EFFECTS OF FINGOLIMOD AND NATALIZUMAB ON SLOWLY EXPANDING LESION OCCURRENCE OVER TWO YEARS OF TREATMENT IN RELAPSING-REMITTING MULTIPLE SCLEROSIS

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Short title: SELs occurrence in natalizumab *vs* fingolimod

Objectives. Fingolimod and natalizumab are highly effective treatments to reduce disease activity in relapsing-remitting multiple sclerosis. However, their ability to limit smouldering inflammation has not been evaluated yet. We compared their longitudinal effects on the occurrence of white matter lesions showing a progressive linear enlargement over 2 years of treatment.

Methods. RRMS patients starting fingolimod (n=25) or natalizumab (n=30) underwent 3T brain MRI scans at baseline (T0), month 6, 12 and 24. We identified slowly-expanding lesions (SELs) among baseline T2-hyperintense lesions, by linearly fitting the Jacobian of the non-linear deformation field between timepoints, obtained using T1- and T2-weighted scans. A threshold ≥10% of annual increase was applied and neighbour voxels were grouped in clusters. Total number, percentage, volume of lesions defined as SELs, and their average magnetization transfer ratio (MTR) were calculated considering clusters ≥10 voxels.

Results. Treatment-groups were matched for baseline variables. The proportion of fingolimod-patients showing ≥1 SEL was higher compared to natalizumab (96% *vs* 50%, p<0.001). Compared to natalizumab-patients, fingolimod-patients showed a higher mean number (6.44 *vs* 3.40, p=0.004), and volume (0.20 *vs* 0.13 ml, p=0.002) of SELs, and mean percentages of lesions (7.30% *vs* 4.32%, p=0.007) and of lesional volume (2.12% *vs* 0.92%, p<0.001) defined as SELs. In both groups, compared to not-SELs, SELs showed significantly lower mean MTR values at T0 (26.87 *vs* 34.36 in fingolimod-group; 26.79 *vs* 34.41 in natalizumab-group, p<0.001), with no significant between-group differences and longitudinal changes.

Conclusions. SELs assessment using T1-, T2-weighted and MTR sequences is feasible in MS and allow to identify chronic active lesions typically described in pathology and characterized by smouldering inflammation, ongoing demyelination and axonal loss. Natalizumab seems to have a stronger effect in limiting the number and burden of SELs, while both drugs similarly prevent the accumulation of microstructural tissue damage in both SELs and not-SELs.