No association between decreases in serum immunoglobulin (Ig) levels below lower limit of normal (LLN) and serious infections (SI) with long term ublituximab (UBL) treatment in patients with relapsing Multiple Sclerosis (RMS)

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American Academy of Neurology (AAN) Annual Meeting, April 5-9, 2025, San Diego, CA

TG Therapeutics

OBJECTIVE

- To evaluate the immunological safety profile of prolonged ublituximab (UBL) treatment.

KEY FINDINGS

- Mean serum IgG and IgM levels in the cohort that received continuous UBL for at least 5 years remained above the lower limit of normal (LLN) [mean (SE) were 8.06 (0.13) g/L and 0.69 (0.04) g/L respectively].
- There was no apparent association between decreases in serum immunoglobulin (Ig) levels below LLN and rates of serious infections (SI) with long term UBL treatment.
    - Rates of SI per 100 patient-years (95% CI) in patients with Ig values <LLN and ≥LLN during 5 years of continuous UBL treatment had overlapping CI's. IgM <LLN was 3.26 (2.10, 5.05) versus 2.44 (1.94, 3.07) for IgM ≥LLN. IgG <LLN was 2.57 (2.09, 3.16) versus 2.92 (0.94, 9.06) for IgG ≥LLN. IgA <LLN was 3.66 (1.37, 9.76) versus 2.55 (2.07, 3.13) for IgA ≥LLN.
- Out of the total duration of ublituximab exposure (3603.90 patient years), the proportion of time spent ≥LLN were 97.2% for IgG, 83% for IgM and 97% for IgA.
- None of the patients on continuous UBL treatment for 5 years had IgG drops below LLN that were severe. At year 5, decreases in IgG levels below LLN were only mild to moderate in nature. The proportion of patients with decreases in IgM levels below LLN were mostly mild to moderate in nature.
- The frequency of serious Infections remained constant over time and was not affected by increases in the proportion of participants <LLN.

BACKGROUND:UBLITUXIMAB

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC).[1]
- Ublituximab exhibits enhanced ADCC and Fcγ-receptor (FcγR) binding relative to all other currently approved anti-CD20 therapies used in multiple sclerosis (MS).[2,3]
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies,[1] administered in 1-hour infusions after the first infusion.[4]

BACKGROUND: ULTIMATE I/II and OLE

- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) are identical, Phase 3, randomized, multicenter, double-blind, active-control studies evaluating the efficacy and safety of UBL versus TER in participants with relapsing multiple sclerosis (RMS).

- In ULTIMATE I and II studies, UBL demonstrated significant reduction in disease activity vs TER over 2 years, demonstrating a statistically significant reduction in ARR for UBL compared with TER as well as significant improvements in the number of Gd+ T1 lesions and the number of new/enlarging T2 lesions.[5]

- After 2 years of randomized, active-controlled, double-blind phase (DBP), RMS patients either continued UBL treatment (UBL-UBL) or switched from TER to UBL (TER-UBL) in the open-label extension (OLE) phase.

- During OLE participants demonstrated significant reduction in disease activity. ARR in Year 5 of continuous treatment with UBL was 0.02, equivalent to one relapse occurring in 50 PY, and participants exhibited lower rate of disability progression compared to those initially treated with TER. Overall safety profile of UBL remained consistent over 5 years of continuous treatment.[6]

