COMMENTARY

Vedolizumab provides a new hope of acute graft-versus-host disease prophylaxis through immune regulation

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the curative therapy for most of the hematologic malignancies, and more and more patients benefit from allo-HSCT and achieved long-term survival. According to the reports of Chinese Blood and Marrow Transplantation Registry (CBMTR), over 12000 patients received allo-HSCT in 2021 (Figure 1A). Acute graft-versus-host disease (aGVHD) is a major early complication following allo-HSCT and is associated with a significant higher risk of transplant-related mortality, particularly among those with lower-gastrointestinal involvement. The treatment for gastrointestinal aGVHD is difficult because of the severe gastrointestinal hemorrhage, imbalances of fluid, mal-nutrition caused by absorption obstacle, and severe infection followed by translocation of intestinal flora. Thus, it is important to prevent the gastrointestinal aGVHD, which is a serious challenge for clinical practice (Figure 1B).

Vedolizumab, a monoclonal antibody targeting the α4β7 integrin, can disrupt the homing of T cells to gut lymphoid tissue by blocking the binding of α4β7 in cell adhesion molecule-1. It can block the Th1, Th2, Th17, and Treg

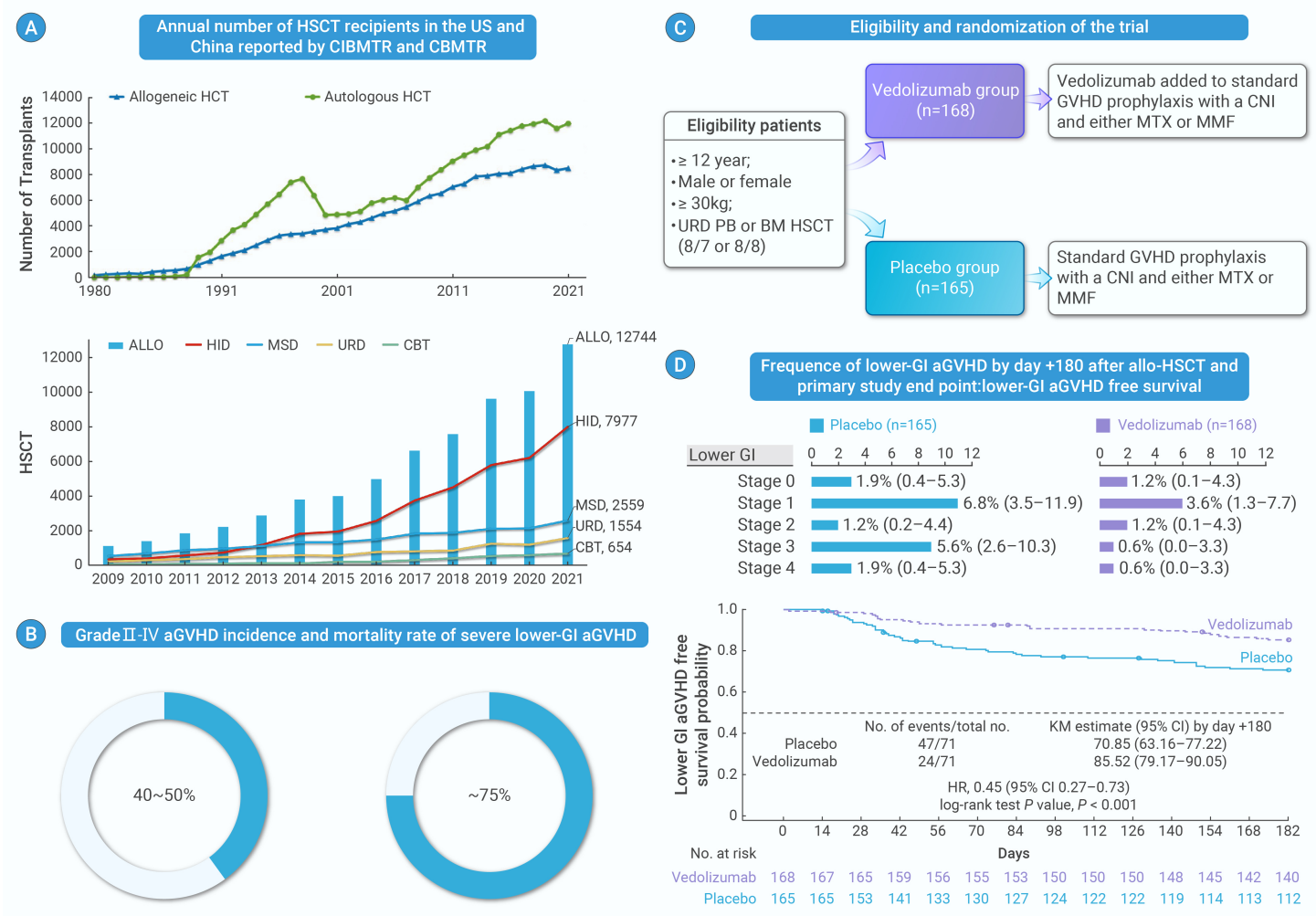

Figure 1. (A) Annual number of HSCT recipients in the US and China reported by CIBMTR and CBMTR. (B) Grade Ⅱ-Ⅳ aGVHD incidence and mortality rate of severe lower-GI aGVHD. (C) Eligibility and randomization of the trial.[2] (D) Frequence of lower-GI aGVHD by day +180 after allo-HSCT and primary study end point:lower-GI aGVHD free survival.[2]

cells homing to inflamed colon and their accumulation in the tissue, which reduces the gastrointestinal tract inflammation. Many studies have demonstrated the efficacy and safety of vedolizumab as an induction and maintenance treatment for inflammatory bowel diseases (IBD). Similarly, aGVHD is also mediated by donor effector T cells, which exit lymphoid tissues, traffic to target organs, and cause tissue damage. Some authors observed that α4β7

