Natalizumab in secondary progressive multiple sclerosis

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Natalizumab in secondary progressive multiple sclerosis: an evolving story

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The ASCEND trial[1] was a two-part study that assessed whether natalizumab slows disease progression unrelated to relapse in patients with secondary progressive multiple sclerosis. Part 1 was a randomised, placebo-controlled, double-blind study, comprising 888 patients with secondary progressive multiple sclerosis (439 in the natalizumab group and 449 in the placebo group) who were followed up for 2 years. Part 2 was an optional 2-year, open-label, extension study, comprising 565 participants (291 continuing natalizumab and 274 initiating natalizumab). Part 2 was terminated by the funder of the study after the results of part 1 emerged, before completion of year 4 of the study, thus limiting available data to 156 weeks of follow-up.

The ASCEND trial did not meet the multicomponent primary endpoint for part 1 assessed at 2 years. No treatment effect was observed on two components of the primary endpoint that measure progression of ambulatory disability: the Expanded Disability Status Scale (EDSS) and the Timed 25-Foot Walk (T25FW). However, natalizumab treatment was associated with a nominally significant 44% reduction in the relative risk of confirmed upper-limb disability progression as measured by 9HPT, the third component of the primary endpoint (15% with natalizumab *vs* 23% with placebo; adjusted odds ratio 0·56 [95% CI 0·40–0·80]; p=0·001).

The results of this phase 3 trial are in line with those of the IMPACT trial,[2] which investigated interferon beta 1a in secondary progressive multiple sclerosis, in patients with similar baseline demographics (mean age 47 years, mean disease duration 16 years) to those enrolled in the ASCEND trial. A reduction in the relative risk of confirmed upper-limb disability progression, as measured by 9HPT, but no clinical effect on ambulatory disability, were documented in both IMPACT[2] and ASCEND.[1]

The observed discrepancies between lower-limb and upper-limb disability need addressing. Raju Kapoor and colleagues[1] pointed out that residual degeneration should abate more quickly in shorter axon pathways than in longer ones because shorter axons have a lower lesion burden. However, another potential explanation not offered by the authors might be that the progressive phase presents as gradual, insidious ambulatory worsening (ie, lower-limb disability expression [EDSS 3.5–6.5]). Conversely, in the ASCEND trial, there was no clear evidence of a gradual, insidious, progressive course unrelated to disease activity for upper-limb disability worsening. This consideration lends itself to two possibilities: natalizumab treatment had a positive clinical effect on upper limbs either through its effects on disease activity (which is strongly supported by its well documented effect on both annual relapse rate and MRI activity) or through its effects on the insidious neurodegenerative process, independently of focal inflammatory disease activity.

To address this important question, the effect of natalizumab versus placebo on upper-limb disability performance could be assessed in patients younger than 50 years versus those older than 50 years and according to the duration of the progressive phase after the onset of progression (duration <5 years *vs* >5 years), since disease activity is substantially dependent on age and time.[3] If natalizumab has a similar positive effect on upper-limb performance regardless of the age of the patients or the duration of the progressive phase, this result will be a clear demonstration that natalizumab has a real effect on the neurodegenerative process independently of the focal inflammatory process (the fundamental feature of multiple sclerosis progression). If, however, the reduction of upper-limb worsening is restricted to patients with secondary progressive multiple sclerosis who are younger than 50 years and who have a duration of the progressive phase shorter than 5 years, as observed with the interferon beta[4,5] and anti-CD20[6,7] phase 3 clinical trials, one could conclude that natalizumab affects disability worsening in secondary progressive multiple sclerosis by influencing disease activity, which is still present in the early phase of secondary progressive multiple sclerosis.

The debate around initiation of natalizumab treatment in patients with secondary progressive multiple sclerosis with worsening disability unrelated to relapse remains unresolved. Taking into account the benefits, risks, and costs of treatment, it might

be reasonable to first consider on an annual basis the phenotype descriptors, as defined by Lublin and colleagues,[8] including references to disease activity (based on clinical relapse rate and imaging findings) and disease progression. One might propose the use of natalizumab in secondary progressive multiple sclerosis mainly in those patients who have active and progressing disease.

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