The RESPECT study: a multi-centRE observational analysiS of PErsistenCe to Treatment in the new MS drugs era.

R. Lanzillo (1), L. Prosperini (2,3), R. Fantozzi (4), M. Moccia (1), V. Nociti (5), C. Gasperini (2), C. Tortorella (2), P. Annovazzi (6), P. Cavalla (7), M. Radaelli (8), S. Malucchi (9), V. Torri Clerici (10), L. Boffa (11), F. Buttari (4,11), P. Ragonese (12), G. Maniscalco (13), M. Di Filippo (14), M. Buscarinu (15), F. Pinardi (16), A. Gallo (17), E. Cocco (18), G. Coghe (18), I. Pesci (19), A. Laroni (20), A. Gajofatto (21), M. Calabrese (21), V. Tomassini (22), C. Solaro (23); **R.I.Re.MS study group**

(1) Dept. of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University, Naples; (2) Dept. of Neurosciences, S. Camillo-Forlanini Hospital, Rome; (3) Dept. Of Neurology and Psychiatry, Sapienza University, Rome; (4) Neurology Unit, IRCCS Neuromed, Pozzilli (IS); (5) Dept. of Geriatrics, Neurosciences and Orthopedics, Catholic University, Rome; (6) MS Study Center, ASST Valle Olona, Gallarate Hospital, Gallarate (VA); (7) MS Center, Neurology 1 Unit, City of Health and Science University Hospital, Turin; (8) Institute of Experimental Neuroscience (INSpe), Division of Neuroscience, S. Raffaele Scientific Institute, Milan; (9) SCDO Neurologia 2-Regional MS Center, University Hospital S. Luigi Gonzaga, Orbassano (TO); (10) Dept. of Neuroimmunology and Neuromuscular Diseases, IRCCS C. Besta Foundation, Milan; (11) Dept. of Systems Medicine, Tor Vergata University, Rome; (12) Dept. of Experimental Biomedicine and Clinical Neurosciences, University of Palermo , Palermo; (13) MS Center, Caldarelli Hospital, Naples; (14) Neurology Unit, Medicine Dept., University of Perugia, Perugia; (15) Center for Experimental Neurological Therapies, S. Andrea Hospital, Rome; (16) UOSI SM Rehabilitation, Bellaria Hospital, Bologna; (17) I Clinic of Neurology, University of Campania, Naples; (18) Dept. of Medical Sciences and Public Health, University of Cagliari, Cagliari; (19) Neurology Unit, AUSL PR, Osp. di Vaio, Fidenza (PR); (20) Dept. of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa; (21) Dept. of Neuroscience, Biomedicine and Movement Sciences, University Hospital, Verona; (22) Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Cardiff (UK); (23) Neurology Unit, Centro di Recupero e Rieducazione Funzionale, Moncrivello (VC).

INTRODUCTION

In recent years there is an increasing availability of disease-modifying treatments (DMTs) for treating multiple sclerosis (MS), including new oral therapies.

The common perception is that first-line oral therapies (teriflunomide [TER], dimethyl fumarate [DMF]) may be more accepted and tolerated by patients than self-injectable DMTs (interferon beta [IFNB], glatiramer acetate [GA]), merely due to their simpler route of administration.

Therefore, oral therapies are believed to be able to enhance treatment adherence, a key factor to reduce relapse rate, delay disability worsening and lead to better clinical outcomes. However, oral therapies are also associated with systemic side effects such as flushing, gastrointestinal disturbances and laboratory abnormalities.

As a consequence, there is not yet established evidence that oral therapies are superior to self-injectable DMTs in terms of adherence and persistence to treatment.

Aim of our study is to investigate the short-term persistence to treatment with first-line self-injectable or oral DMTs in patients with RRMS.

METHODS

We retrospectively collected data of patients regularly attending 22 MS Centers. Patients were considered eligible if they started a self-injectable or oral DMT (excluding fingolimod) from January to December 2015.

We estimated the proportion of patients discontinuing the treatment within a follow-up period of 12 months and analysed reasons for discontinuation.

A Cox regression model (stratified by Centre) was run to explore baseline predictors of treatment discontinuation.

RESULTS

We analyzed data of 1,841 consecutive patients (1,293 F, 548 M) with a mean age of 40 years and median EDSS of 2.0. Of them, 631 (34%) were treatment-naïve, while the remaining 1,210 (66%) were switched from another DMT.

The most frequently prescribed treatment was DMF (n=1,050; 57%), followed by TER (n=174, 15%), GA 20 or 40 mg (n=175; 10%), s.c. IFNB-1a or 1-b (n=165, 9%); i.m. IFNB-1a (103, 5%), s.c. pegylated IFNB-1a (n=71, 4%).

A total of 366 (20%) patients discontinued the prescribed DMT after a median time of 6 months due to lack of tolerance (n=185), clinical or radiological disease activity (n=95), adverse events (n=64) or pregnancy planning (n=22). Shorter time to treatment interruption was observed in case of poor tolerability (p<0.001) and adverse events (p=0.02) [**FIG. 1**].

Reasons for discontinuation did not differ between naives and switchers (p>0.4).

Overall, there was no significant difference in discontinuation rate between oral drugs and self-injectable DMTs (p>0.1). However, the highest discontinuation rate was observed in patients treated with pegylated-IFNB (p<0.02 *vs.* each other DMT) [**FIG. 2**].

Female sex (HR=1.45, p=0.003) and previous exposure to >2 DMTs (HR=1.66, p=0.009) were other independent risk factors for treatment discontinuation.

FIG. 1. Time to treatment interruption according to reasons for discontinuation.

