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# Teriflunomide Selectively Impacts the Immune System and Does Not Impair Protective Responses: Preclinical and Clinical Data

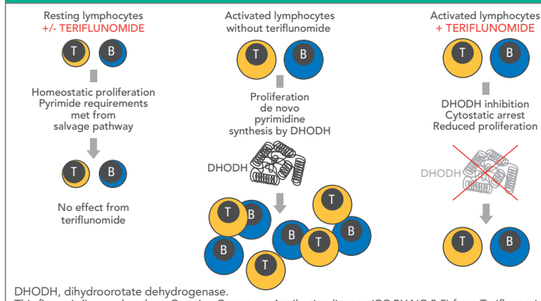
Amit Bar-Or,[1] Johanne Kaplan,[2] Andrea Edling,[2] Françoise Menguy-Vacheron,[3] Philippe Truffinet,[4] Heinz Wiendl[5]

[1]Montreal Neurological Institute and Hospital, Montreal, QC, Canada; [2]Genzyme, a Sanofi company, Framingham, MA, USA; [3]Sanofi, Chilly-Mazarin, France; [4]Genzyme, a Sanofi company, Chilly-Mazarin, France; [5]University of Münster, Münster, Germany

## INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing–remitting MS
- Teriflunomide reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, required for de novo pyrimidine synthesis in rapidly dividing lymphocytes, thereby limiting proliferation of activated T and B cells.[1,2] Teriflunomide has no direct effects on DNA.[1] Through its effect on proliferation, teriflunomide has the potential to limit pathogenic immune responses that can contribute to MS disease activity
- Resting and slowly dividing cells, including lymphocytes and nonlymphoid cells, rely on the pyrimidine salvage pathway to meet their pyrimidine needs.[1] 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**)
- Various lines of evidence suggest that the selective immune modulatory activity of teriflunomide does not adversely affect protective immunity

**Figure 1.** Hypothesized Mechanism of Action of Teriflunomide




DHODH, dihydroorotate dehydrogenase.


## OBJECTIVE

- To present preclinical and clinical evidence related to the selective mechanism of action of teriflunomide, supporting preservation of protective immunity under teriflunomide treatment

## METHODS

### Preclinical

- Using ovalbumin-peptide-specific murine T cells and ovalbumin peptide variants, teriflunomide inhibition of T-cell proliferative responses to peptides of various affinities were measured in vitro[3]
- In vivo memory (secondary) and neoantigen (primary) antiviral antibody responses were evaluated in teriflunomide-treated mice inoculated with adenovirus[4]

### Clinical

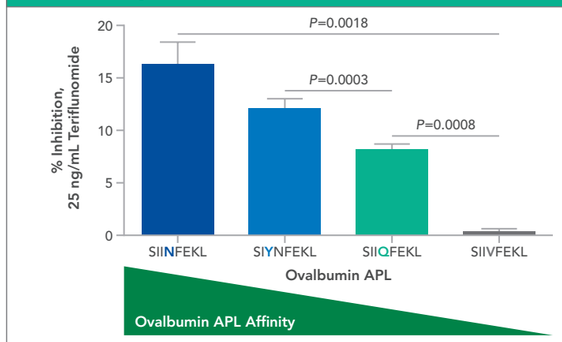
- Information on leukocyte counts and incidences of malignancy and infections (including serious opportunistic infections) were collected during the teriflunomide clinical development program. In clinical trials, patients received either teriflunomide 14 mg or 7 mg, or placebo once daily. Here we present data from the phase 2 trial (NCT01487096)[5] and the phase 3 trials TEMSO (NCT00134563),[6] TOWER (NCT00751881),[7] and TOPIC (NCT00622700)[8]
- Safety data were collected during extensions of these trials, and data from the phase 2 (NCT00228163)[9] and TEMSO (NCT00803049)[10] extensions are presented here
- The immune response to seasonal influenza vaccine was examined in patients treated with teriflunomide for at least 6 months before vaccination (TERIVA, NCT01403376)[11]
- The immune response to rabies vaccination (used as a neoantigen) was examined in healthy individuals treated with a loading dose of teriflunomide 70 mg once daily for 5 days and followed by teriflunomide 14 mg once daily[12]

