PL-08, Crosstalk between Renin-Angiotensin System and Neuropilin Pathways in Adjuvant-Induced Rheumatoid Arthritis in Rats

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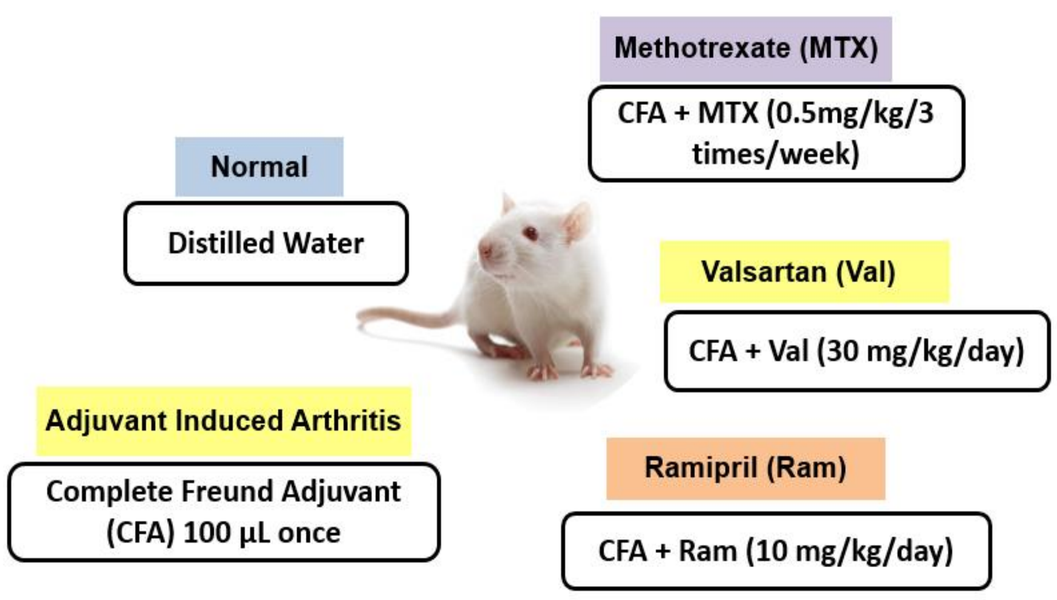
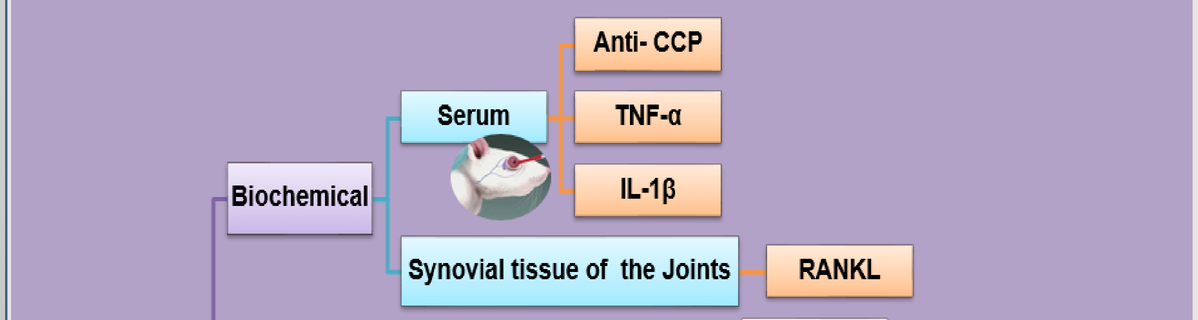
Introduction

Rheumatoid Arthritis (RA) is a serious autoimmune disease, characterized by aggressive synovial hyperplasia causing articular joint destruction. The renin-angiotensin system (RAS) is an important inflammation and tissue damage modulator whose components are expressed in the synovial tissues. Neuropilin-1 (NRP-1) is also expressed in synovial tissue and was recently found to be involved in RA pathogenesis. In our study, we studied the crosstalk between RAS and NRP-1 pathways in RA by testing the influence of RAS disruption, using valsartan/ramipril, on NRP-1 ligands binding, dimerization, and downstream signaling. The potential efficacy of valsartan/ramipril on RA regression was compared to the standard of care; methotrexate.

Materials and Methods

Rats were randomly divided into 5 groups (6 rats each)





Statistical Analysis

Data were expressed as means ± S.E. Statistical significance was taken as $p<0.05$, using one-way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test to verify the difference between various groups.

