PREDICTIVE VALUE OF MRI FOR CLINICAL OUTCOMES

Summary of presentations from the Genzyme-supported satellite symposium, held at the 22nd Annual Meeting of the European Charcot Foundation, Baveno, Italy, on 20th-22nd November 2014

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MEETING SUMMARY

The meeting outlined the evidence that the use of magnetic resonance imaging (MRI) markers as surrogate endpoints in clinical trials of relapsing-remitting multiple sclerosis (MS) is both valid and informative. The mechanisms of action of teriflunomide (Aubagio®) and alemtuzumab (Lemtrada®), both treatments for relapsing-remitting MS, were discussed, and their Phase II and III safety and efficacy data were reviewed alongside the MRI-derived outcome measures.

MRI Markers of Disability

Professor Maria Pia Sormani

MRI-derived markers of MS are enabling a deeper understanding of the pathophysiology of MS. They provide prognostic and diagnostic markers to improve clinical practice, and can detect changes in the brain and spinal cord, indicative of clinical improvements due to disease-modifying agents. Surrogate endpoints are often used in clinical trials when the treatment goals of an intervention are difficult to assess, and when modification of the surrogate marker by the intervention is predictive of its efficacy. The nature of the disability in MS necessitates the use of a surrogate marker in clinical trials: disability is very difficult to measure, it is slow to progress, and it is irreversible – so allowing trial participants to continue on a potentially ineffective intervention is not justifiable if a surrogate marker is available.

For a surrogate marker to be valid, it must capture the full effect of treatment on the clinical outcome. In two independent meta-analyses, this requirement was found to be met for MRI lesion changes (measured with conventional tesla [T]2-weighted imaging) as a surrogate marker of reduced relapse rates.[1,2] The first analysis compiled all randomised trials in relapsing-remitting MS for the period prior to, and including, 2009; the second analysis included all studies completed since that date until 2013. Both revealed that while there may be poor correlation at an individual level between T2 lesion size and relapse rate, there was a very strong and consistent correlation between reductions in lesion size and reduced relapses due to treatment.

Lesions measured with T2-weighted imaging have a weaker, though still significant, relationship with disability progression in MS.[3,4] For this clinical outcome, a recently published meta-analysis, which included 13 clinical trials on relapsing-remitting MS, found that brain atrophy (change in brain volume) and T2 lesion size entered together as predictive variables in a regression model can account for 75% of the variance in treatment effects on disability progression.[5] This finding suggests that by including both surrogate markers in the analysis, variability in each marker's relationship with a particular drug has less impact on the overall model. For example, disability progression after treatment with teriflunomide was unrelated to brain atrophy change, but was closely predicted by the T2 lesion number reduction. In contrast, disability progression decreased after alemtuzumab was predicted reliably by brain atrophy reduction, but to a lesser extent by T2 lesion number change.

For a surrogate marker to be valid across individual patients, it must pass a set of four statistical criteria, commonly referred to as the Prentice criteria.[6] These dictate that the treatment must have an effect on the surrogate; the treatment must have an effect on the clinical outcome; the surrogate and the clinical outcome must be correlated; and this correlation must capture the variance in the clinical outcome due to the treatment. This last criterion also offers a method to evaluate the quality of the surrogate; the greater the proportion of the treatment effect that is explained by the surrogate, the more 'perfect' the surrogate marker. Using the methods just described, the combination of MRI lesions and relapse rate was evaluated as a surrogate endpoint for reduced disability worsening in MS due to treatment with interferon β-1a (IFNb1a).[7] More than 60% of the variance in the treatment effect was accounted for by each endpoint in isolation, but when combined, 100% of the variance could be explained. This suggests that the combined endpoints, both of which are measurable over the short term, are a useful surrogate for disability progression over the long term.

A similar analysis was performed to evaluate the same combination of endpoints, as well as the extent of brain volume change, as surrogate markers for the reduction in disability progression after treatment with fingolimod.[8] Taking the potential surrogate endpoints by themselves, the separate regression models revealed that reduction in the mean number of MRI lesions accounted for around half of the treatment effect on disability, and around 60% and 23% of the variance in the treatment effect was shared by the reduction of relapses and the reduction in brain atrophy, respectively. When combined, it was found that MRI lesions did not have any unique predictive power for the reduction in disability progression due to fingolimod. However, relapses and brain volume change could account for 73% of the variance in the treatment effect. The analyses described suggest that the effect of a particular treatment on disability progression in relapsing-remitting MS can be explained by a reduction of MRI lesions and/or brain atrophy accumulation, but the degree to which these markers are appropriate as surrogate endpoints will be drug-specific. Further studies (with standardised methodologies) are needed to strengthen the role of MRI markers as surrogates for disability in MS.

