

# Therapeutic effect of gevokizumab, an anti-IL1 $\beta$ mAb, in a mouse model of anti-GBM glomerulonephritis

Thiago T Maciel<sup>1</sup>, Aurélie Fricot<sup>1</sup>, Renato C Monteiro<sup>2</sup>, Ivan C Moura<sup>1</sup>.

<sup>1</sup>INSERM U1163, Imagine Institute, Paris, France.

<sup>2</sup>INSERM U1149, Center for Research on Inflammation, Paris, France.

## OBJECTIVES

- Glomerulonephritis (GN) is one of the main causes of end-stage renal disease.
- Experimental GN induced by serum against glomerular basal membrane (GBM) is a well-recognized experimental model to induce rapidly progressive GN in rodents.
- It results in an immediate inflammatory response characterized by an early infiltration of the innate immune system into the kidney and the involvement of several cytokines.
- Among these, IL-1 $\beta$  plays an important role in the clinical development of renal injury.
- **Gevokizumab is a recombinant humanized monoclonal antibody targeting human IL-1 $\beta$** , which was shown to prevent renal inflammation in this model in mice. (1)
- **This study assesses whether gevokizumab can limit the progression of renal inflammation in more severe conditions i.e. when mice present with overt albuminuria.**

## METHODS

- **Induction of GN:** C57BL/6J mice (8/group) pre-immunized with normal goat IgG in complete Freund's adjuvant 4 days before an intravenous administration of anti-GBM serum.
- **Treatments:** started 3 days after administration of anti-GBM serum when mice had significant albuminuria (ACR >2 mg/mmol), up to day 14. Mice received **gevokizumab (S78989) i.p. (1 and 10 mg/Kg)** or a **control IgG2 (anti-KLH) every 3 days (4 injections)** or **oral prednisolone (1 mg/kg) daily** as a positive control.
- **Kidney damage:** assessed at day 14 by measuring albuminuria, proteinuria, serum and urinary NGAL and BUN. Inflammatory cytokines IL-1 $\beta$ , TNF- $\alpha$ , IL-6, CCL2 and CRP were measured in serum. Data were analyzed by an ANOVA followed by a post-hoc Dunnett test.
- **Glomerular and tubular injuries:** evaluated on kidney sections after Masson Trichrome and Sirius Red stainings.
- **Myeloid cell infiltration:** verified by immunohistochemical staining with CD11b antibodies.
- **Renal fibrosis :** assessed by collagen type I Western blot.

## RESULTS

At day 14, mice treated with gevokizumab at 10 mg/kg showed:

- significantly **lower ACR** than mice treated with a control IgG2 ( $10.3 \pm 1.2$  mg/mmol vs  $18.9 \pm 3.0$  mg/mmol,  $p < 0.01$ ).
- decreased proteinuria, BUN and urinary NGAL compared to control IgG2 group (non significant effect)
- significantly **reduced serum NGAL** ( $667 \pm 84$  ng/ml vs  $1131 \pm 126$  ng/ml in control IgG2,  $p < 0.01$ ).
- significantly **decreased serum levels of:**  
**CRP** ( $10.8 \pm 1.4$  vs  $15.8 \pm 1.1$   $\mu$ g/ml in control IgG2 group,  $p < 0.05$ ),  
**CCL2** ( $8.6 \pm 0.9$  vs  $14.5 \pm 1.7$  ng/ml in control IgG2 group,  $p < 0.01$ ),  
**TNF $\alpha$**  ( $1.4 \pm 0.2$  vs  $2.4 \pm 0.3$  ng/ml in control IgG2 group,  $p < 0.05$ ).
- decreased IL-1b and IL-6 (non significant)

Histological analysis confirmed that gevokizumab at 10 mg/kg **decreased glomerular and tubulointerstitial injuries**, and **attenuated the infiltration of CD11b+ cells and collagen type I deposition** when compared to control IgG2.

## CONCLUSIONS

Overall, results obtained showed that gevokizumab improved markers of renal damage and inflammation through the limitation of the inflammatory processes in a severe model of renal injury, validated with prednisolone (effective in all parameters).

**This study confirmed that gevokizumab might have a therapeutic role in the limitation of renal injury and fibrosis, by decreasing the inflammation induced in a mouse model of anti-GBM disease even after the onset of renal inflammation. Gevokizumab might be useful as a potential therapy for GN and renal pathologies involving inflammation.**

(1) T Maciel T, et al. Nephrology Dialysis Transplantation 29 (Supplement 3): iii25–iii26, 2014

thiago.trovati@inserm.fr

