COMPARATIVE EFFICACY AND SAFETY OF NEXT-GENERATION JAK INHIBITORS (FEDRATINIB, PACRITINIB, AND MOMELOTINIB) IN MYELOFIBROSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Basil Joy[1], Jeffrey Mathew Boby[1], Esha Umair[2], Ajina Joy[1], Vijay Murali[3]
1 Government Medical College Kozhikode, Kozhikode, India
2 Nishtar Medical University, Multan, Pakistan
3 Stanley Medical College, Chennai, India

INTRODUCTION

Myelofibrosis is a high-risk myeloproliferative neoplasm marked by progressive splenomegaly, debilitating constitutional symptoms, and disease-related anemia. Ruxolitinib was the first-approved JAK inhibitor, but three newer agents — fedratinib, pacritinib, and momelotinib — now address distinct unmet needs. Comprehensive comparative evidence across efficacy and safety domains has remained limited, particularly in anemic or severely thrombocytopenic patients.

AIM

To compare the efficacy and safety of fedratinib, pacritinib, and momelotinib versus ruxolitinib, placebo, or best available therapy in adults with intermediate- or high-risk primary or secondary myelofibrosis.

METHOD

Systematic review and meta-analysis of RCTs and prospective studies of fedratinib, pacritinib, or momelotinib vs. ruxolitinib, placebo, or best available therapy.

- 9 studies included (N = 1,917): JAKARTA, JAKARTA2, FREEDOM2 (fedratinib); PERSIST-1, PERSIST-2 (pacritinib); SIMPLIFY-1, SIMPLIFY-2, MOMENTUM (momelotinib); plus a supporting network meta-analysis
- Primary endpoints: spleen volume reduction ≥35% (SVR35) and symptom response ≥50% (TSS50) at week 24
- Secondary endpoints: transfusion independence (TI) and grade ≥3 hematologic/nonhematologic toxicity
- Pooled risk ratios estimated via random-effects DerSimonian–Laird model

CONCLUSIONS

Next-generation JAK inhibitors show significant, consistent efficacy over comparators. Fedratinib leads on spleen and symptom endpoints; momelotinib offers a reproducible transfusion-independence benefit in anemic patients; pacritinib fills a therapeutic gap in severe thrombocytopenia.
These findings support a precision-based, biomarker-informed treatment selection strategy, with anemia and platelet count as primary decision variables.

RESULTS

Overall Efficacy
All three agents significantly outperformed comparators for spleen volume reduction ≥35% (pooled RR 3.84; 95% CI, 2.1–7.0; I^2=62%) and symptom response ≥50% (pooled RR 2.72; 95% CI, 1.7–4.4; I^2=74%).
Fedratinib achieved the highest absolute spleen response rates: 47% in JAK inhibitor–naïve patients and 36% post-ruxolitinib (drug-specific RR 5.8).
Momelotinib uniquely achieved superior transfusion independence across all three phase 3 trials (pooled RR 1.64; 95% CI, 1.12–2.41; I^2=28%; P=0.011), with substantially lower grade ≥3 anemia versus ruxolitinib (14% vs 38%, SIMPLIFY-1).
Pacritinib provided clinically meaningful spleen and symptom responses (SVR35 18%–19%) with a favorable hematologic safety profile in severely thrombocytopenic patients (platelets <50×10⁹/L).
Observed heterogeneity was attributable to differences in comparator type, line of therapy, and patient population rather than trial quality.

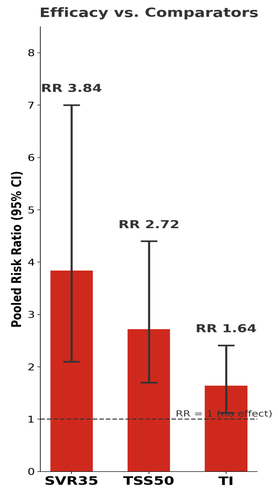

Figure 1. Pooled risk ratios (RR) and 95% CI for spleen response (SVR35), symptom response (TSS50), and transfusion independence (TI) vs. comparators.

ACKNOWLEDGEMENTS

The authors declare no conflicts of interest and received no specific funding for this study.

CONTACT INFORMATION

Email: drbjoe@gmail.com

REFERENCES

Trials pooled in this meta-analysis:
JAKARTA • JAKARTA2 • FREEDOM2 • PERSIST-1 • PERSIST-2 • SIMPLIFY-1 • SIMPLIFY-2 • MOMENTUM • Supporting network meta-analysis