Case Report
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NLRP3 Inflammasome Activation in Renal Injury: Long-Term Effectiveness and Safety of Blocking the IL-1 System in a Kidney Transplanted Patient Affected by AA Amyloidosis Secondary to Cryopyrin-Associated Periodic Syndromes (CAPS)

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ABSTRACT

NLRP3 inflammasome activation is recognized to play a key role in the pathogenesis of several chronic diseases such as chronic tubulointerstitial diseases, glomerulonephritis and calcium oxalate crystal nephropathy. Genetic variants of NLPR3 are likely associated to pro-inflammatory/autoimmune disorders, by the altered self-regulation of inflammasome with overproduction of inflammatory cytokines. Recently experimental and human studies have focused on the interest in both acute and chronic renal diseases. Inhibition of the Interleukin-1 (IL-1) system has become an attractive potential therapeutic target in a variety of renal disorders, including IgA nephropathy, ischemic reperfusion injury, after unilateral ureteral obstruction, rhabdomyolisys-induced Acute Kidney Injury (AKI), contrast-induced AKI, crystalline nephropathy, and recently also in diabetic nephropathy.NLRP3 activation in kidney diseases magnify inflammation and subsequent fibrosis, and this effect is abrogated by genetic or pharmacologic deletion of NLRP3. Inflammasome-dependent NLRP3 mediates the progression of kidney diseases by rapidly increasing the inflammatory response in immune cells as demonstrated also in hereditary autoimmune syndromes, like CAPS.

We describe the renal involvement in one patient affected by Muckle-Wells syndrome (MWS), biopsy-proven reactive AA amyloidosis and proteinuric renal failure, by focusing the interest above all on the efficacy and safety profile of therapy with anti-IL1 antibody on a clinical continuum from the reduced renal function to the kidney transplant.

Keywords: *NLR3 Inflammasome, Renal AA Amyloidosis, Kidney Transplant, Muckle-Wells Syndrome, Interleukin-1, Autoinflammatory Syndrome, Immunosuppressive Therapy*

Introduction

Inflammation is considered a central process in the pathogenesis of renal damage and includes non-dialysis as well as dialysis-related factors, through the cellular infiltration of T lymphocytes and

macrophages in the parenchyma, with the production of cytokines (Scarpioni *et al*., 2016).

The key role of inflammation is confirmed by the involvement of mononuclear inflammatory cells in the damaged renal interstitium, a frequent finding in renal failure that correlates inversely with renal function (Mezzano *et al*., 2000; Grandaliano *et al*., 2000).

In the kidney, interstitial inflammation and fibrosis are main predictors for the risk of progression towards and-stage renal disease (ESRD) and, as in non-renal diseases, inflammation worsen the atherosclerotic progression (Becker and Hewitson, 2000; Zacho *et al*., 2008; Liu *et al*., 2006).

To further complicate the complex scenario, more often an impaired control of innate immune system there occurs, generating the so-called autoinflammatory disorders (AIDs) mediated by antigen-independent activation of the immune system (Masters *et al*., 2009).

The latter are a group of heritable diseases characterized by unprovoked attacks of sterile systemic inflammation in the absence of autoantibodies and autoreactive T cells which relies in altered regulation of inflammasome with consequent overproduction of pro-inflammatory cytokines, especially IL-1b, elevated in CKD (Lucherini *et al*., 2018).

The inflammasome is a large, multiprotein complex that drives proinflammatory cytokine production in response to infection and tissue injury; the best-characterized inflammasome is the Nod-Like Receptor Protein 3 (NLRP3). Once activated, inflammasome leads to the active form of caspase-1, the enzyme required for the maturation of IL-1 beta (Scarpioni *et al*., 2016).

The latter, previously known as endogenous pyrogen, osteoclast activating factor, catabolin, hemopoietin-1, lymphocyte activating factor, or epidermal-derived thymocyte activating factor, is produced as an inactive precursor form upon cell activation (Turner *et al*., 2014). Its release requires the activation of different molecules gathered under the name of “inflammasome”. The activation of inflammasome leads to the active form of caspase-1, the enzyme required for the maturation of IL-1 (Lorenz *et al*., 2014). The release of IL-1 beta requires the activation of the cell by ATP through its P2X7 receptor, the involvement of K+ and Ca+ channels and the action of a phoshatidylcholine-specific phospholipase (Scarpioni *et al*., 2016).

