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Early non-disabling relapses are associated with a higher risk of disability accumulation in people with relapsing-remitting multiple sclerosis

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Introduction: The prognostic significance of non-disabling relapses (NDRs) in people with relapsing-remitting multiple sclerosis (pwRRMS) is unclear, yet guidance from the European Medicines Agency restricts the use of certain disease-modifying therapies (DMTs) to only those with disabling relapses (for example natalizumab and fingolimod in untreated pwRRMS).
Objective: To determine whether NDRs early in the course of RRMS herald faster accumulation of disability.
Methods: Using prospectively collected data from the MSBase international registry, we examined pwRRMS with complete early relapse severity information. Relapse severity was defined by clinicians on a 3-point scale, where "mild" was deemed non-disabling. We compared people with exclusively NDRs in the 2-year period after attaining clinically-definite RRMS to those with no relapses within this time. To mitigate the confounding effect of DMTs, analyses were performed (i) in those untreated during follow-up; then (ii) in those who received only platform therapies (interferon-beta, glatiramer acetate, dimethyl-fumarate or teriflunomide) during follow-up. For each group, a mixed effects Cox model was used to investigate whether early NDRs were associated with 3-month confirmed disability accumulation events, defined as an increase in Expanded Disability Status Scale (EDSS) score of 1.0 (or 1.5 if the baseline EDSS=0, or 0.5 if the baseline EDSS>5). Age, sex, year of inclusion, interval between first symptom and RRMS diagnosis, EDSS score at RRMS diagnosis and treatment centre (as a random effect) were assessed as predictors of disability in all models.
Results: Untreated pwRRMS who experienced NDRs during the 2 years post-RRMS attainment (n=285) had a marginally increased risk of disability accumulation compared to those with no relapses (n=4717; hazard ratio [HR]=1.29, 95% confidence interval [CI]: 1.00-1.68). Patients treated with platform DMTs who experienced NDRs (n=1074) had a significantly increased risk of disability accumulation compared to those who experienced no relapses within 2 years post-RRMS attainment (n=7262; HR=1.33, 95% CI: 1.15-1.54).
Conclusions: Early non-disabling relapses are associated with a higher risk of disability accumulation in pwRRMS. Therefore, non-disabling relapses should be taken into consideration when making treatment decisions.

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Multi-center, randomized, double-blinded assessment of dimethyl fumarate in extending the time to a first clinical demyelinating event in radiologically isolated syndrome (ARISE)

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Introduction: The radiologically isolated syndrome (RIS) represents the earliest detectable pre-clinical phase of multiple sclerosis (MS).
Objectives: This study evaluated the impact of therapeutic intervention in preventing first symptom manifestation at this stage in the disease spectrum. We hypothesized that early treatment would delay a first clinical event related to CNS demyelination.
Methods: We conducted a multi-center, randomized, double-blinded, placebo-controlled study involving people with RIS. Within 12 MS centers in the U.S., participants were randomly assigned 1:1 to oral dimethyl fumarate (DMF) 240mg twice daily or placebo. The primary endpoint was the time to onset of clinical symptoms attributable to a CNS demyelinating event at week-96. Secondary endpoints included the number of new or newly-enlarging T2-weighted hyperintense lesions, change in T2-lesion volume, and the number of gadolinium-enhancing lesions over 96 weeks. An intention to treat analysis was applied to all participating individuals in the primary and safety analyses. The study is registered at ClinicalTrials.gov, NCT027395420 (ARISE).
Results: Participants were recruited from March 9, 2016 to October 31, 2019 with 87 patients randomized to dimethyl fumarate or placebo. Following treatment with DMF, the risk of a first clinical demyelinating event during the 96-week study period was highly reduced both in the unadjusted (hazard ratio (HR)=0·18, 95% confidence interval (CI)=0·05-0·63, p=0·007) and in the adjusted (HR=0·07, 95% CI= 0·01-0·45, p=0·005) Cox proportional-hazards regression model. Adjusting for the number of gadolinium-enhancing lesions at baseline, there was a significant reduction in the number of new or newly-enlarging T2-weighted hyperintense lesions in the DMF arm as compared to placebo (HR=0.20, 95% CI=0.04-0.94, p = 0.042). More moderate adverse reactions were present in the DMF (14 (31·8%)) than placebo groups (9 (20·9%) but severe events were similar (DMF, 2 (4·5%); placebo, 4 (9·3%)).
Conclusions: This is the first randomized clinical trial demonstrating the benefit of disease modifying therapy in people with RIS. Treatment with DMF resulted in over 80% risk reduction relative to placebo in the prevention of a first clinical event related to CNS demyelination. These data add to the benefit of early treatment in the spectrum of demyelinating disease.
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