression on the Expanded Disability Status Scale and number of relapses in favor of methotrexate. However, as yet, there are not enough studies of methotrexate in RRMS to reach any firm conclusions.[27]

Hyperbaric oxygen therapy

This treatment modality involves people breathing pure oxygen in a specially designed chamber. Hyperbaric oxygen therapy has sometimes been used for MS, especially in cases of lack of oxygen to the affected nerves leading to worsening MS, but this theory is unproven. There is no consistent evidence to confirm a beneficial effect of hyperbaric oxygen therapy for the treatment of MS, and its routine use is not justified. The analyses suggestive of benefit were isolated, biologically implausible, and would need to be confirmed in well-designed trials in the future.[28]

Other therapies

Emerging immunosuppressive therapies in oncology and organ transplantation have been associated with life-threatening risks, including serious opportunistic infections and/or new malignancies.[39] Among these drugs are cladribine, alemtuzumab, rituximab, and fingolimod. With alemtuzumab, the greatest risk seems to be the development of autoimmune syndromes. The effects of cladribine, alemtuzumab, and rituximab on the immune system are more long term, and must be monitored years rather than for days or weeks. Other drugs, such as laquinimod and dimethyl fumarate, appear to be largely immunomodulatory, whereas teriflunomide is mainly immunosuppressive, i.e. preventing lymphocyte proliferation. Laquinimod, dimethyl fumarate, and teriflunomide are not associated with these life-threatening risks, and they seem to be safer. However, some questions remain about how robust the efficacy of these therapies will be.[39,40] There are not enough systematic reviews supporting evidence on the effect of daclizumab, amtuzumab, and alemtuzumab in RRMS.[29] Alternative therapies, including bone marrow autologous transplantation and plasmapheresis, did not showed definitive results neither. A number of small clinical trials[24–27] supported the modest effect of IVIG, azathioprine, methotrexate, and cyclophosphamide, either alone or in combination with standard therapy.

Randomized clinical trials

Twelve RCTs were found[4,8,33,47–54] and their results are shown in the Table 1.

SC IFNβ1a versus SC IFNβ1b

IFNβ1a has shown better outcomes in RRMS, causing fewer side effects and less immunogenicity. SC IFNβ1a and SC IFNβ1b were similarly effective in reducing the frequency of relapses and slowing disease progression, whereas IM IFNβ1a was less effective. However, these findings were contradicted by trials which compared each drug with placebo. IM IFNβ1a was similar to IFNβ1b for preventing relapses, while SC IFNβ1b was not significantly better than placebo for slowing disease progression.

IFNβ1 used alone or as combination therapy

There was weak evidence showing that IFNβ1a in combination with other drugs increases favorable outcomes in MS. Many preliminary studies have produced favorable results for various combination regimens. For instance, add-on, high-dose daclizumab treatment reduces the number of new or enlarged gadolinium contrast-enhancing lesions, and might reduce MS disease activity to a greater extent than IFNβ1a alone,[29] and oral methylprednisolone given in pulses every four weeks as an add-on therapy to SC IFNβ1a in patients with RRMS led to a significant reduction in relapse rate.[30] However, several subsequent large, randomized, controlled trials have had negative or conflicting results.[31] Therefore, the usefulness of combination therapy in MS remains uncertain.

Subcutaneous versus intramuscular IFNβ1

There is no clear evidence that the SC route is better than the IM route, although tolerability problems, especially related to injections and injection site reactions with the IM route (including lipoatrophy), continue to be an important issue. However, in general terms, the SC route has had better acceptance by patients and the most favorable adherence to treatment. Two trials suggested a benefit of SC IFNβ1a over interferon IM IFNβ1a in terms of relapse outcomes. In addition, another study has shown that SC IFNβ1 had dose-dependent cognitive benefits in mildly disabled patients with RRMS, and supported the idea of early initiation of high-dose IFNβ1a treatment.[32] On the other hand, the ASSURANCE study concluded that for some patients with MS, long-term use of IM IFNβ1a was associated with significantly less disability progression, better quality of life, and greater independence in activities of daily living.[33] Therefore, the only real, but weak, difference between the SC and IM routes would be acceptance and convenience for patients.

Optimal duration of effect of IFNβ1

One RCT showed that SC IFNβ1a would yield greater health benefits over four years than IM IFNβ1a, at a cost that would seem to be a reasonable trade-off. In the long term, IM IFNβ1a also showed a beneficial safety-tolerability profile. IM IFNβ1a was well tolerated, and no new safety concerns were identified over 15 years of use. [33] Despite that, there have not been enough trials that show significant beneficial effects in delaying disability progression with long-term therapy (over 20 years or more), with any of the IFNs. The methodological difficulties faced in designing a trial of such an extended duration would be hard to overcome.

