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Switch Analysis of Teriflunomide from Other Multiple Sclerosis Disease Modifying Therapies

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OBJECTIVES

To evaluate the effectiveness and safety of teriflunomide in the first switch analysis study.

BACKGROUND

•Teriflunomide is an oral once-daily immunomodulatory agent with anti-inflammatory properties, that blocks the proliferation of activated B and T lymphocytes.[1]

•Although the effects of teriflunomide on relapse-related neurologic sequelae are known, there is no published study evaluating the effectiveness and safety of teriflunomide when switched from other multiple sclerosis (MS) disease modifying therapies (DMTs).

METHODS

•Patients were included in this study if they:
1. Switched to teriflunomide from another MS DMT, and
2. On teriflunomide for at least 6 months (unless treatment discontinuation due to side effects, relapse, and/or at the patient's request)
3. Note: Treatment duration for each patient will vary as each patient had different teriflunomide start date.

•For prior therapy with natalizumab (NTZ), teriflunomide was given one month after the last NTZ infusion. No washout period was used for conversion of other MS DMTs to teriflunomide.

•Analysis included baseline demographics, reasons for switching, pseudo-relapses, relapses requiring steroids treatment, Cox proportional hazards on probability of remaining on therapy across time, side effects, and discontinuation rate on teriflunomide.

RESULTS

•Ninety-five patients met the inclusion criteria. All were started on teriflunomide 14mg. Baseline demographics and primary reasons for switching are listed in Table 1.

•While the majority of patients were Caucasian, almost 20% of patients were non-Caucasian (mostly African-American and Hispanics). (Table 1)

•Average duration of therapy was 10.1 ± 4.4 months.

Table 1: Baseline Demographics and Switch Reasons

Variable	N = 95
Age (yr) – mean ± SD Range	55.4 ± 10.6 24 to 81
Female Gender – N (%)	83 (87%)
Caucasian – N (%)	78 (82%)
EDSS – mean ± SD Range	3.5 ± 1.7 1 to 8
Disease Duration (yr) – mean ± SD Range	15.0 ± 10.2 2 to 40
Prior Therapies – N (%) Glatiramer acetate (GA) Interferon β (IFN β) Natalizumab (NTZ) Other orals	 70 (73.7%) 14 (14.7%) 9 (9.5%) 2 (2.1%)
Primary Reason for Switching – N (%) Lipoatrophy or injection site reaction Preference for an oral agent Injection or infusion exhaustion Increase in relapse JCV positive serology Increase in EDSS Nabs to IFN β Nabs to NTZ	 32 (32.6%) 22 (23.2%) 19 (20.0%) 10 (10.5%) 6 (6.3%) 5 (5.3%) 1 (1.1%) 1 (1.1%)

Nabs = neutralizing antibodies

Table 2: Clinical Outcomes

Outcomes	N = 95
Pseudo-relapse – N (%)	2 (2.1%)
Relapse requiring steroids – N (%) Annualized relapse rate (ARR)	3 (3.2%) 0.04
% relapse-free	96.8%

•Over 50% switched to teriflunomide due to injection-associated reasons, almost 25% due to preference for an oral agent, and about 16% due to sub-optimal therapies (increase in relapse or EDSS). (Table 1)

•Almost 90% of patients were clinically stable on teriflunomide therapy, without any relapse or side effects leading to discontinuation. (Figure 1)

•The probability of patients remaining on teriflunomide at 12 months is almost 90%, regardless of EDSS score ≤3 or >3. (Figure 2)

Figure 1: Patient Outcomes

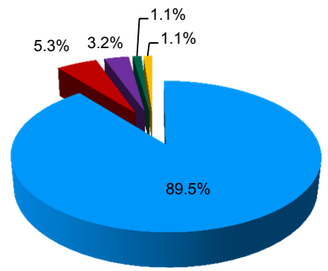
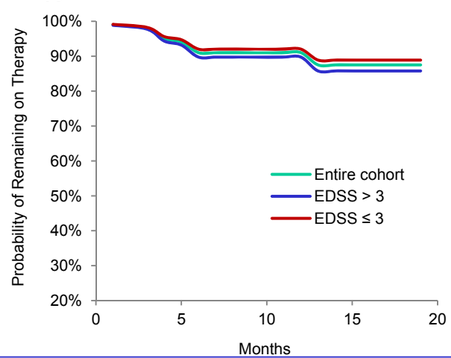


Figure 2: Probability of Remaining on Teriflunomide Therapy over Time



•The percent of patients who relapsed on teriflunomide was low, all were on prior NTZ therapy and occurred at month 6. All had complete recovery after steroid treatment and switching back to NTZ. (Tables 2 and 3)

•Patients on prior sub-optimal DMTs were relapse-free on terifluonimide.