Case Report

In a previous paper we reported our experience in two Caucasian patients, father and son, heterozygous for both V198M and R260W NLRP3 mutations who had AA amyloid deposits on renal biopsy. In the manuscript, we demonstrated that canakinumab, a fully human monoclonal antibody,

providing selective and prolonged IL-1 beta blockade, allowed to obtain a sustained clinical response in terms of reducing renal damage progression and proteinuria (in an overall period of 18 months) and removing symptoms, such as arthralgias, myalgia, fever and skin rashes, without adverse events, namely infectious episodes (Scarpioni *et al*., 2015).

The older patient, the father, affected by renal insufficiency (serum creatinine 2 mg/dl, eGFR= 37 ml/min) and nephrotic proteinuria (7 g/daily), started therapy with canakinumab (Sozeri *et al*., 2016; van der Hilst *et al*., 2016) on September 2011, at the dose of 150 mg subcutaneously every 60 days. Previously he had been treated with prednisone, cyclophosfamide and colchicine (Gul, 2016), without clinical benefit or slowing of progression of renal failure or reduction of proteinuria. Immediately, after that the patient showed subjective well-being and rapid increase in glomerular filtration rate. The improvement of inflammatory parameters started soon after the first administration (Fig. 1-3).

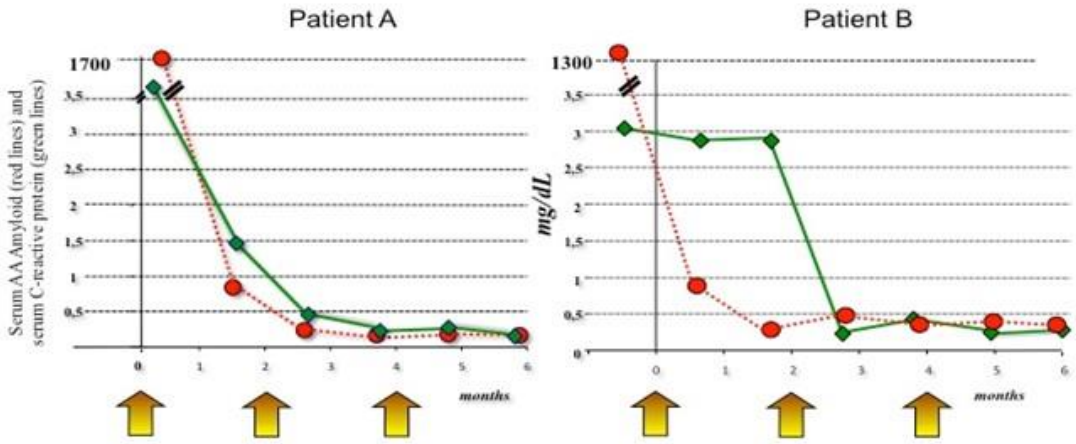


Figure 1: The effects of IL-1 block on serum AA Amyloid (red lines) and on serum C-Reactive Protein (green lines)