Teriflunomide: Efficacy by MRI Measures

Professor Andrew Chan

Teriflunomide inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), which is a key enzyme for *de novo* pyrimidine synthesis, itself in high demand by activated and proliferating lymphoblasts.[9] In MS, teriflunomide is thought to reduce the activity of proliferating T lymphocytes and B lymphocytes, thereby diminishing the overall inflammatory response. The drug may also exert its effects via DHODH-independent pathways, which presumably include inhibiting protein tyrosine kinases, altering

cytokine production, and modulating the expression of cell-surface molecules.[9] There have been two pivotal Phase III trials (TEMSO[10] and TOWER[11]) of teriflunomide in relapsing MS, each showing a dose-dependent reduction of the relapse rate and the reduction in disability progression. An extension phase of TEMSO revealed that disability progression was stabilised with teriflunomide over 9 years of the study. Furthermore, in a trial (TOPIC[12]) recruiting very early stage patients with clinically isolated syndrome (a single episode of demyelination) teriflunomide reduced the risk of conversion to clinically definite MS (i.e. the occurrence of a second relapse). This efficacy was achieved across all studies without major short or long-term safety signals.[13]

The TEMSO and TOPIC studies, as well as the preceding Phase II study,[14] also included MRI imaging as an outcome parameter. In the Phase II trial, the number of unique active lesions (i.e. T1 gadolinium [Gd]-enhancing lesions and the number of unique new or enlarging T2 lesions) was clearly reduced over 36 weeks. In the Phase III TEMSO trial there was a dose-dependent reduction in total lesion volume after 108 weeks of teriflunomide treatment[10] that was primarily dependent on T2-hyperintense lesion volumes, but with a significant independent contribution from the T1-hypointense lesion volumes.[15] More traditional MRI measures also favourably responded to teriflunomide over placebo in a dose-dependent manner. With the teriflunomide dosage of 14 mg, which is approved by EMA, there was an 80% reduction in T1 Gd-enhancing lesions[10,15] and a 69% reduction in the number of combined unique, active T1 and T2 lesions. Global brain atrophy, defined as total parenchymal volume change, also progressed more slowly after teriflunomide compared with placebo; this was largely dependent on the impact on white matter.[15,16] Furthermore, in a post-hoc analysis of the TEMSO trial data, it was found that there were more patients free of both clinically and MRI-measured disease activity after teriflunomide compared with placebo (Figure 1).[17]

In the TOPIC study, treatment of patients at a very early stage of MS with teriflunomide reduced the number of Gd-enhancing lesions by 59% and reduced the volume of T2-hyperintense and T1-hypointense lesions.[12] These findings were consistent across sex, age, and baseline lesion loads.[18] In summary, clinical efficacy on disability progression and relapse rate are corroborated by MRI-based outcome measures. In the future, MRI may also be able to inform our measurement of drug efficacy in more detail in order to identify non-responding patients in need of an alternative approach. However, there are many aspects of these measures that need to be examined further if we are to fully understand their biological significance.

