Treatment of Relapsing-Remitting Multiple Sclerosis: Current and Future Algorithms

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Key Words

Decision model · Monoclonal antibody · Relapsing remitting multiple sclerosis · Treatment algorithm

Prevalence and Incidence of MS are Increasing

Both the prevalence and incidence of multiple sclerosis (MS) are increasing worldwide [1–3]. The 2- to 3-fold rise in prevalence over the past 50 years can be explained in part by improved diagnostic tools and the increasing life expectancy of individuals with MS, whereas the 2-fold increase in incidence over the same timeframe can be attributed to a marked decrease in infectious diseases and a corresponding increase in autoimmune diseases [4].

Early Treatment of RRMS Improves Outcomes

The MS disease course is characterized by both inflammatory and degenerative elements, with different mechanisms underlying each phase (fig. 1). Early treatment in the inflammatory phase is associated with better long-

term outcomes. A long-term study examined survival in a cohort of patients ($n = 372$) who had participated in a pivotal randomized, placebo-controlled clinical trial of interferon beta in relapsing-remitting MS [5]. After a median of 21.1 years from the time of enrollment, 98% of patients were identified and 81 deaths were recorded. Early treatment was associated with prolonged survival, as evidenced by a 46.8% reduction in the hazard rate of all-cause mortality among patients treated with interferon versus placebo.

New MS Therapies Drive New Treatment Algorithms

The evolution of disease-modifying therapies (DMTs) for relapsing-remitting MS has escalated during the past few years. The first highly-selective monoclonal antibody against VLA-4, natalizumab, entered the market in 2006. By producing an almost 70% reduction in the annualized relapse rate, natalizumab was a quantum leap forward compared with existing agents (interferons, glatiramer acetate, mitoxantrone). Its shortcoming, albeit in only a few cases, was the occurrence of a rare viral disease – progressive multifocal leukoencephalopathy –

Fig. 1. A two-phase model of multiple sclerosis: inflammatory and degenerative. Underlying mechanisms for each phase differ.

with an associated mortality rate of 20%. The first oral DMT, fingolimod, was introduced in 2011 and was followed in 2013 by approval of two additional oral drugs (teriflunomide and dimethyl fumarate) as first-line treatments. The MS treatment algorithm was amended accordingly to incorporate these newer options. Also in 2013, the European Medicine Agency approved alemtuzumab for ‘patients with active relapsing-remitting MS ... with signs of disease activity clinically or on MRI ...’ The MS treatment algorithm was tweaked further to accommodate alemtuzumab as a first-line therapeutic option (fig. 2).

The ‘Multiple Sclerosis Decision Model’

The introduction of new and potent DMTs for relapsing-remitting MS has increased the desire for therapeutic success and shifted the treatment goals from ‘reducing the relapse rate’ to ‘achieving an absence of clinically relevant disease activity’. In order to standardize measurement of this newer therapeutic aim and support early treatment decisions, a panel of German experts proposed a multifactorial decision model based around the domains of relapse, disability progression, neuropsychology and magnetic resonance imaging [6]. The Multiple Sclerosis Decision Model uses a ‘traffic light’ system with different weightings applied to measures of disease

Fig. 2. Therapeutic concepts for multiple sclerosis: 2014. IFN-β = interferon-beta; iv = intravenous; IG = immunoglobulin; BG-12 = dimethyl fumarate; MP = methylprednisolone.

activity in each of the four domains (fig. 3). Evaluation of therapeutic success incorporates measurements from each domain and serves as a guide for clinical decision-making.

In the event that the decision model indicates that a change of therapy is warranted, the timing of the switch is an individual decision (i.e. it is not proscribed). Some factors to consider when taking a decision to switch include:

Fig. 3. Multiple Sclerosis Decision Model: evaluation of therapeutic success. MRI, magnetic resonance imaging. Reproduced from [6] with permission.

Fig. 4. Therapeutic concepts for multiple sclerosis: 2015. Mitox = mitoxantrone; Cyclo = cyclophosphamide; IFN-β = interferon-beta; Peg IFN = pegylated interferon; MP = methylprednisolone; iv = intravenous; PLEX = plasmapheresis.

- Progression occurred but was not permanent
- Tolerability affects compliance?

An immediate treatment switch is essential in the event of: two relapses; one relapse and any new MRI lesion; or in the presence of significant confirmed disease progression.

In the near future, MS treatment algorithms will be directed by disease activity (i.e. high or low) (fig. 4); this will necessitate redefining the clinical criteria. There are numerous opportunities to be explored and a substantial amount of work ahead for clinicians treating patients with MS.

Disclosures/Conflict of Interest

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- Relapse in the first year (but not in the first 3 months after treatment initiation)
- Relapse responding poorly to corticosteroids
- ≥ 2 new MRI lesions (T2/ gadolinium-enhancing) without relapses

References

- 1 Simpson S Jr, Pittas F, van der Mei I, Blizzard L, Ponsonby AL, Taylor B: Trends in the epidemiology of multiple sclerosis in Greater Hobart, Tasmania: 1951 to 2009. *J Neurol Neurosurg Psychiatry* 2011;82:180–187.
- 2 Fernández O, Fernández V, Guerrero M, León A, López-Madróna JC, Alonso A, Bustamante R, Tamayo JA, Romero F, Bravo M, Luque G, García L, Sanchís G, San Roman C, Romero M, Papais-Alvarenga M, de Ramon E: Multiple sclerosis prevalence in Malaga, Southern Spain estimated by the capture-recapture method. *Mult Scler* 2012;18:372–376.
- 3 Otero-Romero S, Roura P, Solà J, Altimiras J, Sastre-Garriga J, Nos C, Vaqué J, Montalban X, Bufill E: Increase in the prevalence of multiple sclerosis over a 17-year period in Osona, Catalonia, Spain. *Mult Scler* 2013;19:245–248.
- 4 Bach JF: The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002;347:911–920.
- 5 Goodin DS, Reder AT, Ebers GC, Cutter G, Kremenchutzky M, Oger J, Langdon D, Rametta M, Beckmann K, DeSimone TM, Knapertz V: Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFN β -1b trial. *Neurology* 2012;78:1315–1322.
- 6 Stangel M, Penner IK, Kallmann BA, Lukas C, Kieseier BC, Gold R: Multiple Sclerosis Decision Model (MSDM): development of a multifactorial model to monitor treatment response and disease course in relapsing remitting multiple sclerosis [Article in German]. *Akt Neurol* 2013;40:486–493.