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"Evaluation of the potential nephroprotective effect of phosphodiesterase 4B inhibition on Cyclosporine induced nephrotoxicity in male rats"

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Introduction

Cyclosporine, a potent immunosuppressant, used to prevent organ rejection in transplant recipients. However, its application is limited by nephrotoxicity. This study explores nephroprotective approaches using apremilast, a PDE4 enzyme inhibitor, to mitigate the nephrotoxic effects of cyclosporine, a potent immunosuppressant used in transplant recipients and treating autoimmune disorders.

Materials and Methods

Four groups of male Sprague-Dawley rats were randomly assigned.

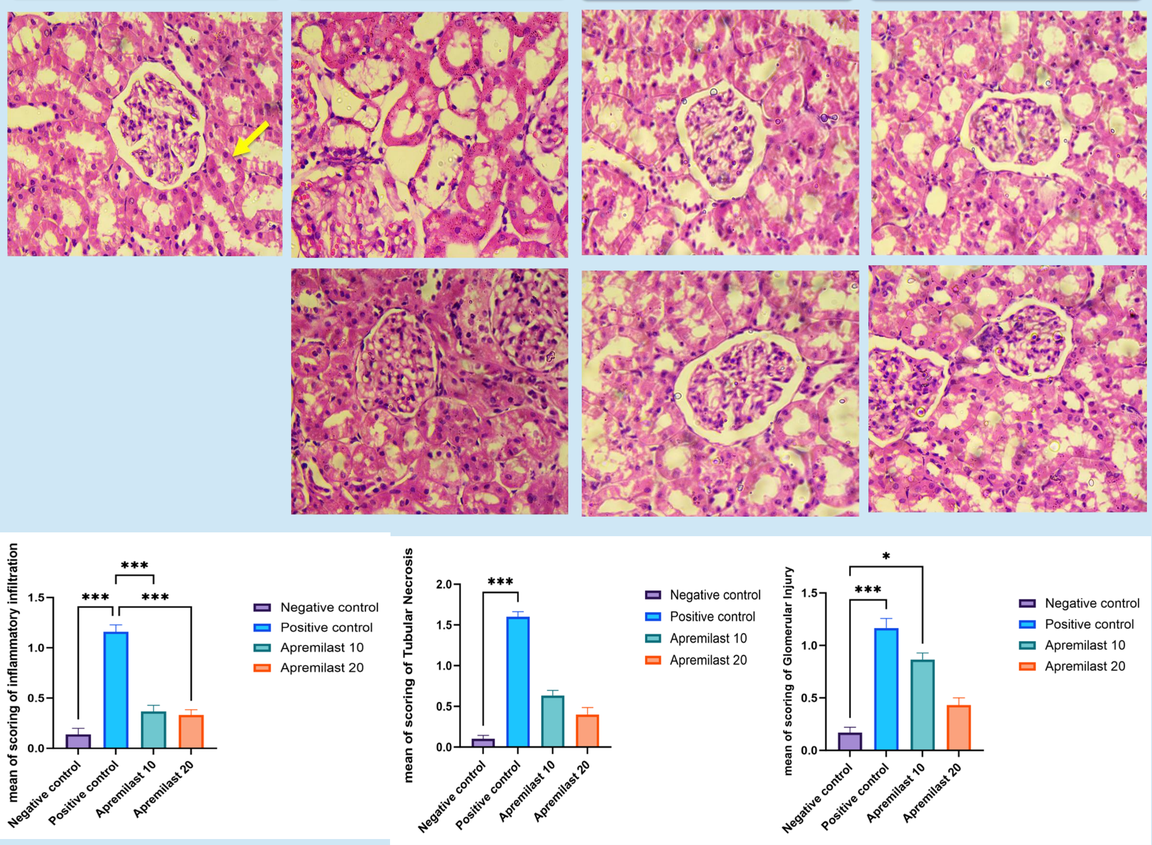
1- The negative control group received DMSO/cremophor.