Table 1 Randomized controlled trials and other studies of the effects of IFNβ1a

Study	Duration/ follow-up	Type of study and subtype of MS	Drug and route	n	Main results
Jacobs et al[8]	3 years	-RCT - RRMS	IM IFNβ1a 30 μg versus placebo	301	Reduced activity, volume, and number of lesions on MRI in 71% of cases (0 lesions), showed moderate side effects and short-term effect, less than 2 years; it reduced the accumulation of permanent physical disability, exacerbation frequency, and disease activity as measured by gadolinium-enhanced lesions on brain MRI
Bermel et al[33]	15 years (follow-up of MSCRG study)[8]	Multicenter, single timepoint	At follow-up, 46% (56 of 122) of patients were receiving IM IFNβ1a and 54% (66 of 122) were not	122	For some patients with MS, long-term use of IM IFNβ1a is associated with significantly less disability progression, better quality of life, and greater independence with self-care; IM IFNb-1a is well tolerated, and no new safety concerns were identified over 15 years of use; long-term effect (more than 10 years)
Jacobs et al[4]	3 years	RCT CIS	IV and oral steroids, followed by placebo versus IFNβ1a IM 30 μg weekly	383	Delay in disability progression was significantly lower on IM IFNβ1a than on placebo; compared with placebo, patients on IFNβ1a had a relative reduction in volume of brain lesions, fewer new or enlarging lesions, and fewer gadolinium-enhancing lesions at 18 months; moderate side effects and short-term effect (less than 2 years)
Kinkel et al[47]	5 years (follow-up of CHAMPS) study[4]	RCT CIS	IM, IV, and oral steroids, followed by placebo versus IFNβ1a IM 30 μg weekly	203	Delayed disability progression, delay of conversion to CDMS, reduction in activity, volume, and number of lesions on MRI in 71% of cases (0 lesions), moderate side effects, short-term effect (less than 2 years); modest beneficial effects of immediate treatment compared with delayed initiation of treatment
PRISMS[48]	2 years	RCT RRMS	SC IFNβ1a 22 μg versus placebo or SC IFNβ1a 44 μg SC versus placebo	560	Significantly lower relapse rates at 1 and 2 years with both doses of SC IFNβ1a than with placebo; time to first relapse was prolonged by 3 and 5 months in the 22 μg and 44 μg groups, respectively, and the proportion of relapse-free patients was significantly increased; SC IFNβ1a delayed progression in disability, and decreased accumulated disability during the study; the accumulation of burden of disease and number of active lesions on MRI was lower in both treatment groups than in the placebo group; short-term effect (less than 2 years)
Schwid et al[49]	2 years	RCT RRMS	IM IFNβ1a 30 μg versus SC IFNβ1a 44 μg	439	SC IFNβ1a 44 μg TIW was associated with a significant reduction in clinical and imaging measures of disease activity over 1 to 2 years, when compared with IM IFNβ1a 30 μg QW treatment; the SC group also had a decreased number of relapses, and reduced activity, volume, and number of lesions on MRI with SC IFNβ1a, moderate side effects, short-term effects (of less than 2 years)
Durelli et al[50]	2 years	RCT RRMS	IM IFNβ1a 30 μg weekly versus SC IFNβ1b SC QOD	188	High-dose IFNβ1b administered every other day was more effective than interferon IFNβ1a given once a week; delayed disability progression and a significant reduction in activity, volume, and number of lesions on MRI; short-term effects (less than 2 years)
Koch-Henriksen et al[51]	2 years	Multicenter, controlled, open-label, randomized, head-to-head	IFNβ1a SC 22 μg weekly versus IFNβ1b 250 μg QOD	278	250 μg of IFNβ1b administered every other day did not prove clinically superior to once-a-week administration of 22 μg of IFNβ1a; relapse rates, sustained progression, and time to first relapse were eqivalent; short-term effect, less than 2 years
Mikol et al[52]	2 years	Multicenter, randomized, comparative parallel-group, open-label study RRMS	IFNβ1a 44 μg SC TIW, Glatiramer 20 mg SC weekly	764	There was no significant difference between IFNβ1a and glatiramer acetate in the primary outcome; relapse rates were equal between groups, fewer gadolinium-enhancing lesions in IFN β1a group; lesions per patient, similar side effects in number and type, both showed similar delay disability progression and moderate side effects; short-term effect (less than 2 years)

(Continued)

Table 1 (*Continued*)

