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# Real World Use of Teriflunomide in South Africa: A Medium Prevalence Multiple Sclerosis Area

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## Abstract

**Back ground:** South Africa, which has a multi-ethnic population of over fifty million, is considered to have a medium (5-30/100 000) prevalence rate of Multiple Sclerosis. Teriflunomide is one of two oral disease modifying agents that have been registered in this country. We describe the real-world experience of this drug in South Africa with respect to efficacy, tolerability and side effects.

**Methods:** A retrospective analysis was undertaken of the demographics, clinical presentation, number of preceding relapses, date of last relapse, degree of disability (Expanded Disability Status Scale-EDSS- score) and the magnetic resonance imaging (MRI) changes at initiation of therapy with teriflunomide (14 mg daily orally) and the subsequent course. Tolerability and side effects were recorded. Any preceding disease modifying therapy was recorded. The treating neurologists were asked about the effectiveness of teriflunomide in the patients under their care.

**Results:** Data for 32 patients was analysed. The majority were women (75%) and of white race (78.1%). The mean age ( $\pm$ ) was 41.1 (11.5) years at the time of initial assessment. Twenty six of the 32 (81%) patients were on prior disease modifying therapy (DMT) which consisted of an interferon-beta 1a or 1b and glatiramer acetate. One patient was on teriflunomide at initiation of the study. The duration on treatment with DMTs prior to teriflunomide ranged from 7.0 to 236.6 months with a mean ( $\pm$ ) of 96.5 (71.2) months.

The duration of therapy with teriflunomide varied from 3 to 24 months with a mean ( $\pm$ ) of 12.3 (5.0) months. Fourteen patients experienced mild to moderate relapses while on teriflunomide treatment, with 56% remaining relapse free over the study period. The mean ( $\pm$ ) EDSS score on teriflunomide was 2.5 (1.6), remaining relatively stable compared to the baseline score 2.6 (1.3). The drug was well tolerated in 24 patients, satisfactorily tolerated in 7 and not tolerated in 1. The treating neurologists' assessment was that the drug was an effective treatment choice in 87.1% of patients, with 96.9% of patients remaining on therapy at the time of analysis. One patient experienced 2 relapses in the year of treatment and one experienced a relapse and progression of the gait disturbance.

**Conclusions:** This small "real world" study confirms that teriflunomide is an effective DMT for patients with mild to moderate MS, prolonged disease duration and switching from other DMTs. It has a tolerable side effect profile. The oral administration compared to the interferons will appeal to many patients. The drug was also effective in patients who were on previous DMTs.

**Keywords:** Multiple sclerosis; Teriflunomide oral therapy; Patient

## Introduction

Teriflunomide is an oral disease-modifying therapy (DMT) indicated for the treatment of relapsing remitting multiple sclerosis (RRMS), administered as a single daily oral dose of 14 mg. It causes reversible inhibition of dihydro-orotate dehydrogenase, a mitochondrial enzyme required for pyrimidine synthesis, thus reducing the number of activated lymphocytes. It has little influence on resting cells [1]. Two phase three trials, TEMSO and TOWER and a more recent pooled data and extended follow up study have shown that teriflunomide is effective with acceptable tolerability [2-4].

South Africa is a multi-ethnic population of over fifty million individuals and is considered to have a medium prevalence rate of MS (5-30/100 000) [5]. Teriflunomide was registered and approved for use in South Africa in February 2017. Prior to the registration of teriflunomide in this country, it was made available to over 40 patients at no cost on a named-patient program. We report on the real-world experience of this drug in South Africa with respect to efficacy, tolerability and side effects.

## Methods

Ten Neurology centres participated in the study. Patient demographic data, start of MS symptoms, time to diagnosis, relapse rate, EDSS score at baseline and use of prior medication were recorded in the case report form (CRF). The duration of teriflunomide therapy and the patient progress until the most recent visit were also noted.

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Information on tolerability and side effects were recorded. Where available the baseline and most recent MRI reports were scrutinized. The treating neurologists were asked to provide reasons for switching patients to teriflunomide, and for their impression of the efficacy of teriflunomide in these patients.

