aGvHD

Vedolizumab treatment for the prevention of acute GvHD following allogeneic hematopoietic stem cell transplantation

| Jan 20, 2020

T cell trafficking to gut-associated lymphoid tissue has been shown to play a key role in acute graft-*versus*-host disease (aGvHD) establishment in experimental models.[1] A key mediator of T-cell adhesion to gut endothelial cells is the integrin α4β1, which binds to mucosal addressin cell adhesion molecule 1 (MAdCAM-1) found specifically on gut endothelial cells.[2,3] Vedolizumab, an anti-α4β1 humanized monoclonal antibody, has been shown to elicit gut-specific immunomodulatory activity and is currently approved for the treatment of moderate to severe ulcerative colitis and Crohn's disease in adults.[4]

Yi-Bin Chen, Massachusetts General Hospital, Boston, US, and colleagues explored the potential benefits of coadministration of vedolizumab with standard GvHD prophylaxis in a phase Ib, open-label study (NCT02728895).[4] The study evaluated the tolerability, safety, pharmacokinetic profile, and efficacy of vedolizumab in 24 patients undergoing allogenic hematopoietic stem cell transplantation (allo-HSCT) and was recently published in *Blood Advances*.

The GvHD Hub recently covered GvHD prophylaxis as a monthly theme. Read more here.

Study Design

Treatment:

- All patients underwent either a myeloablative or reduced-intensity conditioning (**Table 1**) followed by standard GvHD prophylaxis (tacrolimus [recommended goal serum trough concentration of 5–10ng/dL] and MTX [recommended 10 mg/m^{2}IV on Days +1, +3, +6 and +11 after allo-HSCT])
- Patients received 75 mg (n= 3) or 300 mg (n= 21, dose-escalation) IV vedolizumab, on Days -1, +13, and +42 subsequent to the allo-HSCT procedure
- Dose escalation:
  - Three participants were primarily enrolled on the 75 mg IV vedolizumab dosing regimen, on Days -1, +13, and +42 after the allo-HSCT procedure
  - If the first patient tolerated the basal dose and reached full neutrophil engraftment, two further participants were enrolled and observed for dose-limiting toxicities (DLTs)
  - A lack of DLTs across three patients resulted in the initiation of a dose-determining phase where additional 21 patients received 300 mg IV vedolizumab

Endpoints:

- Primary endpoints: to identify the tolerability and safety of vedolizumab and determine the recommended dose
- Secondary endpoints: characterize PK profile of vedolizumab in participants and determine the cumulative incidence and the severity of aGVHD by 100 days after allo-HSCT

Results

- Patient characteristics
  - Patients (n= 24), median age 55 (range, 18–72) years, undergoing allo-HSCT were recruited (**Table 1**)

Table 1. Characteristics of study sample defined by vedolizumab dose cohort

Characteristic	Vedolizumab 75 mg (n= 3)	Vedolizumab 300 mg (n= 21)	Total (N= 24)
Median age, years (range)	22 (18–50)	58 (19–72)	55 (18–72)
Disease Type			
Myeloproliferative neoplasm	0	3	3
Myelodysplastic/myeloproliferative neoplasm	0	3	3
Myelodysplastic syndrome	0	2	2
AML or related precursor neoplasm	3	6	9
Precursor Lymphoid neoplasm	0	5	5
Precursor T-ALL/LBL	0	3	3
Precursor B-ALL/LBL	0	2	2
Other	0	2	2
Conditioning Regimen			
Myeloablative, busulfan + fludarabine	2	5	7
Myeloablative, cyclophosphamide + TBI	1	5	6
Reduced-intensity, busulfan + fludarabine	0	6	6
Reduced-intensity, fludarabine + melphalan	0	5	5
Source of stem cells			
Bone Marrow	3	6	9
Peripheral blood	0	15	15
HLA compatibility			
Matched	3	20	23
Mismatched	0	1	1
Donor relationship to study participant			
Related	0	4	4
Unrelated	3	17	20

B-ALL, B-cell acute lymphoblastic leukemia; HLA, human leukocyte antigen; LBL, lymphoblastic lymphoma; T-ALL, T-cell acute lymphoblastic leukemia; TBI, total body irradiation

- Safety[4]
  - All participants experienced at least one grade III or higher TEAE, eight of which were considered related to vedolizumab (n= 2 and n= 6 in the 75 mg and 300 mg dose cohorts, respectively).
  - Serious TEAEs were observed in 13 of 24 participants. However, only in one patient in the 300 mg dose cohort it was considered to be related to study drug
  - No DLTs were observed for participants in either dose cohort
  - Cytomegalovirus- and *Clostridium difficile*-related infections were the most common TEAEs in the 300 mg dose cohort
  - Neutrophil engraftment was observed by Day +100 for all 24 participants. Time to engraftment was not significantly different between the 300 mg dose cohort (median 14; interquartile range 13–17 days) and the 75 mg dose cohort which saw one patient reaching engraftment at Day 15 and two at Day 22
  - Of the three deaths observed over the course of the study, none were believed to be related to vedolizumab
- Efficacy
  - No participants in the 75 mg dose cohort developed grade II–IV aGvHD by 100 days post allo-HSCT
  - By Day 100, three of the 21 participants in the 300 mg dose cohort developed grade II aGvHD while one developed grade III acute GvHD (location: two skin only, two skin + intestinal tract, one skin + intestinal tract + liver). Grade I intestinal aGVHD occurred in three participants
  - At 12 months following allo-HSCT, three patients had grade II aGvHD and two patients had grade III aGvHD. However, no further participants developed aGvHD of the lower intestinal tract
  - One of the four deaths observed over the 12-month course of the study was a result of aGvHD
  - In the 300 mg dose cohort at 12 months, the overall survival was 84.7% and non-relapse mortality was 5.6%
- PK profile
  - Vedolizumab IV at a dose of 300 mg was considered sufficient to maintain good α4β1 saturation. Therefore, no further dose escalation was required

Conclusions

- Vedolizumab was well tolerated and did not interfere with engraftment when combined with standard GvHD prophylaxis in patients undergoing allo-HSCT
- Despite the small study size, there were encouraging signs for a low intestinal aGVHD and overall grade III to IV aGVHD
- The heterogenous nature of clinical characteristics, such as stem cell sources and conditioning intensities, was a further limitation associated with the study
- Results from this study have justified a phase III randomized study (NCT03657160) investigating the administration of vedolizumab 300mg alongside standard GvHD prophylaxis in patients undergoing allo-HSCT

References

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