Multiple Sclerosis Therapy
A Practical Guide

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Contents

Summary .......................................................... 200
1. Magnetic Resonance Imaging ............................... 201
2. Pathogenesis .................................................. 202
   2.1 Evidence for Immunological Involvement .......... 202
   2.2 T Cell Function in Multiple Sclerosis .......... 202
3. Treatment ..................................................... 203
   3.1 Treatment of Relapse .................................... 203
   3.2 Prevention of Relapse and Progression .......... 204
   3.3 Symptomatic Treatment in Multiple Sclerosis . 206
4. Future Developments ......................................... 208
   4.1 Improvement of the Course of the Disease ...... 208
   4.2 Promotion of Remyelination ........................... 210
   4.3 Symptomatic Treatment ................................. 210
5. Conclusion: A Practical Guide to Treatment .......... 210

Summary

A growing amount of evidence suggests that a disturbance of immunological function is of importance in the pathogenesis of multiple sclerosis. This is reflected in the drugs used to slow progression and to treat relapses. Immunosuppressive drugs such as azathioprine, cyclophosphamide and cyclosporin might have some potential to slow down progression of multiple sclerosis, but their use is limited by potentially serious adverse effects. Recently, it was shown that interferon-β-1b can diminish the exacerbation rate in multiple sclerosis without leading to unacceptable adverse effects. Nevertheless, symptomatic treatment remains of crucial importance in the management of multiple sclerosis patients. Spasticity, depression, fatigue and urinary, paroxysmal and sensory symptoms can all be alleviated to some extent with pharmacological interventions, although rehabilitation procedures and psychosocial consultations are no less important.

Further therapeutic approaches to multiple sclerosis will be directed at either the specificity of the immune response or the grade of activation of the immune response. Magnetic resonance imaging techniques will play an important role in the evaluation of efficacy of new therapeutic agents.
Multiple sclerosis is an inflammatory demyelin­
ating disease of the CNS. In its early stages the
 disease in general follows a relapsing and remitting
 course. The majority of patients have recognisable
 clinical syndromes, because multiple sclerosis le­
sions have a predilection for certain sites within the
 CNS: the most common presenting symptoms are
 paraesthesia in the extremities, optic neuritis and
 weakness of the limbs.

Although some patients fully recover after each
 relapse, in many patients recovery tends to be in­
 complete after some exacerbations and they are left
 with disability. Many of these patients sub­
 sequently enter a progressive phase of the disease
during which motor abnormalities (weakness,
 spasticity), brainstem involvement (internuclear
 ophthalmoplegia, pseudobulbar palsy) and cere­
bellar disturbances (ataxia, tremor) can be very dis­
 abling. Other symptoms, such as fatigue, loss of
 bladder and bowel control and neuropsychological
 abnormalities, are commonly encountered. In
 about 10 to 20% of patients the disease has a pro­
 gressive course from onset.

The diagnosis of the disease remains essentially
 clinical, with demonstration of signs and symp­
toms disseminated in time and space being re­
 quired, although a number of investigative proce­
dures have come into use as diagnostic aids to
 exclude other diseases and help fulfil diagnostic
 requirements. Cerebrospinal fluid (CSF) examina­
tion (elevated IgG index, oligoclonal banding),
evoked potential testing (conduction disturbances)
and especially magnetic resonance imaging (mul­
tiple white matter lesions, indicating dissemination
 in place) have been shown to increase diagnostic
 sensitivity.

The pathological hallmark of the disease is the
 white matter plaque, a clearly defined patch of de­
 myelination within the CNS. In normally myeli­
nated tracts the axons are wrapped in myelin
 sheaths that are produced by a specialised cell, the
 oligodendrocyte. Following demyelination, con­
duction is slowed or lost and symptoms ensue. His­
tologically, acute lesions are characterised by in­
flammatory cell infiltration (mainly lymphocytes
 and macrophages) and demyelination. Chronic le­
sions show only little inflammatory activity; the
 myelin sheaths and oligodendrocytes are absent
 and axonal loss tends to occur.

At present it is not known whether the progres­
sive phase of the disease is mainly due to persistent
 demyelination, to failure of remyelination, or to
 occurrence of axonal loss.

1. Magnetic Resonance Imaging

Magnetic resonance imaging shows areas of in­
creased signal intensity on standard images in 95% of
patients with clinically definite multiple sclero­
sis. Histopathologically, these abnormalities cor­
respond well with the presence of plaques. The fact
that every stage in the development of plaques in­
creases the signal on standard magnetic resonance
images explains the poor specificity of these signal
changes per se. Following injection of gadolinium
salts, signal enhancement can be observed in active
lesions, indicating the presence of blood-brain bar­
er disruption in the inflammatory phase. Monthly
magnetic resonance imaging studies have revealed a
considerable amount of clinically silent disease ac­
tivity in patients with relapsing-remitting and sec­
dary progressive multiple sclerosis. Serial magnetic
resonance imaging is 5 to 10 times more sensitive than
clinical monitoring in the detection of disease ac­
tivity. In addition, the nature of the information is
more objective than clinical scoring. Magnetic resonance
imaging is therefore well suited to serve as an outcome
measure in treatment trials. In phase III trials the ac­
cumulation of lesions can be used as a secondary end­
point, whereas in early phase II studies magnetic
resonance imaging activity can be used as a mea­
sure of efficacy.

Guidelines have been developed on how to
perform magnetic resonance imaging–monitored
 treatment trials. Based on natural history data,
magnetic resonance imaging–monitored treatment
trials have been simulated to obtain power esti­
mates. Using a placebo-controlled, parallel group
design, moderate treatment effects can be demon­
strated in relatively small patient groups within 6