CLINICAL SCIENCE JOURNAL CLUB OF EUSTAR YIG

June 2019

This first edition of the clinical science journal club of the EUSTAR Young Investigators (YIG) summarizes some of the recent studies that have been published regarding systemic sclerosis related renal crisis. Scleroderma renal crisis (SRC) is a rare but potentially life-threatening complication of systemic sclerosis (SSc). SRC is described to occur in approximately 5% of all patients. Before introduction of angiotensin-converting enzyme (ACE)-inhibitors (ACEi) as treatment SRC was the leading cause of death in SSc. But also nowadays, SRC is still a feared complication of SSc with considerable risk for mortality and loss of kidney function. The clinical picture at first presentation may differ between patients complicating early and adequate diagnosis. In addition, the absence of a gold standard complicates early and uniform identification of patients with SRC, and also complicates the research how to further improve this severe complication.

This issue will cover different aspects of SRC in SSc, by summarizing recent literature:

- Summary of two different studies that retrospectively identified clinical risk factors for SRC development
- Overview of core sets to define SRC identified by the SRC working group of SCTC (Scleroderma Clinical Trials Consortium)
- Summary of retrospective study evaluation outcomes of SSc patients that needed renal replacement therapy

We hope you will enjoy reading!

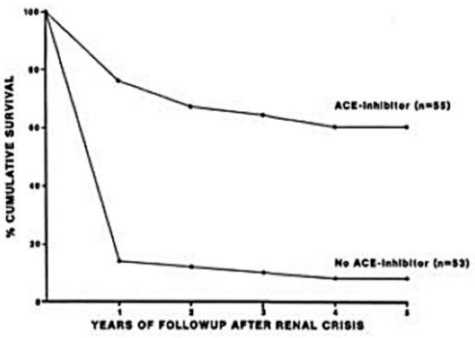
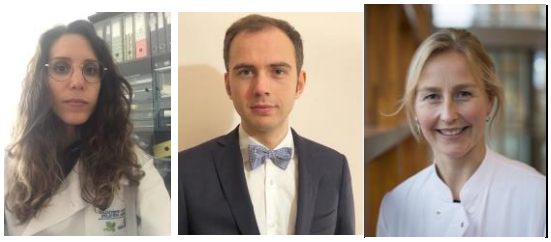


Figure 1. Survival after scleroderma renal crisis in patients with systemic sclerosis who were (n = 55) and were not (n = 53) treated with an angiotensin converting enzyme (*ACE*) inhibitor.

Figure 1: Survival after scleroderma renal crisis in patients treated with ACEi (n=55) compared to patients not treated with ACEi (n=53); derived from the landmark study on use of ACEi in SRC; Ann Int Med 1990; 113:352



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Risk factors for future scleroderma renal crisis at systemic sclerosis diagnosis

Gordon et al.; J Rheumatol. 2019 46(1):85-92.

In this study the authors aimed to identify possible risk factors at the diagnosis of SSc for future development of SRC. The population they investigated was derived from a global United States Department of Defense healthcare network involving active and retired service members and their family. Three-hundred and fifty-two SSc patients were identified, of which 31 had SRC. This complication was defined by at least one of these criteria without other explanation: *1) acute kidney injury requiring renal replacement therapy; 2) a doubling of serum creatinine (SCr); 3) 50% increase in SCr with new onset of hypertension (HYN); 4) hypertensive urgency or emergency defined by an abrupt onset of a blood pressure > 180\110 mmHg with hospitalization or end organ damage.*

Multivariate analysis showed that **SRC patients had more often proteinuria, anemia, HTN, chronic kidney disease (i.e. eGFR<60 ml\min\1.73m^2), elevated erythrocyte sedimentation rate (i.e.>27 mm\h), thrombocytopenia (i.e. platelet count<150000\µl), hypothyroidism, anti-Ro antibody seropositivity** at time of diagnosis. In addition, three or more of these risk factors present at SSc diagnosis was sensitive (77%) and highly specific (97%) for future SRC. No SSc without SRC disease controls had ≥ 4 risk factors.

Although needing an external validation, this panel of risk factors may be a useful clinical tool to identify patients at increased risk of SRC that may benefit from a closer follow up.

Scleroderma renal crisis (SRC): risk factors for an increasingly rare organ complication

Moinzadeh et al.; J Rheumatol. 2019; doi: 10.3899; [Epub ahead of print]

In this study the authors aimed to determine frequency of SRC and its association with clinical and therapeutic characteristics in a large prospective SSc registry, the German Network for Systemic scleroderma. SRC was defined as *(1) increased systolic pressure (>140/90 mmHg), a fast increase of the systolic/diastolic pressure of more than 30 mmHg/20 mmHg compared to baseline in addition to (2) an increase of serum creatinine and a decrease of the glomerular filtration rate of more than 30%.* To determine patients characteristics associated with SRC patients with and those without SRC were compared cross-sectionally. In addition, General Estimation Equation (GEE) was used to evaluate associations longitudinally including all available data.

Data of in total 2873 SSc patients could be analyzed, of whom n= 70 (2.4%) developed SRC. Patients with SRC more often had diffuse cutaneous SSc, and in this group disease duration was shorter at moment of first registration. All other characteristics were comparable between the groups. Multivariate analyses show that a recent **history of proteinuria, presence of anti-RNA polymerase antibodies, diminished DLCO levels, PAH and GI involvement are independently associated with SRC development**. Recent onset hypertension and recent onset proteinuria were predictive of future SRC development. Use of ACEi and of use corticosteroids were both predictive for SRC in the future in univariate analyses; in the multivariate model these associations were no longer significant.

