IL1 Blockage in Renal Diseases

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RENAL INFLAMMATION

• Renal inflammation is a universal response to infectious and noninfectious triggers.

• Renal inflammation always involves antigen-independent innate immune system, whereas antigen-specific (adaptive) immunity may or may not be present.

• It is still unclear how innate immunity translates infectious and noninfectious danger into the various forms of kidney diseases.

  – Intracellular multiprotein proteolytic complexes termed “inflammasomes” play the most important role in injury.

INNATE IMMUNE SYSTEM

• The humoral part of innate immunity. Complement factors, mannose binding lectin, and pentraxins (CRP, serum amyloid P, pentraxin 3)
  • opsonize pathogens or apoptotic cells to induce phagocytosis
  • also directly kill pathogens or cells by forming the membrane attack complex (MAC)

• The cellular components of innate immunity. Monocyte/macrophage and neutrophil recruitment
1. The inflammasome is a proteolytic caspase-1-activating platform.
   - Activated caspase-1 processes numerous cellular substrates including the cytokines IL-1 and IL-18.

2. In addition, inflammasomes mediate an inflammatory form of cell death termed “pyroptosis”
   - Pyroptosis was recently described in macrophages and consists of programmed cell death involving loss of membrane integrity, unlike apoptosis.
INNATE IMMUNE SYSTEM

• Innate immune system involves several soluble and cellular receptors
  – Toll-like receptors; TLRs
  – Retinoic acid-induced gene (RIG)-like receptors
  – Nucleotide-binding domain (NOD)-like receptors; NLRs
  – Scavenger receptors

• These receptors are activated by
  – various bacterial and viral “pathogen-associated molecular patterns” (PAMPs)
  – nonmicrobial stimuli, particularly to intracellular molecules that are released from necrotic cells “danger-associated molecular patterns” (DAMPs)
Many diverse microbial, nonmicrobial, and even endogenous stimuli activate the inflammasome

- Streptolysin O and other bacterial toxins (Strep. pyogenes and other bacteria)
- ATP, DNA (Dying cells)
- Reactive oxygen species (oxidative stress, hypoxia, hyperglycemia, etc.)
- Uric acid crystals (hyperuricemia, gout)
- Silica/asbestos crystals (Environment)
How pattern recognition receptors induce innate immunity?

Extracellular or intracellular pattern recognition receptors recognize PAMPs and DAMPs at the cell surface and in intracellular endosomes and induce the expression of NF-κB-dependent genes, including most proinflammatory cytokines including IL-1 and IL-18. IL-1 and IL-18 need caspase-1 activation before they can be released. **Caspase-1 activation is under the control of NLRP3 inflammasomes.** Potassium efflux, lysosomal cathepsin leakage in the cytosol or oxidative stress can trigger inflammasomes. All cytokines amplify innate immunity by interacting with their receptors.
The NLRP subfamily of NLR (nucleotide-binding oligomerization domain like receptor) genes consists of 14 members. They are typified by an N-terminal PYD, NACHT and leucine-rich repeat domains.

Inflammasomes also consist of adaptor protein ASC and cystine protease caspase-1.
Simplified model of NLRP3 activation

1. Exposure to a DAMP or PAMP releases NLRP3, which oligomerizes via its NACHT domain.

2. NLRP3 oligomerization recruits the adaptor protein ASC and then protease caspase-1 to form a protein complex termed the “inflammasome”.

3. Recruitment to the inflammasome triggers caspase-1 autoprocessing and generation of the active p10/p20 heterodimeric enzyme.

4. Active caspase-1 cleaves pro-IL-1 and pro-IL-18 into their activated forms.
Inflammasome and IL-1/IL-18 axis

- Accumulating data document a role of the NLRP3 inflammasome and IL-1/IL-18 axis in many diseases, including
  - autoinflammatory disorders, amyloidosis, atherosclerosis, diabetes, malaria, crystal-related diseases, almost all acute and chronic kidney diseases
  - identifying this innate immune pathway and IL-1/IL-18 axis as an attractive therapeutic target.
Crystal-induced pathologies

- Monosodium urate or calcium pyrophosphate dihydrate crystals activate the NLRP3 inflammasome, which is a central pathogenic mechanism of gout and pseudogout.
- IL-1 antagonism immediately ameliorates the clinical symptoms of these crystal arthropathies.

