Neutralizing Antibodies and Antidrug Antibodies in the Ublituximab Phase 3 ULTIMATE I and II Studies in Relapsing Multiple Sclerosis

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OBJECTIVE

- To evaluate the incidence of neutralizing antibodies (NAbs) and antidrug antibodies (ADAs) against ublituximab in the pooled Phase 3 ULTIMATE studies

KEY FINDINGS

- 1.1% and 16.5% of ublituximab patients had treatment emergent (TE)-NAbs and TE-ADAs at Week 96
- The proportion of patients receiving ublituximab who tested positive for NAbs and ADAs was 2.4% and 17.8% at baseline and 6.4% and 86.5% at any time postbaseline, respectively
- Annualized relapse rates (ARRs) were 0.03 in NAb-positive (postbaseline), 0.11 in NAb-negative (postbaseline), 0.10 in TE-ADA–positive, and 0.12 in TE-ADA–negative patients
- The mean number of new/enlarging T2 lesions by Week 96 was 0.299 in NAb-positive (postbaseline), 0.422 in NAb-negative (postbaseline), 0.425 in TE-ADA–positive, and 0.362 in TE-ADA–negative patients
- Infusion-related reactions (IRRs) occurred in 48.4% of TE-ADA–positive patients and 42.0% of TE-ADA–negative patients (P=0.2487)

CONCLUSIONS

- In the Phase 3 ublituximab studies:
  - A low incidence of TE-NAbs was observed, and NAbs and ADAs did not impact efficacy as measured by ARR or the number of new/enlarging T2 lesions
  - The proportion of patients with TE-NAbs and TE-ADAs declined after 24 weeks, with continued reductions at subsequent timepoints
  - TE-ADAs were generally transient and had no observable impact on B-cell depletion or ublituximab's efficacy or tolerability

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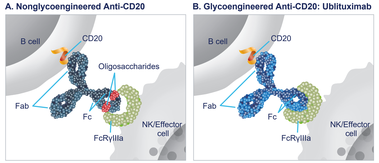
ACKNOWLEDGMENTS

The authors thank the patients and their families for participating in the ULTIMATE I and II studies. The authors also thank Apollo Medical Communications for providing medical writing and editorial support, which was funded by TG Therapeutics. The ULTIMATE I and II studies were sponsored by TG Therapeutics.

BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC) **(Figure 1)**[1,2]
- 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) are identical, Phase 3, randomized, multicenter, double-blind, active-control studies evaluating the efficacy and safety of ublituximab vs teriflunomide in patients with relapsing multiple sclerosis (RMS)[7]
- ULTIMATE I and II met their primary endpoint, demonstrating a statistically significant reduction in ARR for ublituximab compared with teriflunomide[7]
- Ublituximab also provided significant improvements in the number of gadolinium-enhancing T1 lesions and in the number of new/enlarging T2 lesions, and improvements in the proportion of patients with no evidence of disease activity vs teriflunomide at 96 weeks[7]

Figure 1. Ublituximab Is Glycoengineered to Enhance ADCC



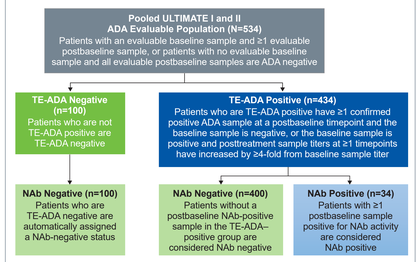
(A) In nonglycoengineered anti-CD20 antibodies, the core fucose of Fc-linked oligosaccharides sterically blocks interaction with FcγRIIIa, reducing affinity.[3,4] **(B)** Ublituximab is glycoengineered to have a low fucose content in the Fc region, which allows for closer interaction and enhanced affinity for all variants of FcγRIIIa.[4-6]

ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer.

