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.1–4 Viral infections have been associated with increased risk of relapse in MS.3,4–7 A77 1726, also known as teriflunomide, is the active metabolite of leflunomide, a treatment choice and treatment sequencing in order to optimize patient outcomes in MS 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.

• AT-1726, also known as teriflunomide, is the active metabolite of leflunomide, a treatment for patients with rheumatoid arthritis.

• Teriflunomide promotes cytostasis in T and B cells via selective inhibition of dihydroorotate dehydrogenase (DHODH), a key mitotic enzyme in the novel pyrimidine synthesis required by rapidly dividing lymphocytes.6

• Inhibition of DHODH is induced by the addition of uracil−

• Viral replication requires host 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 unavailable6,8 (Figure 1).

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

• Only administered teriflunomide is largely metabolized to its active metabolite, AT-1726, also known as teriflunomide.9

• 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).

• Due to the potential antiviral effects of teriflunomide reviewed here, it may be useful to review the studies that have demonstrated antiviral activity in vitro and in vivo.

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

Table 1. Evidence of Antiviral Effects of Leflunomide and Teriflunomide

<table>
<thead>
<tr>
<th>Virus</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-1</td>
<td>Teriflunomide</td>
<td>Dose-dependent reduction of HSV-1 production in Vero (monkey epithelial) cells and human umbilical vein endothelial cells (HUVEC)</td>
</tr>
<tr>
<td>CMV</td>
<td>Leflunomide</td>
<td>Reduction of viral loads in cardiac transplant patients with CMV infection</td>
</tr>
<tr>
<td>BKV</td>
<td>Teriflunomide</td>
<td>Dose-dependent suppression of BKV load in renal epithelial cells</td>
</tr>
<tr>
<td>HCMV</td>
<td>Leflunomide</td>
<td>Dose-dependent suppression of BKV load in human primary tubular epithelial cells</td>
</tr>
</tbody>
</table>

Teriflunomide has a well-characterized safety and tolerability profile, as demonstrated across phase 2 and 3 clinical studies,4–7 and their extensions.41–43 Furthermore, these clinical trials demonstrated that teriflunomide had no significant impact on protective treatment.44–46

• While the mean lymphocyte counts decreased by 15% for teriflunomide treatment, values remained within the normal range, and there was no evidence of a relationship between decreased lymphocyte or haematological counts and infection.47

• Individuals treated with teriflunomide mounted an effective immune response to seasonal influenza vaccination,48 and had nonsuppressive responses to rabies neonatally and response to recall antigens.49

• 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.

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, it is important to consider the potential antiviral effects of teriflunomide reviewed here, may, therefore, have implications for treatment sequencing strategies when patients transition from other DMTs.

• 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 (for Table 2).

Table 2. Patients Switching to Teriflunomide Following Treatment With Natalizumab

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Teriflunomide Treatment</th>
<th>PML Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Study type</td>
<td>Retrospective</td>
<td>Perspective</td>
</tr>
<tr>
<td>Number of patients with specific PML risk factors at baseline, JCV+</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>JCV+ vs. JCV−</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>Duration of prior natalizumab treatment, months</td>
<td>48 (11)</td>
<td>45 (24)</td>
</tr>
</tbody>
</table>

• In studies of leflunomide administered to 136 renal transplant recipients with BKV infection, the infection was cleared in the majority of patients (71%–102%).50

• Inhibition of BK viral replication in these patients was correlated with increased serum levels of teriflunomide.50

Progressive Multifocal Leuкоencephalopathy (PML)

• PML is a new degenerating disease of the CNS caused by JC virus and has been linked to treatment with some DMTs that modulate the immune system for the treatment of autoimmune diseases such as MS.51

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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, PML has also been reported with other DMTs, including fingolimod.52,53 and cyclosporine A.54

• 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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