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Extended interval dosing of natalizumab: is efficacy preserved?

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Introduction: Some clinicians in Italy extended the dose of natalizumab infusions after 24 doses,with the hypothesis of reducing PML risk; this idea was supported by recent reports.
Objective:To make this strategy feasible, it is necessary to ascertain the therapeutic durability of the extended dosing strategy.
Aim: To evaluate the non-inferiority in controlling disease activity of an extended interval dosing (EID) of natalizumab.
Methods: Patients who received natalizumab for at least 24 weeks in 14 Italian centers were included in the analysis. Patients were grouped in 2 categories according to the mean number of weeks between doses (< =5.5 weeks, standard interval dosing (SID);>5.5 weeks, EID). Only the dose intervals before the first relapse was used to estimate the mean intervals between doses, to minimize the bias associated to a possible return to SID in patients under EID after they experienced a relapse. The non-inferiority of EID vs SID was a priori defined as satisfied if the upper limit of the 95%CI of the annualized relapse rate (ARR) in the EID group did not exceed the mean ARR of the SID group by 0.02 relapse/year. Baseline characteristics were comparedbetween groups by aMann Whitney U test. ARR during follow up was estimated and compared between groups by a multivariate Poisson regression model.
Results: 341 patientswere included in this analysis. The median interval between doses was 4.9 weeks (range 3.7-8.4), with a clear bimodal distribution (modes at 4 and 6 weeks) associated with individual centers strategies (the median was 4.5 weeks in 220 patients from 12 centers and 6.2 in 121 patients from 2 centers). 221 patients were in the SID (median dose interval=4.5 weeks) and 120 in the EID group (median dose interval=6.3 weeks). The ARRduring follow up adjusting for all the baseline variables (age, disease duration, relapses in 2 years pre-natalizumab start, EDSS, number of previous treatments) was 0.042 (95%CI=0.026-0.067) in the SID group, and it was 0.007 (95%CI=0.002-0.028) in the EID group. The non-inferiority of EID vs SID was satisfied.
Conclusions: In this cohort there is no evidence of a reduced efficacy of natalizumab by extending the intervals between doses from a median of 4.5 to a median of 6.3 weeks. This observation confirms previous results and together with the emerging evidence of a reduced risk of PML associated to an EID supports the need of a randomized study to change the standard of the natalizumab dosing schedule.
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