GUIDELINE

Guideline for the use of beta-interferons in patients with multiple sclerosis — a South African proposal

Multiple Sclerosis Advisory Committee of the Neurological Association of South Africa (NASA)

Aim. To determine guidelines for use of beta-interferons in South African patients with multiple sclerosis.

Method. Review of existing international protocols. Opinions of South African neurologists who have an interest in multiple sclerosis.

Conclusions. The main indication for interferon use is the relapsing and remitting form of multiple sclerosis.

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Multiple sclerosis (MS) is an inflammatory immune-mediated demyelinating disease that affects the central nervous system (brain, optic nerves and spinal cord). It is the leading cause of chronic neurological disability in young adults worldwide. It has a high prevalence in Caucasian people, in particular across the northern parts of Europe, Northern Scotland, Scandinavia and North America. It is much less common in the tropical areas of the world.

The mean age of onset of the disease is in the early thirties, with a female preponderance. The aetiology remains unknown but there is strong evidence that the disease is caused by a combination of environmental, genetic and as yet undetermined factors.

The disease has a variable course and is categorised into different forms based on natural history. Remitting and relapsing MS (RRMS) is the commonest form of the disease. Primary progressive (PPMS) and secondary progressive (SPMS) are the two other recognised types of MS. A further category defined as clinically isolated syndromes (CIS) has been described in which patients suffer a single attack (e.g. optic neuritis) with objective clinical evidence of a lesion (on magnetic resonance imaging (MRI) scan of the brain). If dissemination can be shown in time and space on MRI then in the appropriate context MS may be diagnosed in these patients. Alternatively a second attack will also suffice to establish MS diagnosis. Benign MS refers to a group (10%) of patients (typically with RRMS) who do well for many years and hence are defined as 'benign'. Typically these patients have many attacks but little cumulative deficit. Some also have few attacks separated by long intervals.

In the past, the diagnosis of MS was essentially clinical. However, the advent of MRI has made a major impact in terms of diagnosis. With MRI becoming more widely available, early diagnosis of MS has become a reality. MRI has become the principal diagnostic tool in investigation of patients with suspected MS. Other modalities that may assist in diagnosis include cerebrospinal fluid (CSF) oligoclonal antibodies and evoked potential tests. Criteria for the diagnosis of MS based on clinical, MRI and these ancillary tests have now been established. The first of these criteria for diagnosis were based on Poser's 1983 criteria[1] (Appendix A). More recently in 2001 newer criteria based more strongly on MRI findings have been proposed by McDonald *et al*. (Appendix B).[2] These revised criteria allow for early diagnosis and diagnosis of monosymptomatic disease.

The treatment of MS has been refined and redefined over the past few decades. The hallmarks of treatment are immunosuppression and immunomodulation. Immunosuppression uses high doses of intravenous steroids (methylprednisolone). This is used to treat acute relapses. The treatment is nonspecific and targets the generalised expected disturbance in immune mechanisms during an acute attack. Given the high doses, the side-effect profile of this kind of treatment can be considerable and therefore its use is restricted to a pulse for a maximum of 5 days. There is no evidence for the use of prolonged treatment with intravenous or oral steroids.

Immunomodulatory therapy is more specifically directed at altering the natural history and course of the disease. Essentially two groups of agents have been established to have beneficial effect in this regard. The first and most widely used of these are the interferons (IFNs). The other agent that has similar beneficial effect is the drug glatiramer acetate. As this drug is not currently available in South Africa, we will not discuss it any further.

The IFNs are available in South Africa in two forms, IFN-beta-1a (Avonex and Rebif) and IFN-beta-1b (Betaferon). These are different forms of recombinant IFN-beta. The IFNs are cytokines that form a natural part of the human immune system. Two major types are identified: type 1 — IFN alpha/interferon beta, and type 2 — interferon gamma. The IFNs are secreted after activation by invading organisms. The type 1

Please forward all comments to: **Professor G Modi, PO Box 909, Lenasia, 1800 (tel 083 601 2878, fax (011) 484-7576, e-mail gmodicns@mweb.co.za)**

IFNs have anti-inflammatory effects through IFN-stimulated gene products. The anti-inflammatory effect of these IFNs forms the basis of their immunomodulatory effects in MS. The IFNs have been shown to:[3-9] *(i)* increase the time of development of a second relapse in early MS; *(ii)* reduce the frequency and severity of relapses in RRMS; *(iii)* slow the accumulation of physical disability (4-year follow-up study); and *(iv)* reduce the MRI burden of the disease.

There is strong evidence that these agents are beneficial in patients with RRMS. There is no recognised benefit in patients with PPMS, but there is evidence of benefit from IFN therapy in SPMS with frequent relapses. There is now accumulating evidence (not yet as conclusive as evidence for RRMS) for benefit in patients with CIS.[3-9] A relevant issue, especially in our country and perhaps even worldwide, is the cost of immunomodulatory agents. In South Africa, regardless of the type used, the average cost per annum for an IFN is in the region of R85 000. In RRMS the benefits of the IFNs have been shown to outweigh costs.[3-9] This has prompted the National Health Service (NHS) in the UK to allow IFN use in patients with RRMS and SPMS with frequent relapses.