Results

Biochemical Markers

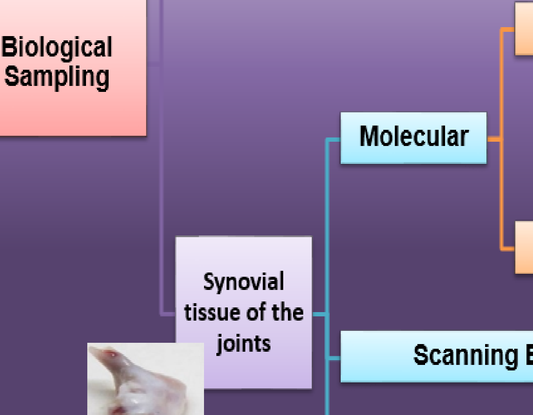


Fig.1: Effect of MTX, Val, Ram on serum Anti-CCP Levels.

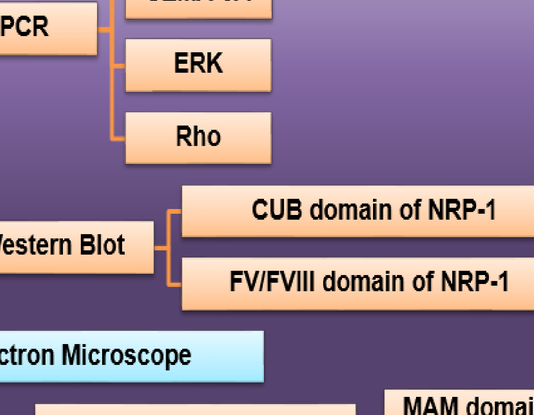


Fig.2: Effect of MTX, Val, Ram on serum TNF-α Levels.

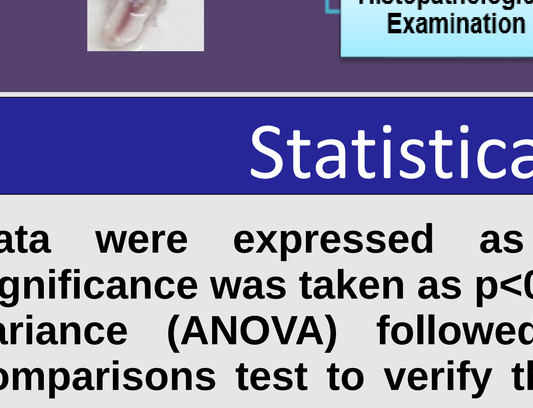


Fig.3: Effect of MTX, Val, Ram on serum IL-1β Levels.

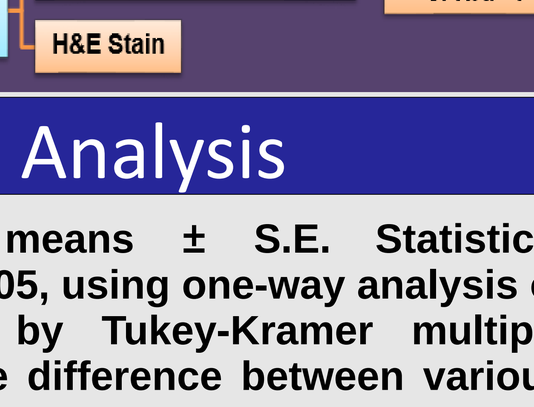


Fig.4: Effect of MTX, Val, Ram on RANKL Levels in joint tissue.

PCR and Western Blot

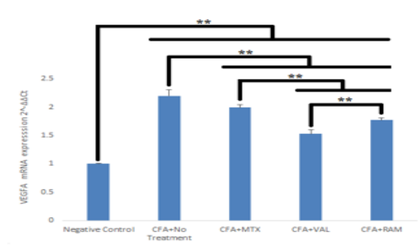


Fig.5: Effect of MTX, Val, Ram on VEGFA mRNA expression.

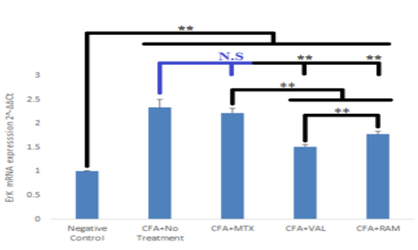


Fig.6: Effect of MTX, Val, Ram on Erk mRNA expression.

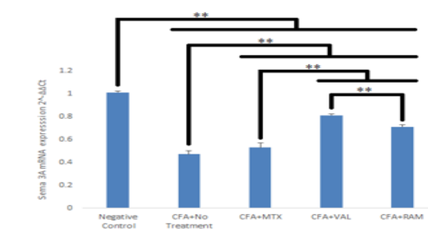


Fig.7: Effect of MTX, Val, Ram on Sema 3A mRNA expression.