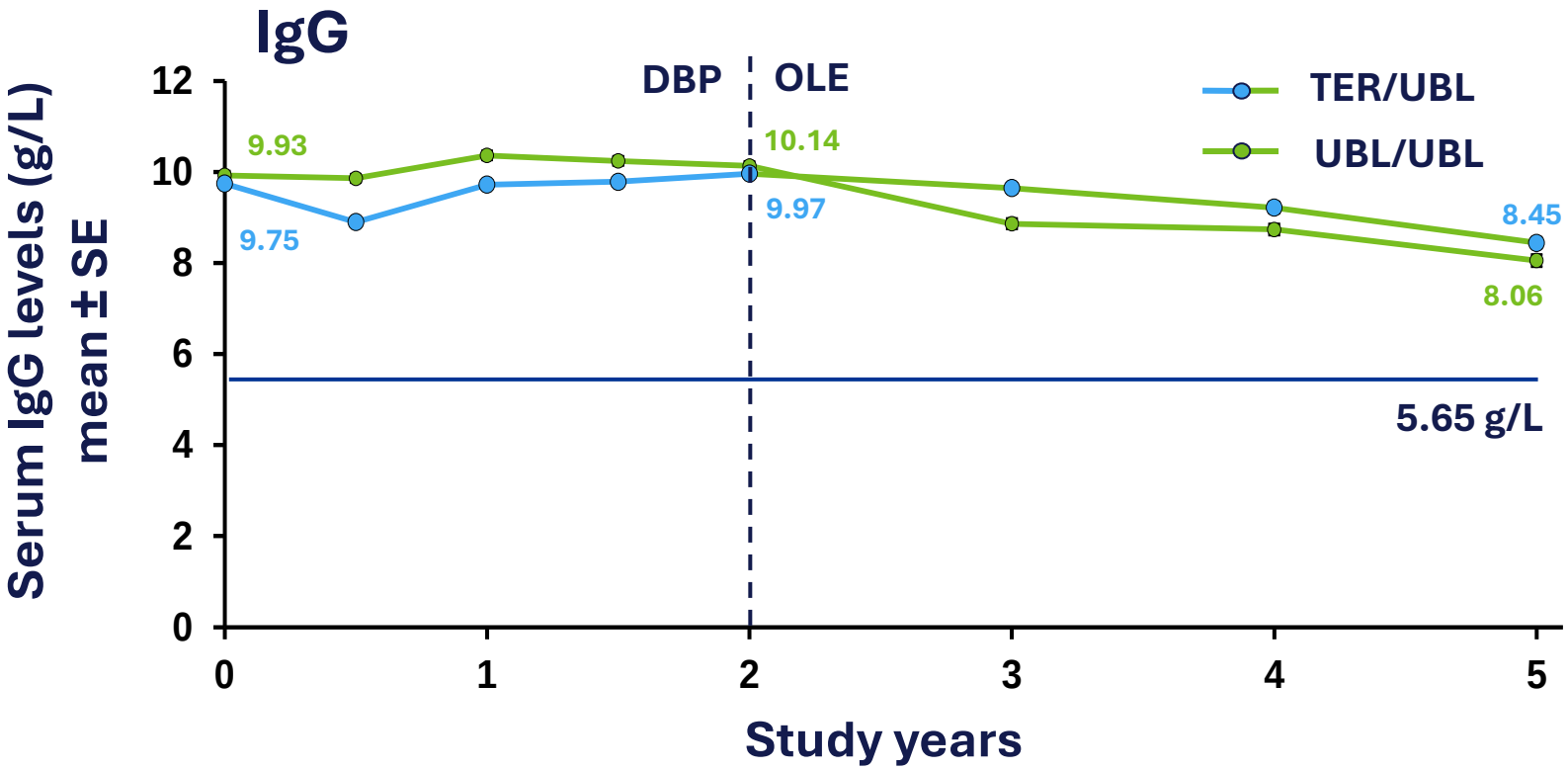
- Immunoglobulin and infection profile with prolonged UBL treatment from DBP and OLE are presented here.

METHODS

- The active-controlled ULTIMATE I (N=549) and II (N=545) studies evaluated UBL 450 mg intravenous infusion every 24 weeks (following Day 1 infusion of 150 mg and Day 15 infusion of 450 mg) vs TER 14 mg orally once daily for 96 weeks.[5]
- After 2 years of randomized, active-controlled, DBP, RMS patients either continued UBL treatment (UBL-UBL) or switched from TER to UBL (TER-UBL).
- Mean serum Ig levels were calculated through the 5-year period (data cut off: 1-January-2024), and patients with Ig levels above or below the lower limit of normal (LLN) threshold at any time during UBL therapy and rates of serious infections (SI) were analyzed. Per protocol, Ig's were sampled on Day 1, 15 and every 24 weeks during DBP, and every 48 weeks during OLE, and SIs associated with such Ig sampling were analyzed.
- Per protocol, patients in ULTIMATE I and II and OLE continued treatment if Ig values fell below LLN and were allowed to enter OLE with no restriction on Ig values being above or below LLN.
- LLN thresholds were set at 5.65 g/L for IgG, 0.4 g/L for IgM, 0.7 g/L for IgA and severity of LLN drops in g/L was classified as mild: <5.65 to ≥ 4.0, moderate: <4.0 to ≥ 2.0, severe: <2.0 for IgG, and mild: <0.4 to ≥0.36, moderate: <0.36 to ≥ 0.2, and severe: <0.2 for IgM.
- Rates of SIs per 100 PYs and 95% CI were estimated by Poisson regression model. Multiple SIs in one participant are counted multiple times. The terms "COVID-19" and "COVID-19 pneumonia" were excluded.

