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Disease Management in Multiple Sclerosis

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During the last 15 years new immunomodulatory agents have been developed for the long-term treatment of patients with multiple sclerosis (MS). They have shown efficacy in several class I treatment trials [1] but the overall effect is modest and cost effectiveness is still under review.

A conference held in Vienna in October of 2004 gathered 15 international experts on MS and its treatment from the US, Canada, the UK, Italy, Switzerland, Spain and Germany to discuss relevant issues in the management of people with MS. The aim of the meeting was to consider controversial issues in therapy and prepare a platform for an international consensus on the treatment of people with MS.

In the past few years the medical advisory boards of several national MS societies and the 'American Academy of Neurology Task Force on MS Treatments' have published reports. The following key issues were discussed:

(1) The Goal

There was consensus that the goal of MS treatment should be defined: disease activity, as evidenced by exacerbations and progression, should be stopped to prevent irreversible disability; damaged tissue should be repaired and injured tissue protected to improve impaired function in the nervous system. It was recognised that none of these goals are yet achieved.

There was consensus that new disease activity demonstrated on magnetic resonance imaging (MRI), including active inflammatory lesions and the evolution of other possible indicators of disease progression, such as black holes, should be reduced or prevented by effective treatment, despite the lack of validation of such markers for long-term outcome. The extrapolation of available observations from multi-centre treatment studies, usually of 2–3 years' duration, with follow-up periods from 4 to 10 years, supports this hypothesis but the observations need to be extended. We recognise

that there is no prospective long-term evaluation of the clinical impact of MRI changes in the individual patient, but accept that MRI is currently the best available marker for disease activity and consider it could be used in monitoring disease progression and assessing treatment efficacy provided that a standard protocol be used with scans performed at regular, frequent intervals.

It is hoped that the current early treatment trials with interferon- β -1b (BENEFIT) [2], glatiramer acetate (PRECISE) and statins will shed new light on the implication of MRI lesions in early MS for the clinical burden and disease evolution in the longer term. Currently we recognise that the treatment effect of immunomodulatory drugs in relatively early disease is to delay further MS exacerbation in people with early MS, but are less certain whether ultimate disease progression and permanent disability can be prevented by any of the licensed immunomodulatory treatments.

(2) Initiation of Therapy

There was consensus that long-term immunomodulatory treatment should probably be commenced early in the disease to delay, or hopefully prevent, further attacks as demonstrated by earlier clinical trials. There is as yet limited data to support the attractive concept that early treatment of clinically isolated syndromes will be more effective than delaying treatment until the patient satisfies the McDonald Criteria in preventing long-term disability.

(3) Choice of Treatment

If therapy is to be used early in the course of the disease it is likely that patients will only accept those treatments with a low-risk profile and few unpleasant side-effects. In contrast, once the patient has become disabled, a higher risk profile may be considered but treatment may be less effective. All participants agreed that the choice of the patient was the key issue in treatment decisions, taking into account medical factors such as the natural history of the type of MS, trial evidence and the views of the physician. Moreover, the influence of treatment on quality of life, recommendations from other people with MS, and the specific experience of the treating physician, or MS Specialist Nurse, will influence the decision making process.

There was no consensus within the expert group as to which drug should be used for initiation of therapy because there is little class I comparative trial evidence. The ongoing NIH-funded combi-Rx trial comparing interferon- β 1a to glatiramer acetate and combination therapy in early MS should provide such class I evidence in due course.

Attendees: B. Arnason, USA; D. Arnold, CA; D. Bates, UK; P. Durelli, FR; L. Durelli, IT; G. Ebers, UK; M. Feedman, CA; D. Goodin, USA; H.-P. Hartung, DE; R. Hohlfeld, DE; L. Kappos, CH; X. Montalban, ES; S. Reingold, USA; K.V. Toyka, DE; J. Wolinsky, USA.

(4) Cessation of Therapy

The experts agreed that when treatment was perceived to be ineffective or futile it should be discontinued, but found it difficult to define 'suboptimal response' and noted that none of the suggested definitions have been validated. All recognised a 'treatment responder' as a patient with multiple attacks whose exacerbations stopped or were at least reduced markedly after treatment, and who remained stable. Similarly they recognised as a 'non-responder' a patient with numerous disease exacerbations before treatment whose attacks continued at a similar or increased rate after commencing therapy and whose underlying condition progressively deteriorated.

'Partial' response, or 'suboptimal' response, is not defined and although there was consensus that clinical effects, after sufficient time has elapsed since initiating therapy, could be used to assess a 'suboptimal response' it was felt that a surrogate marker, when validated, would aid in this process. It was recognised that a better definition would help to establish a disease activity-dependent mode of treatment beginning with initial immunomodulatory therapy, followed by treatment escalation with cytotoxic drugs, plasma exchange, monoclonal antibodies when approved or, when sufficient data demonstrates the value, combination therapies, each of which might be added in a hierarchical way when suboptimal response was identified.

