Adherence to teriflunomide in multiple sclerosis: A Belgian observational study

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INTRODUCTION

- Adherence plays a critical role in optimizing therapeutic response in relapsing-remitting multiple sclerosis (RRMS)[1]
- A real-world phase-4 Teri-PRO study reported high adherence to teriflunomide in patients with RRMS[2]
- However, there is scarcity of data to confirm these findings in real-life setting and to understand the parameters that can impact adherence
- None of the existing studies of teriflunomide have measured adherence prospectively and/or described the adherence in accordance with the state of art taxonomy, which includes[3]:
  - Initiation phase (to identify if the patient initiated the prescribed treatment)
  - Implementation phase (to analyse if the patient delays, omits, or takes extra doses)
  - Persistence phase (to measure the time until the patient discontinues the treatment on their own initiative)
- **OBJECTIVE:** This real-world, open-label, multicenter (across 16 centers in Belgium), single arm observational study was conducted to determine adherence prospectively as per the state of art taxonomy in terms of initiation, implementation, and persistence in RRMS patients who started on teriflunomide in a real-life setting as per standard clinical practice

METHODS

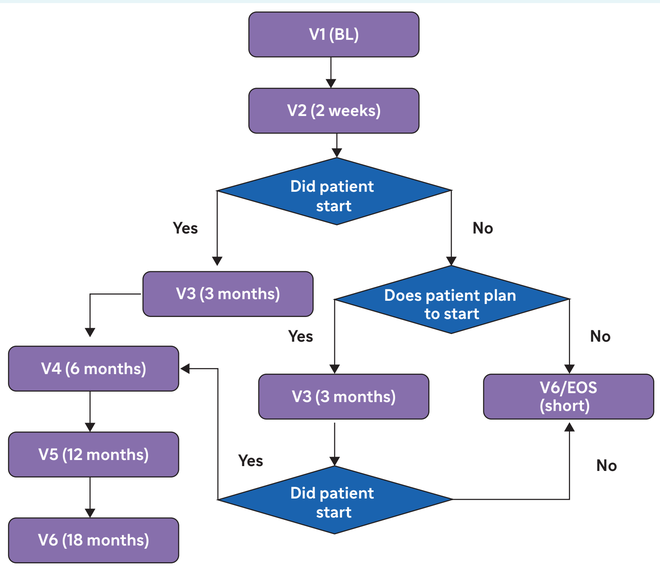
Study design

- In this real-world study, adult patients treated with teriflunomide (14 mg/day) were followed-up until:
  - 18 months (for patients included from 15 June 2018 until 31 October 2019) or treatment termination, whichever came first – **Cohort 1**
  - 12 months (for patients included from 01 November 2019 until 30 March 2020) or treatment termination, whichever came first – **Cohort 2**
- Data was recorded at inclusion visit, at 3, 6, 12, and at 18 months (if applicable)

Study participants

- Adults (>18 years) diagnosed with RRMS using the 2017 revised McDonald criteria, and Expanded Disability Status Scale (EDSS) score ≤ 6.5
- No prior treatment with teriflunomide
- The decision to start teriflunomide was taken independently from the decision to include patients in the observational study

Figure 1. Study design



Note: V5 skipped in case patient is enrolled after November 1st, 2019 and replaced by V6 (anticipated at 12 months); V6 planned at 18 months if patient is enrolled until 31st of October 2019. If patient stops earlier for any reason, in this case, the next planned visit is replaced by the EOS visit
BL, baseline; EOS, end of study; V, visit

Study endpoints

Primary endpoint:

- Adherence in terms of persistence (time to first teriflunomide discontinuation); and continuation rate at 12 and 18 months, as assessed by the modified Basel Assessment of Adherence to Immunosuppressive Medication Scale (mBAASIS) questionnaire

Key secondary endpoints:

- Adherence in terms of initiation (starting treatment from baseline to 3 months visit: Yes/No) and implementation (A good implementation was defined as not forgetting a pill for the entire period as registered in the mBAASIS)
- Reasons for treatment discontinuation (healthcare professional decision / patient decision / joint decision / other reason)
- Comparisons between discontinued and non-discontinued patients in terms of efficacy parameters (number of relapses, EDSS score and magnetic resonance imaging [MRI] result)

Safety:

- Adverse events (AEs), serious AEs (SAEs), AEs related to treatment discontinuation, AEs of special interest (AESI) and AEs leading to death were recorded

Statistical analysis

- Statistical analyses were performed using SAS Version 9.4. statistical software and were descriptive in nature
- Persistence was analyzed as a time-to-event parameter using Kaplan-Meier (KM) survival analysis, while secondary variables were summarized with 95% CI
- Statistical analyses were performed at 5% significance level using 2-sided tests or 2-sided CI
- p-values were provided for descriptive purpose only, and no adjustments for multiple comparisons were performed
- Comparisons between groups for the efficacy metrics were made using Welch's t-test

