P047

Potential Antiviral Properties of Teriflunomide: A Consideration for Optimizing MS Treatment Sequencing

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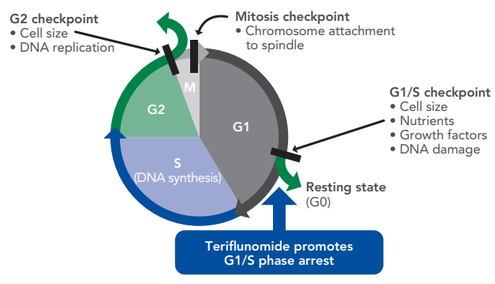
OBJECTIVE

- **To review data on the antiviral effects of teriflunomide and the potential role of these effects in the treatment of MS with teriflunomide**

INTRODUCTION

- The etiology of MS is complex and is likely to result from a combination of genetic and environmental factors, among which viruses have been postulated to play a critical role[1]
- Exposure to Epstein-Barr virus has been linked to increased risk of relapsing-remitting MS[1,2]; a variety of other herpesviruses (eg, human herpesvirus 6) and common viral infections have been associated with increased risk of relapse in MS[3,4]
- Current data suggest that long-term use of certain disease-modifying therapies (DMTs) is associated with an increased risk of opportunistic viral infections[5]; this includes, but is not limited to, cytomegalovirus (CMV) and polyomaviruses such as BK virus (BKV) and John Cunningham virus (JCV)
- Exploring the potential antiviral properties of DMTs could, therefore, be critical in terms of treatment choice and treatment sequencing in order to optimize patient outcomes in MS
- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS
  - A77 1726, also known as teriflunomide, is the active metabolite of leflunomide, a treatment for patients with rheumatoid arthritis[6]
- Teriflunomide promotes cytostasis in T and B cells via selective inhibition of dihydroorotate dehydrogenase (DHODH), a key mitochondrial enzyme in de novo pyrimidine synthesis required by rapidly dividing lymphocytes[6]
  - Inhibition of DHODH is rescued by the addition of uridine[6]
  - Viral replication requires host resources to make viral protein and replicate the viral DNA/RNA genome.[7] Teriflunomide promotes G1/S phase arrest, thus impeding viral replication because these resources are unavailable[6,8] (**Figure 1**)

Figure 1. Inhibition of Mitochondrial DHODH by Teriflunomide Promotes Cytostasis via G1/S Phase Arrest



DHODH, dihydroorotate dehydrogenase.

CONCLUSIONS

- **Preclinical and clinical data provide evidence that teriflunomide shows antiviral activity against a range of viruses, which may arise due to the impact of teriflunomide on host mechanisms. When interpreting these results, consideration should be given to the fact that the antiviral activity of teriflunomide has not been studied in prospective clinical trials**
- **Given the potential involvement of viruses in the etiology of MS, and their potential significance in the disease course and treatment of MS, the antiviral properties of teriflunomide and the implications for treatment sequencing strategies when patients transition from other DMTs merit further investigation**

- Teriflunomide has a well-characterized safety and tolerability profile, as demonstrated across phase 2 and 3 clinical studies,[9–13] and their extensions.[14–17] Furthermore, these clinical trials demonstrated that teriflunomide had no significant impact on protective immunity[13]
  - While the mean lymphocyte counts decreased by ≤15% with teriflunomide treatment, values remained within the normal range, and there was no evidence of a relationship between decreased lymphocyte or neutrophil counts and infection[13]
  - Individuals treated with teriflunomide mounted an effective immune response to seasonal influenza vaccination,[18] and had seroprotective responses to rabies neoantigen and memory responses to recall antigens[19]
- Here, we review data on the antiviral effects of teriflunomide and leflunomide, and the potential role such effects might have in the treatment of MS with teriflunomide

METHODS

- A review was conducted of available literature and current safety data on potential antiviral effects of teriflunomide and leflunomide

LITERATURE REVIEW

Use as an Antiviral Agent

- Orally administered leflunomide is largely metabolized to its active metabolite, A77 1726, also known as teriflunomide[20–22]
- Presented here are a range of preclinical and clinical studies investigating the potential antiviral properties of leflunomide and/or its active metabolite, teriflunomide (**Table 1**)

Herpes Simplex Virus (HSV)-1

- Dose-dependent reduction of HSV-1 production was observed in the presence of pharmacologic concentrations of A77 1726/teriflunomide in Vero (monkey epithelial) cells and human umbilical vein endothelial cells[23]

Cytomegalovirus (CMV)

- In cardiac transplanted rats inoculated with rat CMV, leflunomide treatment reduced viral loads by 4–6 orders of magnitude[24]
- In case reports of renal transplantation patients with CMV infection, including 4,[25] 17,[26] and 31[27] cases, leflunomide treatment resulted in either a clearance of the infection or a clinical response, with healing of involved organs, in the majority of patients

BK Virus (BKV)