Study	Duration/ follow-up	Type of study and subtype of MS	Drug and route	n	Main results
Comi et al[53]	2 years	RCT CIS	IFNβ1a 22 μg SC TIW versus placebo	308	Delayed conversion to CDMS in IFN β1a group versus placebo; significant effect on MRI measures and reduced activity, volume, and number of lesions in MRI; short-term effect (less than 2 years)
Sorensen et al[30]	2 years	Multicenter RCT RRMS	MP 100 mg PO, daily for 5 days every 4 weeks + IFNβ1a 44 μg SC TIW	130	Oral methylprednisolone given in pulses every 4 weeks as an add-on therapy to SC-IFNβ-1a in patients with RRMS led to a significant reduction in relapse rate
Cohen et al[54]	2 years	RCT Phase IV	IM IFNβ1a 30 mg + placebo + IV MP 1000 mg/day for 3 days or IM IFNβ1a 30 mg + MTX 20 mg PO + IV MP 1000 g/day for 3 days	313	This trial did not demonstrate a benefit of adding low-dose oral methotrexate or IV MP every other month to IFNβ1a in RRMS patients; all of the drug combinations showed a reduction in number and size of previous T2-hyperintense lesions; IV MP decreased the formation of anti-IFN NABs

Abbreviations: QOD, every other day; TIW, 3 times per week; RCT, randomized control trial; R, randomized; NR, nonrandomized; IM, intramuscular; SC, subcutaneous; CDMS clinically definite multiple sclerosis (Kaplan-Meier ± 95% CI); CIS, clinically isolated symptom; RRMS, relapsing–remitting multiple sclerosis; MRI, magnetic resonance imaging; IV, intravenous; PO, orally; MP, methylprednisolone; MTX, methotrexate; NABs, neutralizing antibodies.

Low- versus high-dose IFN therapy

SC IFNβ1a 44 μg has shown the highest efficacy in the treatment of RRMS.[34] Long-term Class 1 data from PRISMS supported the use of SC IFNβ1a twice weekly as a first-line treatment for MS, as evidenced by sustained efficacy rates, acceptable safety profiles, and high patient adherence rates.[34]

Frequency of administration

SC IFNβ1a demonstrated better outcomes in RRMS at a dosing frequency of three times per week. Two RCTs concluded that administering high-dose, high-frequency SC IFNβ1a was more effective in preventing relapses in patients with RRMS than low-dose weekly IM IFNβ1 after 64 weeks.[34,35]

IFNβ1 versus glatiramer acetate

Both these drugs have been used as first-line treatment for RRMS in RCTs. The mean difference in relapse rate between glatiramer acetate and placebo was statistically significant in some trials, but the effect on disease progression was unclear.[37] Adverse events rates were higher for glatiramer acetate than for placebo, most notably post-injection systemic reactions and injection site reactions, as were withdrawals due to adverse events. Withdrawal rates were also consistently significantly higher in observational studies when compared with placebo. The use of glatiramer acetate in cases of suboptimal response to IFNs appeared to improve the effectiveness of the latter. However, IFNβ1 has showed better results than glatiramer acetate in most cases.

Suboptimal responses

The frequency of suboptimal responses to MS therapy was as high as 30% in the three years following initiation of first-line therapies.[36] Criteria for defining a suboptimal response vary between the trials. Typical criteria include relapse rates greater than one per year or unchanged from pretreatment rates, incomplete recovery from relapses, new brainstem or spinal cord lesions, and progression of disability or cognitive impairment that leads to a disruption in activities of daily living. There are at least three main causes of suboptimal responses.[37] These are development of neutralizing antibodies (NABs) that reduce or abolish IFNβ bioactivity in a titer-dependent manner, lack of long-term adherence to therapy, and, possibly, switching of disease-modifying therapies to improve patient response or eliminate adverse effects.

Adherence to therapy

Lack of adherence was shown in some RCTs. Notably, four of the six currently available therapies require self-injection, and all have side effects ranging from influenza-like symptoms to injection site reactions. Barriers to adherence included needle phobia, not taking medication because of forgetfulness, complacency, treatment fatigue, changes in socioeconomic status, and perceived lack of efficacy.[36] The most common adverse events overall were injection site reactions, vasodilatation, rash, dyspnea, and chest pain. Localized lipoatrophy occurred in roughly 2% of patients.[37]

Neutralizing antibodies

Some reports[38,39] showed that the appearance of high-titer (< 1:100) neutralizing NABs totally blocked the biological activity of IFNβ. The development of NABs did occur in up to 35% of IFNβ-treated patients, with several studies suggesting that IFNβ1b was most immunogenic (35% of patients NAB-positive), followed by subcutaneous IFNβ1a (23.7% of patients NAB-positive), and, lastly, IM IFNβ1a (7% of patients NAB-positive).[40]

Conclusions

Thus far, the evidence shows that the most effective short- to medium-term, disease-modifying therapy for delaying disability progression, prevention of relapses, reducing the area and activity of lesions seen on MRI, with the least side effects, is high-dose, high-frequency SC IFNβ1a 44 μg three times per week

The Practice

Avoiding pitfalls

- The most effective therapy with the least side effects should be started as soon as possible to prevent or delay the appearance of permanent neurological disability
- Adherence to treatment should be monitored closely, and comprehensive patient information and education is necessary to establish long-term adherence, which is a critical determinant of long-term outcome.
- The best approach to treatment of the disease includes disease management, symptom management, and patient management. A combination of tools is necessary to ease the various symptoms that fall into three broad categories, i.e. rehabilitation, pharmacological, and procedural. It is important to understand that none of these treatment approaches should be used in isolation, unless it is by itself sufficient to remedy the particular symptom/problem.