integrin was involved in lymphocyte trafficking in lower-gastrointestinal aGVHD, and the increase of α4β7 integrin on the surface of activated T cells was related to the subsequent occurrence of lower-gastrointestinal aGVHD.[1] This suggests that lower-gastrointestinal aGVHD shares pathogenesis similar to the IBD, and identifying adhesion molecules involved in lower gastrointestinal aGVHD provides new targets for more specific GVHD prevention. Considering that vedolizumabs can disrupt T cell homing to gut lymphoid tissue, it may be effective for the treatment and prophylaxis of lower GI aGVHD.

A phase 1b trial reported that using vedolizumab for GVHD prophylaxis reduced incidence of gastrointestinal aGVHD with well tolerance (NCT02728895). Recently, a randomized, double-blind, placebo-controlled phase 3 trial (NCT03657160) confirmed the efficacy and safety for adding vedolizumab to standard GVHD prophylaxis (i.e., calcineurin inhibitor plus methotrexate/mycophenolate mofetil). 333 patients were randomized into vedolizumab (n = 168) or placebo (n = 165) group (Figure 1C). For the primary endpoints, vedolizumab showed a significant improvement in the 180-day probability of lower-gastrointestinal aGVHD-free survival (85.5% versus 70.9%, $P < 0.001$) compared with placebo group. For the other secondary efficacy end points, vedolizumab significantly improved 180-day probability of the lower-gastrointestinal aGVHD-free and relapse-free survival, as well as the grade C–D aGVHD-free survival compared with placebo group. The incidence of treatment-related serious adverse events was comparable between the groups (6.5% versus 8.5%), particularly, the incidence of serious infections of abdominal and gastrointestinal was only 5% in vedolizumab group compared with 2% in placebo group (Figure 1D).[2] Thus far, this is the first successful randomized trial for lower-gastrointestinal aGVHD prevention which provide a new hope of GVHD prophylaxis in clinical practice.

This successful clinical trial yielded several insightful findings. Firstly, drugs targeting diseases with a similar pathophysiologic mechanism to GVHD demonstrate potential efficacy in GVHD prevention and treatment. This discovery opens up new possibilities for GVHD prophylaxis and treatment beyond the use of immunosuppressants alone.