The data was analyzed using STATA version 14.2 (STATA Corporation, College Station, TX USA). Simple descriptive statistics were used to characterise the study population, continuous data were summarised by mean and standard deviation (SD), and by median and interquartile range (IQR). Categorical data were summarized as number and proportion. Statistical tests included chi-square test (adjusted if number less than 5) and linear regression which was used to determine the association between EDSS score and enhanced lesions. Statistical tests were two-sided at  $\alpha = 0.05$ . Data for 1 patient was not included in the analysis. The following variables were included in the analysis: age, gender, race, date of onset of symptoms, date of diagnosis, treatment history, treatment change (including date of change and reason for change), reason for treatment switch to study drug, relapse while on study drug (including date of relapse, cause of relapse, severity and if relapse needed hospitalisation), MRI results (lesions enhancing or not), EDSS score, tolerability of study drug, number of participants still on study drug at the end of the study and investigators opinion on study drug. The study was approved by Pharma Ethics, an independent research ethics committee in South Africa.

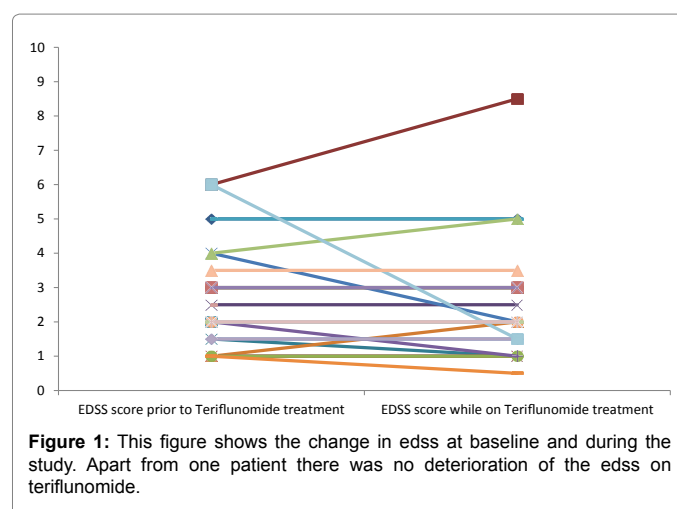
## Results

The demographic and clinical data are summarized in Table 1. The majority of patients were women (75%) and of white race (78.1%). The mean age ( $\pm$ ) was 41.1 (11.5) years at the time of initial assessment. The time from onset of symptoms to MS diagnosis varied from 0 to 13 years with a mean (SD) of 1.5 (2.4) years whilst the mean (SD) time since diagnosis was 9.1 (5.6) years (range: 1-20 years). Time from start of symptoms to diagnosis was longer in females compared to males mean (SD) 1.8 years (3.1) vs. 0.9 (0.9) years, however this was not a statistically significant difference ( $p = 0.468$ ). Twenty six of the 32 (81%) patients were on prior disease modifying therapy (DMT) either interferon 1b, interferon 1a or glatiramer acetate. Of these 14 were on one prior DMT, 8 on 2 and 4 on more than 2. The duration of treatment with a DMT prior to teriflunomide ranged from 7.0 to 236.6 months with a mean ( $\pm$ ) of 96.5 (71.2) months. Average treatment duration (SD) with one, two and three prior DMTs was comparable at 62.4 (43.1), 59.1 (64.8) and 57.0 (48.1) months respectively. None of these patients was on natalizumab or fingolimod prior to starting teriflunomide. Neurologist-reported reasons for switching to teriflunomide included previous therapy unsatisfactory (8), adverse event (12), doctor's recommendation (3) and other reasons (9).

