Early, Transient Shift in Hematologic Parameters Observed With Ublituximab in the ULTIMATE I and II Phase 3 Studies

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OBJECTIVE

- To characterize the early, transient shifts in hematologic parameters the day after ublituximab infusion in the ULTIMATE studies

KEY FINDINGS

- On the day following the first infusion of ublituximab (Day 2), based on laboratory values:
  - 91.0% of participants had low lymphocyte counts; 39.2% had Grade ≥3 lymphopenia
  - <1% of participants had low neutrophil counts; only 1 participant had one Grade 2 event
  - 16.6% of participants had low hemoglobin; all were Grade 1 or 2 events
- Only 7.8% of ublituximab-treated participants had a low lymphocyte count at Day 8 (<1% Grade ≥3), indicative of a transient postinfusion effect
- Decreases in lymphocyte or neutrophil count below the lower limit of normal (LLN) were not observed to be associated with serious infections
- In ublituximab-treated participants, the most common hematologic parameters reported as treatment-emergent adverse events (TEAEs) by investigators across all study time points were lymphopenia, neutropenia, and anemia; Grade ≥3 events occurred in 9.5%, 2.0%, and 0.0% of cases, respectively
- Excluding lymphopenia, rates of Grade ≥3 TEAEs (hematologic and nonhematologic) were 14.1% with ublituximab and 13.5% with teriflunomide

CONCLUSIONS

- Here we report an assessment of hematologic parameters on the day following the first infusion of ublituximab, as has been similarly described in a single-site study with ocrelizumab[1]
- Unique to the ULTIMATE study designs was assessment of laboratory values at Day 2, which revealed a transient decrease in lymphocytes that normalized in the vast majority of ublituximab-treated participants by Day 8
  - The mechanism for this transient observance is being explored, but is hypothesized to represent a temporary compartmental switch, given the rapid recovery, which would not be possible if a lymphocytic event had occurred
- Excluding lymphopenia, the overall rate of Grade ≥3 TEAEs in ublituximab-treated participants was comparable with that of teriflunomide-treated participants

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DISCLOSURES

PQ has received speaking and consulting honoraria from Biogen, BMS, Genzyme, Genentech, Viela Bio, and TG Therapeutics. DH has nothing to disclose. SW has received compensation for consulting from TG Therapeutics; has been a consultant, speaker, and research participant for Celgene/BMS, Biogen, EMD Serono, Genentech/Roche, and Genzyme/Sanofi; has conducted research and been a consultant for Novartis; and has conducted research for Alkermes and TG Therapeutics. TT and DC are employees of TG Therapeutics. KS has received honoraria for speaking, consulting, and serving on advisory boards for Merck, Novartis, Roche, Biogen, Celgene, BMS, and TG Therapeutics.

BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered to exhibit a low fucose content in its fragment crystallizable (Fc) region[2-4,a]
- The exclusion of specific fucose molecules on the Fc region enhances its affinity for all variants of FcγRIIIa receptors, thereby increasing engagement of natural killer (NK) cells and resulting in increased antibody-dependent cellular cytolysis relative to other approved anti-CD20 antibodies[2,5,6]
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies[7]
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) were identical, Phase 3, randomized, multicenter, double-blind, active-control studies that evaluated the efficacy and safety of ublituximab vs teriflunomide in participants with relapsing multiple sclerosis (RMS)[7]
- ULTIMATE I and II met their primary endpoint, demonstrating a statistically significant reduction in annualized relapse rate for ublituximab compared with teriflunomide as well as significant improvements in the number of gadolinium-enhancing T1 lesions and the number of new/enlarging T2 lesions[7]
- Along with sustained B-cell depletion,[8] pharmacodynamic studies of ublituximab have reported a transient decline in the percentage of total T cells and NK cells as well as a reciprocal increase in myeloid cells following the initial dose of ublituximab at Day 2[9]
- Lymphocyte counts at Day 2 have not been evaluated in pivotal trials of other anti-CD20 agents[10,11]
- Additional evaluations of ULTIMATE I and II data were conducted to understand the incidence and kinetics of shifts in hematologic parameters with ublituximab as well as potential association with infections

[a]Ublituximab was approved by the U.S. Food and Drug Administration for the treatment of relapsing forms of multiple sclerosis in December 2022.

METHODS

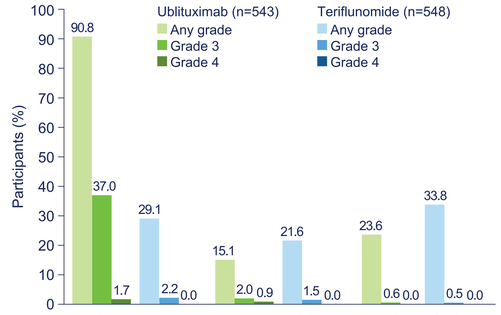
- ULTIMATE I and II enrolled a total of 1094 adults from 10 countries with a diagnosis of RMS (relapsing-remitting or secondary-progressive) with disease activity[7]
- Participants received ublituximab 450 mg administered by 1-hour intravenous infusion every 24 weeks (following Day 1 infusion of 150 mg and Day 15 infusion of 450 mg) or teriflunomide 14 mg orally once daily for 96 weeks[7]
- Laboratory evaluations were conducted at Days 1 (predose), 2 (1 day after initial infusion), 8, and 15 (predose); every 4 weeks at Weeks 4-24; every 12 weeks up to Week 96; and at Weeks 100 and 104
- Hematologic parameters were evaluated both as laboratory abnormalities (grade based on cell counts) and TEAEs based on medical judgment to be clinically significant (severity graded by investigator) according to the Common Terminology Criteria for Adverse Events version 4.0
- The safety population (pooled for both studies) included all participants who received at least 1 dose of study drug

