Injectable versus oral first-line multiple sclerosis therapies: knows and unknowns from observational studies

Emanuele D’Amico*, Aurora Zanghi†, Carlo Avolio

The approval of oral disease modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) has changed considerably the therapeutic scenario and they often represent the first therapeutic choice for patients with RRMS, since their safety and efficacy profile has been extensively validated (D’Amico et al., 2015).

The choice between an injectable and an oral DMT for each patient with RRMS must result from a careful weighting of the risk/benefit ratio, in a view of personalized therapy, considering efficacy, safety profile, dosage, and way of administration (Figure 1).

European medicine agency includes as first-line injectable DMTs either Copaxone (40 mg per mL/three times per week subcutaneously and at least 48 hours apart) or IFNs (interferon β-1a, 30 µg/0.5 mL, once weekly, intramuscularly, interferon β-1b, either 22 µg or 44 µg, three times per week subcutaneously, pegylated interferon β-1a 125/0.5 µg/mL every 2 weeks subcutaneously and interferon β-1b, 250 µg/mL, every other day subcutaneously. The first-line oral DMTs are dimethyl fumarate (DMF) at the dosage of 120 mg twice per day for the first seven days, then 240 mg twice per day; and teriflunomide (TRF) at the dosage of 14 mg once per day. Oral DMTs are gradually replacing the injectable ones for their high tolerability (D’Amico et al., 2015, 2019a; Stuchiner et al., 2020), although injectable DMTs are still widely prescribed, even because they are licensed for the use during childbearing and breastfeeding (Zanghi et al., 2021).

In the last years, real-world observational studies have revealed that treatment with DMF and TRF could impact positively on disease course, both in terms of disease activity (clinical relapses, new lesions on brain magnetic resonance imaging) and disability accrual (D’Amico et al., 2015, 2018b, 2020, 2021). Moreover, the rates of discontinuation have suggested a good persistence (D’Amico et al., 2019b). A recently published Italian study focusing on survival methods for the comparison between oral DMTs revealed that both DMTs controlled similarly magnetic resonance imaging activity and disability progression, whilst the time-varying Cox model for the event “time-to-first relapse” revealed that when the time-on-therapy exceeded 38 months, the patients on DMF had an approximately 0.3 times lower relapse hazard risk than those on TRF (HR\textsubscript{t > 38DMF} = 3.83, 95% CI = 1.11 to 13.23, \textit{P} = 0.033) (D’Amico et al., 2020).

An Italian registry study has directly compared injectables and oral DMTs as first therapeutic choice in a cohort of RRMS-naïve patients with a propensity-score adjusted method (D’Amico et al., 2021). The results suggested that oral DMTs were associated with lower risk of experiencing new clinical relapse and therapy discontinuation when compared to injectable DMTs, whilst no differences were found for the outcome confirmed disability progression (D’Amico et al., 2021). Also, European, and American national registry studies study have analyzed the emerging role of oral DMTs compared to injectable ones (Stuchiner et al., 2020; Vermersch et al., 2020; Buron et al., 2021).

A French registry study revealed a better compliance and persistence to oral therapies in naïve patients starting first-line DMT for RRMS (Vermersch et al., 2020). Furthermore, in a Danish cohort, switching from injectable DMTs platform therapies to oral first-line therapies in patients with clinically stable RRMS does not increase the risk of disability accumulation (Buron et al., 2021). The Pacific Northwest MS Registry analyzed the quality of life (QoL) of patients who switched to an oral DMT from injectable one, showing no significant differences in QoL or self-reported disability status compared to those remaining on injectable DMTs continuously in the same time period (Stuchiner et al., 2020).

The MSbase consortium (https://www.msbase.org/) and online national registries are globalizing questions about disease course, risk/benefit ratios of DMTs and quality of life.

Figure 1 | First-line disease modifying therapy prescription: injectable versus oral.
The real-world data and well-structured registries are of importance because they offer the opportunity to study real-world clinical outcomes in large cohorts of patients. The strengths of such studies include the generalizability and the representation of daily clinical MS practice. However, the observational retrospective studies have biases related to data collection and the choice of the best-fitting model could help to mitigate the imbalance. The analysis of propensity score matched samples can mimic that of randomized clinical trials because propensity score methods allow clinicians to estimate marginal (or population-average) treatment effects.