Figure 1: IgG levels remained above LLN over the 5-year period for patients treated with ublituximab

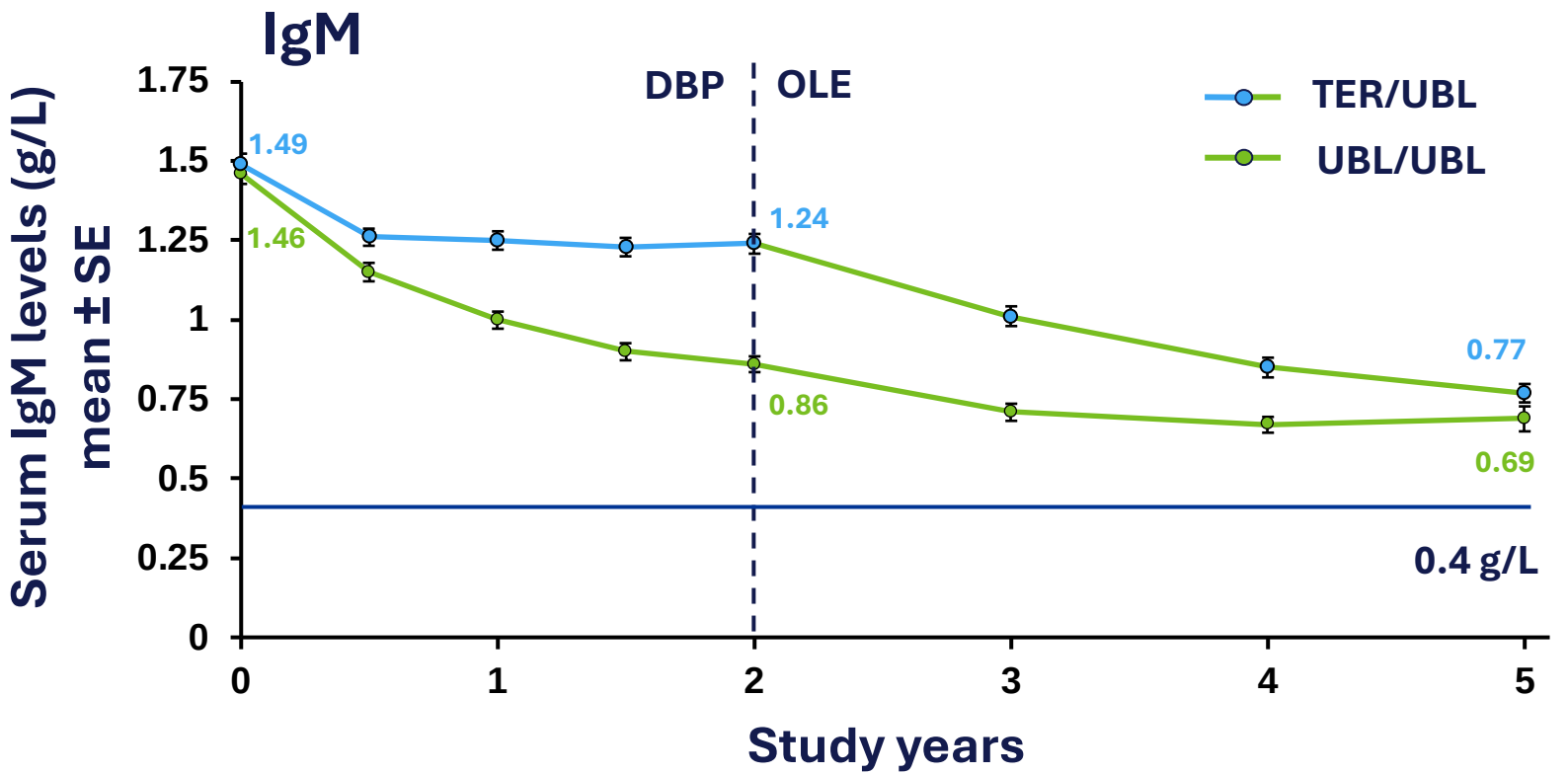
- In the continuous cohort that received UBL for at least 5 years, the mean (SE) IgG levels were 8.06 (0.13) g/L. The IgG levels remained stable and above the LLN (5.65 g/L).



