Infusion-Related Reactions With Ublituximab in the Phase 3 ULTIMATE I and II Studies in Relapsing Multiple Sclerosis

Edward J. Fox, MD, PhD,[1] Lawrence Steinman, MD,[2] Hans-Peter Hartung, MD,[3-6] Enrique Alvarez, MD, PhD,[7] Peiqing Qian, MD,[8] Sibyl Wray, MD,[9] Derrick Robertson, MD,[10] DeRen Huang, MD, PhD,[11] Krzysztof Selmaj, MD, PhD,[12,13] Daniel Wynn, MD,[14] Koby Mok, PhD,[15] Denise Campagnolo, MD,[15] Bruce A. C. Cree, MD, PhD, MAS[16]

[1]Central Texas Neurology Consultants, Round Rock, TX; [2]Stanford University, Stanford, CA; [3]Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [4]Brain and Mind Centre, University of Sydney, Sydney, Australia; [5]Medical University of Vienna, Vienna, Austria; [6]Palacký University Olomouc, Olomouc, Czech Republic; [7]University of Colorado, Aurora, CO; [8]Swedish Medical Center, Seattle, WA; [9]Hope Neurology, Knoxville, TN; [10]University of South Florida, Tampa, FL; [11]Center for Multiple Sclerosis, Mount Carmel Health System, Westerville, OH; [12]Center of Neurology, Lodz, Poland; [13]University of Warmia and Mazury, Olsztyn, Poland; [14]Consultants in Neurology, Northbrook, IL; [15]TG Therapeutics, New York, NY; [16]UCSF Weill Institute for Neurosciences, San Francisco, CA

OBJECTIVE

- To further characterize the time course, severity, and type of infusion-related reactions (IRRs) with ublituximab

KEY FINDINGS

- In pooled analyses of the ULTIMATE studies, 96.6% of participants completed ublituximab infusions without interruption, and 94.6% completed Doses 2-5 maintenance infusions within 1 hour±5 minutes
- 43% of ublituximab-treated participants had an IRR at Dose 1, the proportion of participants experiencing an IRR markedly decreased to <10.0% for all subsequent infusions, and 69.5% did not have an IRR recurrence
- 78.8% of Dose 1 and 69.2% of Dose 2 IRRs with ublituximab occurred during the infusion period or within 1 hour post infusion
- The administration route of premedications (oral, intravenous [IV], intramuscular [IM], or mixed) did not impact the frequency of IRRs

CONCLUSIONS

- IRRs were the prevailing adverse event (AE) with ublituximab in ULTIMATE I and II; the vast majority were mild to moderate in severity
- Most IRRs occurred at Dose 1, markedly decreased with subsequent infusions, and had minimal impact on infusion completion
- The proportion of ublituximab-treated participants with pyrexia, chills, headache, and influenza-like illness was 9.5%, 7.9%, 7.5%, and 5.9%, respectively

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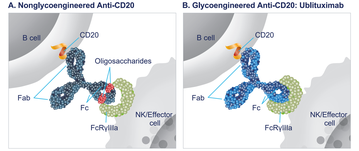
BACKGROUND

- Ublituximab is a novel, next generation monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity **(Figure 1)**[1,2]
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies[3]
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) are identical, Phase 3, randomized, multicenter, double-blind, active-control, double-dummy studies evaluating the efficacy and safety of ublituximab vs teriflunomide in participants with relapsing multiple sclerosis (RMS)[3]
- 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[3]

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.[4,5] **(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.[5-7]