There was agreement that the MRI scan could be used as a marker to identify those people showing suboptimal responses, newly active lesions, total lesion load, reduction in brain volume, and the possible use of newly developed contrast-enhancing agents with molecular targets may all assist in a better definition of suboptimal therapy and allow consideration of the need for change or modification of treatment. The group recognised that presently available data about treatment failure are derived from clinical treatment trials with restricted entry criteria and their results may not apply to other treatments, or to the use of immunomodulatory therapy in people presenting the full range of MS in the clinic. It is suggested that analyses of treatment trial cohorts taking placebo reflecting the natural course of the disease compared with the large cohorts who were given treatment might help in defining 'suboptimal response'.

Other possible markers to identify responsiveness might, with additional study, eventually include antibodies such as those directed at myelin oligodendrocyte glycoprotein; the presence of circulating inflammatory mediators; the production of neopterin and MxA protein as indicators of effective immunomodulation, all potentially interesting, but there is not enough data presently available to assess their value.

Reviews of Treatment

The participants considered four current reviews:

(a) *The American Academy of Neurology Task Force* [1]. This comprehensive review only considered drugs licensed by the US Food and Drug Association (FDA), excluding agents that are not licensed in the US, even though they may be used. The focus of the review was to provide an assessment of the available therapeutics and establish the strength of evidence of effectiveness. Recommendations were to use interferon- β in people with relapsing-remitting MS (RRMS) and secondary progressive MS who were still experiencing relapses, glatiramer acetate in people with RRMS, and interferon- β in those with a 'clinically isolated syndrome' and at high risk to develop MS. The importance of neutralising antibodies to

interferon- β was considered but it was felt that more research was required before they should be used in clinical decision making.

(b) *The National Multiple Sclerosis Society* [3]. The Medical Advisory Board of the National Multiple Sclerosis Society in the United States produced a paper on changing therapy in relapsing MS. They reviewed possible markers of treatment failure, including relapses, acquired neurological deficits and MRI activity, making the point that a single attack whilst on therapy should not be regarded as indicative of treatment failure, nor should such failure be determined within a few months of initiating treatment; they warned of the problems in measuring changes in very low extended disability score (EDSS) ranges, which they considered too variable to be used in isolation to define treatment failure; though they thought that quantitative measures of lesion activity on MRI might prove useful to indicate the risk of future clinical treatment failure, they did not think that the MRI should be used as the sole surrogate indicator of treatment failure. They considered that continued frequent relapses, or non-relapse-associated MRI activity might justify change in therapy, the use of combination therapy or even the use of non-FDA-approved drugs, provided that the risks and indications were understood by the treating physician and patient. They recommended that such patients might be considered for enrolment into properly designed controlled clinical trials.

(c) *The Canadian MS Working Group* [4–6]. The Canadian MS Working Group defined clinical attacks and identified useful prognostic markers for exacerbations, assessing their long-term impact on disease progression and disability. They reviewed data implying that disease progression correlates to the number of relapses and identified that a 1-point progression on EDSS, measured at 6 months, was 80% sensitive and highly specific for sustained disease progression at 4 years. They provided a scheme – 'the three gauge model' – to define a level of concern on the part of a physician, raising consideration of treatment modification based on relapse rate, disability and MRI scan. The support for the model defining levels of concern is derived from observations in the published large clinical trials and may be better substantiated when larger cohorts are available.

(d) *The Multiple Sclerosis Treatment Consensus Group (MSTCG)* [7, 8]. The MSTCG originated in Germany, Switzerland and Austria and has now included 12 other European countries. Its premise is that there is value for patients, health providers and insurance companies to have disease activity-dependent recommendations both for compounds based on Class I evidence and licensed and for those that are widely used, but unlicensed, or are in the 'pipeline'. The MSTCG has devised a simple scheme to escalate therapy from initial and early treatment with the licensed compounds to cytotoxic drugs or experimental treatments including monoclonal antibodies and plasma exchange. By so doing the MSTCG goes further than previous attempts to reach a wider consensus of MS experts.

The workshop participants agreed that a more global consensus would be helpful but recognised that health systems, accessibility to agents and licence are different in different countries, making it unlikely that adaptation of the European recommendations would be practicable in the US or Canada. The workshop participants recognised that a more general consensus would be required if all areas of potential MS treatment were to be covered, or decisions on initiation, cessation, consideration of modification and escalation of therapy would remain variable and individualistic.

Despite recognising the major difficulties, the experts concluded that the medical advisory boards of the national MS societies might be able to modify the existing advice and to draft a statement in which consensus and controversy in the field of MS treatment is defined, thereby encouraging clinical research into the unanswered questions posed by this workshop.

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