Drug Interaction Potential as a Result of Cytokine Release Syndrome Using a Physiologically Based Pharmacokinetic Model: Case Study of Teclistamab

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INTRODUCTION

- The ability of a physiologically based pharmacokinetic (PBPK) model to capture drug-drug interactions (DDIs) was first verified using data from the literature[1,2]
- Teclistamab is the first off-the-shelf B-cell maturation antigen (BCMA) × CD3 bispecific antibody approved, and is a new standard of care (overall response rate, %63) for patients with heavily pretreated relapsed/refractory multiple myeloma[3-5]
- Cytokine release syndrome (CRS) has been associated with teclistamab, with most events being low grade and reported during step-up doses and the initial treatment dose at the recommended phase 2 dose (RP2D)
- Among the different cytokines released during CRS, interleukin 6 (IL-6) is a potent suppressor of cytochrome P450 (CYP450) enzyme activity
- A PBPK model was developed to evaluate the impact of IL-6 following teclistamab (administered at the RP2D in MajesTEC-1) on the exposure to co-administered CYP450 substrates

METHODS

- A PBPK model was developed for IL-6 based on the literature[6]
- DDIs toward different CYP450 substrates (caffeine [CYP1A2], s-warfarin [CYP2C9], omeprazole [CYP2C19], midazolam and cyclosporine [CYP3A4 and CYP3A5], and simvastatin [CYP3A4]) were evaluated where substrates were administered as a single dose when minimum (or maximum for CYP1A2) enzymatic activity was reached
- Inactivation of CYP2C9, CYP2C19, CYP3A4, and CYP3A5, but induction of CYP1A2, has been observed in vitro and in vivo[1,7]
- Prospective simulations were performed using observed IL-6 profiles from 112 patients following teclistamab administered at the RP2D without or prior to administration of tocilizumab (an anti–IL-6 agent) in MajesTEC-1 as of the March 16, 2022 cut-off
- Observed data were recovered by adjusting the dosing regimens of IL-6, modeled as an intravenous infusion. Two scenarios were envisioned:
  - The observed mean serum IL-6 kinetic profile
  - The worst-case scenario (in terms of risk of a DDI) corresponding to the IL-6 profile observed in the patient presenting the highest IL-6 maximum concentration (C_{max}) value
- In addition, time to reach maximum change in CYP450 activity due to IL-6 and return to %80 of the baseline enzymatic activity was evaluated, with the start of cycle 1 as reference
  - %80 was considered as a reasonable cut-off at which DDI liability would be low

MULTIPLE MYELOMA

RESULTS

Model verification

- Transient peak IL-6 concentration and IL-6 concentration at steady state (50 pg/mL) were successfully predicted
- Observed DDIs from literature with CYP1A2, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 substrates in the presence of steady state concentrations of IL-6 at 50 pg/mL were well predicted, providing confidence in the application of the model to assess IL-6 as a perpetrator of these CYP substrates

Model application to teclistamab RP2D

- The mean IL-6 profile following teclistamab at RP2D (mean C_{max}= 21 pg/mL) was predicted to result in a limited change in exposure of CYP1A2, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 substrates (0.87 ≤ area under the curve [AUC] ratio ≤ 1.20) (**Table**)
- The IL-6 kinetic profile with the highest C_{max} (288 pg/mL) was predicted to result in:
  - A mild-to-moderate inhibition on exposure of CYP2C19, CYP3A4, and CYP3A5 substrates (1.90 ≤ AUC ratio ≤2.23) (**Table**)
  - Minimal impact on exposure of CYP1A2 and CYP2C9 substrates (AUC ratio=0.82 and 1.25, respectively) (**Table**)
- For both scenarios, the maximum change in exposure for the studied substrates occurred 3–4 days after the first treatment dose (**Figure 1A**)
  - For the patient with the highest IL-6 C_{max}, return to %80 of the baseline enzymatic activity was observed ~7 days after the first treatment dose (**Figure 1B**)
  - The highest AUC ratio (at %80 of enzymatic activity) reached was ≤1.47 (CYP2C19), which corresponds to a weak interaction

