Circulating TNF receptor levels and renal disease progression in patients with type 2 diabetic nephropathy and blockade of the renin angiotensin system

Authors: Fernández-Juárez G[1], Villacorta J[1], Cachofeiro V[2], Praga M,[3]Barrio V,[4]Tato A,[1] J. Luño [5] on behalf of the investigators of PRONEDI study

[1]Hospital Universitario Fundacion Alcorcón. [2]Facultad Medicina. Universidad Complutense. [3]Hospital 12 Octubre. [4] Hospital Infanta Sofia
[5]Hospital Gregorio Marañón

INTRODUCTION

In the past decade, a number of important research developments in the area of Diabetes Mellitus (DM) and its complications have changed the way we think about this disease. We now know that diabetes mellitus in not only a metabolic disorder and that diverse molecules related to inflammation and innate immune system play a significant rol in the development of diabetes. Several studies have supported the role of some proinflammatory cytokins in the pathogenesis of DM [1,2]: IL6, IL-18, Monocyte chemoattractant protein 1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), transforming growth factor-α (TNFα) …. TNFα is an inflammatory cytokine involved in pro-inflammatory cytokine induction .

The function of TNF is relayed by two structurally distinct receptors, TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). Circulating levels of these soluble receptors have recently emerged as a very robust and independent predictors of the progression of diabetic kidney disease

The purpose of this study has been to analyze the association between circulating levels of TNFR1 and TNFR2 and progression of type II DN in a substudy of the Spanish Progression de Nefropatía Diabética (PRONEDI) trial[10], which was designed to compare the efficacy of combining the angiotensin-converting enzyme inhibitor (ACEi) lisinopriland the ARB irbesartan with the efficacy of each drug in monotherapy (at high and equipotent doses) for slowing progression of kidney disease in patients with established type II diabetic nephropathy (DN).. aim to know if the treatment with drugs that blockage renin angiotensin have any effect on the circulating levels of TNFR1 and TNFR2.

METHODS

We measured circulating of soluble TNF receptor (sTNF-R1) and TNF receptor 2 (sTNF-R2) levels at baseline, 4 and 12 months in 103 patients during the years 2006 to 2011 included in a multicenter randomized controlled trial (EUDRACT 2004-002470-31) . After the washout period, patients were randomly assigned (1:1:2) to receive once-daily doses of lisinopril (10 mg), irbesartan (150 mg), or the combination (lisinopril 5 mg + irbesartan 75 mg), along with conventional antihypertensive therapy. The dose was titrated up to the maximum recommended study dose after 8 weeks (lisinopril 40 mg; irbesartan 600 mg; lisinopril+irbesartan 20+300 mg).

We included 101 patients with type II diabetes and a clinical diagnosis of DN, stage 2 or 3 CKD, and an urinary protein/creatinine ratio (UPCR) ≥300 mg/g (morning urine spot) on two separate occasions.

RESULTS

Hazard ratios of the primary endpoint (>50% increase in serum creatinine concentration, ESRD, or death)

		HR	95% CI
TNFR1 level	(quartil 4 vs quartil 1-3)	2,3	1,02-5,23
Age (years)		1,007	0,95-1,058
eGFR (m/min/1,73m2)		0,977	0,64-1,007
Proteinuria > 1.5 g/24 hours		4,47	1,50-13,268

Figure 1. Cumulative risk of ERSD or dead in patients with DN type 2 according to quartiles of circulating levels of TNFR1 (A) and TNFR2 (B) at baseline examinations

