CAN WE JUDGE THE EFFICACY OF DISEASE MODIFYING MEDICATIONS BASED ON THEIR EFFECTS ON MRI BRAIN ATROPHY? NO, WE CAN'T

Xavier Montalban, Spain

Brain volume loss is a common and early feature in multiple sclerosis (MS) patients. It occurs at an accelerated rate when compared with healthy controls, and it has a high clinical relevance as it has been related to disability. Thus, it is not surprising that recent clinical trials have incorporated atrophy outcomes as a measure of treatment effect. Most of the newest treatments available for MS patients have demonstrated to improve the curve of brain atrophy compared to placebo. That said, brain atrophy measures have some limitations that may difficult their use as a measure of treatment efficacy in clinical practice. First, we lack of a standardized method to determine atrophy rates in MS treated patients. Not only there is no consensus about which technique or software is the best one to use, but also there are many structures to measure (whole brain atrophy – i.e. brain parenchymal fraction, percentage of brain volume loss-; regional atrophy – i.e. cortical grey matter, deep grey matter, white matter volumes- or even spinal cord atrophy) and there again, no consensus about which one is the most reliable and the most clinically relevant. Second, there are different sources of errors that can influence atrophy results such as hydration status or inflammation. This is a very important issue when measuring brain atrophy in MS patients since inflammation at therapy onset may confound early brain volume changes because of the pseudoatrophy effect. In order to better calculate brain volume changes on therapy and to avoid the pseudoatrophy effect, some authors have proposed to delay baseline atrophy magnetic resonance imaging (MRI) scan or to use grey matter volume as a more robust atrophy measure. However, neither delaying baseline MRI scan nor using grey matter atrophy have been evaluated in proper clinical trials or prospective cohorts; hence, we cannot assure that these two strategies were a valid option. The third limitation regards to the duration of the studies performed to date: most of the data evaluating the effect of a specific therapy on brain atrophy is derived from clinical trials. Therefore, the relationship between atrophy and treatment effect is only analyzed while the trial is ongoing (i.e. three years) but there are no long-term follow-up studies evaluating the occurrence of early atrophy on treatment to predict long-term clinical outcomes (i.e. disability progression, etc.). Moreover, daily clinical practice data about MS therapies, atrophy and disability are scarce and with the inherent limitations of the observational studies. And last, but not least, global brain volume measures give us an estimate of a non-specific global effect which may be the result of different processes occurring in the brain such as axonal degeneration, inflammation, new lesion formation, etc. Newer techniques (i.e. diffusion tensor imaging, spectroscopy, magnetization transfer), are more pathologically specific imaging measures that may be able to show real therapy effects on axonal or myelin structures. However, they are more time consuming and therefore, less doable in clinical practice.

In conclusion, I am afraid that before we can judge the efficacy of disease modifying medications based on their effects on MRI brain atrophy we need to: come to and agreement and select the best suitable technique that will allow us to detect small brain volume changes in a robust, fast and feasible way; agree and select the most accurate, reproducible and reliable atrophy measure with a good correlation with clinical parameter and we must validate both of them as predictors of MS clinical evolution in long-term follow-up cohorts taking into account and correcting for all the possible confounders related with both the technique and the measure.