MODULATION OF HEPCIDIN PATHWAY PRODUCES HOMOGENOUS ERYTHROPOIETIC SUPPRESSION BUT HETEROGENOUS IRON REPLETION IN POLYCYTHEMIA VERA: LESSONS FROM REVIVE AND IMPRSSION.

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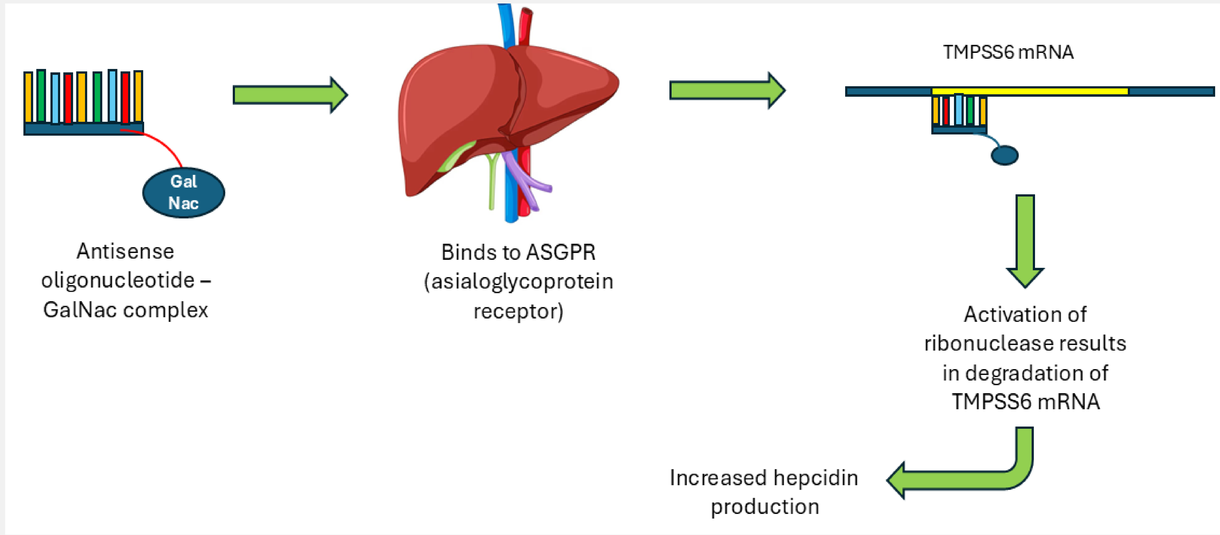
BACKGROUND

- Phlebotomy has long served as a cornerstone in controlling the excess erythrocytosis seen in polycythemia vera (PV). Agents under clinical investigation harness the hepcidin pathway to restrict iron resulting in a "**chemical phlebotomy**".
- Rusfertide, a hepcidin mimetic, and sapablursen, a TMPRSS6 antisense oligonucleotide are two such emerging therapies.

METHOD

- A total of 119 patients with phlebotomy dependent disease PV (± cytoreductive therapy) from IMPRSSION and part-1 of REVIVE trial (49 and 70 respectively) were included.
- We used Cohen's *d* to calculate the effect size of HCT and ferritin using pooled standard deviations (SD).



Intrinsic hepcidin induction using antisense oligonucleotide therapy in polycyhermia vera.

RESULTS

- Hepcidin-iron axis modulation using rusfertide and sapablursen in respective trials resulted in a fall in HCT and a rise in ferritin levels ($p<0.05$).
- HCT and ferritin levels corresponded to a moderate to large effect size with Cohen's $d \approx -1.25$ and $d \approx +1.35$ respectively in REVIVE, and $d \approx -1.11$ and $d \approx +0.71$ respectively in group-A of IMPRSSION trial, while group-B showed a negligible effect size.
- Despite the concordant directionality of HCT and ferritin responses, their variability patterns diverged across all groups. HCT SD contracted with treatment, indicating the patients converged toward a uniform hematological response while ferritin SD expanded, reflecting increasingly heterogenous iron repletion trajectories, thus highlighting uncoupling between suppression of erythropoiesis and recovery of iron stores.

CONCLUSION

- ***We show that a control of HCT is linked to an increase in ferritin when two mechanistically distinct agents modulating hepcidin-iron axis suppress erythropoiesis in PV.***
- ***While interpatient variability in HCT was narrow, increase in ferritin levels are more heterogenous.***
- ***Hence, HCT response does not reliably predict iron repletion status. Individualized monitoring of iron parameters continues to be important to mitigate the symptoms from an iron deficient state.***

REFERENCES

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