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

METHODS

- ULTIMATE I and II enrolled a total of 1094 adult participants from 10 countries with a diagnosis of RMS (relapsing-remitting or secondary-progressive) with disease activity[3]
- Participants received ublituximab 450 mg administered by 1-hour IV infusion every 24 weeks (following Day 1 infusion of 150 mg over 4 hours [Dose 1] and Day 15 infusion of 450 mg over 1 hour [Dose 2]) or teriflunomide 14 mg oral once daily for 96 weeks[3]
- The teriflunomide group received placebo infusions; the ublituximab group received oral placebo[3]
- Participants received premedication 30-60 minutes prior to each dose of ublituximab or IV placebo: antihistamine (diphenhydramine 50 mg or equivalent) and corticosteroid (dexamethasone 10-20 mg or equivalent)
- Acetaminophen (650 mg or equivalent) was not included in the recommended premedication for Dose 1 and was restricted to participants who experienced fever or pyrexia after Dose 1, as clinically warranted. Additional medication for adverse reactions could be used at the physician's discretion
- Participants could receive oral, IV, IM, or mixed routes of premedication
- A 1-hour postinfusion observation period was not required for participants who did not experience IRRs during Dose 1 and Dose 2
- IRRs were defined as infusion-related AEs reported during or within 24 hours of the end of an infusion
- Pooled investigator-reported IRR data from both studies were analyzed. IRRs were evaluated in the safety population of all participants who received ≥1 dose of study drug (ublituximab or teriflunomide, with corresponding placebos)

RESULTS

- The total number of infusions was 2644 for ublituximab and 2637 for placebo. Overall, 96.6% of ublituximab infusions were completed without interruption **(Table 1)**
- The proportion of participants with IRRs was 47.7% and 12.2% in the ublituximab and placebo infusion groups, respectively[3]
- In the ublituximab-treated group, 89.7% of participants completed Dose 1 infusion without interruption within 4 hours 15 minutes, and 94.6% completed their maintenance infusions (Doses 2-5) without interruption within 1 hour±5 minutes **(Table 1)**

Table 1. Infusion Completion

	Teriflunomide (n=548)	Ublituximab (n=545)
Number of infusions, mean±SD	4.8±0.68	4.8±0.62
Total number of started infusions, n (%)	2637 (100)	2644 (100)
Total number of completed infusions, n (%)	2629 (99.7)	2629 (99.4)
Total number of completed infusions without interruption, n (%)	2623 (99.5)	2554 (96.6)
Total number of completed infusions with interruption, n (%)	6 (0.2)	75 (2.8)
Dose 1 infusion		
Total number of started infusions, n (%)	548 (100)	545 (100)
Total number of completed infusions within 4 h 15 min without interruption, n (%)	532 (97.1)	489 (89.7)
Doses 2-5 infusions		
Total number of started infusions, n (%)	2089 (100)	2099 (100)
Total number of completed infusions within 1 h±5 min without interruption, n (%)	2015 (96.5)	1985 (94.6)

Pooled analysis. Safety population.
SD, standard deviation.

Participants With IRR at Dose 1

- 30.1% (164/545) of ublituximab-treated participants experienced an IRR at Dose 1 only and 13.2% (72/545) experienced an IRR at Dose 1 and ≥1 subsequent dose

Participants With 1 IRR

- Of all ublituximab-treated participants with an IRR, 67.7% (176/260) had 1 IRR only; of these, the majority (93.2% [164/176]) experienced the IRR during Dose 1

Participants With >1 IRR

- In ublituximab-treated participants with >1 IRR, 85.7% (72/84) experienced the first IRR during Dose 1

Timing of Dose 1 and Dose 2 IRRs

- 78.8% of Dose 1 and 69.2% of Dose 2 IRRs with ublituximab occurred during the infusion period or within 1 hour post infusion **(Table 2)**

Table 2. Timing of IRRs

	Teriflunomide (n=548)	Ublituximab (n=545)
Dose 1 IRRs, % (n/N)		
Participants with an IRR[a]	9.7 (53/548)	43.3 (236/545)
During the 4-hour infusion period[b]	32.1 (17/53)	69.9 (165/236)
≤1 hour post infusion[b]	15.1 (8/53)	8.9 (21/236)
Dose 2 IRRs, % (n/N)		
Participants with an IRR[a]	3.1 (17/545)	9.6 (52/540)
During the 1-hour infusion period[b]	35.3 (6/17)	48.1 (25/52)
≤1 hour post infusion[b]	11.8 (2/17)	21.2 (11/52)

[a]Percentage based on the number of participants who received that infusion. [b]Percentage based on the number of participants with an IRR at that infusion; IRRs without an exact start time were excluded. Pooled analysis. Safety population.
IRR, infusion-related reaction.

