New and Evolving Treatment Goals in Multiple Sclerosis – the Role of Teriflunomide

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Teriflunomide is an oral immunotherapy agent that acts primarily as an inhibitor of dihydroorotate-dehydrogenase (DHODH), a key mitochondrial enzyme involved in the synthesis of pyrimidines in rapidly proliferating cells such as T lymphocytes and B lymphocytes, thus attenuating the inflammatory response to auto-antigens. The TEMSO and TOWER phase III clinical studies have demonstrated the efficacy and safety of teriflunomide in the first-line treatment of patients with relapsing multiple sclerosis (MS), with long-term follow-up data available up to 9 years. Teriflunomide has also been shown to decrease the risk of conversion to clinically definite MS (CDMS) in patients with a first clinical sign of MS or risk of conversion to CDMS after a clinically isolated syndrome. In addition to reducing disability progression and relapse rate, teriflunomide has also been found to decrease imaging activity and is associated with significant reductions in brain volume loss. The convenience of administration of teriflunomide should establish its role within the growing number of treatment options for MS.

Keywords

Teriflunomide, immunotherapy, multiple sclerosis

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Multiple sclerosis (MS) is a chronic, progressive disease of the central nervous system (CNS), resulting from inflammatory lesions that become sites of demyelination and axonal injury. These lesions are associated with infiltrating T cells and monocytes, as well as B cells and plasma cells.[1] Treatment of MS presents a challenge, since disease-modifying treatments (DMTs) must limit immune responses associated with disease initiation and propagation while also minimising any adverse effect on normal protective immune function. Enhanced understanding of the roles of T and B lymphocytes in the pathophysiology of relapsing MS have facilitated new approaches to managing MS with markedly improved efficacy.[2,3] Treatment goals have changed: halting disability progression and promoting some degree of functional improvement are becoming achievable for many patients.[3–5] The burden of treatment has also been decreased with the approval of a number of oral DMTs for relapsing-remitting MS (RRMS).[6] Teriflunomide (Aubagio® Sanofi-Genzyme, Massachusetts, US) is an oral immunomodulatory agent that selectively targets T and B cells and has been approved both in the US and in Europe for the treatment of RRMS.[7,8] This article will discuss the clinical evidence for the efficacy and safety of teriflunomide in MS, as well as clarifying the role of teriflunomide in the context of current and emerging MS treatment options.

Teriflunomide in the treatment of multiple sclerosis

Teriflunomide is the active metabolite of the parent drug, leflunomide, which has been in clinical use for many years as a treatment for rheumatoid arthritis.[9] Following oral ingestion, leflunomide is rapidly converted almost entirely into teriflunomide. The latter has been found to have highly effective immunomodulatory and anti-inflammatory properties.[7] Its precise effect of reducing T and B cells on the pathophysiology of MS has not been fully elucidated but is related to its action on the proliferation of activated lymphocytes. Teriflunomide selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase in *de novo* pyrimidine synthesis, halting cell division in cells such as autoreactive T- and B-lymphocytes in MS and limiting their involvement in the inflammatory processes underlying MS.[10-15] Mean reductions of white blood cell counts of around 15% occur during the first 6 weeks of teriflunomide initiation and persist during treatment, although mean absolute counts remain within the normal range for most patients.[18] A similar reduction has been reported for dimethyl fumarate (DMF).[16] Cells that do not proliferate in response to activation, e.g. resting lymphocytes, can divide through homeostatic proliferation in which pyrimidines are synthesised by means of the salvage pathway.[10,11] As a result of teriflunomide action, fewer autoreactive T- and B-lymphocytes cross the blood–brain barrier into the CNS but there is no apparent effect on the viability of stimulated T or B cells, a limited impact on lymphocyte activation and no direct effects on DNA.[10,17,18]

The impact of teriflunomide on adaptive immune cell subsets in humans was recently demonstrated in the TERI-DYNAMIC study:[19] patients (n=39) with RRMS received teriflunomide 14 mg once daily for 24 weeks. From baseline to week 12 and week 24, the proportion of CD19+