To address these issues a consensus open meeting was held of South African neurologists (academic and private) interested in MS. The group evaluated the current literature regarding IFN treatment in MS and also assessed the criteria of the British Neurological Association. To assist South African neurologists and health care providers and funders in determining the use of IFNs in our patients with MS, the following criteria were recommended.

1. Remitting and relapsing MS

For this form of MS the Committee agreed that the diagnosis should be based on the occurrence of at least 2 attacks of the disease in the previous 2 years. An attack is defined as a focal neurological event and the diagnosis should meet the McDonald criteria. The Committee also agreed that there was no contraindication to the use of IFNs in this group.

Patients above 18 years of age were to be included in this category. No upper age limit was considered necessary. In this group any patient who can stand and step/walk independently with an Expanded Disability Status Scale (EDSS) (Appendix C) score of less than 5.5 in the stable/remission phase should be included.

2. Secondary progressive MS

Two groups of SPMS are recognised:

Secondary progressive with no relapses. In this group the Committee felt that IFN was not indicated unless, on regular follow-up, relapses were identified. Again, a relapse is defined in terms of McDonald's criteria.

Secondary progressive with relapses. In this group the Committee felt that INF was indicated but that the following should be adhered to:

- relapses should be the dominant cause of disability
- EDSS score of less than or equal to 6.5
- at least 2 disabling relapses (a change in EDSS score of at least 1) in the previous 2 years
- age group — no age restriction
- no contraindications.

3. Clinically isolated syndromes

In this group of patients, 2 separate categories were identified.

3.1 Without any other evidence of disease, i.e. negative MRI and not in keeping with McDonald's criteria. For these patients IFN therapy is not indicated.

3.2 Those with evidence of burden of disease on MRI (white matter lesions) – no IFN treatment is recognised at this stage. However the Committee reserves the right to modify this should further evidence from randomised, controlled trials become available.

In general, in this category of patients the Committee felt that there was insufficient evidence to support use of IFN therapy regardless of paraclinical or any other evidence.

4. Primary progressive MS

IFN use is not indicated in this category of patients at this time.

Certain other comments and recommendations were made by the Committee.

4.1. The diagnosis of MS has to be established by a neurologist. The neurologist has to apply the criteria as proposed by McDonald *et al*., 2001.

4.2. The use of IFN therapy has to be initiated by a neurologist. A general practitioner or other specialist may assist the neurologist in terms of follow-up. It therefore follows that the neurologist will be involved in the motivation for the use of interferon in a selected patient.

4.3. Cost mitigates against the widespread use of IFN as a prophylactic treatment for MS.

4.4. The use of IFN implies that the patient has active or ongoing disease.

4.5. The problem of cost has to be taken out of the equation in patients fulfilling criteria for use of IFN.

4.6. The Committee felt that there is no evidence to support the use of one IFN type over the other. Switching from one IFN type to another would not result in an added benefit. There were insufficient head-to-head data in this regard.

5. Stopping of treatment

The Committee felt that this was an important issue and the following criteria were recommended for stopping IFN therapy in a particular patient:

- intolerable adverse effects (medical contraindications)
- planned/unplanned pregnancy
- lack of efficacy.

These guidelines are based on current literature evidence, and the opinion of the Committee at this time is subject to change with new emerging data.

The Committee consisted of the following members: Prof Girish Modi, Head of Neurology, University of the Witwatersrand (Chairperson); Prof Roland Eastman, Head of Neurology, University of Cape Town; Prof Pierre Bill, Department of Neurology, University of KwaZulu-Natal; Prof Abie Kruger, Head of Neurology, University of the Free State; Prof David Saffer, University of the Witwatersrand; Dr Simon Kessler, private practice, Cape Town; Dr Louis Biermann, private practice, Pretoria; Dr Bhupendra Bhagwan, private practice, Durban; Dr Dominique Giampaolo, private practice, Johannesburg.

All members of the Committee had to disclose any involvement, financial or otherwise, with the IFN pharmaceutical industry. Professor Eastman indicated that he had on occasion advised Serono (manufacturers of the IFN Rebif). He is also on the Medscheme Advisory Board regarding multiple sclerosis. Professor Kruger has attended an advisory meeting for Serono. Dr Biermann had received travel and meeting support previously and had a meeting sponsored by the IFN pharmaceutical industry, with the medical aid industry to try to resolve IFN-related issues. Dr Giampaolo has served on a Serono Advisory Board and also received travel and meeting support from Pharmaplan. Professor Saffer has received travel support for an advisory meeting. No other members received any support to date.

