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POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Model-Based Exploration of the Impact of Prophylactic Tocilizumab on IL-6 Dynamics in Multiple Myeloma Patients Receiving Teclistamab Treatment

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Introduction: Teclistamab is the only approved B-cell maturation antigen (BCMA) × CD3 bispecific antibody (BsAb) with personalized, weight-based dosing for the treatment of patients with triple-class exposed relapsed/refractory multiple myeloma (RRMM).In the MajesTEC-1 study (NCT03145181 and NCT04557098), the incidence of all grade (mostly grade 1 or 2) cytokine release syndrome (CRS) was 72.1% (Moreau et al. 2022). The cytokine interleukin-6 (IL-6) is found to be increased in the serum of patients with CRS (Shimabukuro-Vornhagen et al. 2018). Tocilizumab is a humanized IL-6 receptor-inhibiting monoclonal antibody. As a competitive antagonist, tocilizumab inhibits the IL-6 pathway by competing with IL-6 for binding to IL-6 receptor (IL-6R), resulting in lower IL-6R receptor occupancy (RO) by IL-6, thereby blocking IL-6 signaling. By blocking IL-6R, tocilizumab also reduces IL-6R-mediated IL-6 clearance, which leads to an increase in serum IL-6 levels (Uchiyama et al. 2008). It has been published previously that a single dose of prophylactic tocilizumab reduced the overall incidence of CRS to 26% after teclistamab administration, which represents a 64% reduction compared to the CRS incidence observed in MajesTEC-1 (van de Donk et al. 2023). A mechanism-based PK/PD model was used to evaluate the impact of tocilizumab prophylactic treatment on the soluble IL-6R (sIL-6R), IL-6 and the duration of the blockade of IL-6 signaling pathway in the patients following teclistamab treatment.

Methods: A mechanism-based PK/PD model was built by using reported tocilizumab PK parameters and sIL-6R target engagement. The time course of IL-6R RO for patients receiving prophylactic tocilizumab following teclistamab treatment was estimated from the PK profiles of tocilizumab and competitive binding kinetics. Among the patients with evaluable serum IL-6 levels, the highest peak serum IL-6 concentration in the patients who didn't have CRS (N=9) from prophylactic tocilizumab cohort of MajesTEC-1 was selected as the worst-case scenario. The IL-6R RO in patients receiving prophylactic tocilizumab in the worst-case scenario was characterized by model simulations and the results were compared to the calculated IL-6R RO in the cohorts following teclistamab treatment without prophylactic tocilizumab (N=40).

Results: Time course of serum IL-6 levels following teclistamab treatment showed higher and earlier induction in the cohort with tocilizumab prophylaxis compared to the cohort without tocilizumab prophylaxis. Among the patients who received tocilizumab prophylactic treatment, the median peak serum IL-6 level was 208.6 pg/mL and the highest peak serum IL-6 level was 1701.8 pg/mL in patients who didn't have CRS. The model simulation results showed that a single dose of tocilizumab at 8 mg/kg IV given prophylactically could lower the IL-6R RO by IL-6. In a patient with 1700 pg/mL of serum IL-6 treated with tocilizumab, IL-6R RO was maintained below the level of RO achieved with 10 pg/mL of serum IL-6 in the absence of tocilizumab for approximately 10 days. An IL-6 level of 10 pg/mL was considered as a representative value in the patients who did not have CRS following teclistamab at the approved dosing regimen without prophylactic tocilizumab, as more than half (58%) of these patients showed peak serum IL-6 level below 10 pg/mL. The duration of IL-6R RO reduction covers the two step-up doses (SUD) and the first full treatment dose according to the teclistamab approved dosing schedule.

Conclusions: The modeling and simulation results showed that a single dose of tocilizumab given prophylactically at 8 mg/kg could block IL-6R RO for approximately 10 days following the 1 st step up dose of teclistamab. The results further support this approach for lowering overall risk of CRS during the SUD schedule in multiple myeloma patients treated with teclistamab.

Disclosures Zhou: *Johnson & Johnson:* Current Employment, Current equity holder in publicly-traded company. **Vishwamitra:** *Johnson & Johnson:* Current Employment, Current holder of *stock options* in a privately-held company. **Guo:** *Janssen*

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