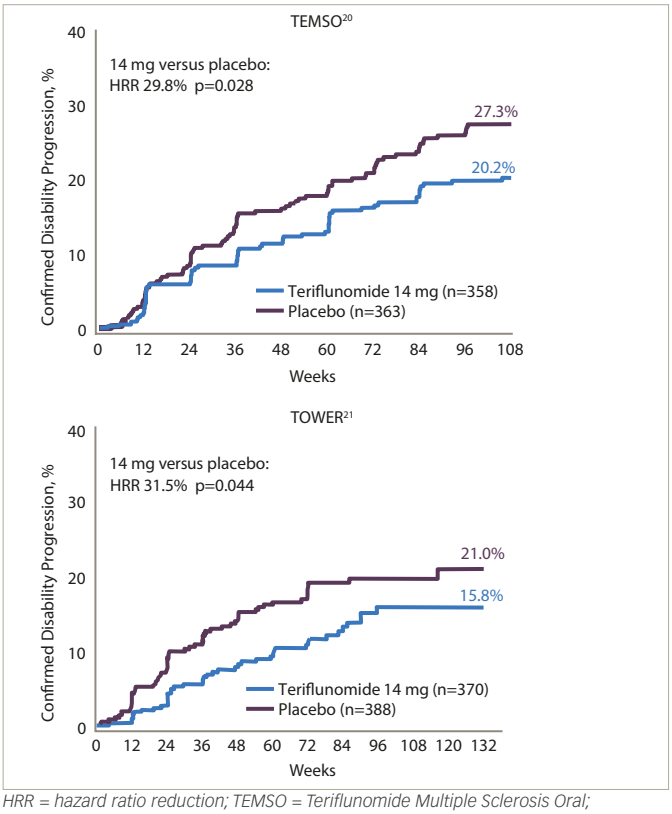
Table 1: The TEMSO and TOWER trials – baseline characteristics

	TEMSO[20]	TOWER[21]
Study design	Multicentre, multinational, randomised, double-blind, parallel-arm, placebo-controlled	
Patients (randomised), n	1,088	1,169
Study duration	108 wk	Ended 48 wk after last patient randomised (mean exposure, 82 wk, max 152 wk)
Patient population	Patients with RMS (McDonald 2001 criteria[22,23]) Aged 18–55 years EDSS score ≤5.5 at screening ≥2 relapses within 2 years or ≥1 relapse within 1 year before randomisation	
Treatment arms	Once-daily, oral (1 : 1 : 1 ratio) Teriflunomide 14 mg : Teriflunomide 7 mg : Placebo	
Primary outcome	ARR (number of relapses per patient-year)	
Secondary outcomes	Key: Time to 12-wk sustained accumulation of disability MRI measures, safety	Key: Time to 12-wk sustained accumulation of disability Safety

ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; RMS = relapsing multiple sclerosis; TEMSO = Teriflunomide Multiple Sclerosis Oral; TOWER = Teriflunomide in Patients With Relapsing Multiple Sclerosis; wk = week; Data sourced from: Genzyme, 2014,[7] O'Connor et al., 2011,[20] Confavreux et al., 2014,[21] Polman et al., 2005,[23]

B cells and absolute counts of Th1 cells decreased and the proportion of CD4+ cells versus CD8+ cytotoxic cells increased. Results also showed that teriflunomide decreases clonal diversity, which provides an immunomodulatory action without impairing immune function.[19]

Figure 1: Confirmed disability progression during teriflunomide or placebo treatment in the TEMSO and TOWER studies



HRR = hazard ratio reduction; TEMSO = Teriflunomide Multiple Sclerosis Oral; TOWER = Teriflunomide in Patients With Relapsing Multiple Sclerosis. Data sourced from: Genzyme, 2014,[7] O'Connor et al., 2011[20] and Confavreux et al., 2014.[21]

Clinical evidence for the efficacy of teriflunomide

Two multicentre, multinational, randomised double-blind parallel-arm, placebo-controlled studies, TEMSO[20] and TOWER,[21] have examined the efficacy and safety of teriflunomide 14 mg and 7 mg/day in patients with MS. The study designs and baseline characteristics were similar in both trials; patients had relapsing MS, were between the ages of 18 and 55 years old, had Expanded Disability Status Scale (EDSS) scores ≤5.5, and at least two clinical relapses in the preceding 2 years, or at least one relapse in the previous year. Patients were randomised to teriflunomide 14 mg or 7 mg/day or placebo once daily for 108 weeks (*Table 1*). In the TEMSO and TOWER studies, compared with placebo, teriflunomide reduced the annualised relapse rate (ARR) relative risk by 32% (p<0.001) and 36% (p=0.0001), for 14 mg and 7 mg respectively. Results showed 29.8% (p=0.028) and 31.5% (p=0.044) relative risk reductions for 14 mg teriflunomide versus placebo for confirmed disability progression in the TEMSO and TOWER studies, respectively (*Figure 1*).[20,21] In the TEMSO study, teriflunomide 14 mg treatment resulted in a 67.4% relative reduction in new T2 lesion volume (p<0.001)[20,24] and an 80.4% reduction in the number of gadolinium (Gd)-enhancing T1 lesions per scan at week 108.[24]