- The proportion of ublituximab-treated participants with pyrexia, chills, headache, and influenza-like illness was 9.5%, 7.9%, 7.5%, and 5.9%, respectively **(Table 3)**

Table 3. IRRs[a]

	Teriflunomide (n=548)		Ublituximab (n=545)	
TEAE preferred term, n (%)	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Participants with any IRR TEAE	**67 (12.2)**	**1 (0.2)**	**260 (47.7)**	**15 (2.8)**
Pyrexia	4 (0.7)	0	52 (9.5)	1 (0.2)
Chills	3 (0.5)	0	43 (7.9)	1 (0.2)
Headache	12 (2.2)	0	41 (7.5)	0
Influenza-like illness	5 (0.9)	0	32 (5.9)	0
IRR	3 (0.5)	0	27 (5.0)	1 (0.2)
Hyperthermia	2 (0.4)	0	25 (4.6)	0
Nausea	2 (0.4)	0	18 (3.3)	0
Sinus tachycardia	3 (0.5)	0	17 (3.1)	0
Body temperature increased	2 (0.4)	0	15 (2.8)	0
Lymphocyte count decreased	1 (0.2)	0	15 (2.8)	9 (1.7)
Throat irritation	0	0	14 (2.6)	0
Tachycardia	4 (0.7)	0	13 (2.4)	0
Pain in extremity	0	0	8 (1.5)	0
Tremor	0	0	8 (1.5)	0
Erythema	0	0	7 (1.3)	0
Dizziness	2 (0.4)	0	6 (1.1)	0
Hypersensitivity	1 (0.2)	0	6 (1.1)	0
Oropharyngeal pain	2 (0.4)	0	6 (1.1)	0
Pruritus	0	0	6 (1.1)	0

[a]Treatment-emergent; occurring in >1% in either group. Pooled analysis. Safety population.
IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

- Most IRRs in the ublituximab-treated group were mild to moderate in severity and decreased in frequency with subsequent dosing[3]
- One participant experienced a Grade 4 IRR (anaphylaxis) with ublituximab at the Dose 2 infusion following two Grade 1 IRRs at Dose 1 (both reported as influenza-like syndrome); the Dose 2 infusion was interrupted and drug withdrawn. All IRRs resolved
- Another participant experienced a Grade 4 IRR reported as lymphocyte count decreased (0.1×10^9/L) at the Dose 1 infusion. The IRR was reported as serious and related to ublituximab. No treatment or dosage change was required, and the outcome was reported as recovered/resolved. The participant continued into the study extension phase with no additional IRRs
- In addition to the participant described above, 5 other participants discontinued ublituximab due to an IRR **(Table 4)**. Of the additional cases, all were Grade 2 and one was considered serious

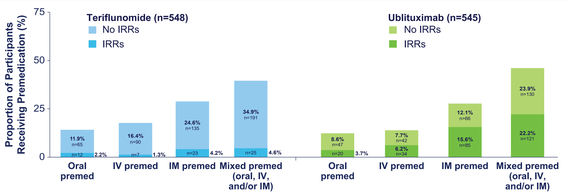
Table 4. Participants Discontinuing Ublituximab Due to an IRR

Participant	Preferred term	Grade	Serious (Y/N)	Outcome
1 (described above)	Anaphylactic reaction	4	Y	Recovered/resolved
2	IRR	2	N	Recovered/resolved
3	Hypersensitivity	2	Y	Recovered/resolved
4	Myocardial ischemia	2	N	Recovered/resolved
5	Toxic skin eruption	2	N	Recovered/resolved
6	Bronchospasm	2	N	Recovered/resolved

IRR, infusion-related reaction.

- The administration route of premedications (oral, IV, IM, or mixed) did not impact the frequency of IRRs **(Figure 2)**

Figure 2. IRRs by Premedication Route of Administration



Pooled analysis. Safety population.
IM, intramuscular; IRR, infusion-related reaction; IV, intravenous; premed, premedication.