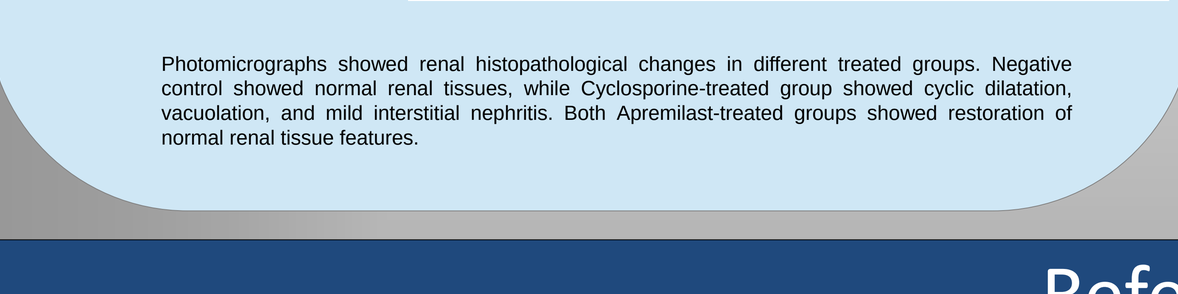
2- The positive control group was administered cyclosporine 20 mg/kg/day only, starting from day 4 till day 14.

3- The third group was treated with Apremilast orally with a dose 10 mg/kg/day.

4- The last group was treated with Apremilast orally with a dose 20 mg/kg/day.

Serum samples were collected at baseline, day 8, and day 14 for urea and serum creatinine analysis. After 14 days, the rats were euthanized, and kidney tissue samples were collected. H&E dye was used for histopathological investigations, and PDE4B Monoclonal Antibody staining was used for immunohistopathology





Photomicrographs showed renal histopathological changes in different treated groups. Negative control showed normal renal tissues, while Cyclosporine-treated group showed cyclic dilatation, vacuolation, and mild interstitial nephritis. Both Apremilast-treated groups showed restoration of normal renal tissue features.

Results

Apremilast effectively ameliorated cyclosporine-induced nephrotoxicity in both treatment groups, as evidenced by a reduction in serum creatinine and urea levels. Additionally, the normal histological features of renal tissue were restored in the groups treated with apremilast. Furthermore, there was a significant decline in the expression of PDE4B, a key trigger of inflammation, compared with its elevated expression in the positive control group

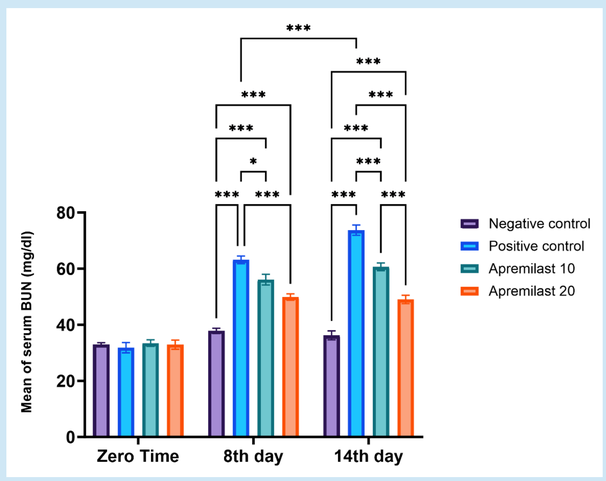


Fig. Effect of different doses of the PDE4 inhibitor, apremilast, against CsA-induced nephrotoxicity on blood urea nitrogen (mg/dl) at zero time and 4 days before treatment with CsA and for the following 10 days after it

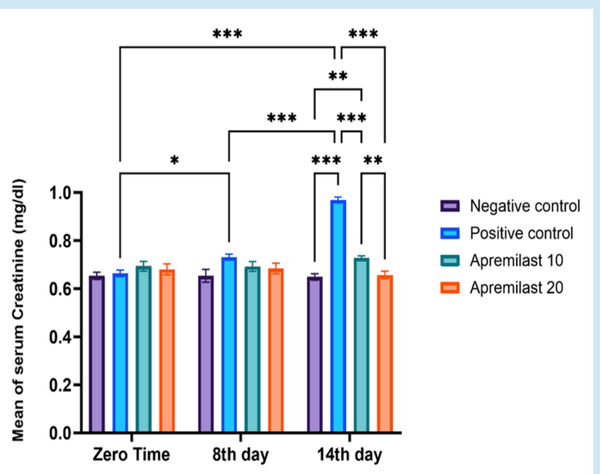


Fig. Effect of different doses of the PDE4 inhibitor, apremilast, against CsA-induced nephrotoxicity on serum of Creatinine (mg/dl) at zero time and 4 days before treatment with CsA and for the following 10 days after it

