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704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Hypogammaglobulinemia and Infection Risk in Relapsed Refractory B Cell Malignancy Patients Treated with Varnimcabtagene Autoleucel (IMN-003A), a CD19-Directed Chimeric Antigen Receptor T (CAR-T) Cell Therapy, in the Phase-2 Study (IMAGINE)

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Background: Varnimcabtagene autoleucel (IMN-003A) is an anti-CD19 CAR-T cell immunotherapy for patients with relapsed refractory B cell malignancies (RR BCM) in the Phase 2 IMAGINE study. Hypogammaglobinemia can result from normal CD19+ B cell depletion (on-target, off-site effect) by CD19 directed CAR-T cells. RR BCM patients (pts) are already at risk for infections due to impaired immune function, lymphodepletion preparative regimen and prior immunosuppressive therapies. Intravenous immunoglobulin (IVIg) replacement is used to reduce the risk of infections due to hypogammaglobulinemia. We report the impact of var-cel on hypogammaglobinemia, infectious complications, risk factors, IVIg usage and clinical outcomes for RR BCM patients treated in first-in-India industry study (CTRI/2022/03/041162).

Methods: RR BCM pts treated with var-cel in this study were reviewed. Hypogammaglobulinemia was defined as IgG <4 g/L. Infections reported during pre-apheresis (post screening), D0 to D+28 post CAR-T infusion and beyond D+29 for study duration were analyzed. IVIg usage for hypogammaglobulinemia was at investigator discretion. Patients were monitored for infection events. RR BCM response was assessed as per NCCN (B-ALL) and IWG (B-NHL) criteria. Appropriate statistical tools were used for data analysis.

Results: At data cut-off, of 25 pts enrolled (median age 31 yrs, range 3 - 66) with RR BCM (n=13 B-ALL; n=12 B-NHL), 24 pts received var-cel (1 withdrawal). Median follow-up after IMN-003A administration was 205 days (range 12 - 434). Overall response rate (ORR) was 91.7% (22/24) at D+28 (B-ALL 91.7%; B-NHL 91.7%) and 80.9% (17/21) at D+90 (B-ALL 80%; B-NHL 81.8%). Treatment related mortality was 4.2% (n=1/24); 3 pts died of disease progression.

Of the 24 pts, none had hypogammaglobulinemia (IgG <4g/L) at baseline. Eleven pts (45.8%) developed hypogammaglobulinemia post var-cel infusion. Of these, 10 pts (90.9%) received prophylactic intravenous immunoglobulin (IVIg). In total, 70.8% (n=17/24) pts received IVIg infusions (Table 1).

The median time to initiation of IVIg after var-cel infusion was 58 days (range 15 to 189 days). Of evaluable pts, IVIg was used in 15 of 17 (88.2%) responders at D+90 (CR / PR) vs 0 of 4 (0%) in non-responders (SD / PD) (p=0.06). 52.9% (n=9/17) pts on prophylactic IVIg reported infections. Patients who received IVIg had more infections (30 events; p=0.76). The mean number of infections with and without IVIg was 1.8 and 1.6 respectively. The median overall survival was significantly higher in pts who received IVIg prophylaxis (p=0.02). There was no difference in survival observed based on presence or absence of hypogammaglobulinemia post var-cel infusion (p=0.46).

A total of 41 infections were reported in 13 pts. Of these, the incidence from screening to D-1; D0 to D+28 and beyond D+29 were 9 events (4 pts); 12 (11) and 20 (7) respectively. Bacterial, viral and fungal infections reported were 28 events (11 pts); 12 (8) and 1 (1) respectively. Bacterial infections were sepsis (n=7); urinary tract infections (n=5), respiratory (n=14) and central line (n=2). There were 12 viral events, 11 of respiratory origin and one involving conjunctiva. There was one episode of probable fungal candidemia. Stool surveillance detected 27 positive events in 13 pts. Table 2 summarizes the reported infectious organisms.

There were 23 infections documented in 13 patients who did not develop hypogammaglobulinemia (median 2 infections; mean 1.8; range 1 - 6). Of 11 pts with hypogammaglobulinemia, there were 18 infections (median 3.5; mean 1.6; range 1 - 9). Complete and partial responders had more infections compared to non-responders ($p = 0.05$).

Conclusions: This is the first-in-India report evaluating hypogammaglobulinemia and infection risk post CAR-T cell infusion. The IVIg usage and documented infections was more in responders. The safety and efficacy outcomes of varnimcabtagene autoleucel (IMN-003A) are consistent with reported outcomes of approved CD19 directed CAR-T cell therapies. The use of prophylactic IVIg, often led by individual practice, to reduce the number of infections and its impact on efficacy outcomes remains uncertain. Potential strategies to reduce infection risk may help improve outcomes.

Disclosures B: *Immuneel Therapeutics Private Limited:* Current Employment. **Arasu:** *Immuneel Therapeutics Private Limited:* Current Employment. **Elluru:** *Immuneel Therapeutics Private Limited:* Current Employment. **Akheel:** *Immuneel Therapeutics Private Limited:* Current Employment. **Kamat:** *Immuneel Therapeutics Private Limited:* Consultancy.

Table 1: Characteristics of patients with and without hypogammaglobulinemia after var-cel infusion

	Hypogammaglobulinemia (IgG <4g/L) after var-cel infusion	
	No (N=13)	Yes (N=11)
Age (yrs) median (range)	43 (7 - 66)	14 (4 - 59)
Age >65: N (%)	1 (7.69%)	0
Number of Infections (events) median (range) mean	23 2 (1 - 6) 1.8	18 3.5 (1 - 9) 1.6
No. of subjects having infections: N (%)	8 (61.53%)	5 (45.45%)
Received IVIg: N (%)	7 (53.84)	10 (90.90)
CR/PR at D90: N (%)	8 (61.53)	9 (81.81)
Survival (PFS days) median (range)	122 (12 - 201)	275 (28 - 360)
Days Follow-up median (range)	182 (12-350)	221 (76-434)
	Overall Response at D+90	
	Responders (N = 17)	**Non-Responders (N = 4)**
Infections (events / pts)	31 / 10	10 / 3
Received IVIg*: N (%)	15 (88.23)	0 (0)
	* Of 17 pts who received IVIg, 15 completed D+90 assessment.	

Table 2: Infectious organisms in patients at different timepoints pre and post var-cel infusion

Timepoint	Bacterial	Viral	Fungal	Stool Surveillance
Screening to D-1 (pre-infusion)	Staphylococcus epidermitis Acinetobacter ursingii Escherichia coli Gram positive cocci in pairs	Covid-19	None	Klebsiella pneumoniae Escherichia coli
D0 to D+28	Staphylococcus aureus Pseudomonas aeruginosa Escherichia coli Acinetobacter baumannii Klebsiella pneumoniae Enterobacter cloacae	Rhino enterovirus Coronavirus OC43	None	Escherichia coli Staphylococcus aureus Citrobacter amalonaticus Klebsiella pneumoniae Enterococcus faecium
>D+28	Pseudomonas aeruginosa Hemophilus influenzae Corynebacterium striatum Burkholderia cepacia Klebsiella pneumoniae - XDR Probable Mycobacterium tuberculosis - MDR Escherichia coli - ESBL Gram positive bacilli Gram negative bacilli Gram negative cocci	Covid-19 Human metapneumovirus Rhino enterovirus Influenza A H3N2	Probable Candida	Escherichia coli Klebsiella pneumoniae - XDR

Figure 1

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