Recently, long-term data from TEMSO has been released: no new or unexpected adverse events (AEs) occurred in patients receiving teriflunomide for up to 9 years. Disease activity decreased in patients switching from placebo and remained low in patients continuing on teriflunomide.[25]

In the TOWER study extension, the improvement in disability progression has been sustained up to 5.5 years. A mean change in EDSS from baseline of <0.15 points[26] and the median EDSS was in the range 2.0–2.5 at all time points.[27] Similar control of disability progression has also been observed in the TEMSO long-term extension study.[28]

A post-hoc analysis of pooled data from both the TEMSO and TOWER studies showed that ARR was reduced by 33.7% with teriflunomide 14 mg versus placebo (p<0.0001) and by 27.0% with teriflunomide 7 mg versus placebo (p<0.0001). Confirmed disability progression was reduced by 30.5% with teriflunomide 14 mg (p=0.0029 versus placebo). However, teriflunomide 7 mg did not show a significant effect on disability progression.[29]

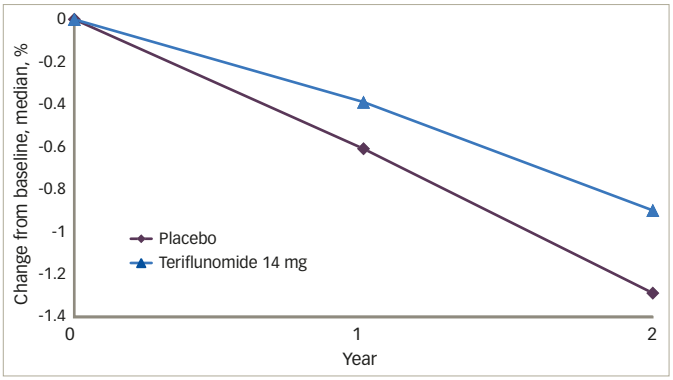
Teriflunomide has also been investigated in MS at different disease stages. The TOPIC study was a phase III clinical trial that evaluated the efficacy of teriflunomide in preventing conversion to clinically definite MS (CDMS) in patients with first demyelinating events suggestive of MS.[30] Patients (n=618) with clinically isolated syndrome (defined as a neurological event consistent with demyelination, starting within 90 days of randomisation, and two or more T2-weighted magnetic resonance imaging (MRI) lesions ≥3 mm in diameter) were randomised to once-daily oral teriflunomide 14 mg, teriflunomide 7 mg, or placebo. At 108 weeks, teriflunomide (14 mg) decreased the risk of conversion to CDMS by 42.6% versus placebo (p=0.0087), as well reduced the risk of another relapse or new MRI lesion by 34.9% (p=0.0003) compared with placebo.[30] Teriflunomide 14 mg reduced risk in the number and volume of Gd-enhancing lesions by 58.5% (p=0.0008). Teriflunomide 7 mg decreased conversion to CDMS by 37.2% versus placebo (p=0.0271) and the risk of recurrent relapse or new MRI lesion formation by 31.4% versus placebo (p=0.0020), and reduced the number but not the volume of Gd-enhancing lesions.[30]

Table 2: Overview of safety of teriflunomide across the clinical development programme

Pooled safety from phase III, TOPIC, TEMSO and TOWER		
n (%)	Placebo (n=997)	Teriflunomide 14 mg (n=1,002)
All AEs	853 (85.6)	885 (88.3)
SAEs	119 (11.9)	133 (13.3)
AEs leading to discontinuation	75 (7.5)	125 (12.5)
Intensity		
Mild	285 (33.4)	281 (31.8)
Moderate	448 (52.5)	477 (53.9)
Severe	120 (14.1)	127 (14.4)

AEs = adverse events; SAEs = severe adverse events; TEMSO = Teriflunomide Multiple Sclerosis Oral; TOPIC = Teriflunomide Versus Placebo in Patients With First Clinical Symptom of Multiple Sclerosis; TOWER = Teriflunomide in Patients With Relapsing Multiple Sclerosis. Data sourced from: Comi et al., 2016,[41] Leist, et al., 2015,[42] Kremenchutzky et al., 2015.[44]

