Exposure–safety analysis from two prospective clinical trials of emapalumab in patients with macrophage activation syndrome in Still's disease

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CONCLUSIONS

- In a pooled analysis of data from two prospective clinical studies of patients with macrophage activation syndrome (MAS) in Still's disease, increasing emapalumab exposure was not associated with an increased risk of moderate or severe events, serious, nor infection treatment-emergent adverse events (TEAEs).
- A statistically significant trend towards decreasing moderate or severe TEAEs, severe TEAEs and infections TEAEs was observed with increasing emapalumab exposure.
- This observation is consistent with a previous safety–exposure analysis in patients with primary hemophagocytic lymphohistiocytosis (pHLH) administered emapalumab[1] and suggests that greater exposure to emapalumab to control hyperinflammation in this patient population may reduce the incidence of moderate and severe TEAEs, as well as infections.
- This pharmacological exposure–safety analysis confirms that repeated administration and/or increasing doses of emapalumab are well tolerated by patients with MAS in Still's disease.

INTRODUCTION

- Interferon-gamma (IFNγ) has a key role in antiviral and antibacterial immunity by promoting macrophage and T-cell activation amongst other immunomodulatory effects.
- Immune dysfunction and immunosuppression have been observed in preclinical IFNγ receptor gene knockout models and patients with IFNγ receptor deficiencies.
- Emapalumab, an anti-IFNγ antibody that binds free and receptor-bound IFNγ has demonstrated efficacy in patients with MAS,[2,3] a potentially life-threatening complication of Still's disease characterized by IFNγ-driven macrophage activation and systemic hyperinflammation.
- Despite emapalumab rapidly neutralizing IFNγ in patients with pHLH, no increased risk of TEAEs, including infections, was observed in clinical data or an exposure–safety analysis.[1,4]

OBJECTIVES

- To evaluate the relationship between emapalumab exposure in patients with MAS in Still's disease and the predicted risk of TEAEs, including infections.

STUDY METHODS

- Data were pooled from two open-label, single-arm interventional studies (NI-0501-06 [NCT03311854] and NI-0501-14 [EMERALD; NCT05001737]) in patients with MAS in Still's disease who had an inadequate response to high-dose intravenous glucocorticoids.
- Herpes zoster antiviral prophylaxis, administered according to the local standard of care, was mandatory in Study 06, but administered at the discretion of the investigator in EMERALD.