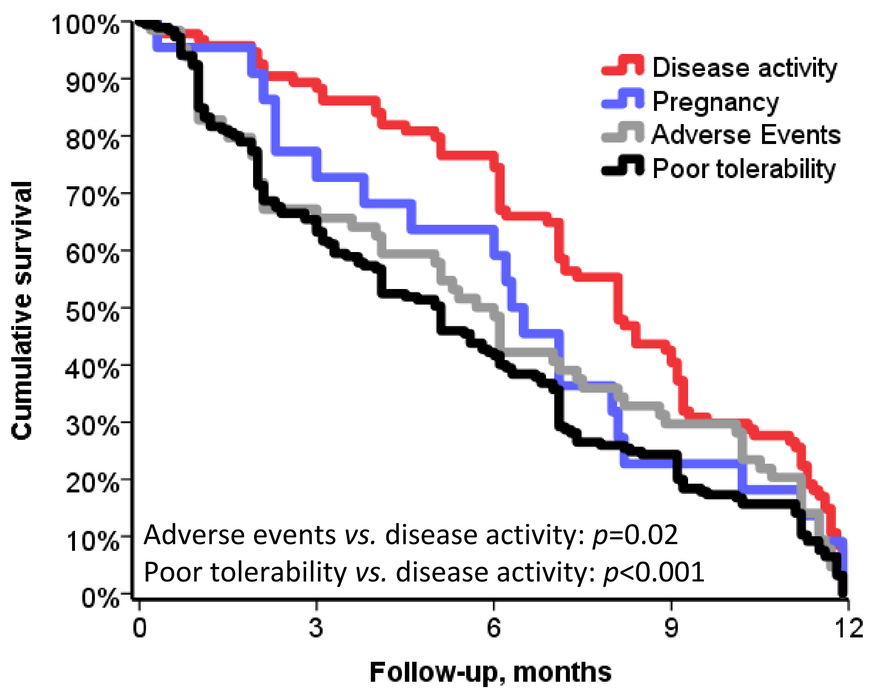
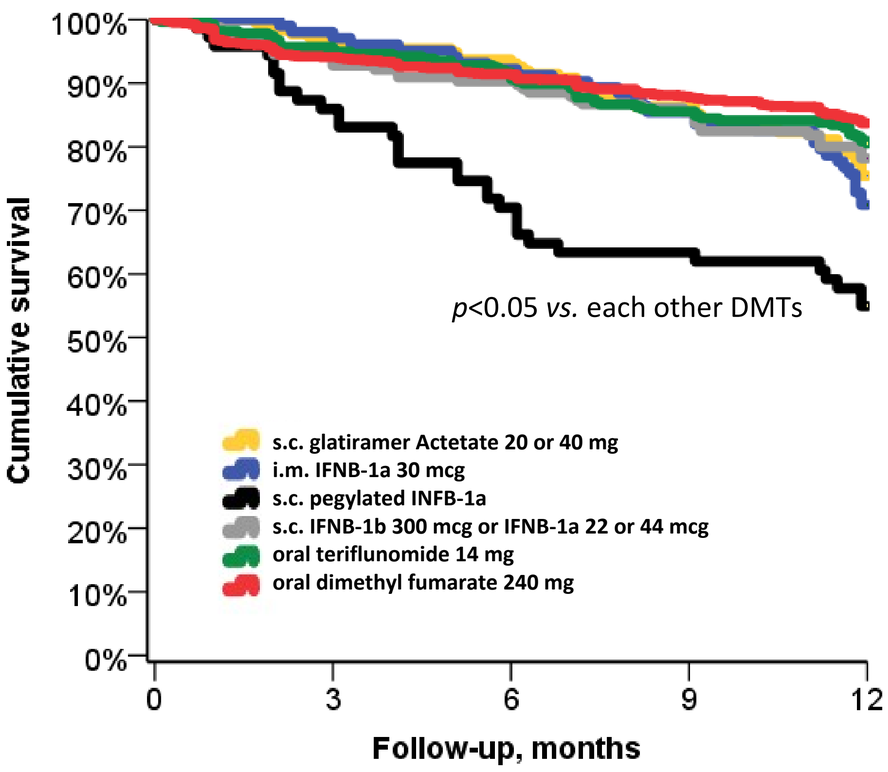


FIG. 2. Time to treatment interruption according disease-modifying drugs.



All p-values are adjusted for sex, age, disease duration, EDSS score and stratified by Centre

CONCLUSIONS

Poor tolerability was the most common cause of treatment discontinuation (>50%) in the short-term period.

Time to discontinuation was significantly shorter in case of poor tolerability and adverse events than in case of disease activity. Oral drugs (discontinuation rate: ~ 16-20%) did not show a better persistence with respect to high-frequency self-injectable IFNB or GA (discontinuation rate: ~ 22-24%), whereas the shortest persistence was observed for pegylated IFNB-1a (discontinuation rate: ~ 36%).

Persistence to treatment in MS still represents a clinical challenge, irrespective of the route and schedule of administration.

REFERENCES

Munsell M, Frean M, Menzin J, Phillips AL. An evaluation of adherence in patients with multiple sclerosis newly initiating treatment with a self-injectable or an oral disease-modifying drug. Patient Prefer Adherence. 2016 Dec 30;11:55-62.

Zettl UK, Schreiber H, Bauer-Steinhusen U et al.; BETAPATH Study Group. Baseline predictors of persistence to first disease-modifying treatment in multiple sclerosis. Acta Neurol Scand. 2016 Oct 30. doi:10.1111/ane.12705.

Moccia M, Palladino R, Carotenuto A et al. Predictors of long-term interferon discontinuation in newly diagnosed relapsing multiple sclerosis. Mult Scler Relat Disord. 2016 Nov;10:90-96.