FIGURE 1: Change in activity of the CYP450 enzyme due to IL-6 for (A) mean IL-6 profile (B) IL-6 profile of patient presenting highest IL-6 C_{max}

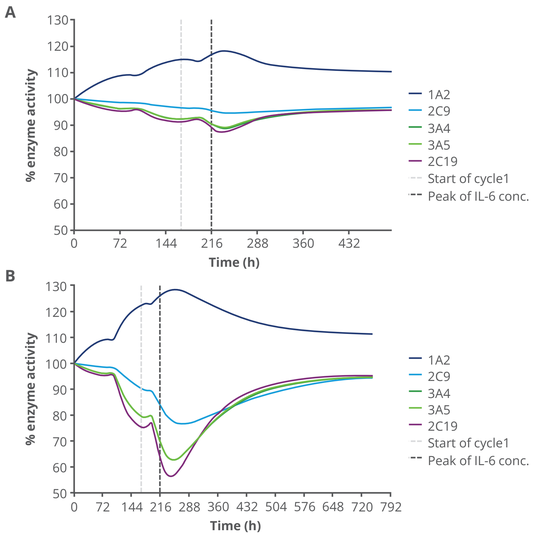

TABLE: Simulated change in CYP450 substrate exposure after single dose administration of the CYP450 substrate in presence of IL-6 kinetics profile observed in MajesTEC-1

CYP substrate	With mean IL-6 kinetics profile[a]			With IL-6 kinetics profile of patient presenting highest IL-6 C_{max}[b]		
	C_{max} ratio, mean	AUC ratio, mean	DDI liability	C_{max} ratio, mean	AUC ratio, mean	DDI liability
Caffeine (CYP1A2)	0.97	0.87	No interaction	0.95	0.82	No interaction
S-warfarin[c] (CYP2C9)	1.00	1.05	No inhibition	1.01	1.25	Weak inhibition
Omeprazole (CYP2C19)	1.10	1.20	No inhibition	1.45	2.23	Moderate inhibition
Midazolam (CYP3A4/CYP3A5)	1.11	1.17	No inhibition	1.46	1.90	Weak inhibition
Simvastatin (CYP3A4)	1.17	1.20	No inhibition	1.86	2.09	Moderate inhibition
Cyclosporine[c] (CYP3A4/CYP3A5)	1.09	1.17	No inhibition	1.35	1.90	Weak inhibition

[a]Mean C_{max} on cycle 1 day 21=3 pg/mL. [b]Highest C_{max} on cycle 1 day 3=288 pg/mL. [c]Narrow therapeutic index.

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KEY TAKEAWAY

Interactions between substrates of CYP450 and IL-6 released when teclistamab is given at the RP2D are predicted to have limited clinical significance

CONCLUSIONS

- The initial release of IL-6 during CRS following teclistamab treatment at the RP2D has minimal or moderate impact on exposure to CYP substrates
- The highest risk of DDI is expected to occur from day 1 of the step-up dosing schedule to 7 days after the first treatment dose and during and after CRS
- During this time period, for substrates with a narrow therapeutic index, such as warfarin and cyclosporine:
  - Patients should be monitored for signs of toxicity
  - Concentrations of these CYP substrates with a narrow therapeutic index should be assessed

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DISCLOSURES

M-EW is employed by Janssen. **SXWL, JDG,** and **SG** were employed by Janssen when this work was done and have stock/other ownership interests in Janssen. **LDZ, LSW, XM, RV,** and **BL** are employed by Janssen. **AB**, **RK**, and **MQ** are employed by and have stock/other ownership interests in Janssen. **DO** is employed by and has stock/other ownership interests in Janssen and has stock/other ownership interests in AbbVie.

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