RESULTS

Participants

- Of 109 included patients, 4 patients did not initiate treatment and 60 (55%) patients completed the study (55/95 in the 18 months cohort [Cohort 1] and 5/10 in the 12 months cohort [Cohort 2])
- Patient demographics and disease characteristics are presented in **Table 1**

Adherence in terms of initiation

- 103/107 (96.26%) patients started the treatment (**Table 2**)

Adherence in terms of implementation

- In the primary analysis set (PAS) population (n=95), more than half of the patients reported not having forgotten one pill during the entire observation period **(Table 2)**
  - At end of the last study visit, 67/90 (74.44%) patients in full analysis set (FAS) mentioned not having implementation issues; 21/90 (23.33%) forgot at least one pill and only 5/90 (5.55%) forgot ≥2 pills on consecutive days in the last 4 weeks

Table 1. Patient demographics and disease characteristics

	FAS (N=109)
Age, mean (SD)	46.86 (12.21)
Gender, female, n (%)	80 (73.39)
Number of relapses in the 2 years prior to enrolment, mean (SD)	0.79 (0.87)
EDSS score, mean (SD)	2.22 (1.32)
MRI, n	84
Stable disease, n (%)	35 (41.67)
Disease activity, n (%)	49 (58.33)
Time since first diagnosis of MS (years), mean (SD)	7.94 (9.34)
Previous DMT, Yes, n (%)	70 (64.22)
Previous DMT in past 2 years, n	109
Switch patient, n (%)	63 (57.80)
Naïve patient, n (%)	46 (42.20)
Time from the last relapse, n	100
<3 months, n (%)	37 (37.00)
≥3 months, n (%)	63 (63.00)
Patients who switched from DMT at least once in past 2 years, n	63
Due to safety, n (%)	38 (60.32)
Other reason, n (%)	25 (39.68)

FAS included patients for whom any follow-up evaluation is available
EDSS, Expanded Disability Status Scale; FAS, full analysis set; MRI, magnetic resonance imaging; MS, multiple sclerosis; SD, standard deviation; DMT, disease modifying therapy

Table 2. Adherence in terms of initiation and implementation

Adherence in terms of initiation	**FAS (N=109)**
Starting treatment from baseline to 3 month, n/N (%)	103/107 (96.26)
Adherence in terms of implementation	**PAS (N=95)**
Patients who have a good implementation, n/N (%)	42/81 (51.85)
mBAASIS at last visit (visit 6)	**FAS (N=109)**
Patients who reported having missed a dose of teriflunomide within the past 4 weeks, n/N (%)	**21/90 (23.33)**
Once	8
More than once	13
Patients who reported having missed 2 or more consecutive doses of teriflunomide within the past 4 weeks, n/N (%)	**5/90 (5.55)**
Once	0
More than once	5
Patients who reported having changed the prescribed amount of teriflunomide in the last 4 weeks, without doctors telling to do so, n/N (%)	**3/90 (3.33)**
Adherence in terms of discontinuation	**FAS (N=109)**
Patients who did not continue treatment, n/N (%)	35/109 (32.11)
Health care professional decision	16
Patient decision	13
Joint decision	5
Other reason	1
mBAASIS at last visit (visit 6)	**FAS (N=109)**
Patients who reported having stopped taking teriflunomide completely within the last year, without doctor telling to do so, n/N (%)	**3/90 (3.33)**

*A good implementation was defined as not forgetting a pill for the entire period as registered in the mBAASIS
PAS included patients completing the study (visit at 12/18 months done or terminating the treatment in the study period. FAS included patients for whom any follow-up evaluation is available. N in n/N refers to the number of patients who completed the questionnaire at the specific visit or at each visit
FAS, full analysis set; mBAASIS, modified Basel Assessment of Adherence to Immunosuppressive Medication Scale; N, overall patients; n, number of patients with available information; PAS, primary analysis set

Adherence in terms of persistence

- The cumulative incidences for discontinuation (95% CI) at 12 and 18 months were 0.28 (0.21; 0.38) and 0.34 (0.26; 0.44), respectively **(Figure 2)**
- Overall, 35/109 (32.11%) patients discontinued treatment: almost half of these patients (16/35) discontinued treatment due to health care professional decision; 13/35 of discontinued patients due to own decision **(Table 2)**

Adherence in terms of continuation rate

- The continuation rates among the patients who remained on treatment at 12 months follow-up (Cohort 1+2) were 73.68% and at 18 months follow-up (Cohort 1) were 64.71%, in the PAS population **(Table 3)**