## RESULTS

### Preclinical

- Teriflunomide was a potent inhibitor of the proliferation of murine ovalbumin-specific T cells stimulated with high-affinity peptides (**Figure 2**). The ovalbumin-specific T cells used had T-cell receptors with high affinity for the ovalbumin peptide SIINFEKL, and lower affinity for the modified SIINFEKL peptides (altered peptide ligands) SIYNFEKL, SIIQFEKL, and SIIVFEKL. Inhibition of proliferation in response to the ovalbumin peptide SIINFEKL was strongest, and the inhibition of proliferation in response to altered peptide ligands was significantly less pronounced. This is of particular interest because higher-avidity T cells are thought to play a pathogenic role in many autoimmune diseases, including MS[13]

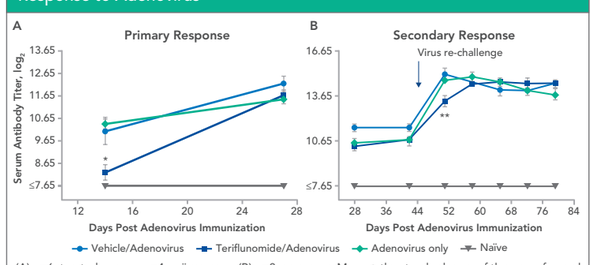
**Figure 2.** Teriflunomide Inhibition of Ovalbumin-Specific T-Cell Proliferative Response to Cognate Peptide Variants




APL, altered peptide ligand.

- Teriflunomide-treated mice effectively mounted specific primary and secondary antibody responses to adenovirus, with only a slight delay in response (**Figure 3**).[4] By the end of the study, teriflunomide-treated mice had comparable anti-adenovirus titers to vehicle-treated mice

**Figure 3.** Time Course of (A) Primary and (B) Secondary Antibody Response to Adenovirus




(A) n=6, treated groups; n=4, naïve group, (B) n=8 per group. Mean ± the standard error of the mean for each group. *$P$<0.05, **$P$<0.01 comparing teriflunomide with vehicle control.

### Clinical

- In clinical trials, patients with MS treated with therapeutic doses of teriflunomide showed no signs of immunosuppression
- Data from the pooled phase 2 and phase 3 TEMSO, TOWER, and TOPIC studies showed similar incidences of infection in patients receiving teriflunomide or placebo (**Table 1**) and did not show any increased incidence of serious opportunistic infection with teriflunomide treatment compared with placebo[14]

**Table 1.** Infections in Pooled Teriflunomide Clinical Studies

| | Teriflunomide 14 mg (n=1002) | Teriflunomide 7 mg (n=1045) | Placebo (n=997) |
|---|---|---|---|
| Any infection TEAEs[a] | 528 (52.7) | 553 (52.9) | 532 (53.4) |
| Serious infection TEAEs[a] | 27 (2.7) | 23 (2.2) | 22 (2.2) |
| Infection TEAEs leading to permanent treatment discontinuation | 10 (1.0) | 8 (0.8) | 5 (0.5) |
| Deaths due to infection | 1 (<0.1) | 0 | 1 (0.1) |

TEAE, treatment-emergent adverse event.
Data are presented as n (%); data from pooled phase 2, TEMSO, TOWER, and TOPIC studies.
[a]Infection or infestation primary system organ class according to the Medical Dictionary for Regulatory Activities.

- Pooled data from phase 2 and phase 3 TEMSO, TOWER, and TOPIC studies showed no increased incidence or unusual patterns of malignancy (**Table 2**)

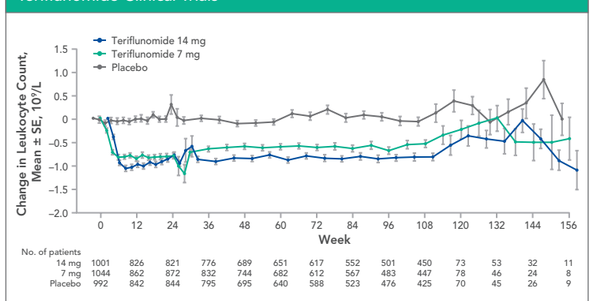
**Table 2.** Malignancies in Pooled Teriflunomide Clinical Studies

| | Teriflunomide 14 mg (n=1002) | Teriflunomide 7 mg (n=1045) | Placebo (n=997) |
|---|---|---|---|
| Any malignancy TEAEs[a] | 3 (0.3) | 2 (0.2) | 5 (0.5) |
| Serious malignancy TEAEs[a] | 1 (<0.1) | 0 | 4 (0.4) |
| Malignancy TEAEs leading to permanent treatment discontinuation | 0 | 0 | 3 (0.3) |
| Deaths due to malignancy | 0 | 0 | 0 |