Fig. photomicrograph showing negative reaction for PDE4B in renal tubular epithelium (IHC-peroxidase –DAB)

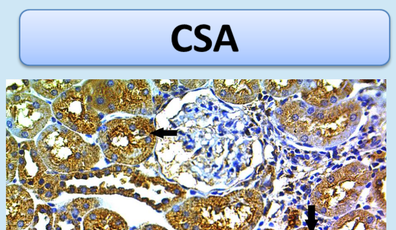


Fig. photomicrograph showing strong positive reaction for PDE4B in one of renal tubular epithelium (arrows) (IHC-peroxidase –DAB)

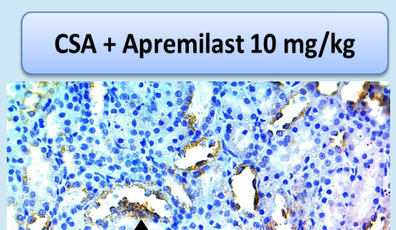


Fig. photomicrograph showing mild positive reaction for PDE4B in renal tubular epithelium (arrow) (IHC-peroxidase –DAB)

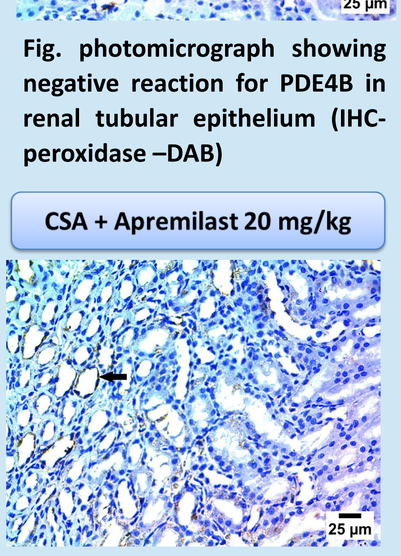


Fig. photomicrograph showing mild positive reaction for PDE4B in renal tubular epithelium (arrow) (IHC-peroxidase –DAB)

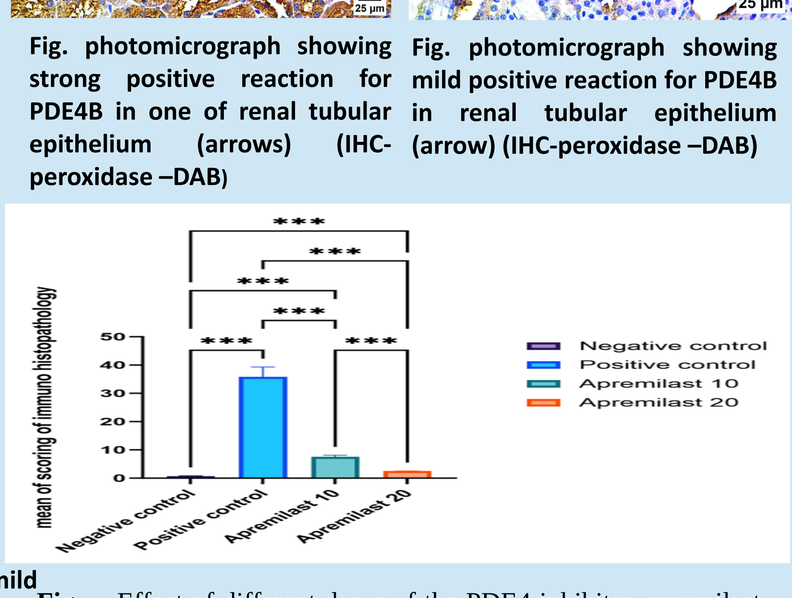


Fig. Effect of different doses of the PDE4 inhibitor, apremilast, against CsA-induced nephrotoxicity on the scoring of immune histopathology investigation

Conclusions

Our findings suggest that apremilast represents a promising therapeutic tool against cyclosporine-induced nephrotoxicity.

References

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