Figure 2: Annualized brain volume loss over 2 years during treatment with teriflunomide or placebo in the TEMSO study



TEMSO = Teriflunomide Multiple Sclerosis Oral. Reproduced under the CC-BY-NC-ND license from: Radue et al., 2015.[39]

To gain a better understanding of the clinical implications of the results of the phase III pivotal teriflunomide studies, compared with those of other disease-modifying therapies (DMTs) pivotal phase III trials, it is useful to calculate the number needed to treat (NNT) to benefit one patient.[31] This takes into account not only the treatment effect, but also the rarity of the event in question (e.g., relapse); thus, a higher NNT would be expected if fewer patients experienced the event in the time period of interest. There has been a downward trend in MS relapse rates over the past decade, making it difficult to compare studies conducted at different times. A post-hoc analysis found that the absolute ARR reductions for TEMSO and TOWER were –0.17 and –0.18, and NNTs were 5.9 and 5.6, respectively.[32] This was similar to findings of the two pivotal studies of DMF 240 mg (DEFINE[33] [Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis] and CONFIRM[34] [Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis]) in which the relapse rates were also significantly reduced versus placebo. The absolute ARR reductions for DEFINE and CONFIRM were –0.19 and –0.18 and NNTs were 5.3 and 5.6, respectively. This similarity in NNTs was observed despite a higher relative relapse risk reduction for DMF compared with teriflunomide.[35] In the TEMSO, TOWER, DEFINE and CONFIRM studies, the NNTs for prevention of disease progression were 13.8, 17.4, 10.8, and 30.2, respectively. These data suggest a potentially greater treatment effect of teriflunomide. However, it should be noted that there was a low number of relapses in the DMF studies, which may confound this comparison. In an analysis of pivotal studies of DMF, fingolimod and teriflunomide, NNTs to prevent any relapse, more severe relapses (such as those leading to hospitalisation or requiring intravenous corticosteroids), and disability worsening. were similar for DMF and teriflunomide, and marginally lower for fingolimod.[32]

Another post-hoc analysis of TEMSO found that teriflunomide reduced relapses leading to hospitalisation (by 36% in the 7 mg group [p=0.015] and 59% in the 14 mg group [p<0.0001]) and intravenous corticosteroid use versus placebo (29% [p=0.001]; 34% [p=0.0003]) and also that teriflunomide-treated patients spent fewer nights in hospital for relapses (p<0.01). In addition, teriflunomide reduced the annualised rate of all hospitalisations (p=0.01) and emergency room visits (p=0.004). This may translate to reduced healthcare costs.[36]

A further demonstration of teriflunomide efficacy was the achievement of no evidence disease activity (NEDA) status during the core phase of the TEMSO study.[37] NEDA was defined as no Gd-enhancing T1 lesions or new/enlarging T2 lesions, and no clinical relapse or 12-week sustained disability progression. In Year 1 significantly more patients receiving teriflunomide achieved NEDA than those receiving placebo (33.1% versus 19.4%, p<0.0001). In Year 2 this difference was maintained (35.3% and 21.2%, respectively, p=0.0002).[37] These data support the continued efficacy benefits of ongoing treatment with teriflunomide.

While clinical measures of efficacy are essential, patient-reported outcomes are also important in establishing the usefulness of a drug in routine clinical practice. The improvement in disability from the patients' perspective has been investigated in the phase IV, single-arm, open-label TeriPRO study (n=1,001).[38] Patients receiving teriflunomide indicated disability level during the past month in eight domains of the Multiple Sclerosis Performance Scales (MSPS). In a 6-month, interim analysis, 52.8% reported an improvement, 10.2% reported no change and 37.0% reported worsening. There were improvements reported for domains of mobility, hand function and vision. A 6-month interim analysis showed that at baseline 41.3% of patients reported normal/minimal disability due to cognitive symptoms; after 6 months of teriflunomide treatment this had increased to 48.1%. In patients switching from another DMT within 6 months of enrolment, mean TSQM (Treatment Satisfaction Questionnaire for Medication) Global Satisfaction score was 74.9, a 22.7-point improvement compared with baseline.[38]

