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Summary

SOLUBLE TL1A/ANTI-TL1A IMMUNE COMPLEXES INDUCE <EM >DE NOVO</EM> PRODUCTION OF TL1A AND INDUCE ANTI-DRUG ANTIBODIES THAT CROSS-BIND APPROVED IBD ANTIBODIES

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Immune complexes formed between anti-TL1A antibodies and TL1A induced a positive feedback loop of increased TL1A production and high-titer anti-drug antibody formation that cross-reacted with risankizumab and vedolizumab, accelerating their clearance in preclinical models.

KEY POINTS

- In mouse studies, TL1A/tulisokibart immune complexes generated high-titer anti-drug antibodies (signal-to-noise ratio 23.86) compared to tulisokibart alone (1.28), and these antibodies cross-reacted with risankizumab in 85% and vedolizumab in 43% of animals.
- Anti-drug antibodies to tulisokibart immune complexes accelerated the clearance of subsequently administered risankizumab and vedolizumab in mice who had developed the antibodies.
- TL1A/tulisokibart immune complexes, but not TL1A or tulisokibart alone, induced up to 100-fold increase in TL1A transcript levels in human monocytes at 6 hours, with return to baseline at 24 hours.
- Anti-TL1A antibody framework regions share 95-97% sequence identity with risankizumab and vedolizumab heavy-chain frameworks, and both cross-linked and non-cross-linked immune complexes restored binding to Fc gamma receptors 1 and 2.
- The authors, who are employees and equity holders of Shattuck Labs, state that further evaluation using patient serum samples will be important to determine clinical relevance of these preclinical observations for treatment sequencing and combination strategies in IBD.

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