DISEASE ENTITIES INVOLVING THE INFLAMMASOME - CASPASE-1 - IL-1/IL-18 AXIS

• In vitro studies and studies performed in mice support a role of the NLRP3 inflammasome in translating the recognition of **crystals, pigments or amyloid microparticles** into IL-1 release and **kidney disease** such as
  – nephrolithiasis
  – renal amyloidosis
  – cholesterol embolism
  – urate nephropathy
  – cast nephropathy
  – acute kidney injury (AKI) secondary to myoglobinuria
Little is known of the expression of inflammasome-related genes in renal cells.

Except for NLRP2 and NLRP10, the human kidney expresses much lower levels of inflammasome-related molecules.

Several studies document the renal tubular epithelial cells express inflammasomes and secrete IL-1 and IL-18.

INFLAMMASOMES and CHRONIC KIDNEY DISEASE

Inflammasome-regulated cytokines are implicated in animal models or human forms of chronic kidney diseases.

- Immune complex glomerulonephritis- IgA nephropathy
- Nephrotoxic serum nephritis
- Nephrotic syndrome


Inflammasomes and Acute Kidney Injury

Acute tubular necrosis

• ischemia-reperfusion during hypotension/shock
• toxins such as drugs (cisplatin) or radiocontrast media
• immune-mediated mechanisms

the release of endogenous components (DAMPs) from necrotic cells such as ROM, ATP (activates NLRP3 inflammasome through P2X 7 receptors), nucleic acids, uric acid and extracellular matrix components (hyaluronan, biglycan)
capable of activating inflammasome.

THE ROLES OF INFLAMMASOMES IN KIDNEY DISEASE

• Markers of inflammasome activation (IL-1, IL-18) are increased over a 14-day time course in mice after unilateral ureteric obstruction (UUO).

• Interstitial fibrosis secondary to UUO

• P2X 7 -/- or biglycan -/- or NLRP3 -/- mice exhibit reduced tubular injury, inflammation and fibrosis after UUO.

• Caspase-1-deficient mice are more resistant to ATN secondary to cisplatin.

FUTURE PERSPECTIVES

1. Studies using human renal biopsies will be useful to determine the expression of inflammasome components in kidney, and to correlate with disease activity or prognosis.

2. The usage of IL-1 blockage to modulate kidney disease would represent the significance of the inflammasome - caspase-1 -IL-1/18 axis in kidney disease.
## NONINFECTIOUS DISEASES RELATED TO INFLAMMASOMES

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<td>MWS</td>
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<td>CINCA</td>
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*GOF, gain-of-function; LOF, loss-of-function mutation*
Autoinflammatory diseases and IL-1

## NONINFECTIOUS DISEASES RELATED TO INFLAMMASOMES

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<tr>
<td>SLE</td>
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<td>PR/CR</td>
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<tr>
<td>idiopathic recurrent pericarditis</td>
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IL-1 BLOCKAGE IN THE RHEUMATİC DİSEASES

- IL-1 blockage is used for the treatment of sJIA, adult-onset Still’s disease, autoinflammatory diseases and acute gouty arthritis.

- “biologic DMARD” (disease-modifying anti-rheumatic drug)
sJIA and IL1 blockage

- sJIA is classified as a subset of JIA, but the pathophysiology is most consistent with an autoinflammatory disorder.

- **The most efficacious biologic agents**, based upon results from randomized trials, are those that **block IL-1 or IL-6**.

- IL-1 or IL-6 inhibitors were **initially reserved for patients refractory to conventional therapy** (NSAIDs, glucocorticoids, mtx)

- However, they are **increasingly the agent of choice** in patients with sJIA since they are highly effective.
  - **The guidelines** are outlined by the ACR **emphasize the earlier use of biologics in children with sJIA**

sJIA and IL1 blockage

Standardized treatment plans was developed through a consensus process by the Childhood Arthritis and Rheumatology Research Alliance (CARRA).

