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Journal

Expert opinion on investigational drugs, 17(4)

ISSN

1354-3784

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Publication Date

2008-04-01

DOI

10.1517/13543784.17.4.451

Published in final edited form as:

Expert Opin Investig Drugs. 2008 April ; 17(4): 451–467. doi:10.1517/13543784.17.4.451.

NOVEL TARGETS AND NEW POTENTIAL: DEVELOPMENTS IN THE TREATMENT OF INFLAMMATION IN CHRONIC KIDNEY DISEASE

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Abstract

Background—Patients with chronic kidney disease (CKD) of all stages experience extremely high mortality, with cardiovascular causes accounting for about half of all their deaths. Traditional risk factors such as hypertension, hypercholesterolemia and diabetes mellitus cannot explain the excessively high cardiovascular mortality in CKD. Chronic inflammation is one of the novel risk factors that appear to contribute to the increased mortality seen in patients with CKD. Therapeutic interventions targeting chronic inflammation in CKD may lead to improved outcomes.

Objectives—To describe the role of inflammation in CKD and to review antiinflammatory pharmacologic therapies that could have a role in its therapy.

Methods—Review of the literature and expert opinion.

Results/Conclusion—Inflammation is a common and significant problem in CKD. There are currently no approved pharmacologic antiinflammatory therapies in CKD, but several agents are being studied in early clinical trials, while others could become viable alternatives in the future.

Keywords

chronic kidney disease; inflammation; therapy

1. Introduction

There are about 20 million patients in the US who suffer from various stages of chronic kidney disease (CKD),[1] of which approximately 400,000 patients with end stage renal disease (ESRD) require chronic renal replacement therapy, consisting of maintenance hemodialysis [over 90%] or chronic peritoneal dialysis[8–10%].[1] Dialysis patients

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experience lower quality of life, greater morbidity, higher hospitalization rates and increased mortality. In spite of recent improvement in dialysis treatment, these patients still experience an annual mortality rate of approximately 20%, and a markedly elevated incidence and prevalence of cardiovascular disease.[2] Indeed, several recent multi-center clinical trials including the HEMO [3] and ADAMEX [4] studies failed to prove a survival advantage from higher dialysis dose or better dialyzer membrane quality in ESRD patients. Interventions designed to improve traditional risk factors of cardiovascular disease such as hypertension, hypercholesterolemia, obesity, and hyperhomocysteinemia have largely failed to reduce mortality in ESRD patients. The recent "Die Deutsche Diabetes Dialyse Studie" (4D study) in 1,255 dialysis patients, randomized to either atorvastatin 20 mg or placebo, did not find a significant improvement in survival with statin use.[5] Modulating other cardiovascular risk factors such as hyperhomocysteinemia in dialysis patients has not led to major improvement in survival in this population either.[6–9] Thus in spite of all our advances, we are still uncertain how to improve the poor clinical outcomes, especially the high rate of cardiovascular disease and mortality, in dialysis and other CKD patients.

2. Inflammation in CKD

Chronic inflammation has been one of many so called novel or non-conventional risk factors that could explain the excess mortality in patients with CKD. Chronic inflammation is common among patients with CKD, and can be found in half or more of ESRD patients receiving maintenance hemodialysis (MHD).[10] The abnormally persistent chronic inflammatory process is seen not only in patients who are on dialysis, but also in patients with earlier stages of CKD.[11]

2.1 Causes of inflammation in CKD

The causes of inflammation in CKD have not been well described, but it is likely that a number of factors contribute to the initiation and maintenance of the inflammatory state, as listed in Table 1, including intercurrent illnesses,[12–14] various comorbidities,[15–17] decreased glomerular filtration rate [18] and various factors related to the dialysis procedure.[19–25] The ideal way to treat chronic inflammation would be to address the cause of it. This can be a very difficult task in patients where many of the factors involved in inflammation are non-modifiable; hence treatment regimens directed against mediators of the inflammatory process are generating significant interest.

