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COMMENTARY

The Innovation Medicine

Balancing cGVHD and GVL with Axatilimab: A macrophage-targeted strategy in allogeneic transplantation

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Received: March 6, 2025; Accepted: August 12, 2025; Published Online: August 18, 2025; https://doi.org/10.59717/j.xinn-med.2025.100152

Citation: Lu H., Wang Y., Mo X., et al. (2025). Balancing cGVHD and GVL with Axatilimab: A macrophage-targeted strategy in allogeneic transplantation. *The Innovation Medicine* **3**:100152.

Chronic graft-versus-host disease (cGVHD) is a frequent, systemic, and multi-organ complication in long-term survivors of allogeneic hematopoietic stem cell transplantation (allo-HSCT), occurring in approximately 30%–70% of recipients. Distinct from acute GVHD, chronic GVHD has complex and variable clinical presentations and is characterized by persistent inflammation and fibrosis. It is also one of the leading causes of non-relapse mortality in transplant survivors. Although several new agents have been introduced into clinical practice, including ibrutinib, ruxolitinib, belumosudil, and abatacept, a durable therapeutic response remains difficult to achieve in more than half of patients, eventually resulting in irreversible end-organ impairment. An effective, durable, and well-tolerated treatment, therefore, is urgently needed.

Chronic GVHD develops through a multi-step process that is usually initiated by tissue injury. Once triggered, the injured tissue releases inflammatory cytokines and activates alloreactive donor T cells, leading to a cascade of inflammatory responses. Dysregulation of the immune response can further activate autoreactive T and B cells during the early post-transplant period, resulting in a breakdown of immune tolerance. Persistent tissue damage is accompanied by tissue repair and fibrosis, largely mediated by activated fibroblasts. Macrophages have an essential role in this process, activating fibroblasts via the secretion of transforming growth factor-β (TGF-β) and platelet-derived growth factor-α (PDGF-α).

In recent years, drug development in GVHD has mainly focused on the suppression of T-cell or B-cell activity, such as ruxolitinib, abatacept, and ibrutinib. Ruxolitinib, a Janus kinase (JAK) 1/2 inhibitor, has shown clinical efficacy in glucocorticoid-refractory cGVHD. In the REACH3 trial, nearly half of patients receiving ruxolitinib achieved an overall response at week 24. However, hematologic adverse events were common, including anemia (29.1%), thrombocytopenia (21.2%), and neutropenia (10.9%), increasing the risk of infections. Opportunistic infections, particularly fungal infections, have also been reported, necessitating clinical monitoring and prophylaxis. Abatacept, which blocks the CD28 co-stimulatory signal required for T-cell activation, demonstrated a 58% overall response rate in a phase 2 trial of steroid-refractory cGVHD. Organ-specific responses were highest in the lung (57%) and liver (54%). Ibrutinib, which inhibits both B-cell and T-cell activity, has shown efficacy in patients with steroid-refractory cGVHD who had failed prior therapies. In the PCYC-1129 trial, ibrutinib demonstrated an overall response rate of 67% and a complete response rate of 21%. A long-term follow-up study reported durable responses lasting more than 44 weeks in 55% of patients.

Such agents can partially reduce inflammation, but often carry a new risk: 1) Infection: As T-cell or B-cell-targeting agents often suppress hematopoiesis and overall immune function, many are associated with increased risks of opportunistic infections. Active screening and appropriate prophylaxis are, therefore, necessary. 2) Fibrosis: While inflammation may be alleviated by T-cell-targeting agents, fibrosis related to cGVHD is often resistant to current therapies and continues to impair patients' quality of life and overall survival. 3) Relapse: Suppressing T-cell immunity may reduce immune surveillance of residual leukemic cells, potentially increasing the risk of leukemia relapse following allo-HSCT. Therefore, Macrophages might be considered as an alternative therapeutic target, as they act both as antigen-presenting cells in cGVHD initiation and as key mediators of fibrosis via fibroblast activation.

CSF1R, also known as macrophage colony-stimulating factor receptor (M-CSFR), is a crucial regulator in the monocyte-macrophage lineage, promoting macrophage polarization toward the M2 phenotype. M2 macrophages secrete TGF-β, PDGF-α, and interleukin-10 (IL-10), and are known to suppress anti-tumor immunity and support tumor cell survival within the tumor microenvironment. While the role of CSF1R in cancer has been widely studied for decades, its importance in autoimmune diseases and in the development of GVHD has only recently been recognized. Axatilimab is a humanized high-affinity anti-colony-stimulating factor 1 receptor (CSF1R) monoclonal antibody that has recently been tested in clinical trials and shown promising efficacy.[1] Using various mouse models of cGVHD, K. Alexander *et al.* demonstrated that $CSF1R^+$ macrophages infiltrate lesion sites in both cutaneous and pulmonary cGVHD in a CSF-1/CSF1R-dependent manner, indicating a close link between tissue-infiltrating macrophages and cGVHD-associated fibrosis.[2]