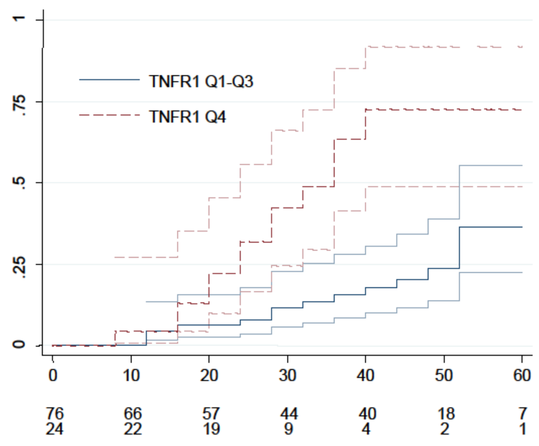
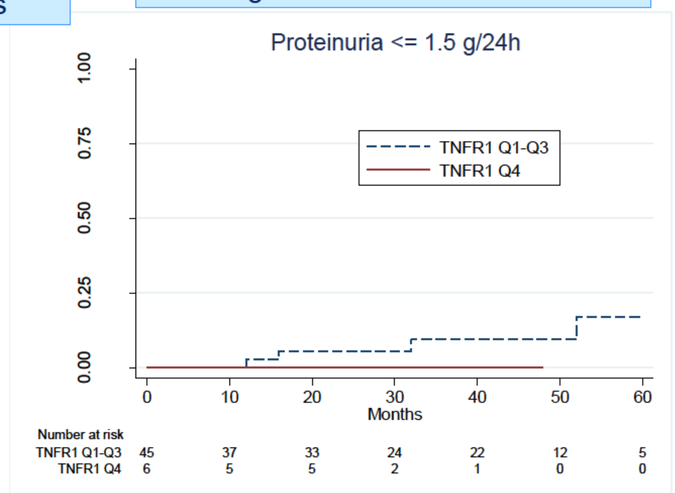


Figure 2. Cumulative incidence of primary endpoint according to quartiles of TNFR1 at baseline and proteinuria > or < 1.5 g/24 hours status.



The study included 101 patients with established type II DN . The 77% of patients were men, the mean age was 69.5±7.7 years, the mean eGFR was 47±16 ml/min per 1.73 m^2 and the geometric mean proteinuria was 1.37±2.14 mg/24 hours.

After an 18-month inclusion period, the median follow up was 32 months (IQR, 18–48), during which 23 patients (22.7%) achieved the renal endpoint (50% increase in serum creatinine concentration or ESRD) and 5 patients died (4.9%). Median serum concentrations of the receptors were 2518 pg/ml and 9750 pg/ml, for TNFR1 and TNFR2 respectively. Serum concentrations of TNFR1 and TNFR2 correlated moderately with each other (r=0.427) and with PTH, CRP, Il-6, eGFR, proteinuria, FGF23, and TNFα, but they did not correlate significantly with HBA1c, BMI, aldosteron, 25 OH vitamin baseline levels, LPO (Lipid hydroperoxide) or oxidate capacitating.

The Kaplan-Meier survival curves for the primary endpoint are shown in Figure 2. Significantly higher renal survival was observed in patients with the highest quartile TNFR1 circulating levels. (Figure 1, A-B)

In the cox regression analysis for TNFR1 , the age-gender adjusted HR of primary and renal outcome was significantly higher among patients in fourth quartile versus lowest quartile (HR 3.92; 95%CI 1.7-8.6 for primary outcome and HR 3.66: 95%CI 1.5-8.8 for renal outcome). The age-gender HR was not significantly difference for TNFR2 (HR 0.99; 95% IC 0.39-2.55). Table 1.

The magnitude of effects of circulating TNFR1 levels on patient and renal survival do not change when in the Cox regression model were included renal function and proteinuria baseline. Age, gender, phosphorus levels, BMI, PTH, FGF23, CPR, treatment with RAS blockers (monotherapy vs combined treatment) and albumin levels were removed as non-confounders

Despite the high renin angiotensin system blockers dosages used in our clinical trial , in the study longitudinal data no differences were observed in circulating TNFR1 and TNFR2 levels before and after the treatment with RAS blockers (4 and 12 months).

CONCLUSIONS

In conclusion, we analyzed the association between circulating TNFR1 and TNFR2 levels and long-term progression of type 2 DN in patients who received optimal treatment with RAS blockers. Our results show that highest levels of TNFR1 are independently associated with renal disease progression and dead.

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