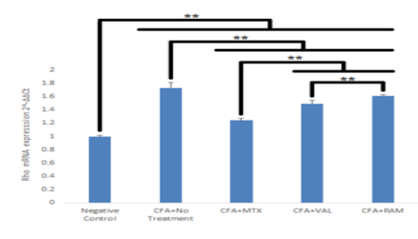
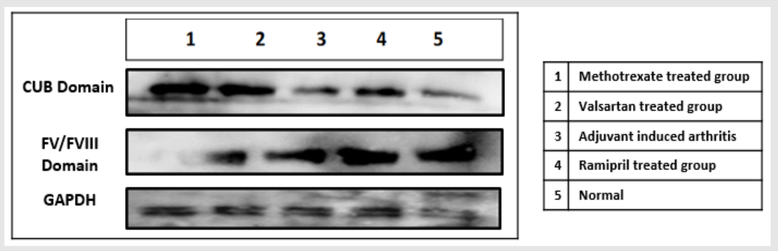


Fig.8: Effect of MTX, Val, Ram on Rho mRNA expression.



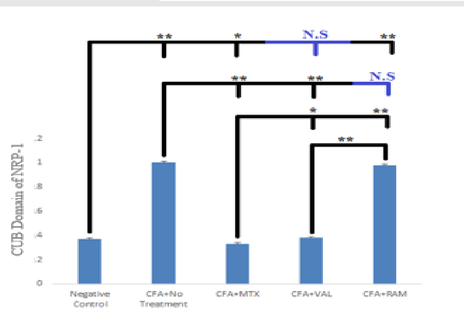


Fig.9: Effect of MTX, Val, Ram on CUB domain of NRP-1

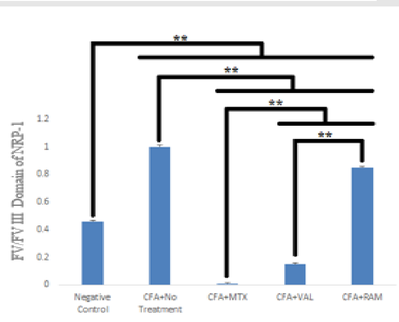


Fig.10: Effect of MTX, Val, Ram on FV/FVIII domain of NRP-1

Scanning Electron Microscope

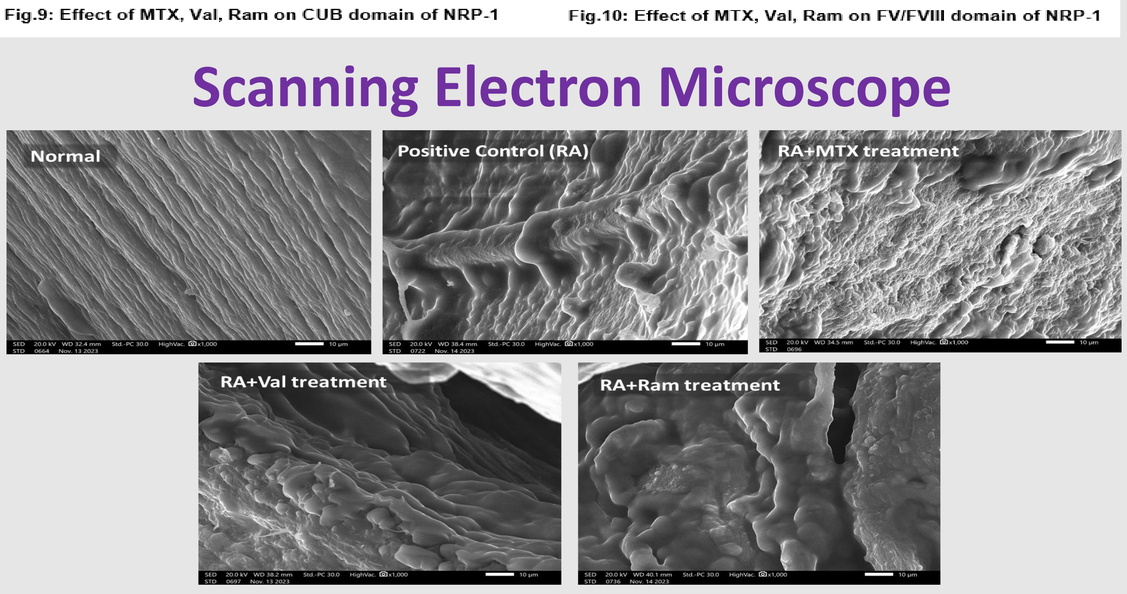


Fig.11: Effect of MTX, Val, and Ram on Interior synovium membrane

Histopathological Examination

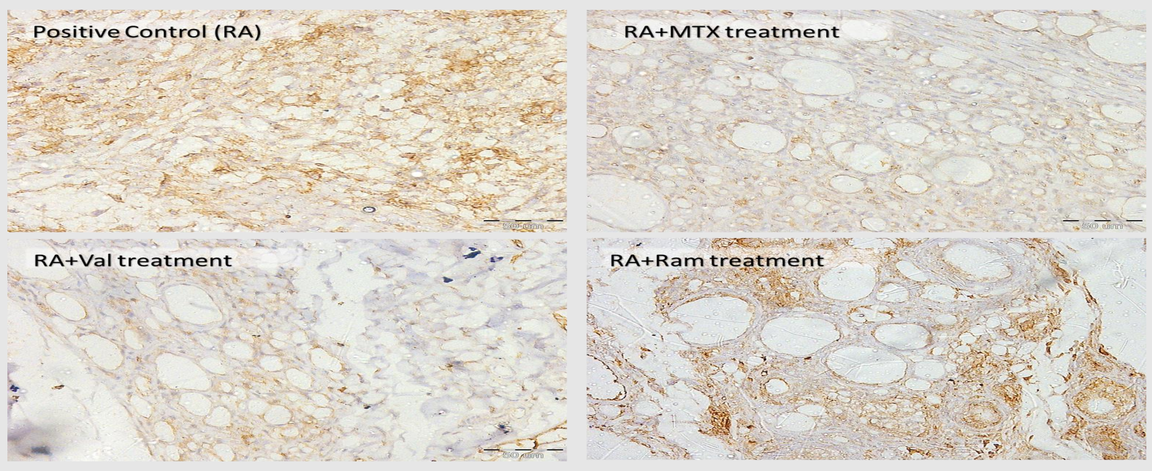