Following confirmation of its effectiveness and safety in a phase I/II trial,[3] axatilimab's potential was evaluated in the AGAVE-201 study, a phase 2, multinational, pivotal, randomized trial in patients with recurrent or refractory cGVHD. A total of 241 patients who had failed at least two lines of systemic anti-cGVHD therapy were enrolled and randomly assigned to three distinct dose groups: 0.3 mg, 1 mg, and 3 mg. After the first six cycles, the overall response rates were 74%, 67%, and 50% in the 0.3 mg, 1 mg, and 3 mg dose groups, respectively. Among them, 60%, 69%, and 41% of patients achieved a clinically meaningful reduction in cGVHD symptoms, defined as more than 5 points on the modified Lee Symptom Scale (mLSS). Patients across all three groups showed rapid and durable responses to axatilimab, with a median time to response of less than 2 months and a median failure-free survival of 11.1 months. Interestingly, the 0.3 mg and 1 mg dose groups demonstrated unexpectedly better therapeutic efficacy and clinical safety compared to the 3 mg group. One possible explanation is that higher doses of axatilimab may lead to elevated CSF-1 levels, as seen in inflammation and autoimmune conditions, which may further exacerbate the inflammatory state. These findings suggest that low-dose or transient CSF1R blockade may offer a better treatment strategy, although the underlying mechanisms remain to be clarified. Organ-specific responses in AGAVE-201 were also notable. In the 0.3 mg dose group, response rates reached 89% in the lower GI tract and 82% in the upper GI tract. Lower response rates were observed in the skin (26%) and eyes (30%), while the liver and lungs showed response rates of 40% and 46%, respectively. Reductions in sclerotic skin were observed in 44%, 34%, and 60% of patients in the 0.3 mg, 1 mg, and 3 mg groups, respectively. Symptoms related to skin thickening were reported by 73%, 77%, and 68% of patients in the respective groups.

Axatilimab, as the first macrophage-targeting agent for cGVHD, shows its effectiveness on the treatment of cGVHD, and offers a different approach to solve these clinical dilemmas, that is, infection, fibrosis, and relapse. First of all, Axatilimab suppresses macrophage-mediated cGVHD while preserves

