Author/s:
Sharmin, S;Roos, I;Malpas, CB;Iaffaldano, P;Simone, M;Filippi, M;Kubala Havrdova, E;Ozakbas, S;Brescia Morra, V;Alroughani, R;Zaffaroni, M;Patti, F;Eichau, S;Salemi, G;Di Sapio, A;Inglese, M;Portaccio, E;Trojano, M;Amato, MP;Kalincik, T;Horakova, D;Prat, A;Girard, M;Duquette, P;Boz, C;Pozzilli, C;Cocco, E;Gallo, P;Yamout, B;Khoury, SJ;Lugaresi, A;Onofrj, M;Lus, G;Clerici, VT;Maniscalco, GT;Romano, S;Tortorella, C;Valentino, P;Rovaris, M;Shaygannejad, V;Ferraro, D;Vianello, M;Grammond, P;Bergamaschi, R;Gallo, A;Cavalla, P;Sa, MJ;Lechner-Scott, J;Pesci, I;Buzzard, K;Gouider, R;Mrabet, S;Aguglia, U;Conte, A;Avolio, C;Bellantonio, P;John, N;Cartechini, E;De Robertis, F;Ferraro, E;Weinstock-Guttman, B;Barcella, V;Van der Walt, A;Butzkueven, H;Coniglio, MG;Granella, F;Kuhle, J;Marfia, GA;Laureys, G;Van Hijfte, L;Maimone, D;Gazzola, P;Blanco, Y;Turkoglu, R;Montepietra, S;Spitaleri, D;van Pesch, V;Gerlach, O;Prevost, J;Ampapa, R;Soysal, A;Altintas, A;Rini, A;Solaro, C;Protti, A;Foschi, M;Surcinelli, A;Gatto, M;Mascoli, N;De Riz, M;Realmuto, S;Rossi, P;Totaro, R;Barnett, M;Oh, J;Nasuelli, D;Ramo-Tello, C;Sanchez-Menoyo, JL;Al-Harbi, T;Fioretti, C

Title:
Disease-modifying therapies in managing disability worsening in paediatric-onset multiple sclerosis: a longitudinal analysis of global and national registries

Date:
2024-05-01

Citation:
Sharmin, S., Roos, I., Malpas, C. B., Iaffaldano, P., Simone, M., Filippi, M., Kubala Havrdova, E., Ozakbas, S., Brescia Morra, V., Alroughani, R., Zaffaroni, M., Patti, F., Eichau, S., Salemi, G., Di Sapio, A., Inglese, M., Portaccio, E., Trojano, M., Amato, M. P. ,... Fioretti, C. (2024). Disease-modifying therapies in managing disability worsening in paediatric-onset multiple sclerosis: a longitudinal analysis of global and national registries. Lancet Child and Adolescent Health, 8 (5), pp.348-357. https://doi.org/10.1016/S2352-4642(24)00047-6.

Persistent Link:
https://hdl.handle.net/11343/345321

Title: Disease-modifying therapies in managing disability worsening in paediatric-onset multiple sclerosis: a longitudinal analysis of a global and national registry

Authors:

Sifat Sharmin, PhD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

Izanne Roos, MD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

Charles B Malpas, PhD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

Pietro Iaffaldano, MD; Centro SM Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Universita' di Bari, Bari, Italia

Marta Simone, MD; Pediatric MS Center, Department of Precision and Regenerative Medicine and Ionian Area, University of Bari Aldo Moro, Bari, Italy

Massimo Filippi, MD; Neurology Unit and MS Center, IRCCS Ospedale San Raffaele, Milan, Italy; Neurorehabilitation Unit, IRCCS Ospedale San Raffaele, Milan, Italy; Neurophysiology Service, IRCCS Ospedale San Raffaele, Milan, Italy; Neuroimaging Research Unit, Division of Neuroscience, IRCCS Ospedale San Raffaele, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy

Dana Horakova, MD; Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic

Eva Kubala Havrdova, MD; Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic

Serkan Ozakbas, MD; Dokuz Eylul University, Konak/Izmir, Turkey

Vincenzo Brescia Morra, MD; Centro Regionale Sclerosi Multipla - Unita' Operativa Semplice - AOU Policlinico Federico II, Napoli, Italia

Raed Alroughani, MD; Division of Neurology, Department of Medicine, Amiri Hospital, Sharq, Kuwait

Mauro Zaffaroni, MD; Centro Sclerosi Multipla, ASST Della Valle Olona, Ospedale Di Gallarate, Gallarate VA, Italia

Francesco Patti, MD; Department of Medical and Surgical Sciences and Advanced Technologies, GF Ingrassia, Catania, Italy

Guillermo Izquierdo, MD; Hospital Universitario Virgen Macarena, Sevilla, Spain

Sara Eichau, MD; Department of Neurology, Hospital Universitario Virgen Macarena, Sevilla, Spain

Giuseppe Salemi, MD; Centro Per La Diagnosi E Cura Della SM E Delle Malattie Demielinizzanti - Dipt. Emergenza, Urgenza E Neuroscienze Universita' Di Palermo, Palermo, Palermo, Italia

Alessia Di Sapio, MD; Centro Di Riferimento Regionale Per La SM (CRESM) - SCDO Neurologia - AOU San Luigi, Orbassano (TO), Italia

Giovanna De Luca, MD; Centro Sclerosi Multipla, Clinica Neurologica Policlinico SS. Annunziata, Chieti, Italia

Matilde Inglese, MD; Centro Per Lo Studio E La Cura Della Sclerosi Multipla E Malattie Demielinizzanti - Dipartimento Di Neuroscienze, Riabilitazione, Oftalmologia, Genetica E Scienze Materno - Infantili, Clinica Neurologica - Ospedale Policlinico San Martino (DiNOGMI), Genova, Italia

Alexandre Prat, MD; CHUM MS Center and Universite de Montreal, Montreal, Canada

Marc Girard, MD; CHUM MS Center and Universite de Montreal, Montreal, Canada

Pierre Duquette, MD; CHUM MS Center and Universite de Montreal, Montreal, Canada

Cavit Boz, MD; KTU Medical Faculty Farabi Hospital, Trabzon, Turkey

Carlo Pozzilli, MD; Centro SM, Policlinico S. Andrea, Universita' Sapienza, Roma, Roma

Eleonora Cocco, MD; Centro Regionale Per La Diagnosi E La Cura Della Sclerosi Multipla ASL8 P.O. Binaghi, Cagliari, Italia

Emilio Portaccio, MD; Department of NEUROFARBA, University of Florence, Florence, Italy