Another important enlightenment of this study is confirming the importance of immune regulation in GVHD prophylaxis. Current strategies for aGVHD prophylaxis typically involve calcineurin inhibitors, methotrexate and/or mycophenolate mofetil. Particularly, antithymocyte globulin (ATG) or posttransplant cyclophosphamide (PTCy) is used in patients at a higher risk of GVHD (e.g., those receiving haploidentical related donor [HIDs] HSCT). Traditional, using multiple immunosuppressants is the major method to increase the efficacy of aGVHD prophylaxis, which may increase the risk of post-transplant infections and relapse offset the benefit from decreasing the GVHD.[3] Unliked the common immunosuppressants, vedolizumab disrupts the homing of alloreactive T cells and transmigration to gastrointestinal lymphoid tissue without causing severe systemic immunosuppression. Therefore, the safety of vedolizumab-based protocol is more satisfactory than traditional immunosuppressive agents. Similarly, incorporating costimulation blockade with abatacept (cytotoxic T lymphocyte antigen 4-immunoglobulin) or mesenchymal stem cell can also prevent aGVHD without increasing the risk of relapse and infections. These novel approaches provide valuable insights for future advancements in GVHD prophylaxis.

Lastly, the success of this trial may also due to a meticulously primary endpoint. Traditionally, the primary endpoint of clinical trial for GVHD prophylaxis is the incidence of grade II to IV or grade III to IV aGVHD. In this study, the primary study endpoint was designed as the lower-gastrointestinal aGVHD-free survival by day +180 after allo-HSCT. Although it is not a common endpoint, this endpoint help to focus on controlling lower-gastrointestinal aGVHD, amplify the advantage of vedolizumab, and reduce the challenge of controlling or censoring competing events. On the other hand, this compound endpoint assigns equal weightage to the lower-gastrointestinal aGVHD and death; nevertheless, certain new drugs (e.g., ruxolitinib and basiliximab) have demonstrated efficacy in treating gastrointestinal aGVHD and more an more patients with severe lower-gastrointestinal aGVHD can be cured. This may alter the significance attached to these events. Actually, 9.3% versus 4.8% patients experienced stage 3 to 4 lower-gastrointestinal aGVHD by day +365, and only 1.2% versus 0% patients died of lower-gastrointestinal aGVHD after allo-HSCT, respectively, in placebo and vedolizumab group, suggested that the assumption of lower-gastrointestinal aGVHD and death carrying equal significance may be debatable. Anyways, this confirmed that an ingenious design is critical for successful clinical trials.

This phase 3 study enrolled patients who underwent 8/8 or 7/8 human leukocyte antigen (HLA)-matched unrelated donor (URD) allo-HSCT. However, HIDs have become the most important alternative donor. Since 2019, HID HSCT accounted for over 60% of transplant cases in China.[4] Despite using ATG and/or PTCy, which significantly reduce occurrence of GVHD, HID HSCT still exhibits higher incidences of aGVHD compared with matched sibling donor HSCT. In addition, we developed a comprehensive model for predicting aGVHD in HID HSCT recipients, and the incidence of grade I to IV, grade II to IV, and grade III to IV aGVHD could be as high as 67.1%, 39.6%, and 19.4%, respectively, for the high-risk groups, which were all significantly higher than those in low-risk group. Particularly, this model can predict the risk of stage 3 to 4 gastrointestinal aGVHD after HID HSCT.[5] These present a subgroup of HID HSCT recipients with especially high risk for severe aGVHD. Consequently, it is worth of further identifying the efficacy and safety of vedolizumab-based regimen in these high-risk patients.

In summary, this study provides a new idea for preventing aGVHD after allo-HSCT, that is, by focusing on immune regulation rather than increasing the intense of immunosuppression alone. In future, studies conducted in other allo-HSCT recipients (e.g., HIDs) will further confirm the efficacy of this strategy.

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AUTHOR CONTRIBUTIONS

All the co-authors contributed equally in conceptualization, data curation, formal analysis, software, resources, funding acquisition and writing.

DECLARATION OF INTERESTS

The authors declare no competing interests.