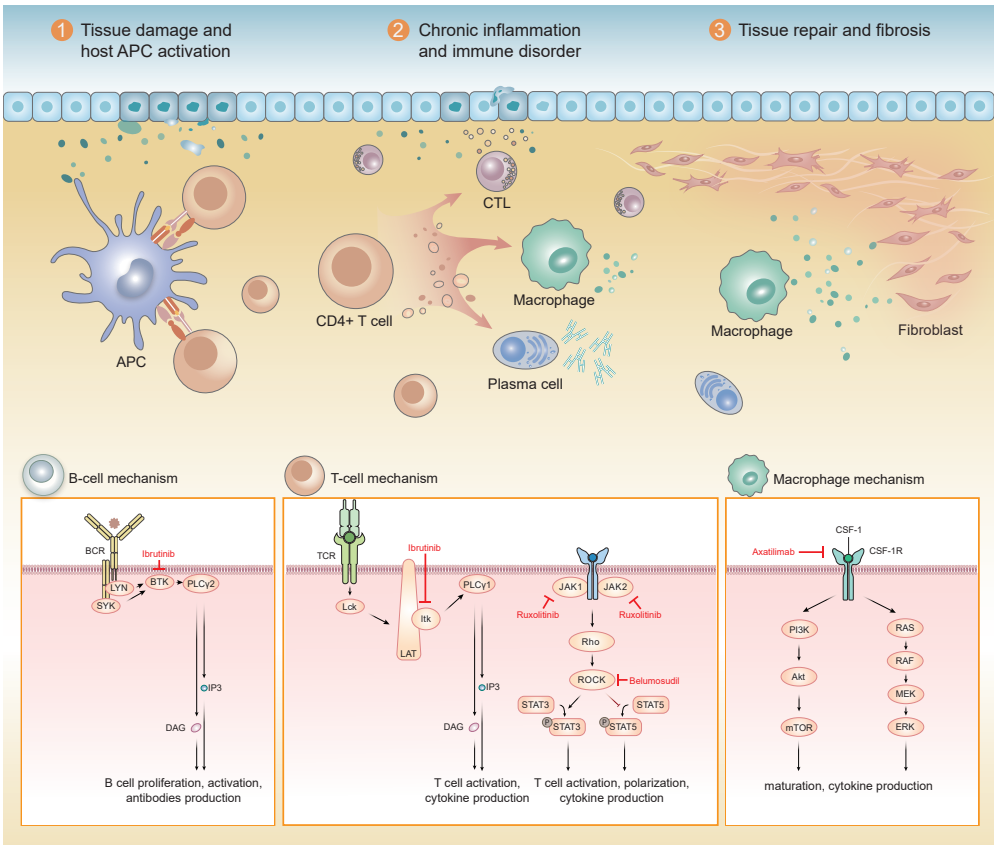

Figure 1. Schema of cGVHD development : signaling pathways and therapeutic targets.

overall immune function. According to the AGAVE-201 trial, axatilimab is associated with a lower incidence of fungal infections and viral reactivation compared to ruxolitinib, with fewer than 5% of patients developing aspergillosis or CMV/EBV reactivation. Although pneumonia was reported in approximately 10% of patients, this adverse event did not seem to be dose-dependent and may be explained by prior long-term immunosuppressive therapy.

By targeting fibrosis-promoting CSF1R signaling in macrophages, axatilimab has demonstrated effectiveness even in organs with extensive fibrotic changes. In the AGAVE-201 trial, reductions in sclerotic skin were observed in 44%, 34%, and 60% of patients in the 0.3 mg, 1 mg, and 3 mg dose groups, respectively. Symptoms related to skin thickening were reported by 73%, 77%, and 68% of patients in the respective groups. Given its dual anti-fibrotic and immunomodulatory mechanisms, axatilimab may have relevance for other fibrotic diseases. For instance, a clinical trial for the treatment of idiopathic pulmonary fibrosis has been initiated (NCT06132256). Furthermore, systemic sclerosis, a life-threatening autoimmune disease characterized by progressive fibrosis of the skin and internal organs, might be alleviated by the use of axatilimab.

Unlike conventional T-cell-targeting strategies, axatilimab preserves T-cell-mediated graft-versus-leukemia (GVL) activity. This feature makes it especially suitable for patients with cGVHD who are at high risk of relapse. In addition, as CSF1R is expressed on tumor-associated macrophages (TAMs), axatilimab may also possess anti-tumor properties. Ongoing clinical trials are currently evaluating its use in HER2-negative breast cancer (NCT06488378) and relapsed or refractory classical Hodgkin lymphoma (NCT05723055).

Approved by FDA, axatilimab was used for the treatment of cGVHD after failure of at least two prior lines of systemic therapy. It shows comparable effectiveness but higher cost (around $18,900 per month) compared to ruxolitinib (around $5,000 per month) and belumosudil (around $11,000 per 6 month). As a monoclonal antibody, the recommended administration route is intravenous injection every two weeks, which necessitates regular hospital visits. As with other monoclonal antibodies, axatilimab may cause infusion-related reactions. However, these were generally mild and led to discontinuation in only two patients. Like other agents, axatilimab is facing the problem of drug resistance. A recent preclinical study suggests that temporal IL-17 and CSF-1 signatures could be defined in cGVHD patients, and it might be helpful for the identification of non-responders and the selection of targeted agents.[4]

Overall, axatilimab fills an important gap in the current cGVHD treatment landscape. Nevertheless, several clinical questions remain. A recent trial showed that the addition of ruxolitinib to GVHD prophylaxis resulted in a lower incidence of moderate to severe GVHD and cGVHD.[5] Whether axatilimab could also be used in front-line GVHD treatment or prophylaxis is still unknown. Given its distinct mechanism of action, a combination of axatilimab with T-cell-targeted agents may be synergistic, and a clinical trial of axatilimab in combination with ruxolitinib is undergoing (NCT06388564).

In conclusion, axatilimab represents an exciting breakthrough in the management of steroid-refractory cGVHD. With its unique macrophage-targeting mechanism, it not only addresses fibrosis-related symptoms but also preserves the critical GVL effect. Future studies exploring its use as front-line therapy, in combination strategies, or for other fibrotic and autoimmune diseases are highly anticipated (Figure 1).

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by the National Key Research and Development Program of China (2022YFC2502600), the National Natural Science Foundation of China (82170206, 82170208), and Shanghai "Rising Stars of Medical Field" Outstanding Young Medical Talents Training Program (20224Z0022). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

HY.L. reviewed the literature and wrote the original draft. YW.W. reviewed and edited manuscript. XD.M. and XX.H. conceived, reviewed and edited the manuscript, and also contribute to the funding acquisition.

DECLARATION OF INTERESTS

The authors declare no competing interests.