Paolo Gallo, MD; Centro Specializzato Regionale per la Sclerosi Multipla (CeSMuV) - Regione Veneto-Dipartimento Di Neuroscienze DNS-Azienda Ospedaliera - Universita' degli Studi Di Padova, Padova, Italia

Bassem Yamout, MD; Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut, Lebanon; Harley Street Medical Center, Abu Dhabi, United Arab Emirates

Samia J. Khoury, MD; Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut, Lebanon

Alessandra Lugaresi, MD; Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italia; IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italia

Marco Onofrj, MD; Department of Neuroscience, Imaging, and Clinical Sciences, University G. d’Annunzio, Chieti, Italy

Giacomo Lus, MD; Centro Clinico per la Sclerosi Multipla, II Clinica Neurologica, II Universita' di Napoli, Napoli, Italia

Murat Terzi, MD; Medical Faculty, 19 Mayis University, Samsun, Turkey

Valentina Torri Clerici, MD; Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italia

Giorgia Teresa Maniscalco, MD; Centro Regionale di Diagnosi e Terapia della Sclerosi Multipla, Napoli, Italia

Silvia Romano, MD; CENTERS Centro Neurologico Terapie Sperimentali - Sapienza Universita' Di Roma, Azienda Ospedaliera S. Andrea, Roma, Italia

Carla Tortorella, MD; Centro Sclerosi Multipla - Az. Osp. S. Camillo Forlanini, Roma, Italia

Paola Valentino, MD; Centro Sclerosi Multipla - Policlinico Universitario - Campus Germaneto, Catanzaro, Italia

Marco Rovaris, MD; Centro SM, IRCCS Fondazione Don Carlo Gnocchi, Milano, Italia

Vahid Shaygannejad, MD; Isfahan University of Medical Sciences, Isfahan, Iran

Diana Ferraro, MD; Centro Malattie Demielinizzanti - Dipartimento Di Neuroscienze, Azienda Ospedaliero-Universitaria/OCSAE, UO Neurologia, Universita' Di Modena E Reggio Emilia, Modena, Italia

Marika Vianello, MD; Centro Sclerosi Multipla UO Neurologia - Ospedale, Treviso, Italia

Pierre Grammond, MD; CISSS Chaudière-Appalache, Levis, Canada

Roberto Bergamaschi, MD; S.S. Sclerosi Multipla dell'IRCCS Fondazione Istituto Neurologico Nazionale C. Mondino, Pavia, Italia

Antonio Gallo, MD; Universita' Degli Studi Della Campania Luigi Vanvitelli, Napoli, Italia

Paola Cavalla, MD; Centro SM - Neurologia 1 D.U. - AOU Citta' Della Salute E Della Scienza Di Torino, Torino, Italia

Maria Jose Sa, MD; Department of Neurology, Centro Hospitalar Universitario de Sao Joao, Porto, Portugal; Faculty of Health Sciences, University Fernando Pessoa, Porto, Portugal

Maura Chiara Danni, MD; Centro SM - Clinica Neurologica - Ospedali Riuniti di Ancona, Ancona, Italia

Jeannette Lechner-Scott, MD; Hunter Medical Research Institute, University Newcastle, Newcastle, Australia; Hunter New England Health, John Hunter Hospital, NSW, Australia

Ilaria Pesci, MD; Centro SM UOC Neurologia Ospedale VAIO di Fidenza (PR), AUSL PR, Fidenza (PR), Italia

Katherine Buzzard, MBBS; Department of Neurosciences, Box Hill Hospital, Melbourne, Australia; Monash University, Eastern Health Clinical School, Box Hill, Australia

Olga Skibina, MBBS; Department of Neurology, Box Hill Hospital, Melbourne, Australia; Department of Neurosciences, Eastern Health Clinical School, Monash University, Melbourne, Australia; Department of Neurology, The Alfred Hospital, Melbourne, Australia

Riadh Gouider, MD; Department of Neurology, LR 18SP03, Clinical Investigation Centre Neurosciences and Mental Health, Razi University Hospital, Tunis, Tunisia; Faculty of Medicine of Tunis, University of Tunis El Manar, Tunis, Tunisia

Saloua Mrabet, MD; Department of Neurology, LR 18SP03, Clinical Investigation Centre Neurosciences and Mental Health, Razi University Hospital, Tunis, Tunisia; Faculty of Medicine of Tunis, University of Tunis El Manar, Tunis, Tunisia

Umberto Aguglia, MD; Department of Medical and Surgical Sciences, Magna Graecia University of Catanzaro, Italy

Antonella Conte, MD; Department of Human Neurosciences, Sapienza, University of Rome, Italy. IRCCS Neuromed, Pozzilli, IS, Italy.

Carlo Avolio, MD; Centro Interdipartimentale Malattie Demielinizzanti - AOU Ospedali Riuniti Di Foggia, Foggia, Italia

Paolo Bellantonio, MD; Centro Sclerosi Multipla - IRCCS Neuromed, Pozzilli (IS), Italia

Nevin John, MBBS; Department of Medicine, School of Clinical Sciences, Monash University, Melbourne, Australia; Department of Neurology, Monash Health, Clayton, Australia

Elisabetta Cartechini, MD; UOC Neurologia, P O Unico Macerata, ast Macerata, Macerata, Italia

Francesca De Robertis, MD; Divisione di Neurologia - Ospedale Vito Fazzi, Lecce, Italia

Elisabetta Ferraro, MD; Centro SM - PO San Filippo Neri - ASL Roma 1, Roma, Italia

Bianca Weinstock-Guttman, MD; Department of Neurology, Jacobs MS center for treatment and research, Buffalo, United States

Valeria Barcella, MD; Department of Neurology, MS center, ASST Papa Giovanni XXIII, Bergamo, Italy

Anneke van der Walt, MBBS; Department of Neurology, The Alfred Hospital, Melbourne, Australia; Department of Neuroscience, Central Clinical School, Monash University, Melbourne, Australia

Helmut Butzkueven, MBBS; Department of Neurology, The Alfred Hospital, Melbourne, Australia; Department of Neuroscience, Central Clinical School, Monash University, Melbourne, Australia

Maria Gabriella Coniglio, MD; Centro Sclerosi Multipla P.O. Madonna delle Grazie, Matera, Italia

Franco Granella, MD; Centro Sclerosi Multipla - Azienda Ospedaliero-Universitaria di Parma, Parma, Italia

Jens Kuhle, MD; Department of Neurology, University Hospital and University of Basel, Basel, Switzerland; Multiple Sclerosis Centre and Research Center for Clinical Neuroimmunology and Neuroscience (RC2NB), Departments of Biomedicine and Clinical Research, University Hospital and University of Basel, Basel, Switzerland