For patients whose initial symptoms include high fevers, other systemic manifestations including serositis and possible early MAS, and/or moderate-to-severe polyarthritis, they suggest adding one of the biologic agents that inhibit interleukin IL-1 or IL-6 rather than the nonbiologic DMARD.

sJIA and IL1 blockage

The biologic DMARDs are

1. more effective than nonbiologic DMARDs

2. have more favorable side-effect profiles than long-term use of glucocorticoids

3. early use may change the course of disease


sJIA and IL1 blockage

The role of IL-1 in sJIA and the clinical outcome of treatment with anakinra were documented in an early study of 9 patients with sJIA.

The following findings were noted:

• All 9 patients became afebrile within the 1st week of anakinra therapy.
• 8 patients had active arthritis at the start of therapy. After 2 months of therapy, 6 had complete resolution, and 2 had improvement in symptoms.
• All 9 patients had normalization of elevated leukocyte and platelet counts.
• 8 patients had normalization of an ESR after 2 months of therapy.
• Anakinra may be more effective if used early in the disease course, rather than as "rescue" therapy once other therapies have failed.

One international group gathered 46 patients who had received anakinra as initial therapy for sJIA.

- **Chronic arthritis did not develop in 90% compared with 30-50% among historical controls.**

sJIA and IL1 blockage

Results from randomized trials, in addition to observational data, indicate that canakinumab is an effective therapeutic option for patients with sJIA.

• 84 children with active sJIA were randomly assigned to canakinumab or placebo.
  – a significant difference in JIA ACR 30 response between the canakinumab (84%) and placebo groups (10%)

• Canakinumab was approved by the US FDA for use in sJIA patients in 2013.

Familial Mediterranean fever (FMF) and IL1 blockage

• FMF is the most common of the monogenic periodic fever syndromes

• There is a *mutation in the MEFV gene encoding the protein pyrin*
  – Pyrin has an important role in the innate immune system. It is a major regulatory component of the *inflammasome*, when activated, trigger the release of IL-1 beta.

• It is important to reduce the attacks of FMF in order to avoid kidney failure resulting from secondary amyloidosis.

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Canakinumab Investigated for Treating Familial Mediterranean Fever

Ruby Haviv & Philip J. Hashkes

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EULAR recommendations for the management of familial Mediterranean fever

Seza Ozen,1 Erkan Demirkaya,2 Burak Erer,3 Avi Livneh,4 Eldad Ben-Chetrit,5 Gabriella Giancana,6 Huri Ozdogan,7 Illana Abu,8 Marco Gattorno,9 Philip N Hawkins,10 Sezin Yuce,11 Tilmann Kallinich,12 Yelda Bilginer,13 Daniel Kastner,14 Loreto Carmona15

Biologics: Targets and Therapy

Efficacy of anti-IL-1 treatment in familial Mediterranean fever: a systematic review of the literature

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Efficacy of Interleukin-1 Targeting Treatments in Patients with Familial Mediterranean Fever

Pınar Cetin,1 Ismail Sarı,1,4 Betul Sozeri,2 Özlem Cam,2 Merih Birlik,1 Nurullah Akkoc,1 Fatos Onen,1 and Servet Akar3
Cryopyrin-associated periodic syndromes (CAPS) and IL1 blockage

- A report of a 2-year follow-up of canakinumab treatment in 166 patients with CAPS revealed the long-term efficacy of canakinumab in decreasing the number and severity of episodes even in neurological abnormalities

  - Loss of hearing is partially reversible with IL-1 blockade, and is more effective when started soon after the first manifestations of the disease.

Cryopyrin-associated periodic syndromes

Randomized-controlled trials also revealed the benefit of anti-IL 1 treatment in CAPS and in the Eurofever registry, anti-IL 1 drugs were the first option in treatment of CAPS and 70% of patients responded to IL 1 inhibition.