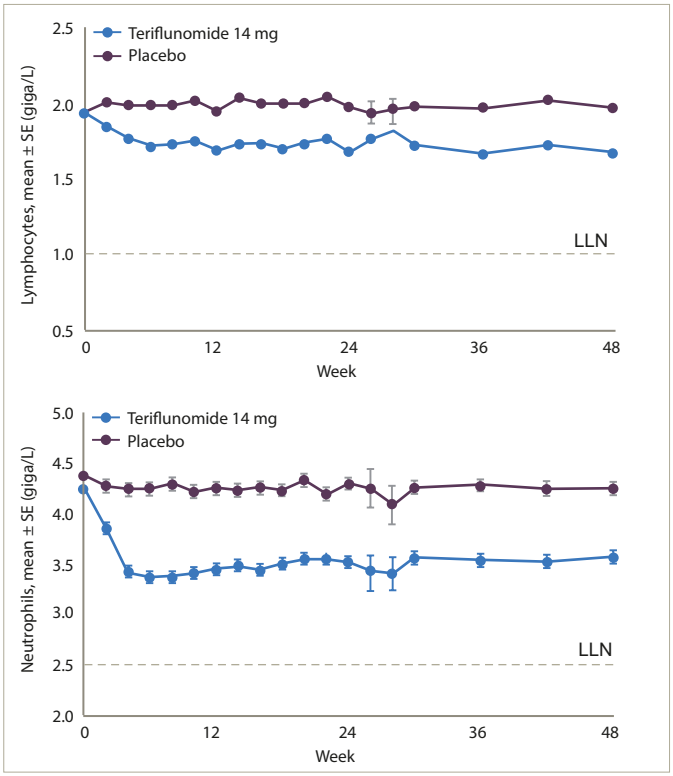
Effect of teriflunomide on brain volume

There is increasing interest in brain volume (BV) atrophy and its effects on disability in MS, largely due to wider adoption of protocols that specify its measurement. In the MRI investigations of the TEMSO study, an analysis using the SIENA (Structural Image Evaluation using Normalization of Atrophy) protocol revealed significant treatment effects.[39] With teriflunomide 14 mg, there was a 39.6% reduction in BV loss after 1 year (p<0.0001) and 30.6% reduction after 2 years (p<0.0001) versus placebo (*Figure 2*). Median BV was reduced by 0.39% with teriflunomide and 0.61% with placebo after 1 year and by 0.90% and 1.29% after 2 years (p=0.0001 for both comparisons). These findings using an established measure of brain tissue loss, are consistent with the effects of teriflunomide on delaying disability progression.

Safety findings of studies of teriflunomide

The safety profile of teriflunomide is based on a population of over 5,000 patients, mostly with RRMS.[27] A pooled analysis of TEMSO, TOWER, and

Figure 3: Mean neutrophil and lymphocyte counts in a pooled analysis of data from the TEMSO, TOWER and TOPIC studies



LLN = lower limit of normal; SE = standard error; TEMSO = Teriflunomide Multiple Sclerosis Oral; TOPIC = Teriflunomide Versus Placebo in Patients With First Clinical Symptom of Multiple Sclerosis; TOWER = Teriflunomide in Patients With Relapsing Multiple Sclerosis. Reproduced with permissions from Comi et al., 2014.[40]

TOPIC study data investigated the effect of teriflunomide on lymphocyte and neutrophil counts.[40] The mean lymphocyte and neutrophil counts decreased during the first 6 or 12 weeks of treatment versus placebo. After the initial treatment period, levels remained stable (*Figure 3*) and were well above the lower limit of normal, suggesting preserved immune function. Neutrophil and lymphocyte count decreases were mostly mild to moderate (Grade 1–2).[41] There was no association between infection and decreased lymphocyte counts in all three clinical studies.

Infection rates were similar for patients receiving teriflunomide 14 mg versus placebo (52.7% versus 53.4% for any infection and 2.7% versus 2.2% for any serious infection).[41,42] Two serious opportunistic infections occurred in the teriflunomide 14 mg group.[43] One patient experienced gastrointestinal tuberculosis, leading to permanent discontinuation of treatment. Another patient developed hepatitis with cytomegalovirus infection, again leading to treatment discontinuation. Two patients died as a result of infections: one was in the placebo group (respiratory tract infection) and one in the teriflunomide 14 mg group (gram-negative bacterial sepsis).[43]