•Ten patients (10.5%) reported side effects early in the treatment course (within 2 months). Of these, 5 (5.3%) discontinued teriflunomide and resumed prior DMT. Side effects in the other 5 patients resolved while remaining on teriflunomide. (Tables 3 and 4)

•Two patients (2.1%) experienced mild hair thinning (both with onset at month 2) and resolved within 1 and 3 months, respectively, while remaining on teriflunomide. Two (2.1%) had elevated liver enzymes (>3x ULN), both resolved within 2 and 3 months, respectively, after discontinuation. (Table 4)

Table 4: Adverse Events

Adverse Events	N (%)
Anxiety	1 (1.1%)
Diarrhea	2 (2.1%)
Hair thinning*	2 (2.1%)
Hypotension	1 (1.1%)
Increased LFTs**	2 (2.1%)
Nausea / Vomiting	1 (1.1%)
Pregnancy	1 (1.1%)

LFTs = liver function tests
*One resolved after 1 month and one resolved after 3 months
**Both cases resolved 2 and 3 months, respectively, after drug discontinuation

Table 3: Reasons for Treatment Discontinuation

Reasons	N (%)	Comments
Side effects	5 (5.3%)	Reasons: 1 anxiety*, 1 hypotension/diarrhea, 1 nausea/vomiting*, and 2 increased in LFTs
Relapse requiring steroids**	3 (3.2%)	All were on prior NTZ therapy and occurred at month 6
Pseudo-relapse***	1 (1.1%)	Was on prior NTZ therapy and occurred at month 4
Pregnancy	1 (1.1%)	Patient discontinued teriflunomide and underwent accelerated elimination at week 6 of pregnancy and experienced spontaneous abortion at week 7

*Discontinued at patient's request.
**All returned back to baseline after steroid treatment and switching back to NTZ
***Both patients returned back to baseline while remaining on teriflunomide. One patient subsequently requested to be switched back to NTZ

DISCUSSION

•The ARR for teriflunomide 14mg in this switch study was 0.04 compared to 0.37 in the TEMSO study, 0.32 in the TOWER study, and 0.26 in the TENERE study.[2-4] This difference may be due to differences in study design, baseline characteristics, and study duration.

•One-third of patients on prior NTZ experienced relapse requiring steroids. Recurrence of disease activity after NTZ discontinuation is common and effective therapy after NTZ discontinuation has not been identified. Recent studies reported 31% to 60% of patients on prior NTZ experienced relapses after switching to fingolimod and 41% to other treatments.[5-6]

•In this study, the incidences of hair thinning (2%), increased liver enzymes (2%), diarrhea (2%), and nausea/vomiting (1%) were lower than the incidences reported in the TEMSO study for teriflunomide 14mg (13%, 14%, 18%, and 14%, respectively).[2]

CONCLUSION

•Teriflunomide is an effective and well tolerated oral medication for the management of MS.

•Side effects were mild and rarely led to treatment discontinuation.

•A 97% relapse-free rate during the first year of treatment compares favorably to other DMTs in our clinical practice and makes teriflunomide a logical choice for first line switch therapy in the management of MS.

REFERENCES

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Statistical Analysis: Simple descriptive statistics were done using Microsoft Excel and Cox Proportional Hazards survival model was performed using Software R.

Cox Proportional Hazards:

The Cox model estimates the survival probability S(t) of a patient surviving at least until time t, $S(t) = \Pr(T > t)$ via the hazard function defined by: $\lambda(t) = \lim_{dt \to 0} \frac{\Pr(t \le T < t+dt)}{dt \cdot S(t)} = \frac{f(t)}{S(t)} = -\frac{S'(t)}{S(t)}$.

The hazard function is modeled as a function of input variables (e.g., EDSS score) via the equation:

$$\lambda(t|X) = \lambda_0(t)\exp(\beta_1 X_1 + \cdots + \beta_p X_p) = \lambda_0(t)\exp(\beta' X).$$

Disclosure:
The authors have nothing to declare