Girolama Alessandra Marfia, MD; UOSD Sclerosi Multipla, Policlinico Universitario Tor Vergata, Roma, Roma, Italia

Guy Laureys, MD; Department of Neurology, Universitary Hospital Ghent, Ghent, Belgium

Liesbeth Van Hijfte, Msc; Department of Neurology, Ghent University Hospital, Ghent, Belgium

Davide Maimone, MD; Centro Sclerosi Multipla, UOC Neurologia, ARNAS Garibaldi, Catania, Italia

Paola Gazzola, MD; SC Neurologia - Ospedale P. Antero Micone - ASL 3 Genovese, Genova Sestri P., Italia

Yolanda Blanco, MD; Center of Neuroimmunology, Service of Neurology, Hospital Clinic de Barcelona, Barcelona, Spain

Maria Edite Rio, MD; Centro Hospitalar Universitario de Sao Joao, Porto, Portugal

Recai Turkoglu, MD; Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

Sara Montepietra, MD; Centro SM, U.O.C. Neurologia, Ospedaliera Santa Maria Nuova, AUSL Reggio Emilia, Reggio Emilia, Italia

Marie D'hooghe, MD; Department of Neurology, Nationaal MS Centrum, Melsbroek, Belgium

Daniele Spitaleri, MD; Centro Sclerosi Multipla - U.O.C. Neurologia, AORN San G. Moscati, Avellino, Italia

Vincent van Pesch, MD; Cliniques Universitaires Saint-Luc, Brussels, Belgium; CLouvain

Ricardo Fernandez Bolaños, MD; Hospital Universitario Virgen de Valme, Seville, Spain

Oliver Gerlach, MD; Academic MS Center Zuyd, Department of Neurology, Zuyderland Medical Center, Sittard-Geleen, The Netherlands, Sittard-Geleen, Netherlands; School for Mental Health and Neuroscience, Department of Neurology, Maastricht University Medical Center, Maastricht 6131 BK, Netherlands

Julie Prevost, MD; CSSS Saint-Jérôme, Saint-Jerome, Canada

Radek Ampapa, MD; Nemocnice Jihlava, Jihlava, Czech Republic

Aysun Soysal, MD; Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul, Turkey

Ayse Altintas, MD; Department of Neurology, School of Medicine and Koc University Research Center for Translational Medicine (KUTTAM), Koc University, Istanbul, Turkey

Augusto Rini, MD; Centro Sclerosi Multipla - Ospedale A. Perrino, Brindisi, Italia

Magd Zakaria, MD; Ain Shams University, Cairo, Egypt

Claudio Solaro, MD; Department of Neurology, ASL3 Genovese, Genova, Italy; Department of Rehabilitaiton, ML Novarese Hospital Moncrivello

Alessandra Protti, MD; ASST Grande Ospedale Metropolitano Niguarda, Milano, Italia

Matteo Foschi, MD; Department of Neuroscience, MS Center, Neurology Unit, S. Maria delle Croci Hospital of Ravenna, Ravenna, Italy; Department of Biotechnological and Applied Clinical Sciences (DISCAB), University of L'Aquila, L'Aquila, Italy

Andrea Surcinelli, MD; Department of Neuroscience, MS Center, Neurology Unit, S. Maria delle Croci Hospital of Ravenna, Ravenna, Italy

Maurizia Gatto, MD; Centro Malattie Demielinizzanti - Ospedale Generale Regionale F. Miulli, Acquaviva Delle Fonti (BA), Italia

Ardito Bonaventura, MD; Centro Sclerosi Mutipla UOC Di Neurologia - Ospedale Della Murgia Fabio Perinei, Altamura (BA), Italia

Nerina Mascoli, MD; Centro SM UO Neurologia ASST Lariana Ospedale S. Anna, San Fermo Della Battaglia (CO), Italia

Bart Van Wijmeersch, MD; University MS Centre, Hasselt-Pelt; Noorderhart, Rehabilitation & MS, Pelt and Hasselt University, Hasselt, Belgium

Milena De Riz, MD; Centro Sclerosi Multipla - Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milano, Italia

Sabrina Realmuto, MD; Centro Di Riferimento Regionale Per La Malattie Neurologiche a Patogenesi Immunitaria - A.O.O.R. Villa Sofia-Cervello, Palermo, Italia

Patrizia Rossi, MD; Ambulatorio Sclerosi Multipla e Malattie Demielinizzanti del SNC - UOC di Neurologia - Ospedale San Bassiano, Bassano Del Grappa (VI), Italia

Eduardo Aguera-Morales, MD; University Hospital Reina Sofia, Cordoba, Spain

Rocco Totaro, MD; Centro Malattie Demielinizzanti - Clinica Neurologica, Ospedale San Salvatore, Coppito (AQ), Italia

Michael Barnett, MBBS; Brain and Mind Centre, Sydney, Australia

Jiwon Oh, MD; St. Michael's Hospital, Toronto, Canada

Davide Nasuelli, MD; ASST Della Valle Olona Presidio Ospedaliero Di Saronno Ambulatorio Sclerosi Multipla U, Saronno, Italia

Rocco Quatrale, MD; Ambulatorio Sclerosi Multipla - Divisione di Neurologia - Ospedale dell'Angelo, Mestre VE, Italia

Cristina Ramo-Tello, MD; Hospital Germans Trias i Pujol, Badalona, Spain

Jose Luis Sanchez-Menoyo, MD; Department of Neurology, Hospital de Galdakao-Usansolo, Galdakao, Spain; Biocruces-Bizkaia Health Research Institute

Talal Al-Harbi, MD; Neurology Department, King Fahad Specialist Hospital-Dammam, Khobar, Saudi Arabia

Cristina Fioretti, MD; Ambulatorio Sclerosi Multipla - Unita' Operativa di Neurologia e Neurofisiopatologia, Spedali Riuniti di Livorno 10 padiglione II piano, Livorno, Italia

Sebastiano Bucello, MD; Ospedale Muscatello di Augusta, Augusta (SR), Italia

Daniela Cargnelutti, MD; SOC Neurologia - Day Hospital, ASUIUD P.O. S.Maria Della Misericordia, Udine, Italia

Sandra Vukusic, MD; Lyon University Hospital, Lyon, France

Maria Trojano, MD; School of Medicine, University of Bari "Aldo Moro", Bari, Italy on behalf of the Italian MS Register

Maria Pia Amato, MD; Department of NEUROFARBA, University of Florence, Italy; IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy on behalf of the Italian MS Register

Tomas Kalincik, MD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia on behalf of the MSBase Study Group

Corresponding author

Tomas Kalincik

CORe, The University of Melbourne, Royal Melbourne Hospital

Level 7, 635 Elizabeth St, Melbourne, VIC 3000, Australia

Telephone: +61 3 93424404, Fax: +61 3 93495997

Email: tomas.kalincik@unimelb.edu.au

Word count, manuscript: 3664

Word count, abstract: 371

References: 36

Figures: 2

Tables: 4

Key words: paediatric-onset multiple sclerosis; relapse; disability worsening; disease-modifying therapy; secondary progressive multiple sclerosis

241

242

Background

High-efficacy disease-modifying therapies have been proven to slow disability accrual in adults with relapsing-remitting multiple sclerosis (MS). However, their impact on disability worsening in paediatric-onset MS, 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 MS (SPMS) in patients with paediatric-onset MS.