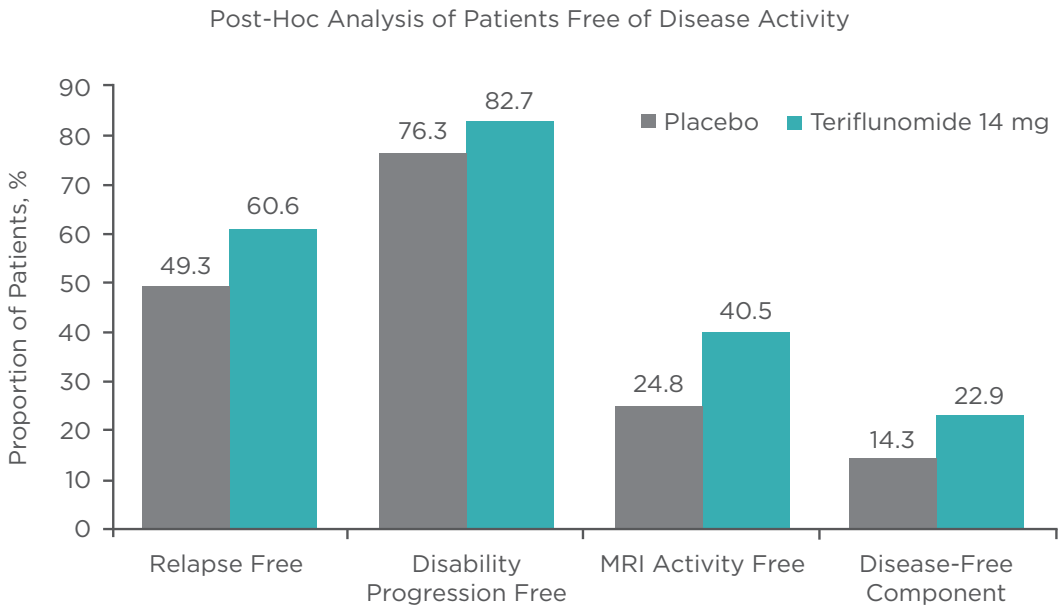

Figure 1: Teriflunomide increased the proportion of patients free from disease activity.[17]
MRI: Magnetic resonance imaging.

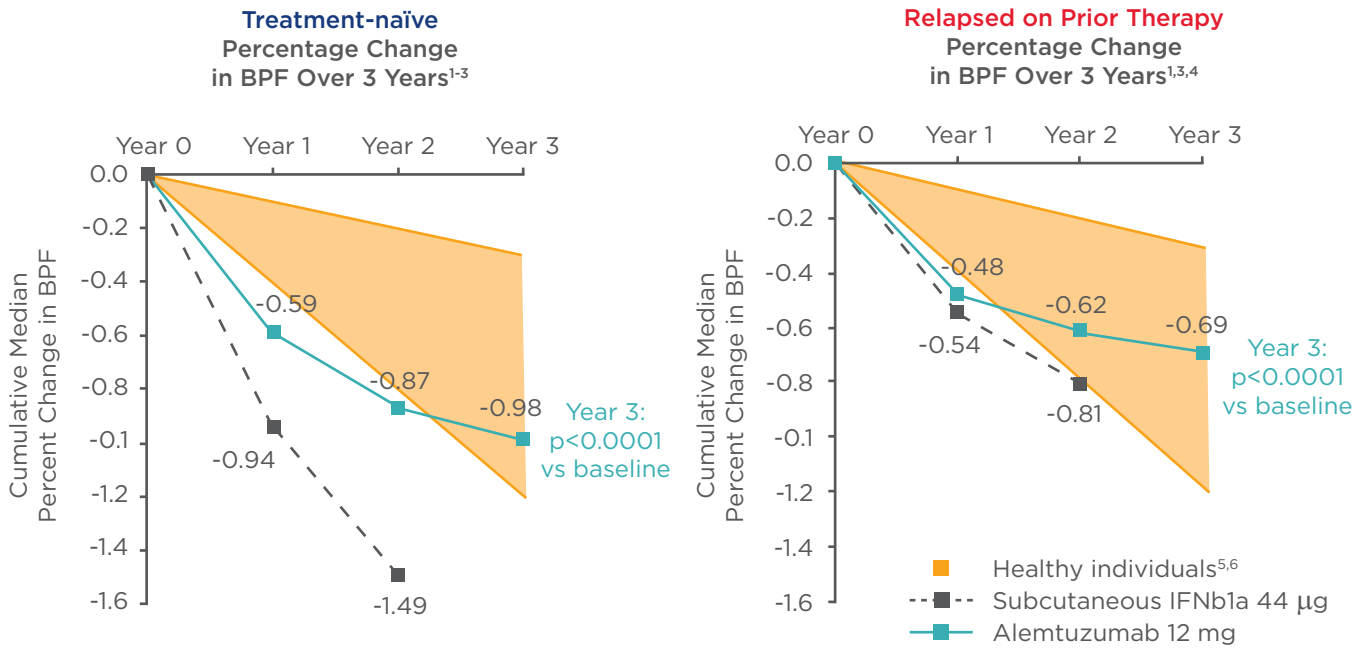

Figure 2: Alemtuzumab was superior in reducing the rate of brain volume loss versus subcutaneous interferon β-1a (IFNb1a).[34,35]

BPF: Brain parenchymal fraction; vs: versus.