CONCLUSIONS

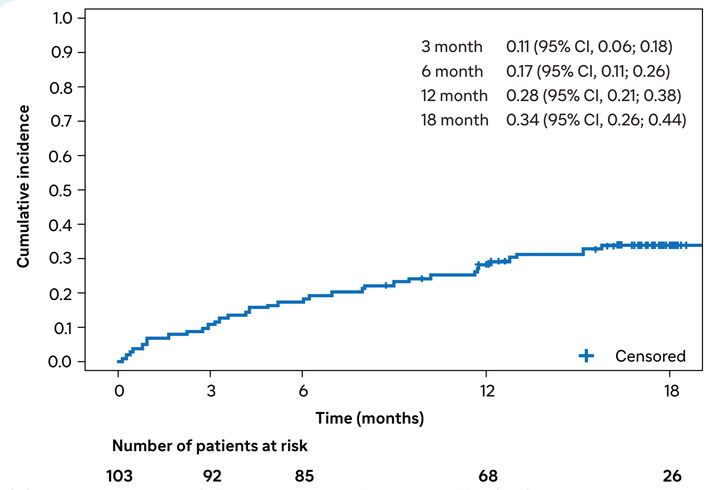
The outcomes of this study demonstrated good adherence to teriflunomide in RRMS patients and are in line with results reported in cross-sectional studies.[4-6] Adherence in accordance with the state of art taxonomy includes:

- **Initiation phase:** About 4% of patients did not initiate treatment
- **Implementation phase:** More than half of patients did not report implementation issues during complete observation period
- **Persistence phase:** 65% of patients remained on treatment until the last follow-up visit. 13/95 (13.68%) patients stopped the treatment on own decision

The prospective nature of this study provides unique insights on patients' medication taking behavior over-time

No new safety concerns were noted

Figure 2. Kaplan Meier plot for persistence in safety population



Safety population consisted of all patients who received at least one tablet of teriflunomide
CI, confidence interval

Table 3. Adherence in terms of continuation rate

	PAS (N=95)	Patient decision* (n=13)
Continuation rate at 12 month (Cohort 1+2), % (n/N) [95% CI]	73.68 (70/95) [63.65; 82.19]	15.38 (2/13) [1.92; 45.45]
Continuation rate at 18 month (Cohort 1), % (n/N) [95% CI]	64.71 (55/85) [53.59; 74.77]	0 [NE]

PAS included patients completing the study (visit at 12/18 months done or terminating the treatment in the study period)
Cohort 1 (n= 10); Cohort 2 (n=85)
*number of discontinued patients due to patient decision excluding those with AEs. CI were calculated based on exact binomial clopper Pearson's method for proportion
AEs, adverse events; CI, confidence Intervals; N, overall patients; n, number of patients with available information; NE, not estimable; PAS, primary analysis set

Differences in efficacy metrics between discontinued and non-discontinued patients

- EDSS score at visit 6 did not change regardless of treatment discontinuation (p = 0.6770)
- There was no difference across groups in the proportion of patients who experienced relapse at visit 6 (p = 0.2645)
- There was no difference in MRI disease activity at baseline between groups (p = 0.88). There was a significant difference at visit 6, with the discontinued group having a higher number of patients with disease activity versus the non-discontinued group (p = 0.01)
- More patients who continued the treatment had stable disease on MRI at visit 6

Safety

- 84.76% (89/105) of patients reported at least one AE
- Most common AEs included diarrhoea, alopecia, headache, and multiple sclerosis relapse
- SAEs were reported in 10 (9.52%) patients
- AEs leading to treatment discontinuation were observed in 27.62% of patients **(Table 4)**
- 62.86% of patients reported an AESI, mainly being diarrhoea, alopecia, nausea, gastrointestinal disorders, and lymphopenia
- No deaths were reported during the study

Table 4. Summary of adverse events

n (%)	Safety (N=105)
Patients with any AE	89 (84.76)
Patients with any SAE*	10 (9.52)
Patients with any related to treatment discontinuation AE	29 (27.62)
Patients with any AESI	66 (62.86)
Patients with any AE leading to death	0
AE leading to treatment discontinuation in ≥ 2 % of patients	
Diarrhoea	7 (6.67%)
Multiple sclerosis relapse	3 (2.86)
Pregnancy	3 (2.86)
Gastrointerstinal disorder	2 (1.90)
Headache	2 (1.90)
Alopecia	2 (1.90)
Lymphopenia	2 (1.90)

*SAEs included appendicitis, erysipelas, pneumonia, tooth abscess, suicidal ideation, headache, multiple sclerosis relapse, optic neuritis, asthma, cholecystitis, intervertebral disc protrusion and prostatitis (in 1 patient each)
AEs, adverse events; AESI, AE of special interest; PAS, primary analysis set; SAE, serious AE

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