Fig.12: Effect of MTX, Val, and Ram on NRP-1 dimerization region immunostaining – Ossification zone

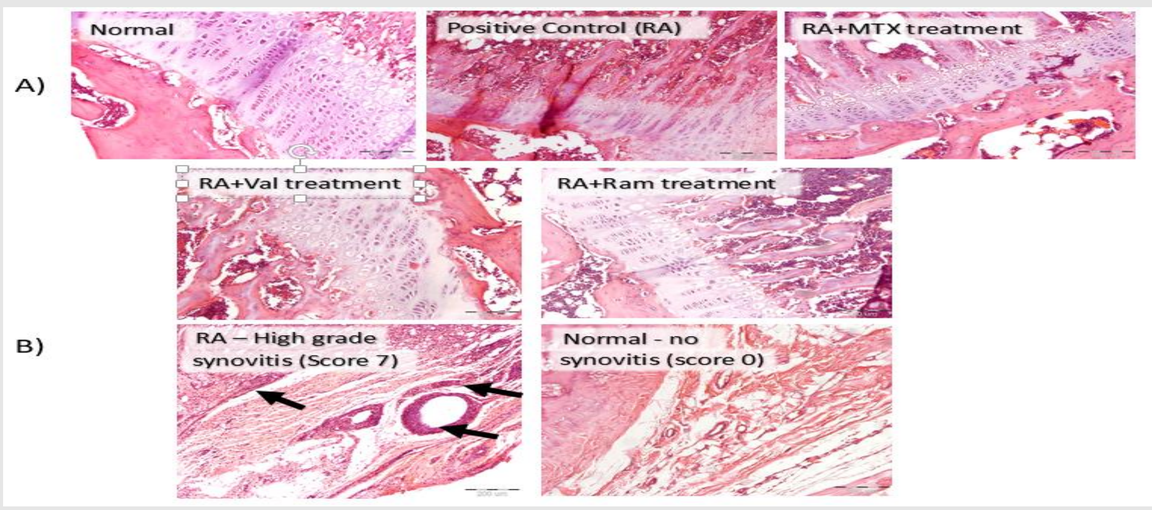


Fig.13: H&E histopathological staining. A: endochondral ossification zone, B: Synovial membrane (Arrows points to immune cells infiltration)

Conclusion

Angiotensin receptor blockade has a great impact on NRP-1 signaling at ligand, receptor, and signal transduction levels with potential efficacy for RA treatment.

References

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