The authors conclude that SRC has become a rare complication and that recent onset proteinuria, a history of hypertension, RNA polymerase antibodies and diminished DLCO are most predictive of future SRC. In addition, they point out that based on these observations, it is still not clear whether or not prior use of ACEi worsens SRC outcome.

Discussion

Both studies presented here identify baseline characteristics that are associated with future SRC development. While in the first study, SRC occurs in 8.8% of patients, incidence was 2.4% in the second study. Proteinuria is the only factor that is identified by both.

Although both studies provide insight in possible risk factors for future SRC, the data also indicate that a consensus definition on SRC is urgently needed to standardize case definition and to standardize clinical data collection of patients with SRC.

Generation of a Core Set of Items to Develop Classification Criteria for Scleroderma Renal Crisis Using Consensus Methodology

Butler et al. Arthritis Rheum 2019; 71(6):964-971

A review evaluating the literature for definitions used to classify SRC identified 40 definitions. Therefore, a group of SSc experts set out to list a core set of items to define SRC by means of consensus. Based on the review 31 items were evaluated for scientific and empirical validity, and for feasibility, by means of a web-based Delphi exercise among 99 international experts in the field, followed by a consensus group meeting (11 experts). All items with a high score for scientific validity and for feasibility (median score ≥ 7 on a 1-9 Likert scale) and where no disagreement existed were included in the final core set. The final core set covers 5 domains (see Table). For each of the items in-depth descriptions and detailed definitions are provided. As such, this core set is the first step in development of classification criteria. Future steps will include validation and weighting of items based on an inception cohort of SSc patients. At this time, data collection in accordance with the proposed core set can already be advocated to standardize clinical data collection in the field.

Table: core set of items for definition of Scleroderma renal crisis*

An acute increase in blood pressure defined as any of	Systolic ≥ 140 mm Hg, Diastolic ≥ 90 mmHg Increase in systolic RR ≥ 30 mmHg or diastolic RR ≥ 20 mmHg
Kidney injury	Increase in serum creatinine ≥ 26.5 µmol/L within 48hour or 1.5 times baseline value in the past 7 days Urine volume < 0.5 ml/kg/hour for 6 hours
Microangiopathic hemolytic anemia and thrombocytopenia	New or worsening anemia not explained otherwise Thrombocytes < 100/ mm^3 Red blood cell fragments on smear Signs of hemolysis (↑LDH, ↑reticulocytes, ↓ haptoglobin) Negative direct antiglobulin test
Target organ dysfunction	Hypertensive encephalopathy or retinopathy; acute heart failure; acute pericarditis
Renal histopathology	Histopathology consistent with SRC and supported by clinical and serological data

*For all items detailed definitions are described in the manuscript

Characteristics and Outcomes of Patients With Systemic Sclerosis (Scleroderma) Requiring Renal Replacement Therapy in Europe: Results From the ERA-EDTA Registry.

Hruskova et al. Am J Kidney Dis. 2018

The authors analyzed characteristics and outcomes of patients with SSc requiring renal replacement therapy (RRT) from a cohort of 342 patients extracted from the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry who initiated RRT between 2002 and 2013. The patients were compared to 2 matched control groups consisting of patients with end-stage renal disease (ESRD) because of diabetes mellitus (DM) or other primary kidney diseases (other PRD). They described an adjusted annual prevalence varying between 0.73-0.95/million, with a significant mean annual increase of 0.02/million. Patients with SSc were less likely to be treated with peritoneal dialysis than with hemodialysis. There was a higher number of deaths during to first 3 months on RRT in SSc patients. The percentage of patients who recovered from RRT dependence after the first 3 months was higher in the SSc group (7.6% in SSc patients vs. 0.7% in DM group and 2.0% in other PRD). Fewer SSc patients on RRT received a transplant when compared to the DM and other other PRD groups. Survival in SSc patients was significantly worse. Adjusted mortality on RRT was significantly higher in the SSc group than in both matched controls groups. Time on dialysis before receiving the first transplant was longer in SSc patients, with a mean time of 2.9 years, compared to 1.6 years in both the DM and other PRD. Adjusted 5-year patient survival and graft survival after first transplant, as well as the adjusted risk of death for SSc patients both after commencing RRT and after kidney transplantation, did not differ from that for patients with DM or other PRD. Interestingly, SSc patients who started RRT had fewer deaths due to cardiovascular events compared to patients with DM, fewer deaths due to malignancy, and cardiac arrest but more deaths due to heart failure compared to patients with other PRD.

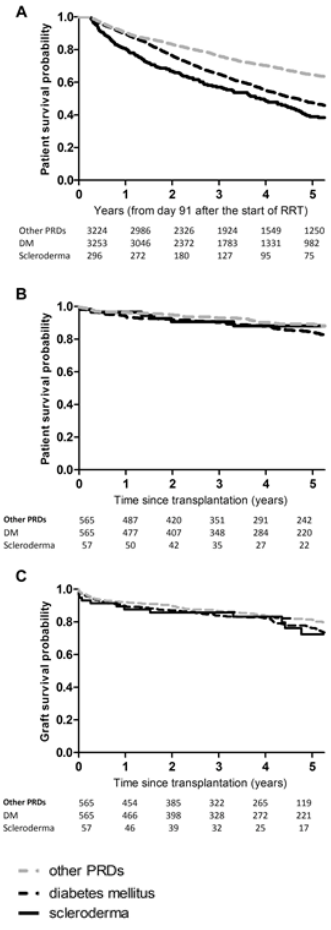

Figure: Kaplan Meier survival curves; A: for patients on RRT; Patient (B) and graft (C) survival after kidney transplantation