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REVIEW

Smoke and mirrors: Limited value of relative risk reductions for assessing the benefits of disease-modifying therapies for multiple sclerosis

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Abstract
A reduction in relapse rate is the main primary outcome in most clinical trials in patients with multiple sclerosis (MS), with the effect of a treatment commonly expressed as relative risk reduction for this outcome. Physicians often assume that a drug with a higher relative risk reduction demonstrated in one trial is more effective than a drug with a lower relative risk reduction in another, and may pass this idea on to younger physicians and to patients. The use of the relative risk reduction as a measure of drug efficacy can be misleading, as it depends on the nature of the population studied: a treatment effect characterized by a lower relative risk reduction may be more clinically meaningful than one with a higher relative risk reduction. This concept is especially important with regard to clinical trials in patients with MS, where relapse rates in placebo groups have been declining in recent decades. Direct, head-to-head comparisons are the only way to compare the efficacy of the different treatments for MS.

Abbreviations: BID, twice-daily administration; BEYOND (trial), BEYOND: Betaferon/Betaseron Efficacy Yielding Outcomes of a New Dose in Multiple Sclerosis (MS) Patients; CARE MS I (trial), Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis; DMT, disease-modifying therapy; EVIDENCE (trial), EVidence of Interferon Dose-response: European North American Comparative Efficacy; INCOMIN (trial), Independent Comparison of Interferon; RCT, randomised, controlled trial; REGARD (trial), REbif vs Glatiramer Acetate in Relapsing MS Disease; TENERE (trial), A Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis; TRANSFORMS (trial), Efficacy and Safety of Fingolimod in Patients With Relapsing-remitting Multiple Sclerosis With Optional Extension Phase

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1. Introduction

Randomized, controlled trials (RCTs) represent the highest level of evidence-based medicine. Appropriate interpretation of the results of these trials is essential to guide the correct application of therapies in everyday clinical practice. Recent years have seen the introduction of novel, oral disease-modifying therapies (DMT) into the management of multiple sclerosis, based on the results of RCTs comparing them directly with interferon-β, the current standard of care for this condition.

Comparisons of annual relapse rates are key outcomes of most RCTs in this area. Relative risk reductions are often used to express differences between treatments in this and other efficacy parameters and, importantly, relative risk reductions are widely used in marketing activities by their pharmaceutical sponsors. It is assumed widely that a higher relative risk reduction means greater clinical efficacy: a dangerous assumption in any field of medicine and especially so in multiple sclerosis, where the nature of the patient population has changed over time. This misconception remains prevalent among healthcare professionals caring for patients with MS and in this article I will discuss the dangers inherent in over reliance on the relative risk reduction as a measure of clinical efficacy, and how we should compare the effectiveness of different DMTs.

2. Absolute risk, relative risk and number needed to treat

Table 1 provides mathematical definitions of absolute risk reduction, relative risk reduction and number needed to treat, while Table 2 shows how these parameters relate to each other, based on a hypothetical evaluation of a new DMT (Spitalnic, 2005; Cutforth, 2015). Intervention in patients at low risk of relapse (Trial 1 in Table 2) provides a much lower absolute risk reduction compared with patients at intermediate (Trial 2) or high risk (Trial 3). However, the relative risk reduction is the same for the intermediate- and low-risk populations, and higher than that for the high-risk population. Numbers needed to treat are consistent with these observations: we would need to treat 50 low-risk patients to prevent a single relapse, but only 3–5 of the higher-risk patient groups.

Thus, the relative risk reduction tells us little about the absolute clinical benefit delivered by the new treatment, as a high value may result from a clinically insignificant change in the event rate in a population at low background risk. It is meaningless to compare relative risk reductions between trials where populations may have a different background risk of relapse. The absolute risk reduction and number needed to treat, by contrast, provide important additional information on the actual magnitude of clinical benefit that a treatment provides. Unfortunately, these parameters are not reported routinely in reports of clinical trials. Incorporating the absolute risk reduction (with the number needed to treat) would lead to more appropriate treatment decisions than those based on consideration of the relative risk reduction alone.

3. Special relevance to clinical trials in patients with MS

The apparent background severity of relapsing-remitting MS, as indicated by the relapse rate, has been declining in clinical trial populations since the pivotal trials that established interferon preparations as the standard of care for pharmacologic intervention in this disease (Klawiter et al., 2009); this has resulted in a clear decline in the relapse rates observed in the placebo groups of clinical trial populations with MS (Table 3). Given the underlying decline in relapse rates over time, it is unsurprising that absolute risk reductions achieved with active treatments relative to placebo have also tended to decline over this period (Table 3). Relative risk reductions vs. placebo for active treatments, by contrast, have increased in later trials

Table 1 Mathematical definitions of absolute risk reduction, relative risk reduction and number needed to treat to prevent one event.

Parameter	Definition
Event rate[a]	Number of patients with the event/ total number of patients in the group
Absolute risk reduction[b]	Control event rate–intervention event rate
Relative risk reduction (%)[c]	100 × (absolute risk reduction [%])/(control event rate [%])
Number needed to treat	1/absolute risk reduction (if the event rate is expressed as a ratio) 100/absolute risk reduction (event rate expressed as a percentage)

[a]Expressed as a ratio or percentage value.
[b]The absolute risk reduction will be expressed in the same units as the event rates on which it was based.
[c]The relative risk reduction is often shown shown as a percentage (as shown) but can also be shown as a ratio (omit the "100 × ").