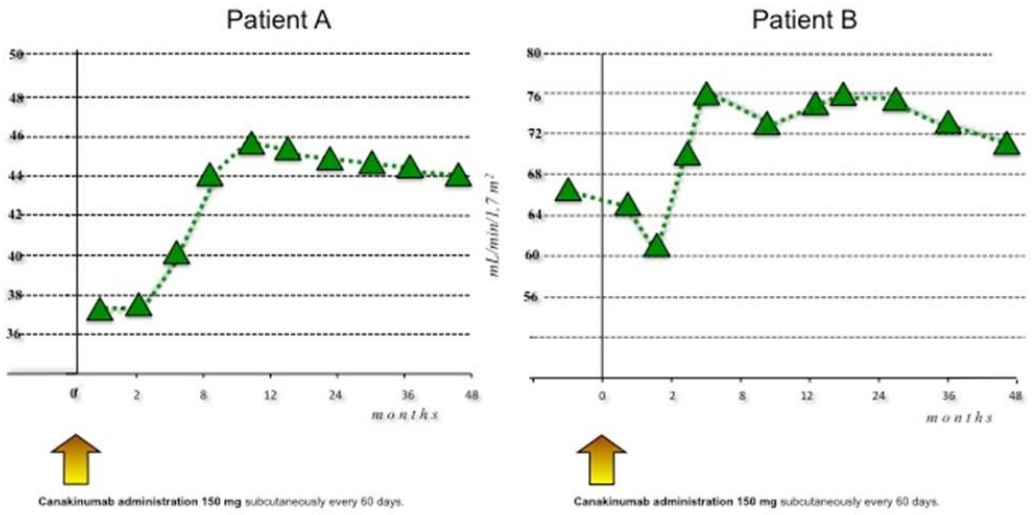


Figure 2: Long-term effects of blocking IL-1 on estimated GFR

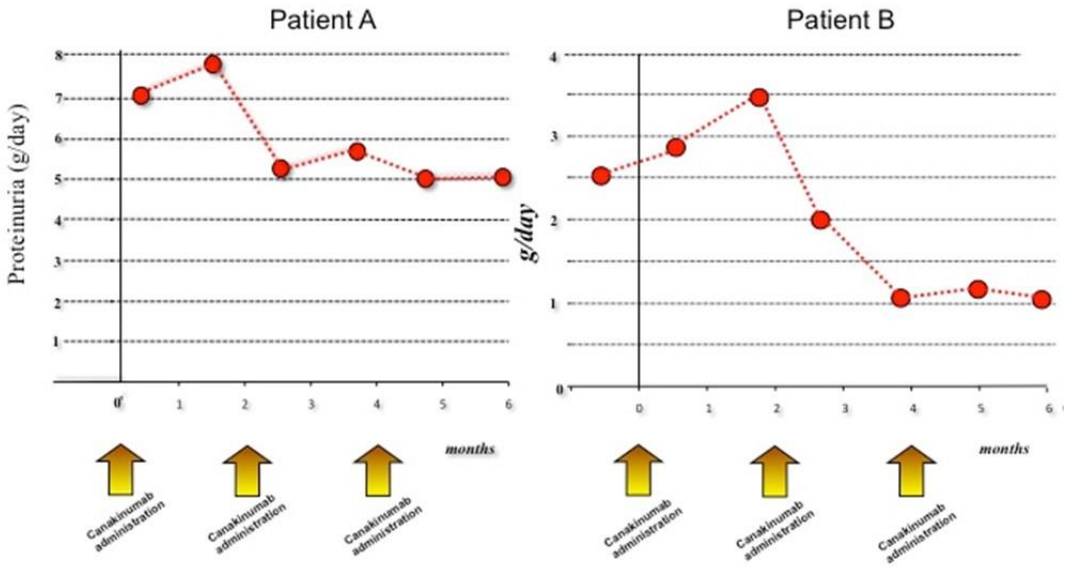


Figure 3: The Effects of blocking IL-1 on proteinuria (g/day)

The younger patient, in the same way as the father, started canakinumab on September 2011, and, at the date, has a moderately reduced kidney function (serum creatinine 1.4 mg/dl, eGFR= 68 ml/min) and persistently proteinuria lower than 2 g/daily, probably because he was exposed over less time to the disease activity.

In the older patient A, the father, therapy with canakinumab was undertaken when the drug was available in Europe for clinical indication for MWS (Quartier, 2011) in a moderate stage of kidney disease (CKD 3b), while there was a marked improvement in the general conditions for a better control of the systemic symptoms. CKD, however, slowly progressed until the need to undertake dialysis replacement therapy on February 2018.

One year later, on 2019, after starting hemodialysis treatment at the age of 58 years, our patient successfully received a cadaveric double kidney transplant, both kidneys housed in right iliac fossa. The initial immunosuppressive therapy consisted of thymoglobuline, as induction, followed by tacrolimus, mycophenolic acid and prednisolone (KDIGO, 2009).

The functional recovery of the graft was delayed because of organ ischemia in the kidneys polar ends, documented by ultrasound, in the context of receiving wide vascular calcifications. The patient underwent three dialysis sessions before renal function recovery until serum creatinine levels decreased to 4 mg/dl at the time of discharge from Bologna Hospital, 15 days after kidney transplantation.

