Rapid Elimination Procedure of Teriflunomide with Colestipol Hydrochloride (TERCOL)

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Introduction

Teriflunomide is an oral disease modifying therapy approved for the treatment of relapsing forms of multiple sclerosis. It works by selectively and reversibly inhibiting dihydroorotate dehydrogenase, which results in the impairment of proliferation of stimulated T and B lymphocytes. Teriflunomide is rapidly absorbed, highly-protein-bound and involved in enterohepatic recycling, which contributes to its long median terminal half-life. This results in slow elimination from plasma, which on average takes 6-8 months, though it can take up to 2 years for plasma concentrations to reach a minimum level (<0.02µg/ml). This slow elimination can become problematic in certain clinical situations, such as in females who become pregnant or plan to become pregnant while on teriflunomide, due to potential teratogenic effects. In these clinical settings an accelerated elimination procedure (AEP) is recommended. Currently, oral administration of cholestyramine or activated charcoal is available. However, these agents are restricted by side effects and limited routes and frequencies of dosing. One possible alternative is colestipol hydrochloride (HCL), a bile acid sequestrant similar to cholestyramine. Colestipol HCL has the potential to exert similar effects on unbound teriflunomide, with potential advantages in ease of administration and less frequent dosing. This study aimed to investigate cholestipol HCL as an alternative to cholestyramine for the elimination of teriflunomide.

Objectives

Primary Objective

- To determine if colestipol HCL tablets can accelerate the elimination of teriflunomide.

Secondary Objectives

- To collect information on the pattern of side effects with use of colestipol HCL after teriflunomide administration, and to determine the best duration of therapy needed for adequate elimination

Methods

Study Design

- This was a single-center, two-period, two-treatment, single-sequence, PK interaction study
- Healthy, non-smoking volunteers ages 18-45 who met the inclusion criteria were treated with teriflunomide for 14 days, followed by a rapid elimination procedure with colestipol HCL for 15 days, as detailed below in Figure 1.
- Percentile changes of teriflunomide concentrations at each PK time point following administration of colestipol HCL tablets were monitored

Figure 1: Study Design Overview

Step One
- Screening/Baseline visit
  - Inclusion/exclusion criteria and informed consent, background demography, review importance of adherence
  - Physical Exam(PE)/Vitals (Pulse, temperature, height/weight, blood pressure)
  - Baseline and Safety Labs (see below)

Step Two (Study Days 1-14)
- Administration of teriflunomide loading dose of 70mg/day, for 3 days
- Followed by administration of teriflunomide maintenance dose of 14mg/day, for 11 days
- Pharmacokinetics (PK) blood draws (starting at Visit 2)
- Review adherence, vitals, labs, AEs

Step Three (Study Days 15-50)
- AEP with colestipol HCL 8g BID for 15 days
- PK blood draws
- Review adherence, vitals, labs, AEs
- Follow-up call (Day 33), review AEs

- **Pharmacokinetic Evaluation**
  - Blood was sampled throughout the study to determine plasma teriflunomide concentrations
  - Assess for decreasing trend of the teriflunomide concentrations over Day 22, Day 28, Day 40 and Day 50 (study protocol amended after completion of 5 subjects to extend collection points of PK out to Day 50)
  - If plasma teriflunomide concentration was >0.02µg/ml at the end of AEP, subjects received cholestyramine 4-8gm three times a day as precautionary measures until teriflunomide concentration was ≤ 0.02µg/ml
- **Safety Monitoring**
  - Subjects were monitored for adverse events, standard clinical laboratory evaluations (CBC/CMP, Beta-HCG at each evaluation in female subjects), vital signs (pulse, temperature, height/weight, blood pressure), physical exam and body weight
  - A Data Safety Monitoring Physician (DSMP) reviewed the data for the first 5 patients to confirm safety parameters. The DSMP also reviewed all charts at the conclusion of each subject's participation.

