Platelet-activating factor (PAF) drives adverse inflammatory effects induced by anti-erythrocyte antibody therapy in murine ITP

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Background

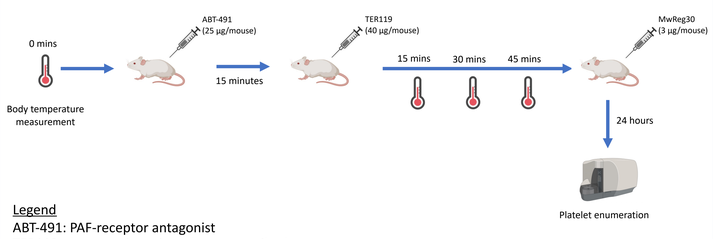
Anti-D is a donor-derived polyclonal anti-erythrocyte antibody used to treat immune thrombocytopenia (ITP)[1]. Although anti-D is effective, its donor-derived nature presents issues of supply and batch-to-batch inconsistencies[2]. Additionally, the adverse inflammatory properties of anti-D contribute to its limited use. **TER119** is a monoclonal anti-erythrocyte antibody which, like anti-D, is therapeutic in murine ITP, although it likewise possesses a highly inflammatory profile[3]. By using TER119 as a surrogate antibody for anti-D, we may progress towards understanding the mechanism of adverse inflammation and simultaneously explore the possibility of using a monoclonal anti-erythrocyte antibody as a replacement therapeutic product.

Platelet-activating factor (PAF) is a highly potent inflammatory compound that mediates hypersensitivity reactions in mice[4]. Therefore, we hypothesize that the inflammatory adverse effects caused by TER119 (and perhaps anti-D) is due to the production PAF, and this inflammation can be mitigated with a PAF-receptor antagonist.

Methods

Murine ITP was induced using an anti-platelet antibody (**MwReg30**). As the primary inflammatory metric, **body temperature** was measured in 15-minute intervals post-treatment with TER119. In addition, serum PAF concentration was assessed at various timepoints by ELISA. To determine the therapeutic activity of TER119, platelets were enumerated 24 hours post-treatment. By administering a prophylactic dose of a PAF-receptor antagonist 15 minutes prior to TER119, we also explored the effects of PAF neutralization on attenuating drops in body temperature.

A summary of the animal model is shown below.



Legend
ABT-491: PAF-receptor antagonist
TER119: therapeutic anti-erythrocyte antibody
MwReg30: anti-glycoprotein IIb/IIIa antibody (anti-platelet antibody to induce ITP)

References

1. Cheung E, Liebman HA. Anti-RhD immunoglobulin in the treatment of immune thrombocytopenia. *Biologics: Targets & Therapy.* 2009;3:57.
2. Lazarus AH. Monoclonal versus polyclonal anti-D in the treatment of ITP. *Expert opinion on biological therapy.* 2013;13(10):1353-6.
3. Crow AR *et al*. Treating murine inflammatory diseases with an anti-erythrocyte antibody. *Science translational medicine*. 2019;11(506).
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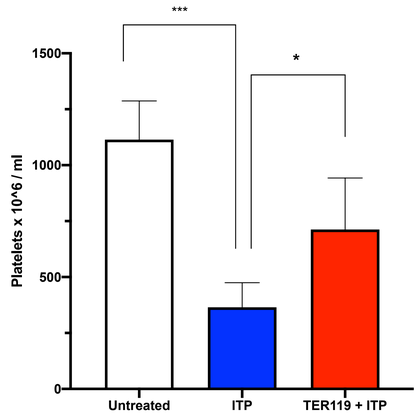
Results

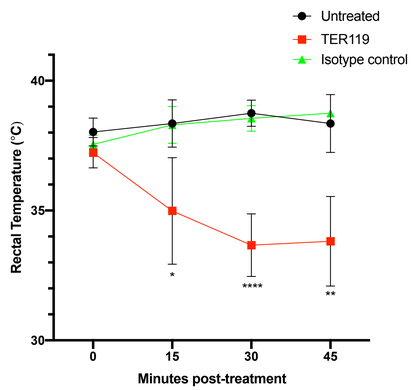
TER119 is an anti-erythrocyte antibody with therapeutic potential in murine ITP but also possesses an inflammatory side effect profile