The mean number of relapses per year at baseline was 1.7, with 1 patient experiencing 6 relapses prior to initiating teriflunomide treatment. A total of 37.5% of patients experienced relapses requiring hospitalisation prior to initiating teriflunomide treatment. At the time of analysis the duration on teriflunomide treatment varied from 3 months to 24 months with a mean ( $\pm$ ) of 12.4 (4.9) months. The mean duration on teriflunomide was longer for patients on 2 or more prior DMTs mean (SD) 14.9 (5.6) vs. 11.1 (3.9)), which suggested a trend but was not significant ( $p = 0.059$ ). Fifty six percent remained relapse free on teriflunomide treatment, while 14 experienced mild (64.3%) and moderate (28.6%) relapses. One patient experienced 2 relapses in the year of treatment and one experienced a relapse and progression of the gait disturbance. The mean ( $\pm$ ) EDSS score at baseline was 2.6 (1.3), and remained relatively stable during teriflunomide treatment 2.5 (1.6). The Figure 1 shows the EDSS score at baseline and at last assessment

<b>Demographic data</b>	
Age in years ( $\pm$ )	41 $\pm$ 11.2
Race White	25
Black	1
Asian	4
Mixed Ancestry	2
Gender (F/M)	3:1
<b>Clinical Features</b>	
Time from first MS symptom years ( $\pm$ )	10.5 $\pm$ 6.66
Time from diagnosis (years $\pm$ )	9.1 $\pm$ 5.47
Use of DMT in the previous year	
None	6
An interferon	23
Glatiramer acetate	1
Methotrexate	1
Teriflunomide	1

**Table 1:** This table Lists the demographic features, times of MS symptoms and diagnosis, and previous DMT use.



**Figure 1:** This figure shows the change in edss at baseline and during the study. Apart from one patient there was no deterioration of the edss on teriflunomide.

whilst on teriflunomide. The drug was well tolerated in 24 patients, satisfactorily tolerated in 7 and not tolerated in 1.

A total of 21 patients had an MRI of the brain during the study. Four of the 21 patients had an MRI of the brain at baseline but not for the period under study and 2 without contrast. There were 2 others for whom MRI brain scans were performed a long time before the study and therefore unreliable for comparison with scans taken during the study. As there were no paired baseline and treatment related MRI scans no comment was possible regarding the change in the number of T2 lesions. We therefore focused on the presence of enhancing lesions to detect activity. Of the 21 scans done during teriflunomide treatment contrast was not used in 4.

Of the 15 patients with a valid MRI result 3/15 (20%) were reported as lesions enhancing and 12/15 (80%) as lesions not enhancing. In the three patients with lesions enhancing, the EDSS scores remained unchanged (1.5-1.5; 3.5-3.5 and 3.0-3.0). All patients continued therapy with teriflunomide barring the 1 who could not tolerate the drug. The treating neurologists' assessment was that the drug was an effective treatment choice in 87.1% of patients, with 96.9% of patients remaining on therapy at the end of the study period.

## Discussion

The pivotal phase 3 trials and the extension studies have confirmed

the efficacy and safety of teriflunomide. Unlike natalizumab and fingolimod no unexpected serious side effects such as the development of progressive multifocal leukoencephalopathy occurred despite at least 12 years of treatment in some patients and a cumulative exposure of more than 6800 patient-years [2-4]. A Danish study examined the real world experience with teriflunomide [6]. Although we studied only 32 patients, our study closely mirrors the findings in the Danish study. Like the Danish study the majority of patients were on DMTs previously, tolerated teriflunomide well, experienced no or little deterioration or had improvements in EDSS score. We had a higher relapse rate (43.7%) than the Danish study but our numbers were small. Five (15% of the whole group) of these relapses occurred within six months of starting teriflunomide. The frequency of relapses is similar to that noted in the pivotal studies. Only one patient (3.1%) discontinued therapy compared to seventeen (16.5%) of Danish patients [7].

## Conclusion

The current study has the limitations of being retrospective, having small number of patients and a short duration of follow up. It does provide information about real world experience with teriflunomide, like the Danish study and is the first to emerge from South Africa (a medium MS prevalence area) and Africa. As it appears to be as effective as the interferons, teriflunomide is a reasonable alternative as first line

DMT for patients who are reluctant to inject themselves. As for the second line DMTs, cladribine holds promise but is as yet unlicensed in South Africa.

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