The Lesson of MS: Is MRI Useful as Surrogate Marker?
Maria Pia Sormani – University of Genoa

mariapia.sormani@unige.it

The primary efficacy outcome in confirmatory clinical trials should be the variable reflecting the most important aspect in terms of quality and/or duration of life of patients. In particular, in multiple sclerosis (MS) the primary outcome should be a clinically measured prevention or delay of disability progression and the incidence of clinical relapses. For practical reasons, clinical trials in MS usually do not last longer than 2 to 3 years, although the accumulation of irreversible disability usually occurs over a longer time period. Moreover, very large samples of patients need to be recruited for such trials, in order to obtain an adequate statistical power to evaluate progression of disability. In addition, with new therapies available, having placebo arms in phase III poses many unsolved ethical problems. Sample sizes may be even larger if superiority over an active comparator or non-inferiority designs are pursued. As a consequence, the use of surrogate outcome measures would be an attractive, if not an inestimable, strategy to overcome the present situation in designing, planning and conducting clinical trials in MS. Moreover, demonstrating the validity of a surrogate marker in MS might prove to be important for daily-life decisions regarding individual patients' treatment.

As a non-invasive and increasingly available approach, magnetic resonance imaging (MRI) offers several advantages over the accepted clinical outcome measures for MS, including an increased sensitivity to disease activity, and a better association with histopathology findings than that with clinical manifestations. MRI also provides highly reproducible measures on ordinal scales, thus allowing a more powerful statistical approach. In addition, the assessment of the MRI scans can be performed at the highest degree of blinding and MRI data are retrievable for new, not pre-planned analyses. [modified from: Bar-Zohar et al, Mult Scler 2008 (1)]

When referring to a variable as a surrogate for a definitive clinical outcome in a clinical trial, it is important to distinguish individual-level surrogacy from trial-level surrogacy.
In the former case, one considers the ability of substituting the surrogate in place of the clinical outcome for the management of a given patient. For trial-level surrogacy, the question is whether the results of a trial using the surrogate outcome can be used to infer the results of the trial if the clinical variable had been observed. This would be useful if the surrogate is observed earlier or can

be measured more conveniently or more sensitively than the clinical outcome. There is no logical imperative that a good individual-level surrogate should be a good trial-level surrogate, or vice versa. In Figure 1 the two concept are illustrated for correlation of two variables: in the first panel in each of the two trials (blue and red dots) there is a good individual level correlation between the surrogate and the clinical outcome (within each trial patients with higher levels of the surrogate have higher level of the clinical outcome); however the two trial have different average levels of the surrogate and identical average levels of the clinical variable. The opposite is true in the second panel, where we see a good trial level correlation, but no correlation at individual level within each trial.
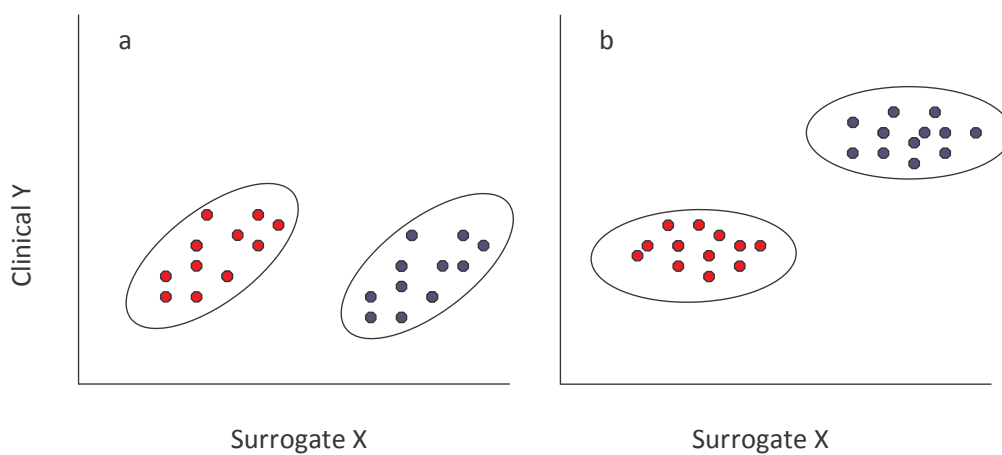

Figure 1: Hypothetical individual data on the surrogate (X) and definitive endpoint (Y) for two clinical trials. (a) X is a poor trial-level correlate but a good individual-level correlate. (b) X is a good trial-level correlate but a poor individual-level correlate.