The overall incidence of AEs was similar for teriflunomide 14 mg and placebo (*Table 2*).[41,42] The frequencies of all AEs for teriflunomide and placebo were 88.3% and 85.6%, respectively. Serious AEs were reported in 13.3% and 11.9%, respectively. The distribution of mild, moderate and severe AEs was also similar between teriflunomide and placebo. The most common AEs reported with teriflunomide were: hair thinning, diarrhoea, alanine aminotransferase (ALT) increase, nausea, and headache; the majority resolved on treatment. A low incidence of malignancy (≤0.4%) was observed in all treatment groups, with no unusual pattern of malignancy, including haematological malignancies and lymphoproliferative tumours.[41] The most common reason for treatment discontinuation in all treatment groups was ALT elevation, reflecting the labelling indication to discontinue treatment on confirmation of ALT >3-times the upper limit of normal (ULN). The proportion of patients with hepatic disorders was higher in the teriflunomide groups (14 mg, 21.5%; 7 mg, 19.8%; placebo, 15.2%), largely due to transient and reversible ALT increases ≤3-times the ULN.[41] Follow-up for 12 years in the phase II study showed the types of AEs were similar to those of the placebo-controlled studies.[44]

Preservation of protective immunity after teriflunomide has been addressed by the TERIVA (teriflunomide and vaccination) study, which investigated the effects of influenza vaccination patients with RRMS.[45] At 28 days post vaccination, the proportions treated with 14 mg teriflunomide who had a ≥40 titre to influenza antigens H1N1, H2N3 and B were: 97.4%, 76.9% and 97.4%, respectively. These proportions in patients treated with IFNβ-1a were 97.7%, 90.7% and 93.0%, respectively. These responses were all above the European Medicines Agency (EMA)-defined threshold for efficacy of influenza vaccination in 18- to 60-year-olds.[46]

No signals for teratogenicity have been reported in the teriflunomide clinical trial database. In a 2014 report, no structural or functional deficits had been reported in 83 patients who had taken teriflunomide during pregnancies leading to live births and 22 pregnancies in partners of male patients.[47] Median birth weight, for 18 newborns, was 3.3 kg, and mean gestational age, documented in 23 cases, was 39 weeks (range 36–44 weeks). All newborns were healthy and did not have any structural or functional abnormalities at birth. The spontaneous abortion rate in teriflunomide-exposed patients was 18.6%,[47] within the range reported for the general population.[48]

In a further study on healthy human subjects (n=46), teriflunomide produced no notable impact on immune response to recall antigens (*Candida albicans*, *Trichophyton*, and tuberculin) or neoantigens (rabies vaccine) versus placebo.[49]

Discussion and Conclusion

Continuing advances in the management of MS have markedly raised the bar in treatment goals in recent years. It is now possible to stabilise disability progression and even reverse it. Selective targeting of T and B cells has proven to be a successful strategy in MS treatment. The oral treatment, teriflunomide, can be used as a first-line therapy in MS. This drug depletes autoreactive T and B cells but does not eliminate precursor or non-autoreactive cells. Decreased inflammation in neuronal tissue is accompanied by normal immune function allowing continued immune responses to infection and vaccination.

The selective action of teriflunomide is reflected in efficacy and safety findings from up to 12-years in a clinical development programme involving over 5,000 patients that showed effective control of MS symptoms and progression, and the risk of infection was little different to either placebo or a comparator treatment interferon beta-1a (IFNβ-1a). Teriflunomide treatment has yielded significant reductions in BV loss compared with placebo or comparator in the TEMSO study. Interim analyses show improvements in cognition and studies are ongoing to further explore this effect.

The role of teriflunomide among the growing number of treatment options for MS is unclear. In the absence of head-to-head trials, its efficacy relative to other first-line parenteral agents is unknown, but phase III clinical trial

data suggest its efficacy is similar to existing injected agents. Its efficacy appears to be lower than that of other oral agents such as fingolimod but its ease of use and favourable safety profile compared to fingolimod make it an attractive treatment option. However, the convenience of oral administration, as well as safety and tolerability, should lead to more widespread use. The use of an oral drug such as teriflunomide may improve adherence and reduce lifestyle restrictions associated with injected therapies. Further studies are needed to determine the optimum sequence of administering teriflunomide and existing therapies and whether it can be used in combination with other agents. There is also a need to identify the ideal responder profile to teriflunomide. Individual genetic or clinical features might predict an optimal response to teriflunomide for a patient at particular stage of the disease. The mechanism of action of teriflunomide suggests that it may be most effective between the early and the relapsing–remitting stage of MS, when immune and inflammatory processes need to be controlled.[11]

In conclusion, there is a need for further clinical data as well as postmarketing studies to fully define the role of teriflunomide among the MS treatment armamentarium. ❑

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