The personalization of treatment in MS is based on a patient-focused approach and from this point of view, the role of observational data is essential to guide the choice of the most suitable DMT. Undoubtedly, oral DMTs offer significant benefits related to adherence and patients on injectable DMTs usually ask for switching to oral ones to improve their quality of life, offering an opportunity of lateral therapeutic switch for convenience (Patti et al., 2010; D’Amico et al., 2016, 2018a; Buard et al., 2019). The unmet need is to define the place-in-therapy for oral DMTs that have been historically associated to naïve patients with mild disability level or in those who switched their initial treatment for poor tolerability. With a wider range of therapeutic opportunities, the question of how to select and sequence different treatments in individual patients arises (Bucello et al., 2021). Balancing risks with the expected efficacy of DMTs will still be key for treatment selection, mostly for the ageing of population with associated chronic comorbidities and polypharmacy treatment (Zanghì et al., 2021).

However, risks as well as efficacy can change when moving from the controlled clinical trial setting to clinical practice. Therefore, monitoring both short-term and long-term effects of therapy sequencing is always necessary, especially in a real-world setting.

In summary, the treatment goal must be settled to the assessment of the treatment response and to the individual patient characteristics. It is important to make reliable algorithms in the clinical practice including measures of disease activity and adherence to the treatment. Furthermore, the assessment of cognition and quality of life are needed to optimize therapy before disability accruals.

**Emmanuele D’Amico**, **Aurora Zanghì**, **Carlo Avolio**
Department “G. F. Ingrassia”; MS Center, University of Catania, Catania, Italy (D’Amico E, Zanghì A, Avolio C)
Department of Medical and Surgical Sciences, University of Foggia; Multiple Sclerosis Center, Department of Neurosciences, Policlinico Riuniti Hospital, Foggia, Italy (Avolio C)

*Correspondence to: Emmanuele D’Amico, MD, emmanuele.damico@unic.it.*
https://orcid.org/0000-0001-7494-9057
(Marco Bucello)

#These authors equally contributed to this manuscript.

**Date of submission:** February 25, 2021
**Date of decision:** March 31, 2021
**Date of acceptance:** May 18, 2021

**Date of web publication:** August 4, 2021

https://doi.org/10.4103/1673-5374.320985

**How to cite this article:** D’Amico E, Zanghì A, Avolio C (2022) Injectable versus oral first-line multiple sclerosis therapies: knowns and unknowns from observational studies. *Neural Regen Res* 17(3):567-568.

**Copyright license agreement:** The Copyright License Agreement has been signed by three authors before publication.

**Plagiarism check:** Checked twice by iThenticate.

**Peer review:** Externally peer reviewed.

**Open access statement:** This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**Open peer reviewers:** Michael Guger, Kepler University Hospital, Austria.

**References**

Buard G, Giovannelli J, Outterckx O, Hadhoun N, Lannoy J, Vermeersch P, Zéphir H (2019) Switching for convenience from first-line injectable treatments to oral treatments in multiple sclerosis: data from a retrospective cohort study. *Mult Scler Relat Disord* 33:39-43.

Bucello S, Annavozzi P, Ragonese P, Altieri M, Barcella V, Bergamaschi R, Bianchi A, Borriolli G, Buscarini MC, Callari G, Capobianco M, Capone F, Cavarpa R, Cavarretta R, Cortese A, De Luca G, Di Filippo M, Dattola V, Fantozzi R, Ferrero E, et al. (2021) Real world experience with teriflunomide in multiple sclerosis: the TER-Italy study. *J Neurol* doi: 10.1007/s00415-021-10455-3.

Bucello S, Annavozzi P, Ragonese P, Altieri M, Barcella V, Bergamaschi R, Bianchi A, Borriolli G, Buscarini MC, Callari G, Capobianco M, Capone F, Cavarpa R, Cavarretta R, Cortese A, De Luca G, Di Filippo M, Dattola V, Fantozzi R, Ferrero E, et al. (2021) Real world experience with teriflunomide in multiple sclerosis: the TER-Italy study. *J Neurol* doi: 10.1007/s00415-021-10455-3.

Buron MD, Kalincik T, Sellierberg J, Sørensen PS, Magyari M (2021) Effect of lateral therapeutic switches to oral moderate-efficacy drugs in multiple sclerosis: a nationwide cohort study. *J Neurol Neurosurg Psychiatry* 92:556-562.