Later, graft function continued to improve until serum creatinine levels of 1.6 mg/dl (eGFR=46 ml/min, by CKD-EPI formula) 45 days after kidney transplantation.

The therapy with monoclonal anti-IL-1b antibody (canakinumab 150 mg subcutaneously every 60 days) (Scarpioni *et al*., 2015; Sozeri *et al*., 2016; van der Hilst *et al*., 2016) has been continued at the same dosage after renal transplantation in order to avoid the amyloid deposition, without relapsing of the underlying disease.

Throughout the follow-up, which has lasted to date two years, we did not observe any clinical rejection episodes, any bacterial or viral infections or any other adverse events needing hospitalization. The same safety profile, with no infectious episode nor need of hospitalization, was observed in the son of the transplanted patient and even in his mother, both affected by MWS, on IL-1 β block therapy, followed over 9 years. Above all, we did not observe any pharmacological interactions between canakinumab and the immunosuppressive therapy.

Two years after renal transplantation, the patient has an excellent graft function with a serum creatinine level of 1.2 mg/dl (eGFR=65 ml/min by CKD-EPI) and proteinuria lower than 500 mg/daily throughout the past year. Since the beginning of therapy in 2011 to date, ten years later, serial controls of the serum amyloid protein were within the normal range (<0.5 mg/dl). Periodic monitoring for Cytomegalovirus, Epstein Barr Virus and Polyoma virus has always been negative.

A renal biopsy was performed 17 months after transplantation. No signs of amyloid deposition on the transplanted kidney or chronic rejection was found (Fig. 4).

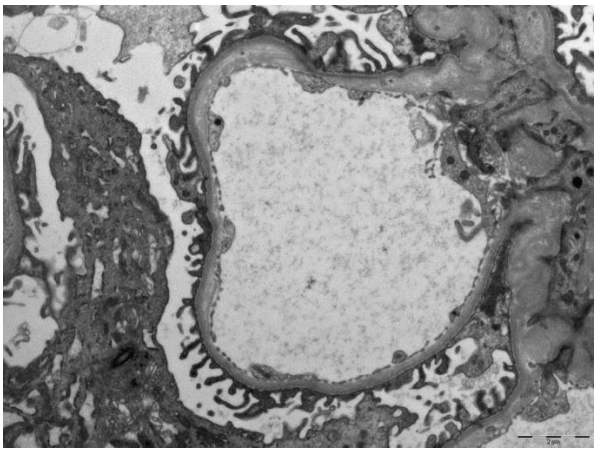


Figure 4: Renal biopsy. Electron Microscopy showing normal glomerular basal membrane

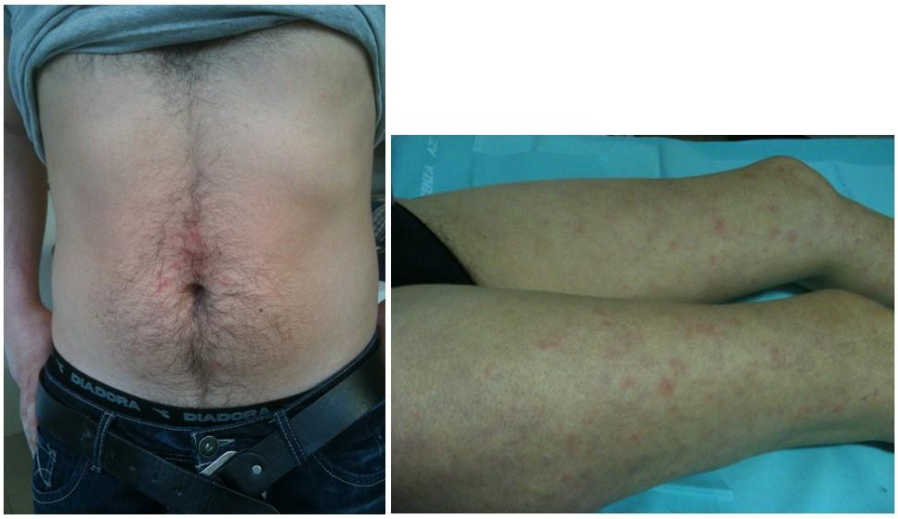
Discussion

The NLP3 inflammasome mediates inflammation in several chronic diseases by processing the cytokines pro-interleukin (IL)-1beta and pro- IL-18. In last years several manuscripts reported the pivotal role played by the NLRP3 inflammasome, whose activation is induced by different pathogens and