Methods

Longitudinal data were obtained from the international MSBase registry and the Italian MS Register. Patients <18 years old at the onset of MS symptoms were included, provided they had a confirmed diagnosis of relapsing-remitting MS 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 0,1·0, and 1·5), mild disability (EDSS 2·0 and 2·5), moderate disability (EDSS 3·0 and 3·5), gait impairment (EDSS≥4·0), and clinician diagnosed SPMS. A multi-state model was constructed to simulate the natural course of MS, modelling the probabilities of both disability worsening and improvement simultaneously. The impact of high-efficacy (alemtuzumab, cladribine, daclizumab, fingolimod, mitoxantrone, natalizumab, ocrelizumab, rituximab, or autologous haematopoietic stem cell transplantation) and low-efficacy (dimethyl fumarate, glatiramer acetate, interferon beta, or teriflunomide) disease-modifying therapies, compared to 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 patients (70·56% female, 29·44% male) with mean (SD) age at MS onset 15·24 (2·52) years were included. High-efficacy therapies reduced the risk of disability worsening across the disability states. The largest reduction (HR 0·41 [95% CI: 0·31,0·53]) was observed in patients who were treated with high-efficacy therapies while in the minimal disability state, compared to those remained untreated. The benefit of high-efficacy therapies declined with increasing disability. Patients with minimal disability who received low-efficacy therapy also

experienced a reduced hazard (0·65 [0·54,0·77]) of transitioning to mild disability, in contrast to those who remained untreated.

Interpretation

Treatment of paediatric-onset relapsing-remitting MS with high-efficacy therapy substantially reduces the risk of reaching key disability milestones. This reduction in risk is most pronounced among patients treated with minimal or mild disability. Children with relapsing-remitting MS should be treated early with high-efficacy therapy, before developing significant neurological impairments, to better preserve their neurological capacity over the long term.

Funding

NHMRC, Australia; MSBase Foundation Fellowship; MS Australia Postdoctoral Fellowship

Research in context

Evidence before this study

We searched the PubMed database from inception to February 13, 2024, using the terms (paediatric multiple sclerosis OR pediatric multiple sclerosis OR ((children OR adolescent) AND multiple sclerosis)) AND (progression OR worsening) AND (recovery OR improvement) AND (disease-modifying treatment OR disease-modifying therapy OR disease-modifying drug). Two natural history studies contributed valuable insights into the attainment of disability milestones in patients with paediatric-onset MS compared to those with adult-onset MS. Three randomised controlled trials and five observational studies assessing the effectiveness of disease-modifying therapies provided evidence supporting their effectiveness in reducing the risk of disability in children with MS. Several other observational studies identified disease-modifying therapies of varying effectiveness as protective factors against disability in paediatric-onset MS. However, the risk of transitions across the entire spectrum of disability and its response to high-efficacy therapies, has not yet been explored. This knowledge gap limits clinicians' ability to prevent irreversible disability through evidence-based treatment strategies.

Added value of this study

This study demonstrates a substantial, clinically meaningful reduction in the risk of disability worsening as a consequence of high-efficacy therapy among patients with paediatric-onset MS, mostly before they develop disability that would limit their capacity. Patients who were treated with high-efficacy therapy during the initial phase of minimal disability experienced the most substantial reduction in the risk of disability worsening, in stark contrast to patients treated with low-efficacy therapy or those who remained untreated.

Implications of all the available evidence

Our findings suggest that patients with paediatric-onset MS presenting with minimal disability derive the greatest benefit from high-efficacy therapies. From the point of view of maximising the effectiveness of therapy, early administration of high-efficacy therapy is a favourable approach to treatment of paediatric-onset MS.

Introduction

Approximately 4-8% of patients with multiple sclerosis (MS) experience symptoms before the age of 18 years, according to data from national registries in Sweden and Italy.[1,2] Prior research revealed that children are more likely to recover from relapses than adults with MS, which is potentially underpinned by their enhanced remyelinating capacity and less pronounced cumulative CNS damage at an early age.[3-6] As a consequence, worsening of disability tends to be initially relatively slower among patients with paediatric-onset MS. Nonetheless, paediatric-onset MS leads to earlier, significant physical limitations, potentially as early as the third decade of life.[7,8] Disease-modifying therapies, including first-line injectables (interferon beta and glatiramer acetate)[9] and oral therapies (dimethyl fumarate and teriflunomide), [10,11] and high-efficacy therapies (fingolimod[12] and natalizumab[13-15]) reduce the risk of disability worsening in patients with paediatric-onset MS.[1,2,16-19] However, it is not fully understood how disease-modifying therapies of varying potency modify the disability trajectory from minimal to more substantial disability in patients with paediatric-onset MS.

The Expanded Disability Status Scale (EDSS) is widely employed to assess disability in MS. It is a categorical measure ranging from 0 to 10 mostly in 0.5-step increments, with 0 representing no impairment and 10 indicating death from MS. Its main limitation is its non-linear nature,

whereby a unit increase in EDSS does not correspond to a constant accrual of disability. For instance, the clinical impact of change from EDSS 2·0 to 3·0 is more significant than an increase from EDSS 0 to 1·0.[20] Furthermore, the lower end of the EDSS spectrum is more variable and assessor dependent.[21,22] Both these characteristics of EDSS pose challenges for comparisons of disability trajectories among individuals. By modelling disability states instead of the crude EDSS scores, we overcame the inherent asymmetry and variability associated with the EDSS, thus enhancing both the precision of our conclusions and their clinical relevance.

In this study, we modelled the natural course of MS in patients with paediatric-onset MS, progressing from a state of minimal disability to pronounced gait impairment and secondary progressive multiple sclerosis (SPMS) using a multi-state Markov model. Further, we evaluated its change due to exposure to high- and low-efficacy disease-modifying therapies, compared to no treatment. We hypothesised that disease-modifying therapies attenuate the natural progression of disability, particularly during the lowest disability states.

