Introduction and Aims

Emapticap pegol (NOX-E36) is a Spiegelmer®. i.e. a PEGylated L-RNA oligonucleotide (Figure 1) that specifically birds and inhibits an pro-inflammatory chemokine CCL2 (MCP-1), which plays a major role in monocyte/macrophage infiltration in the kidney and thus in the pathophysiology of diabetic nephropathy. Emapticap was well tolerated in single and repeat dose Phase I studies in healthy volunteers and diabetics and first hints indicating a renoprotective effect were obtained. The objective of this study was to establish the renoprotective and antidiabetic potential of emapticap in type 2 diabetic patients with proteinuria.

Methods

A randomized, double blind, placebo-controlled multi-site phase IIa POC study in five European countries was initiated in 76 type 2 diabetic patients. The study had to be on stable antidiabetic therapy and RAS blockade and had to present with an ACR >100 mg/g, an eGFR>25 mL/min × 1.73 m² and an HbA1c from 6.0% to 10.5%. Emapticap was administered SC at 0.5 mg/kg twice weekly for 12 weeks, followed by a treatment-free observation period of 3 months (Figure 2). In addition to analysis of the full patient set (FAS), a post hoc analysis was performed for which patients with major protocol violations, treatment with dual RAS blockade and concomitant hematuria and leukocyturia were excluded (primary efficacy analysis set, PEAS).

Results

Emapticap pegol was generally well tolerated, with few mild local injection site reactions as the only relevant treatment-related AEs. Plasma concentrations reached pharmacologically relevant levels of 355 ± 105 nM (Figure 3) and the expected pharmacodynamic effect was observed, i.e. a decrease in the number of monocytes in peripheral blood which is maintained throughout the whole treatment period and a re-increase back to baseline after stop of dosing. Furthermore, the presence of the CCL2 receptor CCR2 on the monocytes was reduced during treatment with emapticap (Figure 4).

Conclusions

Prolonged treatment with emapticap is generally well tolerated, leads to a decrease in the number of monocytes in peripheral blood and their expression of CCR2, and reduces urinary albumin excretion as well as HbA1c in type 2 diabetics with albuminuria.

The sustained effect on albuminuria even after cessation of treatment indicates that important pathophysiological mechanisms of diabetic nephropathy are influenced. This differentiates emapticap from existing therapeutic strategies and indicates the disease-modifying potential of the drug.

In contrast to approved drugs and other novel approaches in this indication, emapticap’s effect on urinary albumin excretion is not associated with changes of blood pressure or eGFR.

The results support an important role of CCL2 and inflammatory mechanisms in the pathogenesis of diabetic nephropathy. Further research to prove emapticap’s potential for prevention of end stage renal disease and cardiovascular events and to further delineate its anti-inflammatory mode of action in the diabetic milieu is clearly warranted.

Disclosures

H Haller and J Menne were investigators in the emapticap study, supported by NOXXON Pharma AG. D Eulberg is an employee and M Baumann is a board member of NOXXON Pharma AG.

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