## Perspective

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

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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, interferonβ-1a, 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 (Zanghì et al., 2020).

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 ($HR_{t > 38DMF}$ = 3.83, 95% CI = 1.11 to 13.23, $P$ = 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.
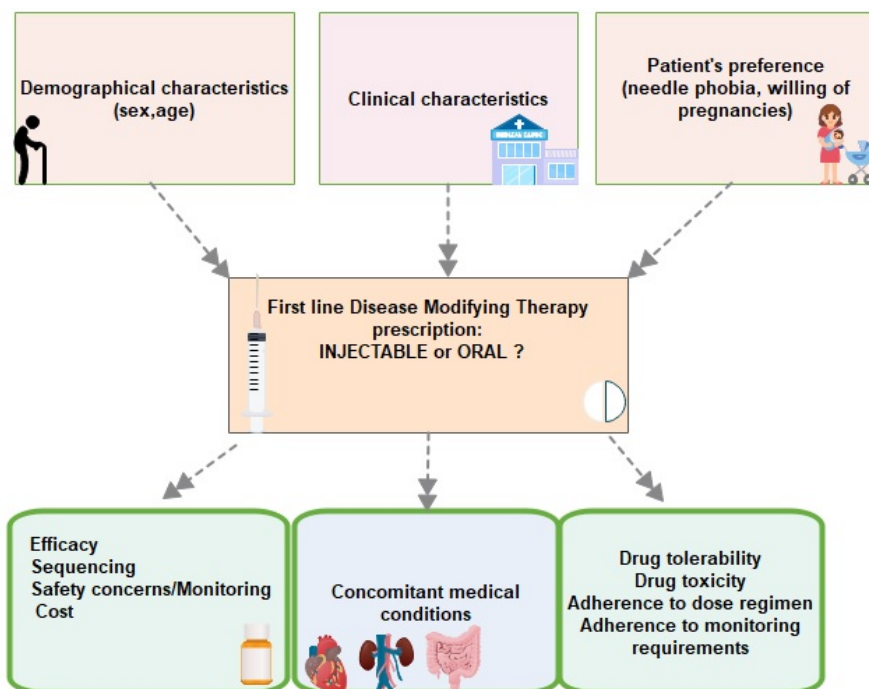


**Figure 1** │ **First-line disease modifying therapy prescription: injectable *versus* oral.**

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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.

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