Methods

Study design and participants

This study is a longitudinal analysis of data from the MSBase registry and the Italian Multiple Sclerosis Register. MSBase (WHO registration ACTRN12605000455662) is an international registry of MS patients from 151 centres across 41 countries[23] and the Italian MS Register is a nationwide database of MS patients from 178 Italian MS centres.[24] Both registries prospectively record longitudinal clinical, paraclinical, and demographic information from patients with MS. Besides participation in the registry, patients did not participate in design and conduct of this study.

Patients aged younger than 18 years at onset of MS symptoms with a confirmed diagnosis of relapsing-remitting MS were included, conditional on the availability of at least four EDSS scores recorded within intervals no longer than 12-months.

Eight centres from the Italian MS Register contributed data to the MSBase registry. To avoid duplication of records, only data from one of the registries were retained for these centres (data from MSBase for six centres and from Italian MS Register for two centres).

Ethics approval for the prospective registries, MSBase and the Italian MS Register was obtained from the Melbourne Health Human Research Ethics Committee and the University/Hospital Ethics Committee of Bari, respectively. Written informed consent was obtained from all enrolled patients or their guardians. Adolescent patients provided written informed assent, co-signed by their guardians. Data for this study was extracted on April 1, 2022 from MSBase and on May 31, 2022 from the Italian MS Register.

Procedures

The primary outcome was defined as the time to transition from entry state to one of the five disability states: minimal disability (EDSS 0, 1.0, and 1·5), mild disability (EDSS 2·0 and 2·5), moderate disability (EDSS 3·0 and 3·5), gait impairment (EDSS ≥4·0), and SPMS. EDSS scores recorded within 30 days of a previous relapse were excluded. Furthermore, EDSS scores and their changes were confirmed over a minimum of 6 months in order to identify transitions between states. Diagnosis of SPMS was made by treating clinicians as per the Lublin definition of clinical course.[25,26]

Statistical analysis

A semi-parametric (Cox) time-homogenous multi-state Markov process model was developed with five states: minimal; mild; and moderate disability; gait impairment; and SPMS. A Markov model predicts the probability of future transitions between different disability states over time based on the current disability status and patient characteristics. We simulated the natural course of MS by modelling both disability worsening and improvement simultaneously. Transitions to higher disability states represent disability worsening and transitions to lower states represent disability improvement. The model assumes that a patient can only exist in one state at a time, and that SPMS acts as an absorbing state, from which a patient cannot return to one of the four relapsing-remitting MS states. The time scale for transitions was the time-on-study, with origin (baseline) being the date of first EDSS score. This definition of origin is not subject to bias in

datasets with variable times of patient entry (i.e., left truncation). Patients were censored at the time of their last recorded visit. No risk of informative censoring was identified.

All possible transitions between the five studied states are presented in Figure 1 which illustrates the natural course of disability in patients with MS. The Markov model assumes that transition rates are dependent on the clinical and demographic characteristics of patients. At each of the possible transitions in the worsening of disability towards SPMS, the model was therefore adjusted for available potential confounders identified based on clinical judgment and existing literature (appendix p 2): sex, age at onset of MS symptoms, time from symptom onset to confirmed diagnosis of relapsing-remitting MS, disease duration at each EDSS assessment, and annualised relapse rate during the time spent at each state. Exposure to therapy was modelled using a categorical variable: (i) treatment with high-efficacy disease-modifying therapy (alemtuzumab, cladribine, daclizumab, fingolimod, mitoxantrone, natalizumab, ocrelizumab, rituximab, or autologous haematopoietic stem cell transplantation), (ii) treatment with low-efficacy therapy (dimethyl fumarate, glatiramer acetate, interferon beta, or teriflunomide), and (iii) no treatment during the time at a disability state (reference). At least 3 months exposure to the treatment was required to account for therapeutic delay.[27] To adjust for geographic heterogeneity, the model was adjusted for country of patients' residence.

Smoothed plots of the scaled Schoenfeld residuals against time was inspected to assess the validity of the proportional hazards assumption. Linearity in the relationship between the outcome and each continuous covariate was assessed by plotting martingale residuals against the covariate.

The multi-state model was estimated using the R package 'mstate'.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Table 1 summaries the demographic and clinical characteristics of patients included in the analyses. A total of 5224 patients with paediatric-onset MS (appendix p 3), predominantly female (70·56%) were studied. Among them, 5170 (98.97%) patients had their first visit recorded between 1990 and 2020. The mean (SD) age at MS onset was 15·24 (2·52) years with a median (first, third quartiles) time from first symptom to diagnosis of MS of 2·03 (0·41, 8·12) years. During the study follow-up, 4570 out of 5224 patients (87·48%) received disease-modifying therapies. Among them, 1834 patients started therapy before the age of 18 years. The median (first, third quartiles) disease duration at the time of initiation of first therapy among the treated was 2·43 (0·30, 8·71) years. Details regarding treatment with different disease-modifying therapies are provided in Table 2. The sequential exposure to therapies throughout the study is presented in an alluvial plot (appendix p 4). The demographic and clinical characteristics of the excluded patients were similar to the included patients, with the exception of the lower proportions of patients with recorded disease-modifying therapy, high-efficacy disease-modifying therapy, and shorter follow-up duration (appendix p 5).

5224 patients collectively contributed 91613 visits. During the median (first, third quartiles) observation period of 5·05 (2·53, 9·09) years, 2622 transitions were recorded in 1701 patients. The most frequent transition (651) was observed from minimal disability to subsequent state of mild disability, followed by 557 transitions in the reverse direction - from mild disability back to minimal disability (appendix p 6). Tables 3 and 4 present the transition specific hazard ratios (HR) and corresponding 95% confidence intervals (95% CI). The benefit of high-efficacy therapy was the greatest in early disease with minimal disability and decreased with increasing disability. Patients who were treated with high-efficacy disease-modifying therapy while having minimal disability were the least likely to transition up to the next disability state (mild disability). Their hazard of transition was 59% lower compared to those who were untreated (HR 0·41 [95% CI: 0·31, 0·53]). Patients who received high-efficacy therapy during the state of mild disability had a 41% lower hazard of transition to the subsequent state of moderate disability, in comparison to those who were untreated (0·59 [0·40, 0·86]). In patients with moderate disability, high-efficacy therapy yielded a clinically significant 33% reduction in the hazard of transition to gait impairment, when compared to untreated patients (0·67 [0·46, 1·00]). However, the corresponding 95% CI marginally includes the null value of 1, indicating uncertainty in the estimate, presumably due to fewer transitions from the moderate disability to gait impairment.