RESULTS

Hematologic Parameters Reported Based on Laboratory Values

- In ublituximab-treated participants, across all study visits, changes in hematologic parameters were observed as lymphocyte, neutrophil, and hemoglobin decreases, and most were Grade 1 and 2 events (**Figure 1**)

Figure 1. Hematologic Laboratory Abnormalities (All Study Visits)



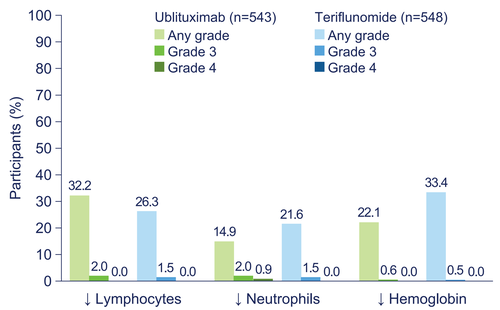
Percentages are based on number of participants with non-missing baseline and at least 1 postbaseline assessment. Pooled post hoc analysis. Safety population. Grade based on CTCAE v4.0. CTCAE v4.0, Common Terminology Criteria for Adverse Events version 4.0.

- Excluding Day 2, the proportion of ublituximab-treated participants with lymphopenia decreased from 90.8% to 32.2% (**Figure 2**)
- On Day 2, 91.0% of ublituximab-treated participants had low lymphocyte counts (39.2% Grade ≥3); this dramatically reduced to only 7.8% of participants with low lymphocyte counts at Day 8 (<1% Grade ≥3), indicative of a transient postinfusion finding (**Figure 3**)
- On Day 2, <1% of ublituximab-treated participants had low neutrophil counts; only 1 participant had one Grade 2 event and 16.6% of participants had low hemoglobin; all were Grade 1 or 2 events (data not shown)

Serious Infections

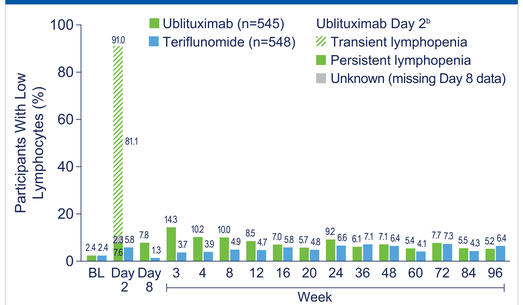
- Serious infections were not commonly associated with a decrease in lymphocyte or neutrophil counts <LLN
  - 10.7% of serious infections occurred with lymphocytes <LLN within 1 month before or after onset of the infection
  - 3.6% of serious infections occurred with neutrophils <LLN within 1 month before or after onset of the infection

Figure 2. Hematologic Laboratory Abnormalities (Excluding Day 2)



Percentages are based on number of participants with non-missing baseline and at least 1 postbaseline assessment. Pooled post hoc analysis. Safety population. Grade based on CTCAE v4.0. CTCAE v4.0, Common Terminology Criteria for Adverse Events version 4.0.

Figure 3. Proportion of Participants With Low Lymphocyte Count by Visit[a]

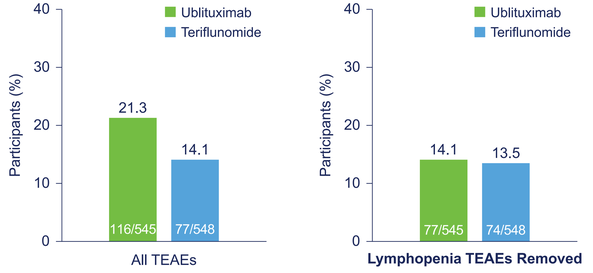


[a]Based on available samples at each time point. [b]Transient defined as <LLN at Day 2 and ≥LLN at Day 8; persistent defined as <LLN at Day 2 and at Day 8; unknown defined as <LLN at Day 2 and missing value at Day 8. Percentages are based on number of participants in the population/treatment group. Pooled post hoc analysis. Safety population.
BL, baseline; LLN, lower limit of normal.

Hematologic Parameters Reported as TEAEs by Investigators

- The most commonly reported hematologic parameters (all grade/Grade ≥3) were lymphopenia (18.7%/9.5%), neutropenia (3.3%/2.0%), and anemia (2.9%/0.0%)
- The median (quartile 1, quartile 3) time to resolution of Grade ≥3 lymphopenia TEAEs with ublituximab was 6.0 days (6.0, 6.0), and 13.0 days (7.0, 21.0) for neutropenia TEAEs, measured at the next laboratory assessment
- Excluding lymphopenia, rates of all Grade ≥3 TEAEs (hematologic and nonhematologic) were similar between ublituximab-treated participants (14.1%) and teriflunomide-treated participants (13.5%) (**Figure 4**)

Figure 4. Grade ≥3 TEAEs With or Without Lymphopenia



Pooled post hoc analysis. Safety population.
TEAE, treatment-emergent adverse event.

HYPOTHESIS

- Transient lymphopenia is hypothesized to be a result of B-cell depletion[8] in combination with a temporary shift in T cells from peripheral circulation into tissues during a state of inflammation, ie, cytokine release[12,13]
  - A prior pharmacodynamic study of ublituximab reported that there was no selective depletion of naive or memory CD4+ T-cell subsets, indicating a relative change in the percentage of total CD4+ T cells in the peripheral blood immediately following an infusion and not an actual depletion of CD4+ T cells[8]
- Insignificant anemia suggests bone marrow disruption is unlikely to be the cause of cytopenias