TER/UBL	546	532	517	505	493	403	317	315
UBL/UBL	540	530	525	511	492	389	297	286

Figure 2: IgM levels remained above LLN over the 5-year period for patients treated with ublituximab

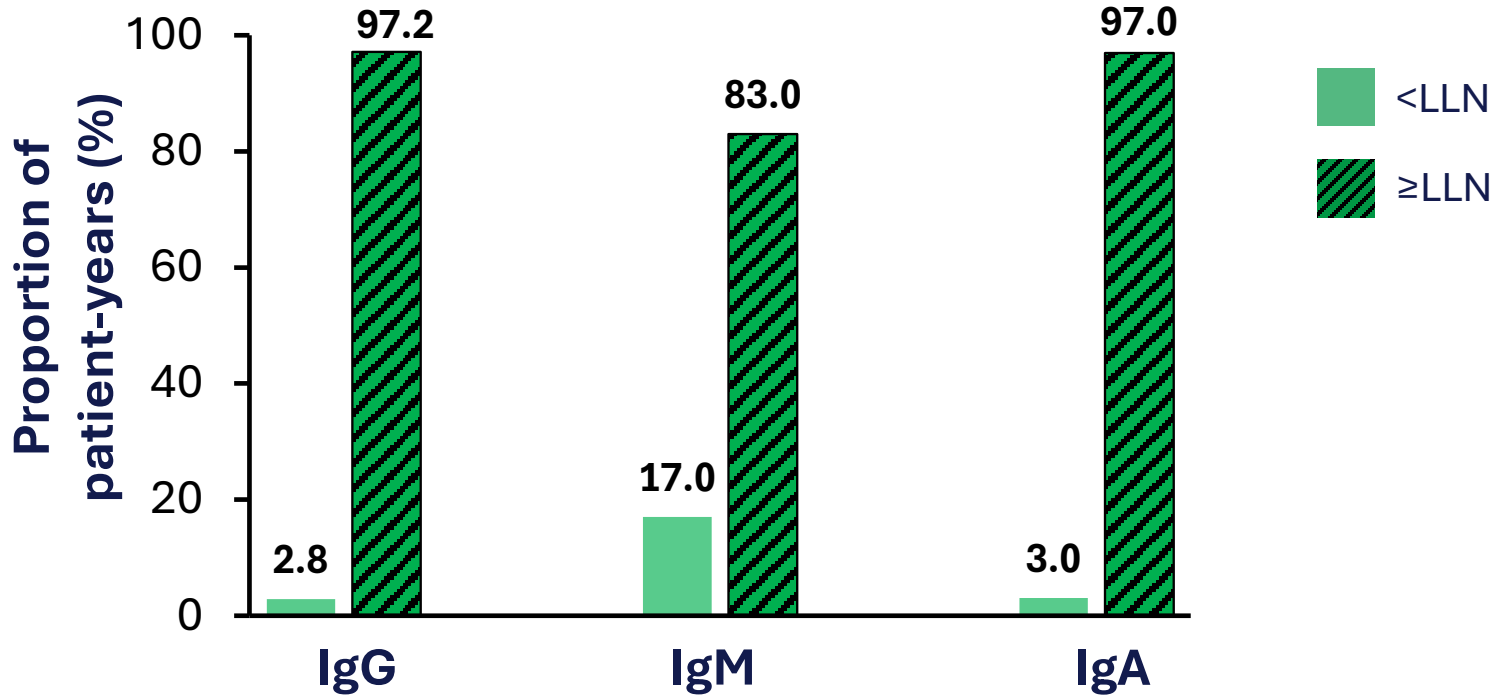
- In the continuous cohort that received UBL for at least 5 years, the mean (SE) IgM levels were 0.69 (0.04) g/L. The IgM levels remained stable and above the LLN (0.4 g/L).