Treatment with low-efficacy therapy also reduced the likelihood of disability worsening compared to those who were untreated, although to a lesser extent in comparison to the high-efficacy therapy. Patients who were treated with low-efficacy therapy during the minimal disability state had a 35% reduced hazard of transition to the next (mild) disability state (0·65 [0·54, 0·77]). Compared with patients who were treated with a high-efficacy therapy during the minimal disability state, patients who were treated with low-efficacy therapy had 1·59 times (HR 0·65 vs. 0·41) higher hazard of transitioning to the next (mild) disability state. Treatment with low-efficacy therapy was also associated with a 41% lower hazard of worsening by two states from mild disability to impairment of gait when compared to no treatment (0·59 [0·39, 0·88]).

Figure 2 (left) provides an illustration of observed disability trajectories of two included patients (patients 'A' and 'B') and (right) corresponding estimated probabilities of transition from minimal to mild disability. To illustrate the estimated impact of early choice of therapy, we explored the hypothetical probability of transitioning to mild disability if the patient 'A' were treated with low-efficacy therapy (counterfactual) instead of high-efficacy therapy (observed) during the minimal disability state. In this hypothetical scenario, the probability of transitioning from minimal to mild disability in patient 'A' would have been clearly higher.

A higher annualised relapse rate was associated with a greater likelihood of transitioning to higher disability states (Table 3). This association was most pronounced for a 3-step transition from minimal disability to gait impairment (5·11 [3·91, 6·68]), followed by a 4-step transition from minimal disability to SPMS (4·96 [1·51, 16·31]). However, a higher annualised relapse rate also conferred a greater likelihood of disability improvement from gait impairment to moderate (1·76 [1·18, 2·62]) and mild (2·52 [1·41, 4·51]) disability (Table 4).

Overall, longer MS duration was associated with increased probability of transition to higher states of disability. However, this association was reversed for transition from gait impairment to conversion to SPMS, suggesting a minimal 6% reduction in the risk of this specific transition (0·94 [0·90, 0·97]). Longer MS duration was also consistently associated with a lower likelihood of improvement for all possible transitions from higher to lower states of disability.

Males were at a higher risk of transition from mild to moderate disability (1·34 [1·06, 1·69]). They were also 46% less likely to experience improvement once gait impairment has been reached (0·54 [0·33, 0·89]).

Older age at onset of MS symptoms was associated with a higher likelihood of disability worsening from minimal to mild (1·04 [1·01, 1·08]), and a lower likelihood of disability improvement from moderate to minimal disability (0·90 [0·81, 0·99]).

A sensitivity analysis that incorporated adjustments for MS diagnostic criteria (categorised as: Poser [reference category], McDonald 2010, McDonald 2017) and diagnostic delay (time from symptom onset to MS diagnosis), corroborated the findings from the primary analysis (appendix p 7-8).

Discussion

This study provides insights into the effectiveness of disease-modifying therapies with different potency on the natural progression of disability from early to severe in patients with paediatric-onset MS. It shows that disease-modifying therapies reduce the risk of worsening of disability from the earliest stage of the disease in this population. Compared to low-efficacy disease-modifying therapy, high-efficacy therapy mitigates the risk of attaining disability more effectively, especially when started before patients have developed moderate or severe disability, corresponding to EDSS score ≥3.

We suggest that patients with paediatric-onset MS should be treated with high-efficacy disease-modifying therapy while they are still only affected by minimal or mild disability. In the phase 3 randomised controlled trial conducted in children aged 10 to 17 years, fingolimod was associated with a lower annualised relapse rate and reduced accumulation of lesions on MRI than interferon beta-1a.[12] Observational studies from the Italian MS Register demonstrated substantial reductions in the annualised relapse rate and disability worsening among children treated with natalizumab.[14,15] More than half of the patients remained free from MRI activity throughout their treatment with natalizumab spanning up to 11 years.[14] A single-centre observational study from Italy showed that high-efficacy therapies (natalizumab and immunosuppressants) considerably reduced the risk of the first relapse as well as the annualised relapse rate in children.[17] A prior multi-centre study of observational data reported a lower relapse rate in children treated with newer therapies (fingolimod, dimethyl fumarate, teriflunomide, natalizumab, rituximab, and ocrelizumab) compared to those receiving injectables (interferon beta and glatiramer acetate).[18]

This is of importance, as the risk of relapses is particularly high in children.[28,29] Another observational study reported that the risk of reaching key disability milestones affecting gait (EDSS 4·0 and 6·0) in paediatric-onset MS has declined by a half between years 1993 and 2013.[1] The authors suggested that the shift in practice towards starting disease-modifying therapies before age 18 may be responsible for this improvement in outcomes.[1] A recent study using data from the French MS Registry has highlighted the superior effectiveness of high-efficacy therapies (alemtuzumab, fingolimod, mitoxantrone, cladribine, natalizumab, ocrelizumab, ofatumumab, and rituximab) when used as first-line treatments for children. These therapies have shown superior control over relapse and radiological activity when compared to moderate-efficacy therapies (azathioprine, cyclophosphamide, dimethyl fumarate, glatiramer acetate, interferon beta, methotrexate, mycophenolate mofetil, and teriflunomide).[19] In adults with MS, early initiation of high-efficacy therapies has been shown to result in improved disease control and superior long-term outcomes when compared to delayed initiation or escalation strategy.[29-32]

Our findings revealed that low-efficacy therapies are also associated with a reduced risk of disability worsening in the earliest state of the disease with minimal disability. While high-efficacy therapies are superior to low-efficacy therapies in reducing disability in paediatric-onset MS, the reduction in the risk of disability worsening associated with low-efficacy therapies is also clinically meaningful. Among patients with minimal disability, high-efficacy therapies were associated with an additional 14% reduction in the risk of disability worsening when compared with low-efficacy therapies. A previous study of 549 patients with paediatric-onset MS from the Swedish MS Registry reported no impact of treatment on disability among patients treated with first-line disease-modifying therapies (dimethyl fumarate, glatiramer acetate, interferon beta, and teriflunomide) but a reduced risk of reaching EDSS 3·0 and 4·0 (moderate disability or impaired gait, respectively) associated with second-line disease-modifying therapies (daclizumab, fingolimod, mitoxantrone, natalizumab, and rituximab), compared to no treatment.[2] However, a randomised controlled trial in children, comparing dimethyl fumarate with interferon beta-1a, demonstrated reduced annualised relapse rate and MRI activity among those treated with dimethyl fumarate.[10]

In this study, relapses were consistently associated with a higher risk of increase in disability. This finding is consistent with the observation that relapses pose a risk for faster disability worsening in MS, including paediatric-onset MS.[2,16] This includes a clinically very significant change from minimal disability directly to gait impairment. On the other hand, children are more likely to recover from relapses than adults,[3] and, accordingly, we have observed that relapses are associated with a higher probability of eventual improvement in disability, including those who developed an impairment of gait after a relapse. This means that relapses represent transient events, whose reversibility depends on the ability of the CNS to recover from transient inflammatory damage. However, the magnitude of the associations of relapses with disability worsening exceeded the associations with disability improvement. This highlights the importance of preventing relapses to minimise the risk of irreversible disability.