Up to now, all the studies aimed at evaluating the potential role of MRI as a surrogate for clinical variables in MS have been focused on individual level surrogacy. The observation of a low individual level correlation between MRI markers and not only disability progression, but also with relapses, the clinical manifestation of MS inflammatory component, generated the so called "clinico-radiological paradox" (2-4). This suggested that MRI cannot be used as a surrogate marker of clinical endpoints (2-3). However, some misconceptions need to be clarified. First, the correlation between the potential surrogate (in this case, MRI lesions) and the clinical outcome (in this case, relapses or disability) is indeed a necessary condition for surrogacy; nevertheless the correlation does not need to be very strong at the individual level, depending not only on the true

relationship between the surrogate marker and the clinical outcome, but also on the variability of these measures (between individuals). Because of this high variability, it is important to evaluate the correlation in studies of a high methodological quality; pooling data retrospectively from different trials or natural history studies can dilute the correlation, that was indeed detected when studied within randomized clinical trials (5,6). Second, the concept of surrogacy is always related to a treatment effect and, in particular, to the amount of the treatment effect on the clinical outcome that is mediated through the surrogate (7). This issue was explored by Prentice, who formulated four criteria for a formal validation of a surrogate endpoint at the individual level in the context of a clinical trial (8). According to this approach a paraclinical measure can be considered as a valid surrogate endpoint of a clinical endpoint in a given disease for a specific treatment when the following conditions are met: 1) the treatment is effective on the surrogate, 2) the treatment is effective on the clinical end-point of interest, 3) the surrogate and the clinical end-point are significantly correlated, and, most importantly, 4) the effect of the treatment on the clinical end-point disappears when adjusting for the surrogate end-point. This approach, applied to data from two clinical trials in relapsing remitting (RR) (5) and secondary progressive (SP) (6) MS, showed that in both cases the treatment effect on MRI lesions accounted for a large portion of the treatment effects on relapses.

For clinical trials design it is more important the concept of "trial level surrogacy" : according to this idea, the effect of a treatment on a valid surrogate marker should satisfyingly correlate with its effect on the clinical endpoint across different randomized trials. Then, trials with large effects on the potential surrogate marker should have also large effects on the clinical outcome and vice versa. This "trial level surrogacy" was tested in MS in a large meta-analysis of all the published trials in RRMS reporting data both on MRI variables and relapses (9).

The results of this meta analysis (23 trials, 6591 patients) indicated a strong correlation between the effect of therapy on active lesions and the effect of therapy on relapses. This correlation accounted for more than 80% of the variance in the relationship (Figure 2). The relationship was also validated on an independent set of trials (Figure 3).
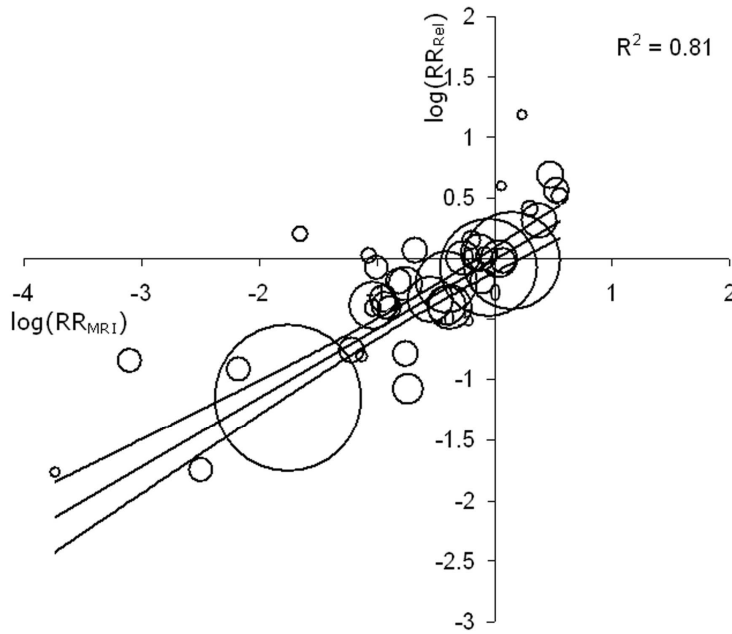
Figure 2: Treatment effect on Magnetic Resonance Imaging lesions (x-axis) versus treatment effect on clinical relapses (y-axis). Both treatment effects are expressed as Rate Ratios on a log scale. Each circle represents a contrast versus placebo and its dimension the weight of the contrast, proportional to trial size and duration. The solid line represents the weighted regression line with the 95% confidence band. RR=Rate Ratio , Log(RR_{Rel})= Logarithm of the relapse rate ratio, Log(RR_{MRI})= Logarithm of the MRI lesions rate ratio .
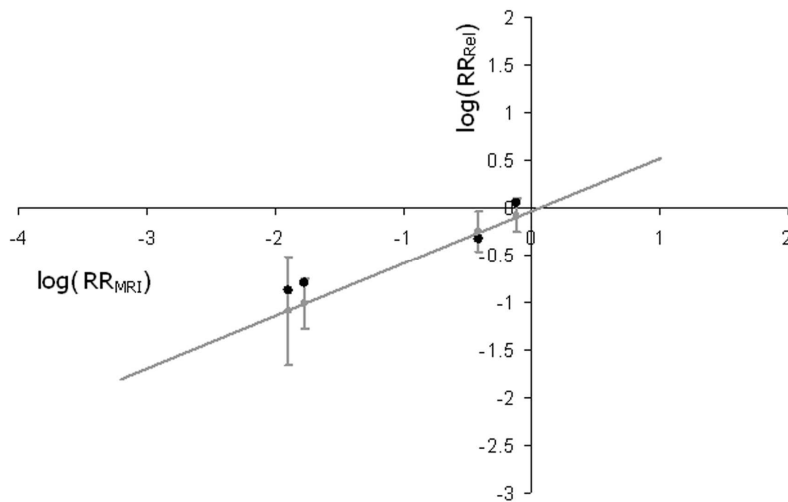