TER/UBL	546	532	517	505	493	402	316	314
UBL/UBL	540	530	524	510	492	389	297	286

Figure 3: Proportion of time ublituximab-treated patients spent with Ig ≥LLN or <LLN

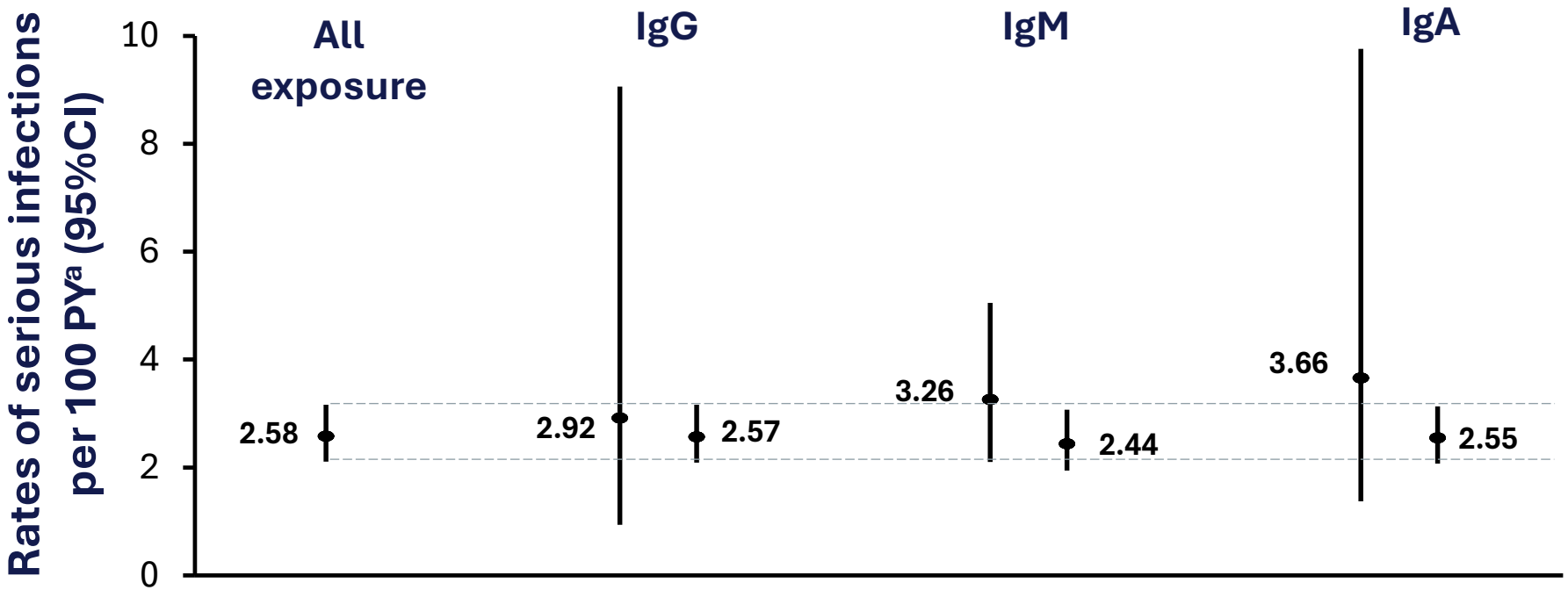
- Out of the total duration of ublituximab exposure (3603.90 patient years), the proportion of time spent ≥LLN was 97.2% for IgG, 83% for IgM and 97% for IgA.



PY as sum of exposures (in years) during each lab episode (<LLN or ≥LLN) from the date of randomization (ublituximab arm in DBP) to the end of DBP and from OLE ICF date (for participants entered in OLE) to the last participant date in OLE or cutoff date 1 Jan 2024 (if ongoing).

Figure 4: Rates of SI per 100 PY in ublituximab-treated patients for Ig values <LLN and ≥LLN

- There was no apparent association between decreased immunoglobulin levels and risk of serious infections in ublituximab-treated patients.
- Exposure-adjusted incidence rates of SIs were comparable in patients with Ig values <LLN and ≥LLN.