This study has benefitted from a large cohort followed over the median (first, third quartiles) of 5 years (2·53, 9·09), representing diverse paediatric populations across multiple geographic regions. This cohort represented a broad spectrum of patients with varying degrees of disability, spanning from minimal to severe. In order to mitigate the shortcomings of the EDSS, we categorised disability into five states: minimal disability (EDSS 0, 1.0, and 1·5), mild disability (EDSS 2·0 and 2·5), moderate disability (EDSS 3·0 and 3·5), gait impairment (EDSS≥4·0), and SPMS. The limitation inherent in this approach is that combining all EDSS scores greater than 4·0 into a single state precludes the analysis of change of disability among patients with advanced MS. Such patients were rare in the present cohort and would require a separate study in population based on different inclusion criteria. Moreover, EDSS is largely insensitive to cognitive impairment that has been reported in nearly one third of paediatric-onset patients[33]; cognitive data were not systematically collected in our cohorts. Further limitation is represented by unavailability of data about several potentially relevant confounders, such as body mass index, smoking status, medical comorbidities, and socio-economic status. Information on ethnicity was incomplete and was therefore not included in the analysis. The unobserved confounders could induce built-in selection bias, leading to a gradual decay of period-specific hazard ratios during the follow-up.[34] This study is also limited by the lack of information about treatment safety and its effectiveness on radiological presentation and disease activity. The international multicentric nature of the data used limited our ability to utilise harmonised quantitative MRI information which may carry additional prognostic information. On the other

hand, this study models the natural course of MS by considering both disability worsening and improvement simultaneously. Separate analyses of disability worsening and disability improvement fail to consider two-way changes in disability status, necessary for holistic evaluation of the influence of treatment on disability and its mediation through the prevention of relapses. To mitigate sparse-data bias resulting from the absence of events in the therapy exposure groups, we opted not to model transitions from minimal disability to SPMS and from mild disability to SPMS in therapy exposure scenarios. In the study cohort, four instances of death were documented. Although death prevents the occurrence of the outcome of interest, acting as a competing risk for transitions between the disability states, it was not accounted for in our study design due to its very low incidence. The requirement of four EDSS scores recorded within intervals not exceeding 12-months may have introduced selection bias. Reassuringly, the excluded patients were very similar to the included patients, with the exception of exposure to disease-modifying therapy and the duration of the available follow-up. Individuals with lived experience contributed to this study by consenting to share their data. However, they were not involved in the design or conduct of this study.

In conclusion, this study of a large, geographically diverse cohort shows that patients with paediatric-onset MS are at risk of acquiring substantial disability, which can be mitigated through early treatment, especially with a high-efficacy disease-modifying therapy. This knowledge has implications for treatment decisions among children with MS, where the evidence from randomised controlled trials about the use of high-efficacy therapies is scarce. From the perspective of maximising the effectiveness of therapy and preserving capacity, it is advisable that high-efficacy disease-modifying therapies are started in children early, during the most inflammatory stages of their disease and before they develop neurological disability. Naturally, the decisions regarding the most appropriate therapy are multifactorial and need to consider the known short-term safety profiles of the available therapies and the individual acceptability of their administration routes. It is imperative to remain mindful of the yet-to-be-understood cumulative long-term risk of immunosuppression. The consensus from both The International Pediatric Multiple Sclerosis Study Group (IPMSSG) and European experts emphasises the paramount importance of prioritising safety in paediatric MS therapies.[35,36] Consequently, there is a critical need to institute an appropriate monitoring protocol in this population, with a strong emphasis on long-term safety considerations.[35,36] The presented new

perspective on the long-term impact of therapies on preserving neurological function among people with paediatric-onset MS provides a useful addition to the information guiding policy governing access to disease-modifying therapies among children with MS.

Contributors

SS conceptualised and designed the study, had access to and verified the raw data from both registries, carried out statistical analyses, interpreted the results, have drafted, and edited the manuscript. TK conceptualised and designed the study, had access to and verified the raw data from both registries, contributed data, interpreted the results, and have edited the manuscript.

IR contributed to the concept of the study, contributed data, interpreted the results, and have edited the manuscript. CBM interpreted the results and has edited the manuscript.

MT and MPA contributed to the concept of the study, recruited patients, contributed data, and have edited the manuscript.

PI, MS, MF, EKH, SO, VBM, RA, MZ, FP, SE, GS, ADS, MI, EP recruited patients, contributed data, and have edited the manuscript. All authors accept responsibility for the decision to submit the manuscript for publication.

Data sharing

MSBase and the Italian MS Register warehouse data from individual principal investigators who agree to share their datasets on a project-by-project basis. Each principal investigator will need to be approached individually for permission to access the datasets.

Acknowledgments

This study was funded by the NHMRC Australia [grants 1129189 and 2026836], MSBase Foundation Fellowship, and MS Australia Postdoctoral Fellowship. The MSBase Foundation is a not-for-profit organisation that receives support from Merck, Biogen, Novartis, Roche, Bayer Schering, Sanofi Genzyme, and Teva Pharmaceutical Industries. We thank the patients who contributed to the registries, the participating neurologists, and the MSBase Operations Team. The list of MSBase Study Group contributors and the MSBase Operations Team are provided in appendix (p 9-11).