TEAE, treatment-emergent adverse event.
Data are presented as n (%); data from pooled phase 2, TEMSO, TOWER, and TOPIC studies.
[a]Malignancy primary system organ class according to the Medical Dictionary for Regulatory Activities.

- Pooled data also showed that mean leukocyte counts were reduced (by approximately 15% from baseline) but remained within the normal range (**Figure 4**). Reductions in leukocyte count occurred during the first 6 months of treatment (3 months for lymphocytes and 6 weeks for neutrophils) then remained stable up to Week 108, with no further decrease.[14] Results from Week 108 onward should be interpreted with caution because few patients remained on study

**Figure 4.** Mean Change in Leukocyte Count Over Time in Pooled Teriflunomide Clinical Trials[a]




SE, standard error.
Normal range defined as 3.8–10.7 x 10⁹/L in TEMSO and TOWER; [a]for Weeks 26 and 28, only data from the phase 2 study were available (n=45–58).

- There were no signals for immunosuppression (no increased incidences of infection, no increased incidence or unusual pattern of malignancies) in patients in open-label extension studies, some of whom have received teriflunomide for up to 12 years[9,10]

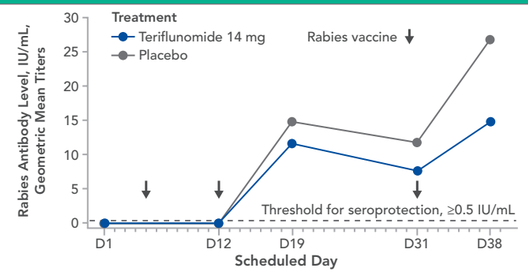
- Patients with MS treated with teriflunomide for at least 6 months before vaccination mounted effective memory immune responses to seasonal influenza vaccine (**Table 3**)[12]
- In healthy subjects, antibody titers to rabies vaccine (used as a neoantigen) were lower in subjects receiving teriflunomide than in those receiving placebo. However, teriflunomide did not impair development of seroprotective immune responses to this neoantigen: all subjects had antibody titers well above the seroprotective threshold of 0.5 IU/mL (**Figure 5**)[10]

**Table 3.** Proportion of Patients With Influenza Antibody Titers ≥40 at 28 Days Postvaccination

| Influenza strain | Teriflunomide 14 mg (n=39) | Teriflunomide 7 mg (n=40) | IFNβ (n=43) |
|---|---|---|---|
| H1N1 | 97.4 (93.3, 100) | 97.5 (93.4, 100) | 97.7 (93.9, 100) |
| H3N2 | 76.9 (65.8, 88.0) | 90 (82.2, 97.8) | 90.7 (83.4, 98.0) |
| B | 97.4 (93.3, 100) | 97.5 (93.4, 100) | 93 (86.6, 99.4) |

IFN, interferon.
Data are presented as means with 90% confidence interval. Per-protocol population. European criteria for efficacy of influenza vaccination in an 18- to 60-year-old population require achievement of a hemagglutination inhibition titer ≥40 by 70% of patients.

**Figure 5.** Titers of Rabies Antibody Over Time




At D (day) 31 and 38, all subjects achieved antibody titers ≥0.5 IU/mL (threshold for seroprotection). n=23 per group.

## CONCLUSIONS

- Therapeutic teriflunomide doses of 14 mg or 7 mg daily demonstrating consistent, beneficial effects on relapses and disability progression in phase 2 and phase 3 clinical trials in patients with MS do not appear to compromise protective immunity or antibody responses to either recall or neoantigen vaccines
- Combined with preclinical data, these findings confirm that teriflunomide has a selective immunomodulatory mechanism of action that preserves protective immune responses

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