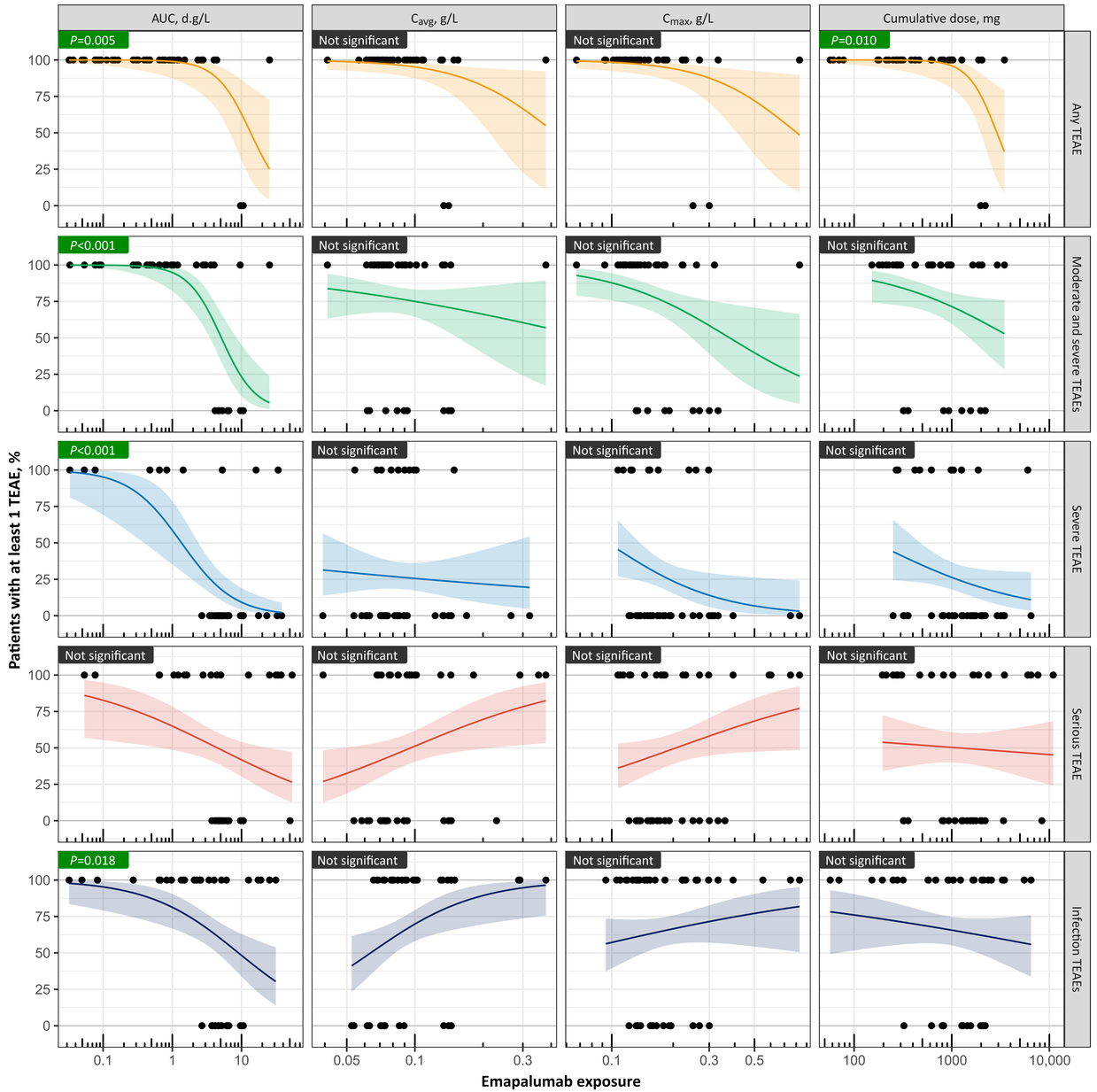
SAFETY-EXPOSURE ANALYSIS

- Logistic regression analyses were performed to quantify the relationship between emapalumab exposure and safety outcomes.
- Safety categories were any TEAE, moderate or severe TEAE, severe TEAE, serious TEAE, and TEAEs with system organ class infections and infestations.
- Three exposure parameters were defined: cumulative area under the emapalumab–time curve (AUC_T), average emapalumab concentration ($C_{avg,T}$), and maximum emapalumab concentration ($C_{max,T}$) during the time between administering the first dose of emapalumab and time T of the first event (or up to 45 days after the last dose in the case of no event).
- The relationship between each safety category and total cumulative emapalumab dose was also analyzed.

RESULTS

- This analysis was performed using data from 38 patients (14 patients from Study 06 and 24 patients from EMERALD) with MAS in Still's disease.
- The frequency of any TEAE was close to 100% in this population, even with very low emapalumab exposure, creating a ceiling effect that prevented meaningful interpretation of this endpoint.
- Moderate or severe TEAEs, severe TEAEs, and infection TEAEs were all significantly less frequent in patients with increasing emapalumab AUC_T ($P<0.001$, $P<0.001$ and $P=0.018$; no adjustment for multiple testing).
- No statistically significant relationship was observed between $C_{avg,T}$, $C_{max,T}$, or total cumulative dose and any safety category or serious TEAEs.

Figure: Exposure-safety analysis for patients with MAS in Still's disease administered emapalumab (N=38)



AUC, area under the curve; C_{avg}, average concentration; C_{max}, maximum concentration; MAS, macrophage activation syndrome; TEAE, treatment-emergent adverse event.

Disclosures

R.T. Krmar, K. Star, A. Stoltenberg, A. Mahmood, U. Ullmann and P. Brossard are employees of Sobi. **B. Jamieson** is an employee of Sobi Inc. **F. De Benedetti:** Consultant and research grants from Sobi, Novartis, Elixiron, Apollo, Sanofi, Abbvie, Kiniksa. **A. Grom:** Consultant to Novartis, Sobi, Kiniksa; Research grants/Contracts from NIH, Novartis, Sobi, sJIA Foundation; Royalties from Up-to-Date. **A. Facius** is a consultant to Sobi.

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Acknowledgements

The authors wish to acknowledge Stefan Duscha, PhD from Sobi (Basel, Switzerland) for publication coordination and Blair Hesp, PhD CMPP of Kainic Medical Communications Ltd. (Dunedin, New Zealand) for medical writing and editorial support, funded by Sobi, based on the authors' input and direction, and in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022).