TER119 recovers platelet counts in murine ITP



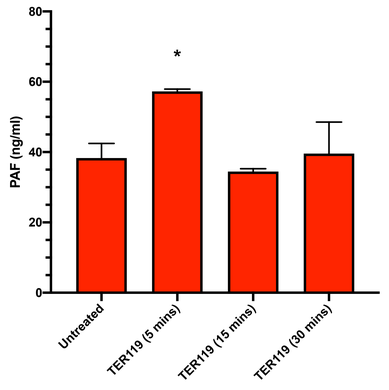
* p<0.05, *** p<0.001

Mice experience an inflammatory drop in body temperature with TER119 antibody therapy



* p<0.05, ** p<0.005, **** p<0.0001 vs. untreated

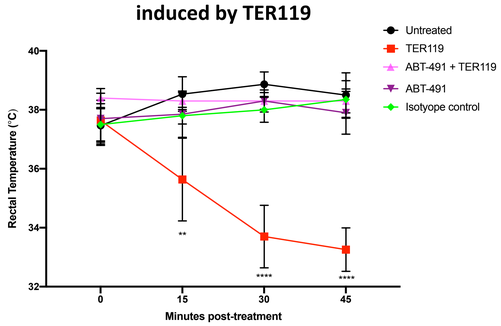
Blood concentration of PAF, a potent inflammatory mediator, is elevated 5 minutes post treatment with TER119



* p<0.05 vs. all other treatment groups

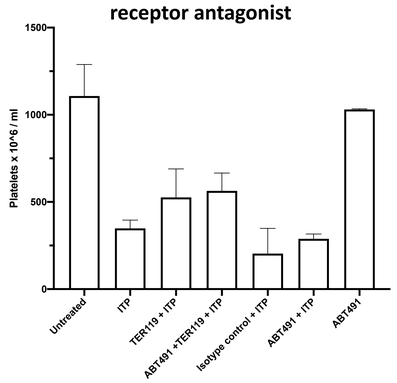
PAF-receptor antagonist ameliorates inflammatory adverse effects without altering the therapeutic potential of TER119

PAF-receptor antagonist prophylaxis mitigates drops in body temperature induced by TER119

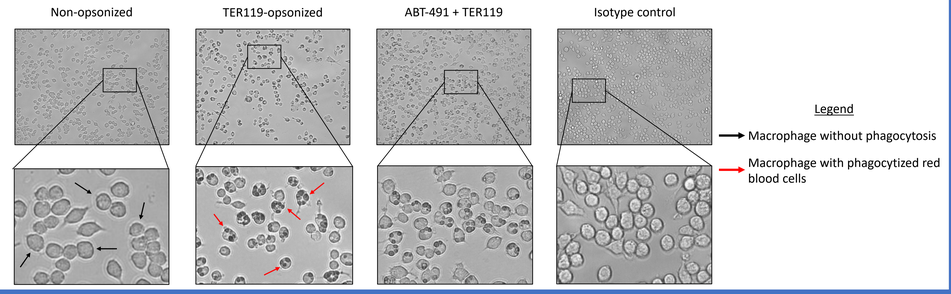


** p<0.005, **** p<0.0001 vs. ABT-491 + TER119

The ability of TER119 to recover platelet counts in murine ITP is not affected by PAF-receptor antagonist



PAF-receptor antagonist does not interfere with phagocytosis of TER119-opsonized erythrocytes



Summary

- TER119 is an antibody with anti-D-like therapeutic activity
- TER119-associated inflammation may be driven by platelet-activating factor (PAF)
- Inflammatory drops in body temperature induced by TER119 can be mitigated with a PAF-receptor antagonist

Implications
- Evaluating the therapeutic and safety profile of TER119 provides insight into the possibility of substituting anti-D with a monoclonal product
- This work may explain the inflammatory profile of anti-erythrocyte antibodies, including anti-D

Acknowledgements

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