(PF690) SOVLEPLENIB AMELIORATES APLASTIC ANEMIA THROUGH THE MODULATION OF CGAS-STING-NF-ΚB PATHWAY

Topic: 12. Bone marrow failure syndromes incl. PNH - Clinical

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Background

Aplastic anemia (AA) is a bone marrow failure syndrome characterized by pancytopenia.Aberrantly activated T lymphocytes and their excessive secretion of cytokines, particularly interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), are key drivers of this excessive hematopoietic cell apoptosis.Studies have confirmed that combining the thrombopoietin receptor agonists (TPO-RAs) eltrombopag with standard immunosuppressive therapy significantly enhances efficacy, accompanied by a significant recovery in bone marrow CD34+ cell counts and the frequency of early hematopoietic progenitor cells.However,some patients show no or insufficient response or relapse TPO-RAs may also be associated with a risk of clonal evolution, particularly the emergence of high-risk cytogenetic abnormalities.Spleen tyrosine kinase (SYK), a key mediator of immune receptor signal transduction, has garnered considerable attention due to its role in autoimmune diseases. SYK inhibitors restore immune homeostasis by blocking the B-cell receptor (BCR) and Fc receptor signaling pathways, thereby suppressing overactivated T cells, B cells and macrophages. Sovleplenib, a novel and highly selective oral SYK inhibitor, has been approved in China for the treatment of primary immune thrombocytopenia (ITP); however, its efficacy and mechanism of action in AA remain unclear.

The innate immune signaling pathway cGAS-STING plays a central role in sensing cellular damage and pathogen invasion. In AA, apoptotic debris in the bone marrow leads to abnormal accumulation of DNA. In turn, cGAS recognizes cytoplasmic DNA and catalyzes the synthesis of the second messenger cGAMP, which activates the STING protein. Persistent activation of the cGAS-STING pathway has been shown to mediate tissue inflammation and drive hematopoietic stem cell exhaustion.This mechanism provides a molecular explanation for the susceptibility of certain patients with DNA repair disorders to bone marrow failure.Furthermore, it offers a novel theoretical perspective on the immunopathological mechanisms of AA.

Aims

To investigate the therapeutic potential of sovleplenib, a selective SYK inhibitor, in aplastic anemia (AA), focusing on its effects on immune modulation and the cGAS-STING-NF-κB inflammatory axis.

Methods

An immune-mediated AA mouse model was established and treated with sovleplenib. Hematopoietic function was assessed via peripheral blood counts and bone marrow mononuclear cell (BMNC) counts. Immune cell profiles were analyzed by flow cytometry. Cytokine levels were measured by ELISA. Underlying mechanisms were explored through proteomics and Western blotting.

Results

Sovleplenib treatment significantly improved peripheral blood counts (HGB, WBC, PLT) and BMNCs, and reduced bone marrow fat vacuolation. It corrected immune imbalance by increasing the $CD4^+/CD8^+$ T-cell ratio and decreasing the M1/M2 macrophage ratio, promoting an M2 phenotype. Concurrently, it elevated Arg-1 level while suppressing ROS, TNF-α, and IFN-β. Mechanistically, sovleplenib inhibited the activation of key pathway components (cGAS, STING, p-TBK1, p-p65).

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Summary/Conclusion

The results demonstrate sovleplenib's dual role in promoting hematopoiesis and immunomodulation. Its efficacy is mechanistically linked to the suppression of the overactivated cGAS-STING-NF-κB pathway, a key driver of inflammation in AA

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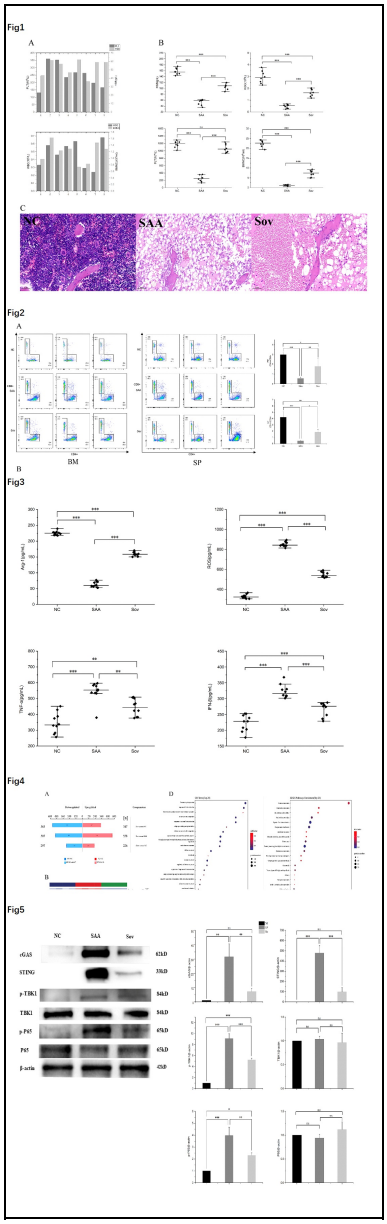


Figure Legends Fig. 1 Sovleplenib treatment significantly improves peripheral blood parameters and bone marrow hematopoietic function in AA mice. (A) Counts of HGB, WBC, PLT, and BMNC in the NC, AA, and Sov groups(n=8) (*P < 0.05, **P < 0.01, ***P < 0.001). (B) Representative sternal bone marrow histology in the NC, AA, and Sov groups (20×, H&E staining). Fig. 2 Sovleplenib promotes bone marrow hematopoietic stem/progenitor cell recovery and modulates immune cell imbalance. (A) Flow cytometric analysis of the $CD4^+/CD8^+$ T cell ratio in bone marrow and spleen of NC, AA, and Sov groups. (B) Flow cytometric analysis of the M1/M2 macrophage ratio in bone marrow and spleen of NC, AA, and Sov groups. (*P < 0.05, **P < 0.01, ***P < 0.001) Fig. 3 Plasma levels of Arg-1, ROS, TNF-α, and IFN-β in mice from each group measured by ELISA. (n=8) (*P < 0.05, **P < 0.01, ***P < 0.001) Fig. 4 Proteomic analysis of NC, AA, and Sov groups. (A) Bar chart showing quantitative differences in protein expression among NC, AA, and Sov groups. (B) Heatmap of differentially expressed proteins across NC, AA, and Sov groups. (C) Volcano plot of differentially expressed proteins between the AA and Sov groups. (D) GO enrichment (Biological Process) and KEGG pathway enrichment bubble plots for all differentially expressed proteins in the Sov versus AA groups. Fig. 5 Western blot analysis of cGAS, STING, p-TBK1, TBK1, p-NF-κB p65, and NF-κB p65 protein expression in femoral bone marrow of mice from each group. (*P < 0.05, **P < 0.01, ***P < 0.001)

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