host-derived signals of cellular damage (De Torre-Minguela *et al*., 2017; Zhong *et al*., 2013) and results in proteolytic cleavage of caspase-1 into its biologically active form, which in turn mediates the production of IL-1beta and IL-18 pro-inflammatory cytokines (Dayer *et al*., 2017).

In a previous review we focused on the multiple, intertwined mechanisms linking autoinflammation and kidney injury (Scarpioni and Obici, 2018). Both experimental and human studies showed a detrimental role for NLRP3 in the development of acute and chronic tubule-interstitial disease (Duewell *et al*., 2010). Several reports document the expression and release of IL-18 from tubular epithelial cells (Faust *et al*., 2002; VanderBrink *et al*., 2011; Franke *et al*., 2012). This would seem to indicate that the NLRP3 inflammasome and caspase-1 axis may also be in renal non immune cells. Moreover, Zhang, *et al*. (2012), using a confocal microscopy, documented NLPR3 and Apoptosis Associated Speck-like protein (ASC) to be expressed by glomerular podocytes. Intrinsic renal cells express components of the inflammasome pathway. This is mostly prominent in tubular epithelial cells and, to a lower degree, in glomeruli.

Among Cryopyrin-associated periodic syndromes (CAPS), we describe renal involvement in patients affected by Muckle-Wells syndrome (MWS), a rare hereditary autoinflammatory disorder, characterized by recurrent fever attacks, arthralgias, myalgia, conjunctivitis, sensorineural deafness, urticarial-like skin rashes (Fig. 5).



Figures 5: Urticarial-like skin rashes at abdomen and legs in two patients affected by MWS

The CAPS disorders (MWS, Familial Cold Autoinflammatory Syndrome (FCAS) and neonatal onset multisystem inflammatory disease -NOMID) are caused by mutations in the NLRP3 gene on chromosome 1q44 which encodes the cryopyrin protein (Hoffman *et al*., 2001). Mutated cryopyrin spontaneously activate the inflammasome complex, leading to caspase-1 activation and subsequent maturation of

interleukin (IL)-1β, which is then inappropriately released, giving rise to most CAPS clinical manifestations (Scarpioni *et al*., 2016).

A major complication for CAPS, including Muckle Wells syndrome (MWS), is the development of systemic reactive type AA amyloidosis due to the accumulation of aggregated amyloid fibrils in the extracellular space of different organs (Van der Hilst *et al*., 2005).

Renal involvement, in terms of proteinuria or renal insufficiency, can be observed in up to 25% of patients (Scarpioni and Obici, 2018) and may be confirmed by renal biopsy (Fig. 6).

AA amyloidosis presents in its early stages with a low grade proteinuria that usually progressively worsens if the inflammatory stimulus persist or recurs over time, leading to nephrotic syndrome and, ultimately, renal failure. Advanced renal dysfunction at diagnosis and persistent elevation of serum amyloid A (SAA) during follow up are powerful risk factors for progression to end stage renal disease and death (Lachmann *et al*., 2007).

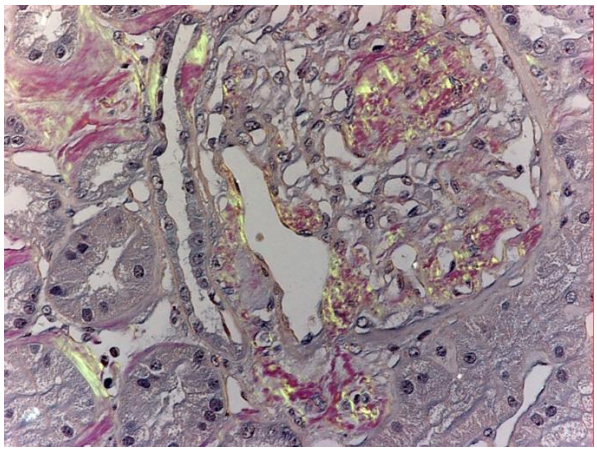


Figure 6: Renal biopsy: Amyloid fibrils bind congo red stain, yielding the pathognomonic apple-green birefringence (see arrow) under cross-polarized light microscopy (Scarpioni *et al*., 2015)

In our opinion this case teach us that early diagnosis of autoinflammatory disease and the research of renal involvement are ultimate because of the potential implications for early therapy, monitoring for the development of secondary (AA) amyloidosis, and the need for genetic counseling.