2.2 Markers of inflammation in CKD

The inflammatory reaction is a complex cascade of events that involves a large number of mediators, and affects several different cell types. The presence of inflammation can be diagnosed by measuring one or more components involved in this process (Table 2). This can be done by assessing readily available and cheap markers such as serum albumin level or the white blood cell count. Unfortunately, such markers are often non-specific, as they can be affected by a variety of other conditions. More specific markers of inflammation such as C-reactive protein (CRP) and interleukin-6 (IL-6) offer a much more specific assessment of the inflammatory system, but are more expensive and some of these tests are not readily available in everyday practice. Unfortunately, the serum measurement of some cardinal

elements of the inflammatory system, such as interleukin-1 (IL-1), is not useful, since plasma levels of this cytokine do not correlate well with it's biological activity; IL-6 levels are in fact more useful as markers of IL-1 activation then IL-1 levels themselves.[26] There is currently no single best test to assess inflammation in CKD for diagnostic purposes; although the emerging wider availability of a laboratory test for highly sensitive CRP, coupled with a large volume of epidemiologic data showing the strong predictive value of a high CRP level for adverse outcomes make this test the most plausible diagnostic tool to assess inflammation. The therapeutic application of certain antiinflammatory medications may warrant the measurement of specific markers (such as the use of B-cell depleting agents, vide infra); unfortunately, the need for additional expensive and complicated tests necessary for therapeutic monitoring purposes may in themselves hinder the practical availability of such treatment modalities.

2.3 Inflammation and outcomes in CKD

Multiple studies have consistently reported a strong association between plasma levels of pro-inflammatory cytokine levels and adverse outcomes such as morbidity, hospitalizations and cardiovascular and all-cause mortality in CKD.[27–31] Poor outcomes have been associated with low albumin levels, elevated CRP or pro-inflammatory cytokine levels in ESRD patients;[32;33] collectively, elements of chronic inflammation and malnutrition appear to be among the strongest risk factors for high morbidity and mortality and low quality of life in CKD patients.[32]

At present, most of the evidence implicating inflammation in adverse clinical outcomes in CKD is epidemiological, but the consistency of the studies is impressive. Furthermore, the involvement of inflammation in the process of atherosclerosis is biologically plausible, and the cellular and subcellular mechanisms whereby inflammation induces and promotes atherosclerosis are now established.[34] Therefore, it is quite possible, although not yet conclusively proven, that an alleviation of inflammation could improve clinical outcomes in CKD patients. Moreover, since the deleterious effect of inflammation is usually exerted within a short period of time, it is possible that short-term interventions would suffice to reverse the inflammation and improve survival.

3. Pharmacologic therapy of inflammation

The strong association between inflammation and adverse outcomes in CKD provides a sound basis for clinical trials that could prove a cause-effect relationship behind the observed associations. Unfortunately (but not surprisingly) such clinical trials have not yet been performed. Opposite to disease states involving short term outcomes (such as rheumatologic diseases, where the end point can be symptomatic improvement), a meaningful end point in CKD is mortality, and it will take large numbers of participants and much longer studies to prove therapeutic benefits from any antiinflammatory intervention. Another roadblock is the balance of risk and benefit in such studies; the use of antiinflammatory agents that have potent immune suppressing capabilities is like navigating between Scylla and Charybdis, and one can see how clinical trials of such treatment modalities will take careful planning and significant determination. On the other hand, the

potential upside of a successful antiinflammatory therapy is significant, given the failure of conventional treatment modalities to achieve meaningful improvement in their outcomes.

The complexity of the inflammatory system has allowed the development of a remarkably diverse armamentarium of antiinflammatory agents. The majority of these agents has not been studied in patients with CKD, but will be presented here nevertheless (Table 3), since clinical application of any of these agents in CKD is possible in the future.

3.1 Tumor necrosis factor-alfa (TNF-alfa) inhibition

A “multifunctional” cytokine, TNF-alfa has attracted significant attention in the process of antiinflammatory drug development, with several agents approved for various indications, and many more in the development process. The exact mechanism of action whereby the inhibition of TNF-alfa exerts a beneficial effect in diseases characterized by inflammation is likely multifactorial, given the broad role of TNF-alfa in the inflammatory reaction.[35] Processes that TNF-alfa is involved in include endothelial cell activation, angiogenesis, the induction of various metalloproteinases and adhesion molecules and the modulation and regulation of other inflammatory cytokines.