- Polyomavirus-associated nephropathy, caused by the BK polyomavirus (which is closely related to JCV[28]), is a leading cause of early renal graft loss[29]
- In vitro, BKV load showed dose-dependent suppression with teriflunomide alone in renal epithelial cells,[29] and with leflunomide in combination with sirolimus (a macrolide agent commonly used to prevent renal transplant rejection) in human primary tubular epithelial cells[30]

Table 1. Evidence of Antiviral Effects of Leflunomide and Teriflunomide

Virus	Treatment	Results
Herpes simplex virus (HSV)-1	Teriflunomide	Dose-dependent reduction of HSV-1 production in Vero (monkey epithelial) cells and human umbilical vein endothelial cells[23]
Cytomegalovirus (CMV)	Leflunomide	Reduction of viral loads in cardiac transplanted rats inoculated with rat CMV[24]
	Leflunomide	Clearance of infection or clinical response in majority of renal transplantation patients with CMV infection[25–27]
BK virus (BKV)	Teriflunomide	Dose-dependent suppression of BKV load in renal epithelial cells[29]
	Leflunomide + sirolimus	Dose-dependent suppression of BKV load in human primary tubular epithelial cells[30]
	Leflunomide	Clearance of infection in majority of 136 renal transplant recipients with BKV infection (71%–100%)[31–35]

- In several studies of leflunomide administered to 136 renal transplant recipients with BKV infection, the infection was cleared in the majority of patients (71%–100%)[31–35]
  - Inhibition of BK viral replication in these patients was correlated with increased serum levels of teriflunomide[31–33]

Progressive Multifocal Leukoencephalopathy (PML)

- PML is a rare demyelinating disease of the CNS caused by JCV. PML has been linked to treatment with some DMTs that modulate the immune system for the treatment of autoimmune diseases such as MS[36]
- Over 2.4 million patient-years of leflunomide exposure in patients with rheumatoid arthritis show that there is no increase in the rate of PML compared to the background rate in the postmarketing setting[37]
- Approximately 67,000 patients have been treated with teriflunomide world-wide (as of December 2016), with the total exposure to the teriflunomide 14-mg dose approaching 100,000 patient-years (as of September 2016).[38] To date, no cases of PML with teriflunomide have been reported in clinical trials or in the postmarketing setting
- In ongoing studies evaluating teriflunomide as a treatment strategy for patients at high risk of PML discontinuing natalizumab therapy, no cases of PML with teriflunomide monotherapy have been reported thus far (**Table 2**)[39, 40]

Table 2. Patients Switching to Teriflunomide Following Treatment With Natalizumab

	Edwards et al.[39]	Cohan et al.[40]
Number of patients	25	40
Study type	Retrospective	Prospective
Number of patients with specific PML risk factors at baseline, JCV+[a] JCV+; no IS[b] Triple +ve[c]	 25 16 9	 40 NA NA
Duration of prior natalizumab treatment, mean (SD), months	48 (11)	45 (26)
Interval between natalizumab and teriflunomide	6 (Range: 0–11) weeks	28 ± 7 days
Follow-up, mean (SD), months	21 (12)	16 (6)
Efficacy	• Relapse: 4 patients • EDSS: Decrease of 0.2 in mean score over 6 months • MRI: New T_2 or Gd+ lesions observed in 2 patients	• Relapse: 6 patients • EDSS: No significant change from baseline at Month 12[d] • MRI[e]: New/enlarging T_2 or Gd+ lesions observed in 14 patients
Safety	• Poor GI tolerability leading to discontinuation (n=2) • Hair thinning (n=5) • No cases of PML	• Mild and transient hepatic enzyme elevation (n=7) • Hair thinning (n=17) • No cases of PML

[a]Anti-JCV antibody–positive patients; [b]anti-JCV antibody–positive patients with no prior immunosuppressant use; [c]anti-JCV antibody–positive patients with prior immunosuppressant use and >24 months' exposure to natalizumab; [d]n=35 with >12 months of teriflunomide treatment. EDSS, Expanded Disability Status Scale; Gd+, Gd-enhancing; GI, gastrointestinal; IS, immunosuppressant; JCV, John Cunningham virus; NA, not available; PML, progressive multifocal leukoencephalopathy; SD, standard deviation.

Optimizing Treatment Sequencing

- Treatment sequencing is becoming increasingly complex with the availability of multiple DMTs with distinct mechanisms of action and diverse impacts on the immune system
- In addition to natalizumab,[41] PML has also been reported with other DMTs, including fingolimod[42–46] and dimethyl fumarate[47–50]
- The potential antiviral effects of teriflunomide reviewed here may, therefore, have implications for treatment sequencing strategies when patients transition from other DMTs

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Teriflunomide is approved in many countries, including the US and the European Union, for the treatment of relapsing multiple sclerosis or relapsing-remitting multiple sclerosis. This material may contain information that is outside of the approved labeling in some countries.

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