Secondary (Reactive) AA amyloidosis

Pathogenesis

• Overproduction of SAA as a consequence of aberrant inflammation

• Proteolytic processing of SAA to AA
  – Internalization of SAA by macrophages
  – intracellular aberrant degradation of SAA to AA protein by specific metalloproteinases
  – release of amyloidogenic peptides into the extracellular space
  – accumulation of insoluble amyloid fibrils in tissue

• Severity of disease

• Early detection and treatment of disease

• Genetic susceptibility
Treatment of secondary AA amyloidosis

Successful treatment of the underlying inflammatory process

• **Surgical resection** of the focus of infection or tumor

• **Antibiotic treatment** of chronic infection

• **Biological agents** in RA and AIDs
  
  – anti-IL 1 or anti-IL 6 drugs can be used in the prevention and treatment of secondary AA amyloidosis.

If untreated, secondary (AA) amyloidosis is a serious disease with a significant mortality due to **end-stage renal disease**, infection, heart failure, bowel perforation, or gastrointestinal bleeding.
Treatment of secondary (AA) amyloidosis

**Biologic treatments** can lead to

- improvement in renal function,
- reduction in protein excretion
- and to partial resolution of amyloid deposits
  - as assessed in some studies by serum amyloid P (SAP) scintigraphy
  - however, these studies have **not confirmed** the improvement at tissue level


Severity of disease

The correlation between the serum SAA concentration and disease course

80 patients with AA amyloid (mostly due to JIA or to RA), followed for 4 years

- 42 patients, **median serum SAA concentration <10 mg/L**
  - amyloid deposits regressed in 25 and stabilized in 14
  - proteinuria fell, serum creatinine concentration stable or improved

- the patients, **median serum SAA concentration >50 mg/L**
  - amyloid load usually increased, and organ function deteriorated

Amyloidosis may complicate AIDs

- Amyloidosis secondary to **FMF** is related to pyrin mutations, in particular, homozygote M694V
- **TRAPS**
- Hyperimmunoglobulinemia D syndrome
- **Cryopyrinopathies**

with varying incidences depending upon disease and ethnic background.

- The impact of anticytokine therapy in preventing AA amyloid in hereditary AIDs is increasingly clear.

*Ombrello AK. Humana Press, New York 2012. p.399*
Secondary amyloidosis in autoinflammatory diseases and the role of inflammation in renal damage

Roberto Scarpioni, Marco Ricardi, Vittorio Albertazzi

The experience of canakinumab in renal amyloidosis secondary to Familial Mediterranean fever

Betul Sozeri, Nesrin Gulez, Malik Ergin and Erkin Serdaroglu

Biological Agents in Familial Mediterranean Fever Focusing on Colchicine Resistance and Amyloidosis

Betul Sozeri and Ozgur Kasapcopur
Secondary AA amyloidosis

In a recent series by Özçakar et al., 6 patients received anti-IL 1 therapy due to FMF-related amyloidosis and their renal and inflammatory biochemical parameters improved.


Bilginer Y et al. reported a patient who was diagnosed with FMF and Behçet’s disease and proteinuria, with normal kidney function after 18 months of anakinra treatment.

Secondary AA amyloidosis

• In a report by Lane et al., the patients who had AIDs were treated with IL1 blockage
  – inflammatory parameters were improved successfully
  – by serum amyloid P (SAP) scintigraphy over the follow-up
    • 17 (46 %) showed amyloid regression
    • 14 (38 %) showed stable amyloid load
    • 2 (5 %) showed increased amyloid deposition, which may be due to ongoing subclinical inflammation

*Arthritis Rheum 2013; 65:1116–1121*
After renal transplantation, the patient with Muckle-Wells syndrome had a very good response to canakinumab with low activity in inflammation markers with an improved quality of life.

5 years after renal transplantation, the patient remains an excellent kidney function without proteinuria. There are no signs of recurrence of AA-amyloidosis in the transplanted kidney.

Kortus-Götze and Hoyer. Pediatric Rheumatology 2015, 13(Suppl 1):P147
A 14-year-old male,

- FMF attacks had begun at the age of 4
- he was diagnosed with FMF at 13 years old (M694V +/+)
- Proteinuria (amyloidosis with renal biopsy)
- CrCL: 89 mL/min. CKD
- Colchicine (1 mg/day) and ramipril (5 mg/day)
- In 6-mos follow up, increased attack rate and proteinuria, colchicine (2 mg/day)
- Colchicine-resistant FMF, severe growth retardation and amyloidosis (canakinumab 150 mg/month)
- One month later, the patient was symptom-free and the inflammatory parameters almost normalized and proteinuria were decreased.
2 children with sJIA or 1 with CAPS and reactive amyloidosis