METHODS

- ULTIMATE I and II enrolled a total of 1094 adult patients from 10 countries who had a diagnosis of RMS (relapsing-remitting or secondary-progressive) and disease activity[7]
- Patients 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 oral once daily for 96 weeks[7]
- NAb and ADA analyses were performed in patients who received ≥1 ublituximab dose (safety population) and were evaluable for NAbs and ADAs; ULTIMATE I and II data were pooled (N=534)
- Blood for NAb and ADA analyses was collected at baseline and Weeks 3, 24, 48, 72, and 96
- ADAs were evaluated by an electrochemiluminescent (ECL) immunoassay using screening, confirmatory, and titering tiers. Ublituximab was presented as a mixture of labeled drug product to allow ADAs in patient samples to bind both ublituximab-labeled materials and form a complex. The complex was captured onto streptavidin-coated ECL microtiter plates through the biotin-labeled drug and detected via a sulfo-label. A similar disease state cut point was established and applied to the data to screen out false positives
- NAbs were evaluated using an ADCC assay, using Raji cells as target cells and KILR® CD16 expressing cells as effector cells. A predefined disease state cut point was applied to the data to appropriately screen out naive interference
- NAbs were evaluated in ADA-positive samples only **(Figure 2)**

Figure 2. ADA and NAb Categories



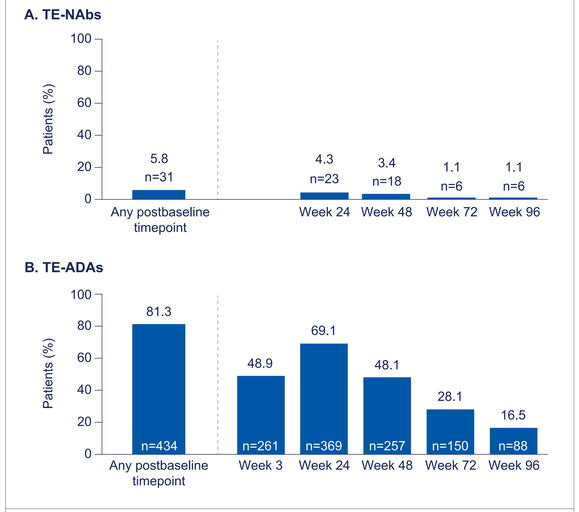
ADA, antidrug antibody; NAb, neutralizing antibody; TE, treatment emergent.

RESULTS

NAbs and ADAs

- 2.4% of patients receiving ublituximab tested positive for NAbs at baseline and 6.4% tested positive at any postbaseline timepoint
- 17.8% of patients receiving ublituximab tested positive for ADAs at baseline and 86.5% tested positive at any postbaseline timepoint
  - Patients testing positive for NAbs or ADAs at baseline did not necessarily test positive at postbaseline timepoints
- 5.8% of patients had TE-NAbs at any postbaseline timepoint and 81.3% of patients had TE-ADAs at any postbaseline timepoint **(Figure 3)**
- The incidence of TE-NAbs and ADAs was highest at Week 24 and declined thereafter **(Figure 3)**

Figure 3. Patients[a] With (A) TE-NAbs and (B) TE-ADAs by Visit

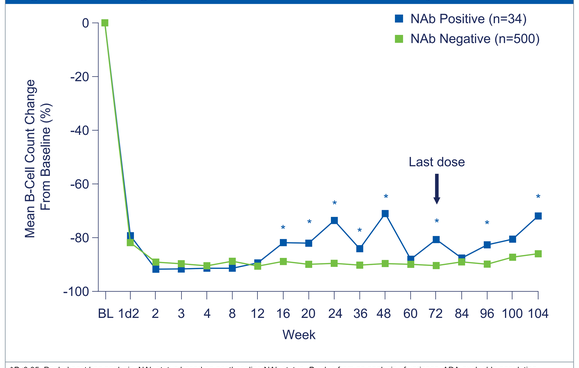


[a]Evaluable patients receiving ≥1 ublituximab dose (N=534).
ADA, antidrug antibody; NAb, neutralizing antibody; TE, treatment emergent.

B-Cell Depletion Levels by NAb Status

- The mean change from baseline in B-cell count for patients who did or did not develop NAbs at any postbaseline timepoint is shown in **Figure 4**
- Patients with or without TE-ADAs at any baseline timepoint had similar levels of B-cell depletion (P=0.3152 for maximum percentage change from baseline; data not shown)

Figure 4. Percentage B-Cell Count Decrease From Baseline by NAb Status



[a]*P*<0.05. Pooled post hoc analysis. NAb status based on postbaseline NAb status. *P* value from an analysis of variance. ADA-evaluable population. 1d2, Week 1 Day 2; ADA, antidrug antibodies; BL, baseline; NAb, neutralizing antibody.

