Therapeutic interventions increasing seizure risk in multiple sclerosis: resolving discordant meta-analyses

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Several disease-modifying treatments increase seizure risk in multiple sclerosis and meta-analyses of randomised trials do not really disagree on this

In their *JNNP* meta-analysis Pozzilli *et al* concludes that sphingosine-1-phosphate receptor (S1PR) modulators substantially increase seizure risk in multiple sclerosis.[1] Conversely, another meta-analysis by Dang *et al*[2] recently concluded that 'no evidence of association was found between disease-modifying therapy and seizure risk'.

Both meta-analyses focused on randomised controlled trials, but used different selection criteria. Pozzilli *et al* were more restrictive in some regards (including large, long-term phase III trials rather than accepting any phase II or III trial); but less restrictive regarding comparisons (including not only placebo-controlled, but also active-controlled trials). Pozzilli *et al* furthermore performed meta-analysis of pairwise comparisons that involved a S1PR modulator, while Dang *et al* preferred network meta-analysis considering all treatments. One may debate which team made the best choices. In fact, probably both teams made some suboptimal combination of choices. For example, given Pozzilli's inclusion of both placebo-controlled and active-controlled trials, a network approach would have been desirable. Otherwise one assumes that non-S1PR disease-modifying treatments (DMTs) have no impact on seizures, similar to placebo. Conversely, Dang *et al*'s network meta-analysis machinery could have nicely accommodated active-controlled trials. However, this benefit was wasted by excluding such trials, hence dismissing half the evidence on S1PR modulators (4/8 trials) and similarly much evidence on other DMTs.

The two teams further diverged on whether and how they grouped treatments. By combining together 4 S1PR modulators (siponimod, fingolimod, ozanimod, ponesimod), Pozzilli *et al* increased their chances of documenting a seizure signal. However, one cannot be sure that this signal applies equally to all S1PR modulators. Moreover, the separation of S1PR versus non-S1PR was an arbitrary choice. Dang *et al*, conversely, examined each drug alone. With sparse seizure events, finding clear risk signals for single drugs is difficult, even if they do exist. Therefore, Dang *et al* was biased upfront towards concluding no associations with seizure risk. Still, their team did actually find much higher seizure risk with siponimod (their forest plot results contradict their text conclusion of no difference), cladribine, and interferon-beta.

Ironically, interferon-beta was used as control in three of the eight trials included by Pozzilli *et al*. These three trials showed no differences in seizure risk between S1PR modulators and interferon-beta, presumably because both drug groups increase seizure risk. Conversely, three of the five other trials showed much higher risk with S1PR modulators (2 vs placebo, 1 vs teriflunomide).

Data extraction may also cause discrepancies. Dang *et al* extracted 12 siponimod and 0 placebo participants with seizures in the EXPAND trial.[3] Pozzilli *et al* captured 19 and 2, respectively, using a broader definition that included also convulsions from central nervous system haemorrhage and cerebrovascular conditions. Both teams also faced the challenge of handling zero event counts in several trials. Their different offered solutions (Bayesian methods, dropping zero-event trials, double-arcsine transformations) were imperfect.[4]

Eventually, the overall conclusion may not be as confusing as these two meta-analyses suggest. S1PR, interferon beta and cladribine increase seizure risk. Small event numbers induce extra caution, but may still be used towards shared clinical decision-making.

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