Figure 3: Validation of the regression line: the treatment effect on relapses as estimated by the regression line is compared by that really observed in four randomized controlled trials not used to estimated the regression equation. The solid line represents the estimated regression line; the bars are the 95% prediction intervals of the estimated treatment effects on relapse rates estimated by the observed treatment effect on MRI lesions; the black dots are the observed treatment effects on relapse rates. RR=Rate Ratio , Log(RRRel)= Logarithm of the relapse rate ratio, Log(RRMRI)= Logarithm of the MRI lesions rate ratio.

A similar approach was applied to study the role of MRI lesions as surrogates for disability progression: all the randomized trials in RRMS patients, lasting at least 2 years, aimed at assessing the efficacy of disease modifying therapies utilizing drugs of any class and reporting data about number of MRI lesions and the proportion of patients with a disability progression over the follow up period were collected. 11 trials were included, for a total of 8527 patients and 15 contrasts (15 comparisons experimental vs standard)

In Figure 4 the relationship between the treatment effect on MRI lesions and the treatment effect on the risk of disability progression is reported.
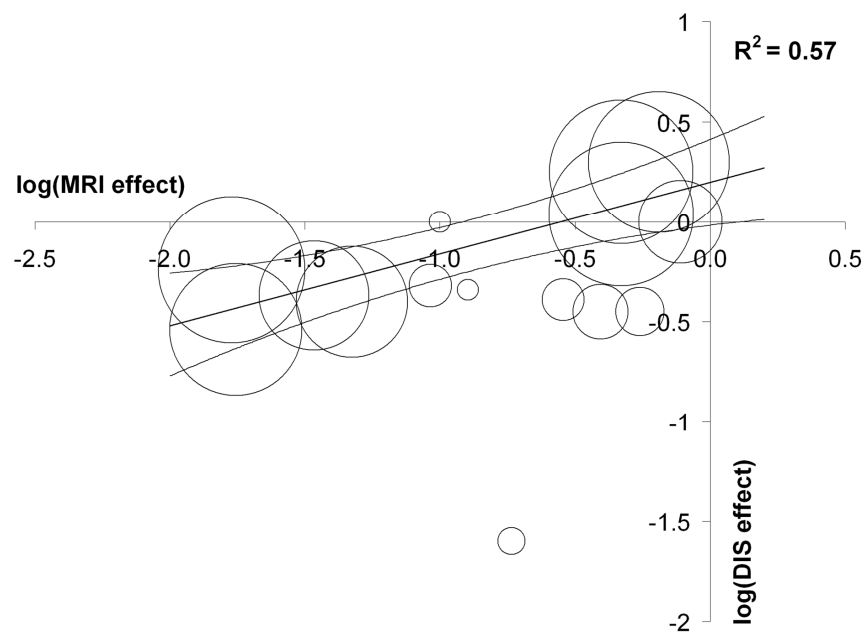

Figure 4: Treatment effect on disability progression (y-axis) versus treatment effect on MRI lesions (x-axis). Both treatment effects are expressed as ratios on a log scale. Each circle represents a contrast of an active versus the control arm and its dimension the weight of the contrast, proportional to trial size and duration. The solid line represents the weighted regression line with the 95% confidence band. Log(MRI-effect)= logarithm of the MRI lesion number ratio, Log(DIS-effect)=logarithm of the ratio of the proportion of progressing patients.

The correlation between effects on MRI and effects on disability progression is much less marked, and despite a relationship with a statistically significant R^2 value (0.57, p=0.001) it should be kept in mind that the observed results are driven mainly by the large trials at the extreme ends of the plot. Therefore, this result, even if encouraging, must be interpreted as preliminary.

These observations could have important implications for the general strategy of clinical trials in RRMS. At present, standard practice is to conduct short term phase II studies based on MRI lesions to determine if a definitive trial with a clinical endpoint as the primary outcome should be contemplated. However, this practice is more based on empirical reasoning than on evidence; the results of the meta-analysis provide a solid scientific evidence for the current trial practice and supports the use of MRI parameters as endpoints in phase II trials. In fact, based on the meta analysis results, once a drug has been shown to be active on MRI lesions in a phase II setting, the prior probability of an effect on relapses is strongly increased and this effect can be indirectly estimated. This information can be used both in the decision to run a phase III trial, and in its design. This gives also support for the use of MRI markers as primary endpoints in trials evaluating analogues or different ways of administration of drugs of proven efficacy, if the available data from previous trials confirms a relationship between their effects on MRI markers and on relapses, according to the estimated regression equation.

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