D’Amico E, Haase R, Ziemssen T (2019a) Review: patient-reported outcomes in multiple sclerosis care. *Mult Scler Relat Disord* 33:61-66.

D’Amico E, Leone C, Zanghì A, Ferro SL, Patti F (2016) Lateral and escalation therapy in relapsing-remitting multiple sclerosis: a comparative study. *J Neurol* 263:1802-1809.

D’Amico E, Patti F, Zanghì A, Chisari G, Lo Fermo S, Zappia M (2018a) Late-onset and young-onset relapsing-remitting multiple sclerosis: evidence from a retrospective long-term follow-up study. *Eur J Neurol* 25:1425-1431.

D’Amico E, Zanghì A, Sciandra M, Borriolli G, Callari G, Gallo A, Salemì G, Cottone S, Bucaccaus M, Valentinò P, Bossio RB, Grimaldi LME, Pozzilli C, Tedeschi G, Zappia M, Patti F (2019b) Discontinuation of teriflunomide and dimethyl fumarate in a large Italian multicentre population: a 24-month real-world experience. *J Neurol* 266:411-416.

D’Amico E, Zanghì A, Callari G, Borriolli G, Gallo A, Graziano G, Valentinò P, Bucaccaus M, Cottone S, Salemì G, Ragonese P, Bossio RB, Docimo R, Grimaldi LME, Pozzilli C, Tedeschi G, Zappia M, Patti F (2018b) Comparable efficacy and safety of dimethyl fumarate and teriflunomide treatment in Relapsing-Remitting Multiple Sclerosis: an Italian real-world multicenter experience. *Ther Adv Neurol Disord* doi: 10.1177/1756286418796404.

D’Amico E, Leone C, Casetta C, Patti F (2015) Oral drugs in multiple sclerosis therapy: an overview and a critical appraisal. *Expert Rev Neurother* 15:803-824.

D’Amico E, Zanghì A, Romeo M, Cocco E, Maniscalco GT, Brescia Morra V, Paolicelli D, De Luca G, Galgani S, Amato MR, Salemì G, Inglese M, Confalonieri PA, Lus G, Avolio C, Gallo A, Vianello M, Chiolfi M, Filippi M, Troiano M, et al. (2021) Injectable versus oral first-line disease-modifying therapies: results from the Italian MS Register. *Neurotherapeutics* doi: 10.1007/s13311-020-00101-6.

D’Amico E, Zanghì A, Sciandra M, Lanzillo R, Callari G, Cortese A, Lus G, Lucchini M, Bucaccaus M, Bonavita S, Gallo A, Curti E, Gajofatto A, Signoriello E, Bisceco A, Gobbin F, Ferrò MT, Ferrazzano G, Sparaco M, Valentinò P, et al. (2020) Dimethyl fumarate vs Teriflunomide: an Italian time-to-event data analysis. *J Neurol* 267:3008-3020.

Patti F, Leone C, D’Amico E (2010) Treatment options of cognitive impairment in multiple sclerosis. *Neuro Sci* 31:265-269.

Stuciner T, Lucas L, Baraban E, Spinnelli KJ, Chen C, Smith A, Hashemi L, Cohan S (2020) Quality of life among injectable and oral disease-modifying therapy users in the Pacific Northwest Multiple Sclerosis Registry. *BMC Neurol* 20:439.

Vermersh P, Suchet L, Golamarino R, Laurendeau C, Detournay B (2020) An analysis of first-line disease-modifying therapies in patients with relapsing-remitting multiple sclerosis using the French nationwide health claims database from 2014-2017. *Mult Scler Relat Disord* 46:102521.

Zanghì A, D’Amico E, Callari G, Chisari CG, Lo Fermo S, Patti F (2021) Exploring polypharmacy phenomenon in newly remitting multiple sclerosis treated with old and new DMTs. *Mult Scler Relat Disord* doi: 10.1177/175628642110483121.

Zanghì A, D’Amico E, Callari G, Chisari CG, Borriolli G, Grimaldi LME, Pozzilli C, Tedeschi G, Zappia M, Patti F (2020) Pregnancy and the postpartum period in women with relapsing-remitting multiple sclerosis treated with old and new disease-modifying treatments: a real-world multicenter experience. *Front Neurol* 11:105.