Effects of Lemtrada® Through the Lens of Radiological Markers

Professor Hans-Peter Hartung

Alemtuzumab (Lemtrada®) is a humanised monoclonal antibody licensed for the treatment of MS that selectively targets CD52, a protein that is abundant on the surface of T and B lymphocytes, monocytes, and macrophages. It has a unique dosing regimen in that it is administered on five consecutive days at baseline and then on three consecutive days after 12 months. Due to its selective depletion of lymphocytes, innate immune cells such as neutrophils, monocytes, eosinophils, and basophils are apparently unaffected,[19] while there is a large and sustained inhibition of CD4 T cells.[20] After administration, reconfiguration of the immune system occurs, so that during repopulation of the T cell pool there is a predominance of 'T regulatory' cells[21,22] that theoretically counteract any auto-aggressive or inflammatory cell population. There is also a return of a memory phenotype T cell population.[23,24] None of these responses are seen with IFNb1a, and it is this change in the balance of the immune system after alemtuzumab treatment that can help rationalise its durable effects.[24]

Amongst the studies conducted in the clinical development program, alemtuzumab was compared to an active comparator (high-dose high-frequency IFNb1a) in a Phase II trial,[25] which included an ongoing, long-term extension study that followed patients over 5 years. Two Phase III trials, also comparing alemtuzumab to subcutaneous IFNb1a have also been completed, one looking at treatment-naïve patients,[26] and the other at patients with continued disease activity despite immunomodulator therapy.[19] The co-primary endpoints for all studies were annualised relapse rates (ARR) and the time to sustained (6 months) accumulation of disability (SAD). In both Phase III trials there was a markedly greater reduction in the ARR after 12 mg alemtuzumab compared with IFNb1a.[19,26] There was also trend-level evidence for superiority of alemtuzumab for decreasing the frequency of SAD in treatment-naïve patients,[26] which was statistically significant in treatment-experienced patients.[19] In the latter study, a 42% reduction in the number of patients with SAD was observed. Furthermore, in the extension phases of these studies the efficacy was shown to be sustained in both treatment-naïve[27] and treatment-experienced patients.[28]

The MRI-based outcome measures (Gd-enhancing lesions, new T1 lesions, and new or enlarging

T2 lesions) in the Phase III trials also favoured alemtuzumab. A majority of patients on alemtuzumab were free from new lesions 3 years after trial onset. This outcome was achieved even though 82% of the patients had not received alemtuzumab for the latter 2 years of the trials,[29] and there was no significant difference in the number of lesions in Year 2 compared with Year 3.[30] In both the treatment-naïve[31,32] and treatment-experienced patients[32,33] alemtuzumab slowed the yearly rate of brain volume loss over 3 years compared with IFNb1a, with atrophy rates being closer to the normal age-related loss seen in healthy individuals (Figure 2).[34,35] Furthermore, after approximately 2 years, it was shown that more patients on alemtuzumab were free from MRI activity, as evidenced by the absence of both Gd-enhancing and new or enlarging T2-hyperintense lesions.[29,30]

The rate of adverse events with alemtuzumab (12 mg), including those leading to treatment discontinuation, was generally similar to that with IFNb1a, and the adverse event profile was similar between treatment-naïve patients and patients who relapsed on prior therapy.[25,26] In the extension study, the adverse event profile was similar to that seen in the core phase of the studies,[27,28] and the rate of overall adverse events, including infections, decreased over time.[36] There is a known risk for the development of thyroid disease after alemtuzumab treatment. The cumulative proportion of thyroid adverse events was estimated to be 36% at 48 months following first alemtuzumab exposure,[37,38] and the annual incidence of thyroid events following alemtuzumab treatment peaked in Year 3 and declined in Year 4.[37,39,40]

In summary, alemtuzumab has demonstrated superior clinical efficacy when compared with high-dose subcutaneous IFNb1a for reducing both ARR and SAD in MS. The majority of alemtuzumab-treated patients in the pivotal Phase III trials were free of MRI activity in their third year of follow-up, and alemtuzumab continued to slow the yearly rate of brain volume loss over 3 years. These findings provide strong support for the durable efficacy of alemtuzumab in both treatment-naïve patients and patients who relapsed on prior therapy, particularly given that the majority of patients received no treatment for 2 years.

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