- With anti-IL 1 treatment, all patients achieved complete remission in inflammatory mediators and proteinuria
- Control renal biopsies were performed median 3 years after the first biopsies.
- Renal amyloid prognostic score (RAPS) ([Arch Pathol Lab Med 2010; 134:532–544](https://pubmed.ncbi.nlm.nih.gov/20482366/)) and damage in the tissue did not improve and even progressed.
- This is the first series showing progression of renal tissue damage after the improvement of proteinuria with anti-IL 1.
• The first biopsy of patient (just before the onset of anakinra treatment), no glomerulosclerosis and no inflammation in the interstitium.

• The second biopsy of patient (2 years after the first biopsy), glomerulosclerosis and interstitial mononuclear infiltration. (HE, ×40)
• The first biopsy of patient (just before the onset of anakinra treatment), amyloid deposition in glomerulus without tubular amyloidosis.

• The second biopsy of patient (3 years after the first biopsy), amyloid deposition in tubular basement membrane (Congo Red, polarized light, ×200)
IL-1 blockage

- **IL-1 receptor antagonist**- Anakinra
- **IL-1 neutralizing antibodies**- Canakinumab
- **IL-1 Trap**- Rilonacept
- **IL-1 beta converting enzyme (ICE) inhibition**- Pralnacasan
IL-1 receptor antagonist

- **Anakinra** is the first selective recombinant human interleukin-1 receptor antagonist (rHuIL-1Ra)
- Unlike the native protein, anakinra is not glycosylated and has an additional N-terminal methionine
- It binds to cell surface IL-1 receptors with high-affinity and **inhibits IL-1-alpha and IL-1-beta binding to IL-1 receptors (IL-1R)**.
IL-1 receptor antagonist

• Anakinra is administered daily via subcutaneous injection.

• It’s dose can be adjusted more readily or withdrawn more quickly if the patient does not respond, because of its short half-life (6 hours).
  
  – This is a potential advantage, especially early on in the course.

• Anakinra received approval from the FDA in 2001 to treat RA.
IL-1 neutralizing antibodies

- Canakinumab, is a **human monoclonal antibody** that **specifically targets IL-1β**, so that IL-1α may still participate in host defence.
- It was approved by the **FDA in 2009** for the treatment of **CAPS**
- Canakinumab is administered **monthly** via subcutaneous injection.
IL-1 Trap

- **Rilonacept** (soluble fusion protein containing human IgG1) linked to IL-1α and β with high affinity
- Rilonacept is administered **weekly** via subcutaneous injection.
- Rilonacept received US **FDA** approval for the treatment of **CAPS** in 2008.
- Rilonacept is not available in our country.
ICE is responsible for cleaving the inactive precursor of IL-1 beta into an active molecule

- Inhibition of ICE decrease the release of active IL-1 and posttranslational protein processing.
- reduce the synthesis of IL-18, TNFα, IL-6 and IFNγ
IL-1 beta converting enzyme (ICE) inhibition

- A preliminary study of an oral ICE inhibitor, pralnacasan, has been conducted in humans with rheumatoid arthritis.
  - Anti-inflammatory effects were noted.
  - However adverse effects such as diarrhea, nausea and hepatotoxic effects were reported frequently and the drug is not being developed further.
Safety issues with IL-1 blockade

IL-1 and host defence against infection

- increased risk of infection, particularly viral-type upper-airway infections, mycobacterial, and fungal infections.
- Severe bacterial infections especially with *Streptococcus pneumoniae* and *Streptococcus aureus* - pneumonia, osteomyelitis, cellulitis, bursitis, gangrene
- The increased frequency of serious infections related with dose and combined usage with other biologic agents
- But there were no related deaths or opportunistic infections including M.tuberculosis infections.
Safety issues with IL-1 blockade

• Although it has not been known how a reduction in IL-1 activity will affect natural defences against cancer yet, there are no an increased risk of cancers to date.

• In the rare cases of neutropaenia being less than 500/mm³, neutrophil counts rapidly rise upon cessation of treatment.