ARR by Postbaseline NAb and TE-ADA Status

- The unadjusted ARR at Week 96 by postbaseline NAb and TE-ADA status is shown in **Table 1**
  - Numbers were small in the NAb-positive group

Table 1. ARR by NAb and TE-ADA Status[a]

Status	n	ARR
All ublituximab-treated	543	0.10
NAb negative (postbaseline)	500	0.11
NAb positive (postbaseline)	34	0.03
TE-ADA negative	100	0.12
TE-ADA positive	434	0.10
Titer[b]		
<Q1	108	0.18
Q1-<Median	109	0.09
Median-<Q3	108	0.08
≥Q3	109	0.05

[a]In evaluable patients receiving ≥1 ublituximab dose.
[b]Q1=49, median=184.5, Q3=662. The titer group cutoff was determined by the quartiles of the maximum ADA titers from all patients with ADA titer measurements in the studies; a patient was assigned to their corresponding titer group using their maximum ADA titer value observed during the study treatment period.
ADA, antidrug antibody; ARR, annualized relapse rate; NAb, neutralizing antibody; Q, quartile; TE, treatment emergent.

Number of New/Enlarging T2 Lesions by ADA and NAb Quartile

- The total number of new/enlarging T2 lesions by Week 96 by postbaseline NAb and TE-ADA status is shown in **Table 2**
- Differences for TE-ADA–negative and TE-ADA–positive populations were not significant (P=0.9986)

Table 2. New/Enlarging T2 Lesions by NAb and TE-ADA Status[a]

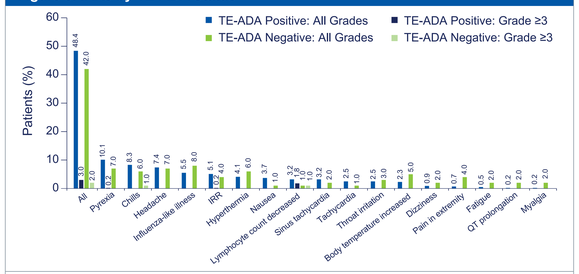
Status	n	Mean Number of New/ Enlarging T2 Lesions
All ublituximab-treated	537	0.426
NAb negative (postbaseline)	495	0.422
NAb positive (postbaseline)	34	0.299
TE-ADA negative	99	0.362
TE-ADA positive	430	0.425
Titer[b]		
<Q1	108	0.532
Q1-<Median	109	0.381
Median-<Q3	107	0.364
≥Q3	106	0.427

[a]In evaluable patients receiving ≥1 ublituximab dose. Total number of new/enlarging T2 hyperintense lesions per MRI scan per patient.
[b]Q1=49, median=184.5, Q3=662. The titer group cutoff was determined by the quartiles of the maximum ADA titers from all patients with ADA titer measurements in the studies; a patient was assigned to their corresponding titer group using their maximum ADA titer value observed during the study treatment period.
ADA, antidrug antibody; MRI, magnetic resonance imaging; NAb, neutralizing antibody; Q, quartile; TE, treatment emergent.

IRRs by TE-ADA Status

- The incidence of IRRs by TE-ADA status is shown in **Figure 5**. The difference in overall IRR incidence in the TE-ADA–positive and TE-ADA–negative groups was not statistically significant (P=0.2487)

Figure 5. IRRs by TE-ADA Status[a]



[a]In evaluable patients receiving ≥1 ublituximab dose; TE-ADA positive (n=434); TE-ADA negative (n=100).
IRR TEAEs occurring in ≥2% of either group.
ADA, antidrug antibody; AE, adverse event; IRR, infusion-related reaction; TE, treatment emergent.

TE-NAb and TE-ADA Status by Demographic Characteristics

- Subgroup analyses showed no obvious association between the incidence of TE-NAbs or TE-ADAs with the baseline demographics of age, gender, race, ethnicity, region, country, weight, height, body mass index, and hepatic impairment or renal impairment; however, no formal statistical testing was performed (data not shown)