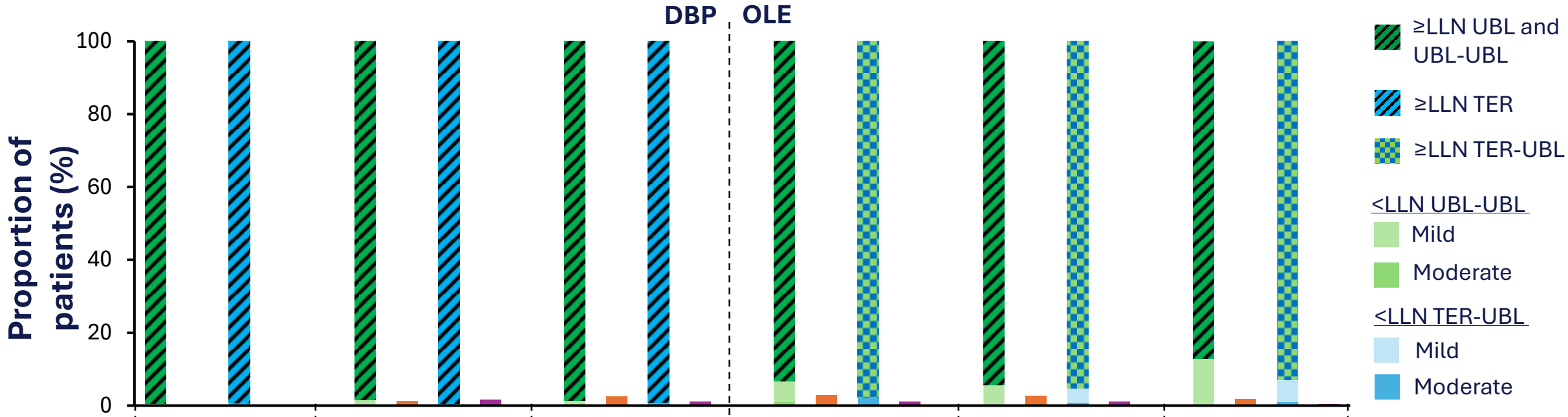


	All exposure	IgG		IgM		IgA	
		<LLN	≥LLN	<LLN	≥LLN	<LLN	≥LLN
Patient-years (PY)[b]	3603.90	102.63	3501.27	613.36	2990.54	109.23	3494.66
No. of SIs	93	3	90	20	73	4	89

SI= serious infection; PY=patient years; LLN = lower limit of normal, defined as: IgG 5.65 g/L, IgM 0.4 g/L, IgA 0.7 g/L. Analysis includes patients who received any dose of Ublituximab during the DBP and OLE periods. Gap period (if any) between DBP and OLE was excluded. [a] Rates of SIs per 100 PYs and 95% CI were estimated by Poisson regression model. Multiple SIs in one participant are counted multiple times. The terms "COVID-19" and "COVID-19 pneumonia" were excluded. [b] PY as sum of exposures (in years) during each lab episode (< LLN or ≥ LLN) from the date of randomization (ublituximab arm in DBP) to the end of DBP and from OLE ICF date (for participants entered in OLE) to the last participant date in OLE or cutoff date 1 Jan 2024 (if ongoing).

Figure 5: Proportion of patients ≥LLN and <LLN by severity for IgG evaluation

- None of the patients showed severe drops in IgG levels below LLN on continuous UBL treatment for 5 years.
- Decreases in IgG levels below LLN were only mild to moderate in nature during 5 years of UBL treatment.
- The frequency of serious infections remained constant over time and was not affected by increases in the proportion of participants <LLN.



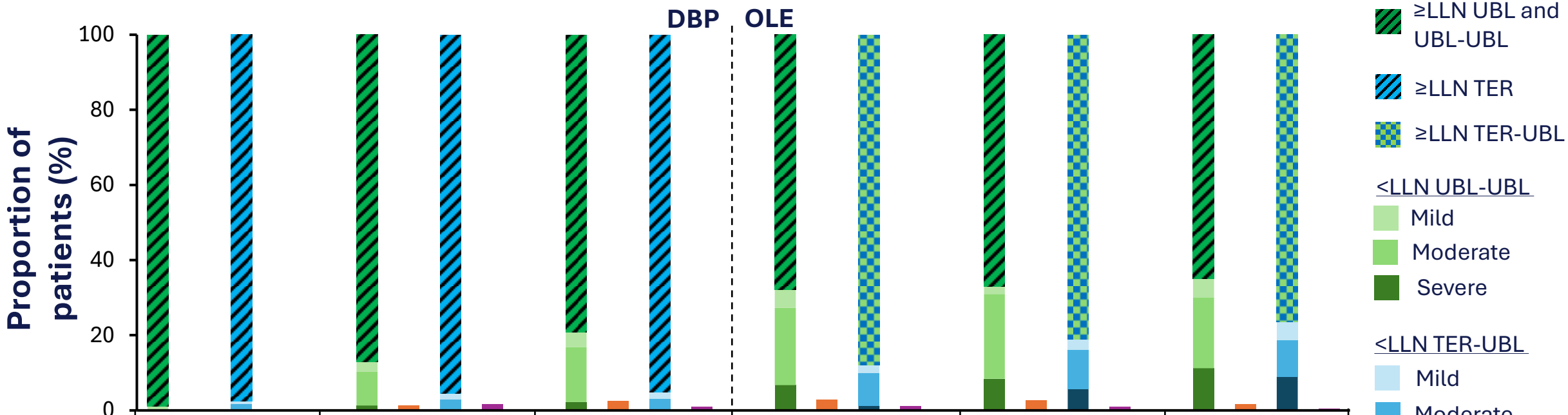
SI (%)			1.3	1.6	2.5	1	2.8	1.1	2.7	1	1.7	0.4				
Normal (≥LLN, %)	99.4	99.3	98.5	99.4	98.6	99.2	93.3	97.8	94.3	95.3	87.1	93.0				
Mild (%)	0.6	0	1.3	0	1	0	5.7	0	5.4	3.8	12.6	6				
Moderate (%)	0	0.7	0.2	0.6	0.4	0.8	1	2.2	0.3	0.9	0.3	1				
Time (weeks)	0		48		96		144*		192		240					