Supplementary Material

Supplementary appendix

Reference

1. Baroncini D, Simone M, Iaffaldano P, et al. Risk of persistent disability in patients with pediatric-onset multiple sclerosis. *JAMA Neurology.* 2021; **78**: 726-735.
2. McKay KA, Hillert J, Manouchehrinia A. Long-term disability progression of pediatric-onset multiple sclerosis. *Neurology.* 2019; **92**: e2764-e2773.
3. Chitnis T, Aaen G, Belman A, et al. Improved relapse recovery in paediatric compared to adult multiple sclerosis. *Brain.* 2020; **143**: 2733-2741.
4. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. *New England Journal of Medicine.* 2007; **356**: 2603-2613.
5. Fay AJ, Mowry EM, Strober J, Waubant E. Relapse severity and recovery in early pediatric multiple sclerosis. *Multiple Sclerosis Journal.* 2012; **18**: 1008-1012.
6. De Meo E, Filippi M, Trojano M, et al. Comparing natural history of early and late onset pediatric multiple sclerosis. *Annals of Neurology.* 2022; **91**: 483-495.
7. Banwell B, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M. Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions. *The Lancet Neurology.* 2007; **6**: 887-902.
8. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain.* 2003; **126**: 770-782.
9. Chitnis T, Pohl D. Pediatric demyelinating disorders: Global updates, controversies, and future directions. *Neurology.* 2016; **87**(9 Supplement 2): S1-S3.
10. Vermersch P, Scaramozza M, Levin S, et al. Effect of dimethyl fumarate vs interferon β-1a in patients with pediatric-onset multiple sclerosis: the CONNECT randomized clinical trial. *JAMA Network Open.* 2022; **5**: e2230439.
11. Chitnis T, Banwell B, Kappos L, et al. Safety and efficacy of teriflunomide in paediatric multiple sclerosis (TERIKIDS): a multicentre, double-blind, phase 3, randomised, placebo-controlled trial. *The Lancet Neurology.* 2021; **20**: 1001-1011.
12. Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *New England Journal of Medicine.* 2018; **379**: 1017-1027.
13. Kornek B, Aboul-Enein F, Rostasy K, et al. Natalizumab therapy for highly active pediatric multiple sclerosis. *JAMA Neurology.* 2013; **70**: 469-475.

14. Baroncini D, Ghezzi A, Guaschino C, et al. Long-term follow-up (up to 11 years) of an Italian pediatric MS cohort treated with Natalizumab: a multicenter, observational study. *Neurological Sciences.* 2022; **43**: 6415-6423.

15. Ghezzi A, Moiola L, Pozzilli C, et al. Natalizumab in the pediatric MS population: results of the Italian registry. *BMC Neurology.* 2015; **15**: 1-6.

16. Amato MP, Fonderico M, Portaccio E, et al. Disease-modifying drugs can reduce disability progression in relapsing multiple sclerosis. *Brain.* 2020; **143**: 3013-3024.

17. De Meo E, Bonacchi R, Moiola L, et al. Early Predictors of 9-Year Disability in Pediatric Multiple Sclerosis. *Annals of Neurology.* 2021;**89**:1011-1022.

18. Krysko KM, Graves JS, Rensel M, et al. Real-world effectiveness of initial disease-modifying therapies in pediatric multiple sclerosis. *Annals of Neurology.* 2020; **88**: 42-55.

19. Benallegue N, Rollot F, Wiertlewski S, et al. Highly Effective Therapies as First-Line Treatment for Pediatric-Onset Multiple Sclerosis. *JAMA Neurology.* 2024; (published online Feb 12.). https://doi:10.1001/jamaneurol.2023.5566

20. Ravnborg M, Blinkenberg M, Sellebjerg F, Ballegaard M, Larsen SH, Sørensen PS. Responsiveness of the multiple sclerosis impairment scale in comparison with the expanded disability status scale. *Multiple Sclerosis Journal.* 2005; **11**: 81-84.

21. Amato MP, Fratiglioni L, Groppi C, Siracusa G, Amaducci L. Interrater reliability in assessing functional systems and disability on the Kurtzke scale in multiple sclerosis. *Archives of Neurology.* 1988; **45**: 746-748.

22. Hughes S, Spelman T, Trojano M, et al. The Kurtzke EDSS rank stability increases 4 years after the onset of multiple sclerosis: results from the MSBase Registry. *Journal of Neurology, Neurosurgery & Psychiatry.* 2012; **83**: 305-310.

23. Kalincik T, Butzkueven H. The MSBase registry: informing clinical practice. *Multiple Sclerosis Journal.* 2019; **25**: 1828-1834.

24. Trojano M, Bergamaschi R, Amato MP, et al. The Italian multiple sclerosis register. *Neurological Sciences.* 2019; **40**: 155-165.

25. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology.* 1996; **46**: 907-911.

26. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014; **83**: 278-286.

27. Roos I, Leray E, Frascoli F, et al. Delay from treatment start to full effect of immunotherapies for multiple sclerosis. *Brain.* 2020; **143**: 2742-2756.
28. Kalincik T, Vivek V, Jokubaitis V, et al. Sex as a determinant of relapse incidence and progressive course of multiple sclerosis. *Brain.* 2013; **136**: 3609-3617.
29. Ontaneda D, Tallantyre E, Kalincik T, Planchon SM, Evangelou N. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. *The Lancet Neurology.* 2019; **18**: 973-980.
30. Brown JWL, Coles A, Horakova D, et al. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA.* 2019; **321**: 175-187.
31. He A, Merkel B, Brown JWL, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *The Lancet Neurology.* 2020; **19**: 307-316.
32. Spelman T, Magyari M, Piehl F, et al. Treatment escalation vs immediate initiation of highly effective treatment for patients with relapsing-remitting multiple sclerosis: data from 2 different national strategies. *JAMA Neurology.* 2021; **78**: 1197-1204.
33. Benedict RH, Amato MP, DeLuca J, Geurts JJ. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *The Lancet Neurology.* 2020; **19**: 860-871.
34. Hernán MA. The hazards of hazard ratios. *Epidemiology (Cambridge, Mass)* 2010; **21**: 13.
35. Waubant E, Banwell B, Wassmer E, et al. Clinical trials of disease-modifying agents in pediatric MS. *Neurology.* 2019; **92**: e2538-e2549.
36. Ghezzi A, Amato MP, Edan G, et al. The introduction of new medications in pediatric multiple sclerosis: open issues and challenges. *Multiple Sclerosis Journal.* 2021; **27**: 479-482.

Figure Legends

***Figure* 1: Transition model for disability worsening and improvement in patients with paediatric-onset MS.**

***Figure* 2: (Left) Observed disability trajectories of two selected patients and (Right) their estimated transition probabilities of entering into the state of 'mild disability' from 'minimal disability'.** The solid line represents the time of treatment with high-efficacy therapy while the dashed line represents the time of treatment with low-efficacy therapy. The dark orange line denotes patient A and the blue line denotes patient B. The light orange line denotes a hypothetical (counterfactual) scenario when patient A's transition probability was modelled with exposure to low-efficacy therapy. The coloured bands denote the 95% confidence interval of the corresponding estimates.