Inflammation in the inflammosomopathies is commonly mediated in part through IL-1-beta, and so blockade of this cytokine can be markedly effective: several drugs are upto day available in order to ameliorate clinical symptoms, substantially reducing levels of inflammatory indices, including serum amyloid A, and sometimes slowing renal disease progression to ESRD, as illustrated by our clinical cases (Scarpioni *et al*., 2015).

A central role for IL-1 beta in these disorders is confirmed by the effectiveness of therapies direct against IL-1 in preventing and alleviating symptoms (Scarpioni *et al*., 2015).

Several experimental data seem to add some hypothetical explanation of the complexity of relations between NLPR3 activation and kidney damage: in the experimental murine model of CI-AKI, for example, it is known that iodinated contrast medium induces vasoconstriction by blocking nitric oxide-induced vasodilatation, the elevation of intracellular calcium, and adenosine. Contrast administration led to NLPR3 inflammasome activation in renal macrophages and CI-AKI was ameliorated in NLRP3 KO mice (Lau *et al*., 2018).

Also in diabetic nephropathy it was found that podocytes and glomerular endothelial cells contain NLPR3 and release cleaved IL-1 beta under high-glucose stimulation. The transcripts of NLPR3, ASC, and proinflammatory cytokines were found to be increased in monocytes from patients with type 2 DM (Lee *et al*., 2013; Yang *et al*., 2019).

Intriguingly, it is reported that the increase in plasma levels of IL-1 beta and IL-18 occurred prior to the presentation of albuminuria and renal histologic changes in murine diabetic nephropathy (Shahzad *et al*., 2015).

Other stimulating pathologic renal diseases are described to be associated with NLPR3 activation, such as in obstructive nephropathy (Guo *et al*., 2017), in crystalline nephropathy (Mulay *et al*., 2013), in Lupus nephritis (Fu *et al*., 2017), in hypertensive nephropathy (Krishnan *et al*., 2019), in rhabdomyolysis-induced AKI (Komada *et al*., 2015), and recently also in IgA nephropathy (Tsai *et al*., 2017).

Conclusions

The NLRP3 inflammasome has been implicated in various kidney diseases, including acute kidney injury (AKI) and chronic kidney disease (CKD). Several experimental (above all) and human data (rare) showed a complexity of relations between NLRP3 activation and kidney damage which at the moment appear to be an interesting and speculative aspect of kidney disease treatment, as supported by numerous experimental and human experiences.

To our knowledge kidney transplantation with a follow up of about two years in a MWS patient on therapy with monoclonal anti-IL-1β antibody for about ten years is the first described in Italy and ,according to previous cases (Kortus-Gotze and Hoyer, 2011), similar to the reports of transplanted patients with Familial Mediterranean Fever (Ozcakar *et al*., 2018), confirms the excellent safety profile of the IL-1β block in addition to standard immunosuppressive therapy.

We can emphasize the observations that monoclonal anti-IL-1β antibody blocking can be used with a very good clinical response in patient with normal or reduced renal function, as well as in patients on renal replacement therapy, either hemodialysis or renal transplantation. Severe side effects nor increased hospitalization rate, compared with patients on "traditional" transplantation therapy, without IL-1 block, were not observed during the two-year follow up. Larger studies are requested in order to confirm the potential role of NLRP3 block in protecting renal function or in preventing the progression of CKD. The high costs actually represents an obstacle to a wide spread of the IL1 block.

Conflict of Interest: Authors declare that they have no conflict of interest.

Ethical Approval: This article does not contain any studies with human partecipants or animals performed by any of the authors.

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