Management

Patients who have an unsatisfactory response to IFNβ1 should be considered for glatiramer acetate therapy. This should be started early in the course of MS to minimize irreversible axonal damage. Patients with worsening MS may be referred for mitoxantrone therapy, but short- and long-term adverse effects, including cardiotoxicity, must be monitored for closely. To shorten the duration of MS relapses and accelerate recovery, corticosteroid therapy should be considered. MRI should be repeated every three months after a clinically suspicious episode to facilitate early diagnosis of MS.

Assessment

Magnetic resonance imaging of brain

MRI scan of the brain is the most useful test for confirming the diagnosis of MS. The lesions appear as areas of high signal, predominantly in the cerebral white matter or spinal cord, on T2-weighted images.[41]

Multimodal evoked potentials

Multimodal evoked potentials may be useful for demonstrating the presence of subclinical lesions in sensory pathways. The presence of three abnormal multimodal evoked potentials increases the risk of reaching moderate disability independently of baseline MRI.[42]

Cerebrospinal fluid analysis

The CSF immunoglobulin G concentration is increased relative to other CSF proteins (eg, albumin), and CSF gel electrophoresis reveals oligoclonal bands that are not present in a matched serum sample.[43]

Local physical findings

Some symptoms could be explained by localized disease: the presence of steadily progressive disease, the absence of clinical remission, the absence of oculomotor, optic nerve, sensory, or bladder involvement, and normal CSF findings. However, none of these findings exclude the diagnosis of MS.[44]

Treatment

The evidence shows that the most effective disease-modifying therapy at this time is high-dose, high-frequency SC IFNβ1 (44 μg three times per week alone). The major difference between the IFNβ1 drugs is that IM IFNβ1a is given once

Table 2. Current drugs used in relapsing–remitting multiple sclerosis.

Drug	Brand name	Delivery systems	Dosage	Side effects	Monitoring
IFNβ-1a (IM)	Avonex®	Reconstitution needed/prefilled syringe	30 μg IM once weekly	Influenza-like symptoms	CBC, LFTs
IFNβ-1a (SC)	Rebif®	Ready to use prefilled syringe	22–44 μg SC three times weekly	Influenza-like symptoms and injection site reactions	CBC, LFTs
IFNβ-1b (SC)	Betaseron®	Reconstitution needed	0.25 mg SC every other day	Influenza-like symptoms and injection site reactions;	CBC, LFTs
Glatiramer acetate	Copoxone®	Ready to use prefilled syringe	20 mg SC once daily	injection site reactions and a benign systemic reaction (flushing, chest tightness with racing or pounding heartbeat, anxiety, and difficulty in breathing)	Local site of injection
Mitoxantrone (immunosuppressive)	Novantrone®	Injection concentrate supplied, dilution required	5 to 12 mg per m^2 IV every 3 months	Mild chemotherapy-related side effects, cumulative cardiotoxicity, small increased risk of leukemia	CBC, cardiological assessment

Abbreviations: IFN, interferon; IM, intramuscular; SC, subcutaneous; IV, intravenous; CBC, complete blood count; LFTs, liver function tests.

a week and SC IFNβ1a and IFNβ1b are given three times a week, or every other day, respectively. The main differences between the available immunomodulatory drugs are shown in Table 2. Treatment with any IFNβ agent can result in the development of NABs. Although study results are variable, once-weekly IM IFNβ1a therapy has been reported to have the lowest incidence of NAB development.[46]

Symptomatic therapy

There is no clear evidence that symptomatic therapy is useful for all patients. Response is dependent on the stage of the disease and on the affective and psychiatric status of the patient, although some medications can be used to improve symptoms partially.[44–46] Influenza-like symptoms, including fever, chills, malaise, muscle pain, and fatigue are the most common side effects, and usually dissipate with continued therapy and premedication with a nonsteroidal anti-inflammatory drug. Dose titration at the initiation of IFNβ therapy is also a useful strategy. Other side effects of IFNβ include injection site reactions, depression, mild anemia, thrombocytopenia, elevated transaminase levels, and worsening of pre-existing spasticity. These are not usually severe and rarely lead to discontinuation of treatment.[45]

Disclosure

The authors report no conflicts of interest in this work.

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