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Ibudilast: a paradigm shift for progressive MS?

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While the armamentarium to treat relapsing-remitting MS is ever expanding, the choice of drugs to treat progressive forms of the disease remains limited. Though (ongoing) inflammation may play a role in neurodegeneration, other mechanisms are likely to contribute to it, and there is a need to identify drugs with a neuroprotective mode-of-action. Ibudilast is a drug that has previously been suggested to have a neuroprotective effect in relapsing-remitting MS¹: ibudilast (60mg) did not reduce the MRI activity or the relapse rate, but reduced brain volume loss accumulation by 34%. The SPRINT-MS trial² was a multicenter study sponsored by the NIH, including patients up to 65 years old with primary and secondary progressive MS. The trial showed that Ibudilast (100mg) reduced brain volume loss by 48% over 2 years.

In this issue of *Neurology*, Naismith et al. report additional endpoints from the SPRINT-MS study³. Secondary and tertiary MRI endpoints included gray matter atrophy, new or enlarging T2 lesions as measured every 24 weeks, and new T1 hypointense lesions at 96 weeks; also, the percentage whole brain volume change was re-assessed using a registration-based software for brain atrophy measure (SIENA) as a sensitivity analysis.

The results of this study are relevant for two reasons. First, the findings of the additional MRI endpoints analysis confirm those of the primary outcome of the trial: gray matter atrophy rate was reduced by 35% in patients treated with Ibudilast vs. placebo, and the percentage brain volume change assessed using SIENA was in the same direction as the one assessed using the segmentation-based technique of brain parenchymal fraction (BPF), even if to a smaller extent (20% reduction). Second, there was no effect of Ibudilast on the development of new T2 lesions, confirming the lack of effect on inflammation of this drug, as reported in the previous trial of ibudilast in relapsing-remitting MS¹.

Of note, in the SPRINT-MS trial, ibudilast showed only a small beneficial effect on confirmed disability progression, based on the Expanded Disability Status Scale (EDSS) score, despite the larger effects on clinical progression observed in the relapsing-MS trial.¹ This slightly disappointing result occurred despite a clearly beneficial effect on gray matter atrophy, which is known to play a key role in disability progression.⁴ Even if none of the phase 2 trials was powered to detect drug effects on disability progression, there is no good explanation for the small beneficial effect on disability progression in the SPRINT-MS trial compared to the larger effect observed in the previous RRMS study. For example, relapses may produce a measurable and sustained effect on disability and therefore the mechanisms of disability worsening between RRMS and progressive MS may be different and somehow favour the impact of inbudilast on progression in the relapsing group. .

Interestingly, a phase 2 trial of simvastatin vs. placebo carried out in secondary progressive MS (MS-STAT)⁵ showed a similar effect on atrophy as the SPRINT-MS trial, i.e. a 43% reduction of the annualized rate of whole-brain atrophy, in the absence of anti-inflammatory effects. Yet the MS-STAT trial did show an effect on disability outcomes. In the MS-STAT trial, though, disability scores were considered as continuous

variables, and (adjusted) differences at 24-month follow-up between treatment groups were computed. Also, a post-hoc analysis⁶ showed an effect on EDSS with mixed-effects models (the rate of annual EDSS worsening was slower in the simvastatin group than in the placebo arm (estimated rate \pm standard-error 0.08 ± 0.04 vs 0.21 ± 0.03 , $p=0.002$) It is possible that the lack of significant clinical effects in the SPRINT-MS trial may -at least partly- be due to the choice of a suboptimal clinical endpoint, like the confirmed EDSS progression.

At the recent MS Virtual 2020 Congress the results of the effect of Ibudilast on neurofilament light (NfL) were presented, and they were negative: the NfL levels had the same time trend in the placebo and in the Ibudilast arm. These results can have two different interpretations: the lack of any effect on NfL can be seen as not confirming the neuroprotective effect of Ibudilast; alternatively, this lack of effect might highlight the weak correlation of NfL with neurodegeneration, as some studies suggest that NfL changes are linked to inflammatory processes⁷. Further studies on NfL will help clarify this issue.

The results of the two phase 2 trials of Ibudilast conducted on patients in different phases of the disease are what the MS community was expecting for years: a drug with a confirmed effect on a surrogate marker of neurodegeneration, that is the brain tissue loss, despite the lack of an effect on inflammation. At present, a number of disease-modifying treatments with remarkable anti-inflammatory effects are already available, whereas drugs that can predominantly tackle neurodegeneration are virtually absent. The key question then is: do neuroprotective drugs provide a valuable option for MS treatment, both in the relapsing-remitting phase, probably added to an anti-inflammatory agent, and particularly in the progressive phase, when neurodegeneration plays a major role? Only a phase 3 trial, with a sufficiently large number of patients and powered on a robust disability progression outcome can give us an answer. Currently, it does not seem that such a trial is being planned.

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