Table 1. Baseline Characteristics and Subject Demographics

	All (N=14)
Age, yr (mean±SD)	24.5 ± 7.9
Male, n (%)	10(71)
Female, n (%)	4(29)
Caucasian/white, n (%)	7 (50)
Hispanic, n (%)	4(29)
Black	2(14)
Asian	1(7)
BMI, mean (SD)	23.9 ± 2.7

Table 3. Summary of Adverse Events(AEs)

	Teriflunomide, n=14	Colestipol HCL, N=13
Total	9	16
Intensity of AE, n(%)		
Mild	8(89)	16(100)
Moderate	1 (11)	0 (0)
Severe	0 (0)	0 (0)
AE type, n (%)		
Upper Respiratory Infection	3(33)	1 (6)
Constipation	0 (0)	3(19)
Diarrhea	3 (33)	1 (6)
Nausea	2(22)	7(44)
Abdominal discomfort	0(0)	3(19)
Heartburn	0(0)	1(6)
Transaminitis	1 (11)	0 (0)

Results

Subjects:
- A total of 25 subjects were anticipated to complete the study. A total of 14 subjects participated in the study before futility analysis confirmed the need for discontinuation. Of these 14, 10 subjects completed the study into the washout phase. One subject was removed due to a moderate teriflunomide AE and 3 subjects were lost to follow-up shortly after beginning the washout phase. The subjects' baseline characteristics are summarized in Table 1.

Pharmacokinetics:
- Mean plasma teriflumomide concentration was 17.95 µg/ml at Day 22, 9.36 µg/ml at Day 28 µg/ml, 2.01 µg/ml at Day 40, and 1.31 µg/ml at Day 50, displaying a mean percent decrease of plasma teriflunomide concentration by 96% (Figure 2 and Table 2).
- To ensure complete elimination of teriflunomide after AEP, all subjects who did not meet complete elimination criteria received cholestyramine to achieve plasma teriflunomide concentrations of ≤ 0.02µg/ml.

Safety:
- A summary of teriflunomide and colestipol HCL related AEs is shown in Table 3.
- None of the patients experienced serious adverse events (SAE).
- One subject was withdrawn from the study early due to a moderate teriflunomide AE (transaminitis) and was treated with AEP with cholestyramine.
- 3 subjects were lost to follow-up and it can not be confirmed if they completed washout or if their AEs were resolved

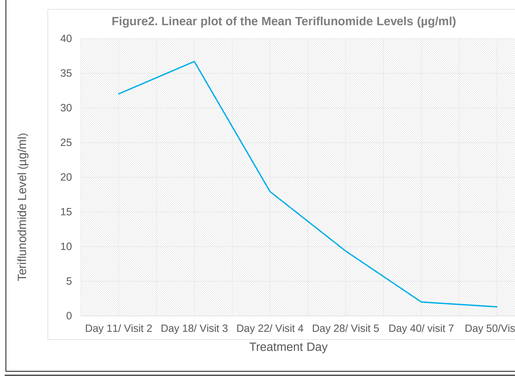

Table 2. Mean Percentage of Elimination Based on Plasma Concentration of Teriflunomide During AEP with Colestipol HCL

Duration of Colestipol HCL	Mean Percentage Change
Day 8 (Study day 22)	51%
Day 14 (study day 28)	75%
Day 26 (Study Day 40)	95%
Day 36 (Study Day 50)	96%

Conclusion/Discussion

Administration of colestipol HCL for 15 days was sufficient to reduce plasma teriflunomide concentrations by an average of ≥ 96%.

Despite the amendment of the protocol to include extended follow-up time of teriflunomde PK levels, colestipol HCL was not able to completely eliminate teiflunomide in the majority of subjects.

AEs experienced by subjects were consistent with known AEs related to both teriflunomide and colestipol HCL, with the vast majority being reported as mild in nature.

Although colestipol HCL did not completely eliminate teriflunomide with the same effectiveness as cholestyramine, for some patients it may offer an alternative method for accelerated elimination of teriflunomide with potentially improved tolerability, a more favorable administration and dosing option, as compared to cholestyramine or activated charcoal. However, given that colestipol HCL did not completely eliminate teriflunomide with the same effectiveness as cholestyramine or activated charcoal, caution should be exercised if needed for certain circumstances (ie. rapid elimination due to pregnancy while on teriflunomide) and the use of cholestyramine or activated charcoal should be strongly considered.

References

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