SI= serious infections; LLN=lower limit of normal, LLN definitions: IgG 5.65 g/L, IgM 0.4 g/L, IgA 0.7 g/L. LLN drops in g/L was classified as mild: <5.65 to ≥ 4.0, moderate: <4.0 to ≥ 2.0, severe: <2.0 for IgG. SI (%) represent total incidences regardless of LLN status and are calculated for the 48-week period preceding the depicted timepoint, i.e., SI (%) at W48 represents SI onset in the treatment window between W1D1 and W48.

* The data for W144 corresponds to treatment window between OLE W1D1 and OLE W48.

Figure 6: Proportion of patients ≥LLN and <LLN by severity for IgM evaluation

- The proportion of patients with decreases in IgM levels below LLN were mostly mild to moderate in nature during 5 years of UBL treatment.
- The frequency of serious infections remained constant over time and was not affected by increases in the proportion of participants <LLN.



SI (%)			1.3	1.6	2.5	1	2.8	1.1	2.7	1	1.7	0.4
Normal (≥LLN, %)	98.9	97.6	87.0	95.4	79.1	95.1	67.9	87.8	67.0	81.0	65.0	76.4
Mild (%)	0.7	0.7	2.7	1.7	4.1	1.6	4.9	2.2	2	2.8	4.9	4.8
Moderate (%)	0.4	1.3	9	2.7	14.6	2.8	20.6	8.7	22.6	10.4	18.9	9.9
Severe (%)	0	0.4	1.3	0.2	2.2	0.4	6.7	1.2	8.4	5.7	11.2	8.9
Time (weeks)	0		48		96		144*		192		240	

SI= serious infections; LLN=lower limit of normal, LLN definitions: IgG 5.65 g/L, IgM 0.4 g/L, IgA 0.7 g/L. LLN drops in g/L was classified as mild: <0.4 to ≥0.36, moderate: <0.36 to ≥ 0.2, and severe: <0.2 for IgM. SI (%) shown here are calculated for the 48-week period preceding the depicted timepoint, i.e., SI (%) at W48 represents SI onset in the treatment window between W1D1 and W48.

*The data for W144 corresponds to treatment window between OLE W1D1 and OLE W48.

Conclusions

- The mean serum Ig levels remained above the LLN through 5 years of DBP and OLE.
- There was no apparent association between decreases in immunoglobulin levels and risk of serious infections in ublituximab-treated patients.
- None of the patients showed severe drops in IgG levels below LLN on continuous UBL treatment for 5 years. Decreases in IgG levels below LLN were only mild to moderate in nature during 5 years of UBL treatment.
- The proportion of patients with decreases in IgM levels below LLN were mostly mild to moderate in nature during 5 years of UBL treatment.
- The frequency of serious infections remained constant over time and was not affected by increases in the proportion of participants <LLN.
- No cases of PML were observed.
- UBL confers a benefit risk balance suitable for long-term clinical management of RMS.

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ACKNOWLEDGMENTS

- The authors thank the patients and their families for participating in the ULTIMATE I and II studies. The ULTIMATE I and II studies were sponsored by TG Therapeutics.