The meeting was sponsored by Pharmaplan, Serono, and Schering. No representative of these companies was present during the meeting or participated in the discussions at the meeting. It was agreed that the Committee would formulate its recommendations independently and would specifically not target any of the IFNs.

Appendix A. The Poser criteria

- **Clinically definite MS**
  - 2 attacks and clinical evidence of 2 separate lesions
  - 2 attacks, clinical evidence of 1 and paraclinical evidence of another separate lesion
- **Laboratory-supported definite MS**
  - 2 attacks, either clinical or paraclinical evidence of 1 lesion, and cerebrospinal fluid (CSF) immunological abnormalities
  - 1 attack, clinical evidence of 2 separate lesions and CSF abnormalities
  - 1 attack, clinical evidence of 1 and paraclinical evidence of another separate lesion, and CSF abnormalities
- **Clinically probable MS**
  - 2 attacks and clinical evidence of 1 lesion
  - 1 attack and clinical evidence of 2 separate lesions
  - 1 attack, clinical evidence of 1 lesion, and paraclinical evidence of another separate lesion
- **Laboratory-supported probable MS**
  - 2 attacks and CSF abnormalities

What is an attack?

- Neurological disturbance of kind seen in MS
- Subjective report or objective observation
- 24 hours' duration, minimum
- Excludes pseudoattacks, single paroxysmal episodes

Determining time between attacks

- 30 days between onset of event 1 and onset of event 2

How is 'abnormality' in paraclinical tests determined?

- Magnetic resonance imaging (MRI) 3 out of 4:
  - 1 gadolinium (Gd)-enhancing or 9 T2 hyperintense lesions if no Gd-enhancing lesion
  - 1 or more infratentorial lesions
  - 1 or more juxtacortical lesions
  - 3 or more periventricular lesions

(1 spinal cord lesion = 1 brain lesion)

- Cerebrospinal fluid (CSF)
  - Oligoclonal immunoglobin (IgG) bands in CSF (and not serum), OR
  - Elevated IgG index
- Evoked potentials (EP)
  - Delayed but well-preserved wave form

What provides MRI evidence of dissemination in time?

- A Gd-enhancing lesion demonstrated in a scan done at least 3 months following onset of clinical attack at a site different from attack, OR
- In absence of Gd-enhancing lesions at 3-month scan, follow-up scan after an additional 3 months showing Gd-lesion or new T2 lesion

Appendix B. McDonald criteria

Clinical presentation	Additional data needed
• 2 or more attacks (relapses) • 2 or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
• 2 or more attacks • 1 objective clinical lesion	Dissemination in space demonstrated by: • MRI • or a positive CSF and 2 or more MRI lesions consistent with MS • or further clinical attack involving different site
• 1 attack • 2 or more objective clinical lesions	Dissemination in time, demonstrated by: • MRI • or second clinical attack
• 1 attack • 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space demonstrated by: • MRI • or positive CSF and 2 or more MRI lesions consistent with MS and Dissemination in time demonstrated by: • MRI • or second clinical attack
Insidious neurological progression suggestive of MS (primary progressive MS)	Positive CSF and Dissemination in space demonstrated by: • MRI evidence of 9 or more T2 brain lesions • or 2 or more spinal cord lesions • or 4 - 8 brain and 1 spinal cord lesion or positive visual evoked potentials (VEP) with 4 - 8 MRI lesions • or positive VEP with < 4 brain lesions plus 1 spinal cord lesion and Dissemination in time demonstrated by: • MRI • or continued progression for 1 year

Appendix C. Expanded Disability Status Scale (EDSS)

The Kurtzke Expanded Disability Status Scale (EDSS) is a method of quantifying disability in MS (for scores see box on p. 921). The EDSS replaced the previous Disability Status Scales which used to bunch people with MS in the lower brackets.

The EDSS quantifies disability in 8 functional systems (FS) and allows neurologists to assign a functional system score (FSS) in each of these. The functional systems are:

- pyramidal
- cerebellar
- brainstem
- sensory
- bowel and bladder
- visual
- cerebral
- other.

EDSS steps 1.0 - 4.5 refer to people with MS who are fully ambulatory. EDSS steps 5.0 - 9.5 are defined by the impairment to ambulation.

EDSS scores

0.0	Normal neurological examination
1.0	No disability, minimal signs in 1 FS
1.5	No disability, minimal signs in more than 1 FS
2.0	Minimal disability in 1 FS
2.5	Mild disability in 1 FS or minimal disability in 2 FSs
3.0	Moderate disability in one FS, or mild disability in 3 or 4 FSs. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in 1 FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk some 500 m without aid or rest
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability; able to walk some 300 m without aid or rest
5.0	Ambulatory without aid or rest for about 200 m; disability severe enough to impair full daily activities (can work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 m; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 m with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 m without resting
7.0	Unable to walk beyond approximately 5 m even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorised wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms, retains some self care functions
9.0	Confined to bed; can still communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

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