Documents

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Disease-modifying therapies in managing disability worsening in paediatric-onset multiple sclerosis: a longitudinal analysis of global and national registries
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Abstract
Background: High-efficacy disease-modifying therapies have been proven to slow disability accrual in adults with relapsing–remitting multiple sclerosis. However, their impact on disability worsening in paediatric-onset multiple sclerosis, particularly during the early phases, is not well understood. We evaluated how high-efficacy therapies influence transitions across five disability states, ranging from minimal disability to gait impairment and secondary progressive multiple sclerosis, in people with paediatric-onset multiple sclerosis. Methods: Longitudinal data were obtained from the international MSBase registry, containing data from people with multiple sclerosis from 151 centres across 41 countries, and the Italian Multiple Sclerosis and Related Disorders Register, containing data from people with multiple sclerosis from 178 Italian multiple sclerosis centres. People younger than 18 years at the onset of multiple sclerosis symptoms were included, provided they had a confirmed diagnosis of relapsing–remitting multiple sclerosis and at least four Expanded Disability Status Scale (EDSS) scores recorded within 12-month intervals. The primary outcome was the time to change in disability state: minimal disability (EDSS scores 0, 1·0, and 1·5), mild disability (EDSS scores 2·0 and 2·5), moderate disability (EDSS scores 3·0 and 3·5), gait impairment (EDSS scores ≥4·0), and clinician diagnosed secondary progressive multiple sclerosis. A multi-state model was constructed to simulate the natural course of multiple sclerosis, modelling the probabilities of both disability worsening and improvement simultaneously. The impact of high-efficacy disease-modifying therapies (alemtuzumab, cladribine, daclizumab, fingolimod, mitoxantrone, natalizumab, ocrelizumab, rituximab, or autologous haematopoietic stem cell transplantation) and low-efficacy disease-modifying therapies (dimethyl fumarate, glatiramer acetate, interferon beta, or teriflunomide), compared with no treatment, on the course of disability was assessed. Apart from recruitment, individuals with lived experience of multiple sclerosis were not involved in the design and conduct of this study. Findings: A total of 5224 people (3686 [70·6%] female and 1538 [29·4%] male) with mean age at onset of multiple sclerosis 15·24 years (SD 2·52) were included. High-efficacy therapies reduced the hazard of disability worsening across the disability states. The largest reduction (hazard ratio 0·41 [95% CI 0·31–0·53]) was observed in participants who were treated with high-efficacy therapies while in the minimal disability state, compared with those remained untreated. The benefit of high-efficacy therapies declined with increasing disability. Young people with minimal disability who received low-efficacy therapy also experienced a reduced hazard (hazard ratio 0·65 [95% CI 0·54–0·77]) of transitioning to mild disability, in contrast to those who remained untreated. Interpretation: Treatment of paediatric-onset relapsing−remitting multiple sclerosis with high-efficacy therapy substantially reduces the risk of reaching key disability milestones. This reduction in risk is most pronounced among young people with minimal or mild disability when treatment began. Children with relapsing−remitting multiple sclerosis should be treated early with high-efficacy therapy, before developing significant neurological impairments, to better preserve their neurological capacity. Funding: National Health and Medical Research Council, Australia; MSBase Foundation Fellowship; MS Australia Postdoctoral Fellowship. © 2024 Elsevier Ltd

Index Keywords
alemtuzumab, beta interferon, cladribine, daclizumab, dimethyl fumarate, fingolimod, mitoxantrone, natalizumab, ocrelizumab, rituximab, teriflunomide, fingolimod; adolescent, Article, controlled study, demography, disability, disease course, disease duration, drug efficacy, Expanded Disability Status Scale, female, follow up, hazard ratio, hematopoietic stem cell transplantation, human, longitudinal study, major clinical study, male, Markov chain, probability, prospective study, register, relapsing remitting multiple sclerosis, simulation, adult, child, complication, multiple sclerosis, progressive multiple sclerosis, relapsing remitting multiple sclerosis; Adolescent, Adult, Child, Female, Fingolimod Hydrochloride, Humans, Male, Multiple Sclerosis, Multiple Sclerosis, Chronic Progressive, Multiple Sclerosis, Relapsing-Remitting, Registries

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