

Project title:

SEQUENTIAL THERAPY WITH **TACROLIMUS** AND **RITUXIMAB** IN PRIMARY **MEMBRANOUS NEPHROPATHY** (THE **STARMEN** STUDY)

Length of the project:

From January 20, 2013 to June 20, 2019

Principal Investigator:

Manuel Praga

Proposed research:

Cyclical treatment with corticosteroids and alkylating agents remains the first therapeutic option in primary membranous nephropathy (MN), after showing in several RCT a higher number of remissions and improved long-term renal survival in comparison with supportive therapy. However, serious concerns exist about the short and long-term side effects of this treatment. Calcineurin inhibitors (CNI) have been recommended as an alternative to cyclical treatments. CNI also induce a high number of remissions, but relapses of nephrotic syndrome (NS) are common after CNI discontinuation. Rituximab (RTX) has shown to induce remissions in primary MN, although no prospective RCT have been performed. Recent observational studies have shown that RTX administered after tacrolimus tapering can decrease the incidence of NS relapse following tacrolimus withdrawal. This sequential therapy tacrolimus-RTX showed a good safety profile, with only minor side effects. Since many nephrologists are still reluctant to use cyclical treatment with steroids and alkylating agents in patients with primary MN due to the severity of side effects, the use of CNI (particularly tacrolimus), RTX, and combined sequential tacrolimus-RTX is increasing. However, no comparative RCT between both therapies have been performed.

A formal, prospective and randomized trial in selected patients with primary MN is needed to determine the efficacy of both therapies regarding NS remissions, time to remissions, number and time of NS relapses, long-term renal survival and side effects. This trial would also provide very important information with better clinical evidence levels about the clinical use of tacrolimus followed by RTX in the treatment of primary MN.

Aim of the research:

Principal objective of the study is to evaluate whether sequential therapy with tacrolimus for 9 months (6 months of full therapy and 3 months of tapering doses) followed by a dose of RTX leads to a greater increase in the proportion of primary MN patients with complete remission (CR) defined as a reduction of proteinuria since baseline level to a value equal or lower than 0.3 g/24 h proteinuria plus stable renal function (eGFR \geq 45 ml/min/1.73m²) and the proportion of patients with partial remission (PR) defined as a reduction of proteinuria since baseline level to a value less than 3.5 g/24 h and 50% lower than baseline proteinuria plus stable renal function (eGFR \geq 45 ml/min/1.73m²) when compared with patients receiving cyclical treatment with corticosteroids and Cyclophosphamide for 6 months. This will be assessed after 24 months.

Secondary objectives will be to evaluate the proportion of CR and PR at 12 and 18 months in both treatment arms, the number of NS relapses, the time to NS relapses, the time to remission, the number (percentage) of patients with preserved renal function (estimated GFR \geq 45 ml/min/1,73m²) after the treatment period, the number of patients with Limited remission, the number of patients with \geq 50% increases of SCr from baseline, the number and severity of side effects, the status of serum antibodies anti-PLA2R levels before and after the treatment period, the status of immune cells (CD4+ and CD8 T cells and CD19+ B cells), and the identification of potential novel clinical, laboratory and histologic predicting factors of response to treatment, relapse and renal outcomes.

List of the papers published in peer review journals:

- Jara Caro, Elena Gutiérrez-Solís, Jorge Rojas-Rivera, Irene Agraz, Natalia Ramos, Cristina Rabasco, Mario Espinosa, Alfonso Valera, Mónica Martín, Miguel Ángel Frutos, Lara Perea, Gema Fernández Juárez, Javier Ocaña David Arroyo, Marian Goicoechea, Laura Fernández, Aniana Oliet, Yolanda Hernández, Ana Romera, Alfons Segarra, Manuel Praga. "Predictors of response and relapse in patients with idiopathic membranous nephropathy treated with tacrolimus". *Nephrology Dialysis Transplantation* 2015; 30: 467-474
- Rojas-Rivera J, Fernández-Juárez G, Ortiz A, Hofstra J, Gesualdo L, Tesar V, Wetzels J, Segarra A, Egido J, Praga M. A "European multicentre and open-label controlled randomized trial to evaluate the efficacy of

Sequential treatment with Tacrolimus-Rituximab versus steroids plus cyclophosphamide in patients with primary Membranous Nephropathy: the STARMEN study". Clin Kidney J. 2015; 8:503-10.

List of the presentations done at major congresses/meetings:

- XLI Congress of the Spanish Society of Nephrology, Sevilla, October 2011
- XVII Symposium of the Instituto "Reina Sofia" de la Fundación Renal and V Joint Symposium with ERA-EDTA, Madrid, November 2011
- 12th Prague Postgraduate Training Course in Nephrology (Nephrology Winter School). ERA-EDTA CME Course "New Trends in the diagnostics and treatment of glomerulonephritis". Prague, January 2012.
- 49th ERA-EDTA Congress, Paris, May 2012
- National Meeting on Glomerulonephritis. Dominican Society of Nephrology. Latinoamerican Society of Nephrology and Transplantation (SLAHN). Santo Domingo 12-14 April 2013
- Meeting of the Nephropathology Club and Spanish Group for the Study of Glomerular diseases (GLOSEN), Madrid 14-15 April, 2014
- ERA-EDTA CME Course "Glomerulonephritis and novel biomarkers", Joint Meeting of IWG (Immunonephrology Working Group), YNP (Young Nephrologist Platform) and TSN (Turkish Society of Nephrology), Istanbul, 6-7 March, 2015
- Meeting of the Nephropathology Club and Spanish Group for the Study of Glomerular diseases (GLOSEN), Madrid 10-11, April 2015
- 53th ERA-EDTA Congress, Vienna, 2016.
- World Nephrology Congress, International Society of Nephrology. México April 2017
- Treatment of Membranous Nephropathy. Update in Glomerular Disease. Fundación Puigvert, Barcelona, May 2017