Teriflunomide Mechanism of Action: Linking Preclinical Evidence to Clinical Activity

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INTRODUCTION
- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS (RRMS).
- Teriflunomide reversibly inhibits the mitochondrial enzyme diamine oxidase (DAO), required for de novo pyrimidine synthesis in rapidly dividing lymphocytes, thereby limiting proliferation of activated T and B cells.1
- Teriflunomide has no direct effects on DNA. Teriflunomide has no direct effects on DNA.
- Resting and slowly dividing cells, including lymphocytes and nonlymphoid cells, rely on the pyrimidine salvage pathway to meet their pyrimidine needs. Because this pathway is not affected by teriflunomide, basic homeostatic functions of resting and slowly dividing cells appear to be preserved and immune cells remain available for surveillance (Figure 1).

OBJECTIVE
- To present the current understanding of teriflunomide's mechanism of action based on preclinical and clinical data.

METHODS
- Preclinical:
  - The impact of teriflunomide on the proliferation and viability of stimulated human peripheral blood mononuclear cells was measured in vitro.1
  - The Dark Agouti Experimental Autoimmune Encephalomyelitis (DA EAE) rat model of RRMS was used to assess the effects of teriflunomide on disease progression (neurological scores).2
  - The DA EAE model was also used to investigate the impact of teriflunomide on central nervous system (CNS) lymphocyte infiltration (measured by flow cytometry of cell preparations and by image analysis of stained sections) and on neuronal conduction (transient motor evoked potentials [TMEREPs] and somatosensory evoked potentials [SSEP]s).3

Clinical
- In the double-blind, placebo-controlled, phase 3 clinical trial TEMSO (NCT01015456) and TOWER (NCT017511881), patients with relapsing MS were randomized (1:1:1) to receive teriflunomide 14 mg, teriflunomide 7 mg, or placebo once daily. Patients received treatment for 108 weeks in the TEMSO trial, and for a variable period of at least 48 weeks in the TOWER trial.4
- The primary endpoint of both trials was annualized relapse rate (ARR). The key secondary endpoint was disability progression, and magnetic resonance imaging (MRI)-measured measures of disease burden were included as co-endpoints in TEMSO (MRI measures were not included in TOWER).5

RESULTS
- Preclinical:
  - In vitro, teriflunomide inhibited proliferation of stimulated human T and B cells, an effect reversed by the addition of uridine, thereby confirming DHODH dependency. (Table 1). Table 1. Teriflunomide inhibition of stimulated human T- and B-Cell Proliferation In Vitro

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CD19+ T Cells</th>
<th>CD19+ T Cells</th>
<th>CD19+ B Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriflunomide 25 µM</td>
<td>0.02 (0.07)</td>
<td>0.03 (0.02)</td>
<td>0.44 (0.19)</td>
</tr>
<tr>
<td>Teriflunomide 25 µM + uridine</td>
<td>1.91 (1.43)</td>
<td>1.37 (0.80)</td>
<td>0.36 (0.19)</td>
</tr>
</tbody>
</table>

- Teriflunomide 14 mg had significant reductions in key secondary endpoints compared with placebo in the TEMSO trial (Table 2).

Table 2. Summary of Key Secondary Endpoints in TEMSO

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Teriflunomide 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate (ARR)</td>
<td>0.69</td>
<td>0.47</td>
</tr>
<tr>
<td>Disability progression</td>
<td>1.0</td>
<td>0.68</td>
</tr>
<tr>
<td>Inflammation</td>
<td>1.0</td>
<td>0.75</td>
</tr>
<tr>
<td>MRI measures</td>
<td>1.0</td>
<td>0.75</td>
</tr>
</tbody>
</table>

- In TEMSO, where MRI measure of disease were collected, the cumulative number of gadolinium-enhancing lesions and the increase in total lesion volume were significantly lower in patients receiving teriflunomide compared with those receiving placebo (Figure 6).

CONCLUSIONS
- Teriflunomide inhibits proliferation of stimulated T and B cells.
- Inhibition of lymphocyte proliferation, associated with a reduction in the number of lymphocytes in the CNS, may account for the reduction of disease severity and preserved neuronal function observed in teriflunomide-treated EAE rats.

REFERENCES

Acknowledgments
Disclosures
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