3.1.1. Blockers of the TNF-alfa molecule—Three TNF-alfa blockers are approved for the treatment of various rheumatic diseases by the United States Food and Drug Administration (FDA); others are undergoing development.

Etanercept is a soluble p75 TNF-alfa receptor fusion protein that consists of two p75 TNF receptors bound to the Fc portion of IgG. One etanercept molecule binds two TNF molecules. Etanercept is effective for the treatment of various forms of inflammatory arthritis like rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis. It is administered once or twice weekly via subcutaneous injection. The effectiveness of etanercept in improving the nutritional status and clinical outcomes of hemodialysis patients as a consequence of its antiinflammatory properties is being studied in a Phase II randomized, double-blind, placebo-controlled clinical trial (ClinicalTrials.gov identifier: NCT 00293202). The primary outcome measure of this study is serum albumin and CRP levels.

Onercept is a p55 soluble TNF-alfa receptor that has been studied in clinical trials of patients with inflammatory bowel disease, psoriasis, and psoriatic arthritis.[36] Due to an unfavorable risk-benefit profile, however, the manufacturer of onercept has recently discontinued three Phase III clinical trials in patients with moderate-to-severe psoriasis. It is unclear what the future fate of this agent will be. There are no plans for studies in CKD.

Infliximab is a chimeric monoclonal antibody directed against TNF-alfa. The antigen-binding portion of infliximab is murine, and the constant Fc domain is human. Infliximab is administered via intravenous infusion approximately once every six weeks. Infliximab is effective for the treatment of a number of forms of inflammatory arthritis, inflammatory bowel disease, and other conditions. There are no plans for studies in CKD.

Adalimumab is a humanized monoclonal antibody that is administered subcutaneously once every two weeks. Due to its humanized construction, adalimumab is associated with a lower risk of anti-drug antibody formation compared with infliximab. Adalimumab has been approved for use in RA, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease. There are currently no plans for studies in CKD.

Certolizumab consists of the pegylated Fab fragment of a humanized monoclonal antibody that is directed against TNF and has been tested in Crohn's disease.[37;38] Unlike infliximab and adalimumab, certolizumab does not contain an Fc portion and is hence devoid of complement activation, antibody-dependent cellular cytotoxicity, or apoptosis. It is unclear what the practical advantages of this difference will be. Certolizumab is injected once a month subcutaneously. No application in CKD is planned.

3.1.2. Inhibitors of TNF-alfa gene transcription—Thalidomide, a once popular antiemetic agent exerts immunomodulatory effects by decreasing the transcription of TNF-alfa and the stability of its mRNA. The usefulness of this agent is limited by its toxicities, including teratogenicity. There are currently no studies of thalidomide in CKD.

Lenalidomide is an analogue of thalidomide that promises greater potency without a teratogenic potential. Currently it is being studied as a potential treatment for multiple myeloma and myelodysplasia.[39] It is unclear if this agent will see an application in the treatment of chronic inflammation, including in CKD.

Pentoxiphylline is a non-specific phosphodiestarase inhibitor that inhibits TNF transcription and was found beneficial in the treatment of arthritis in experimental animals.[40] In a number of small clinical trials of RA it did not produce meaningful benefits and was marred by poor tolerance.[41–43] Pentoxiphylline will be tested in ESRD patients in a randomized, double-blinded, placebo controlled clinical trial (ClinicalTrials.gov Identifier: NCT00561093). The Anti-Inflammatory and Anti-Oxidative Nutrition in Dialysis Patients (AIONID) study is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and will examine the effect of oral nutritional supplements with antiinflammatory and antioxidant properties along with pentoxiphylline therapy in a factorial design on malnutrition and inflammation in 100 patients receiving maintenance hemodialysis.

CF101 is an A3 adenosine receptor agonist that has antiinflammatory effects and reduced production of TNF in animal models.[44] Inhibition of transcription of TNF is a characteristic of adenosine.[45] Adenosine agonists in humans may be limited by dose related adverse effects: flushing, tachycardia, nausea, vomiting, and leukocytosis have been reported.[46] This agent has not been studied in CKD.

3.1.3. Agents using other mechanisms to inhibit TNF-alfa—TMI-1 is a dual TNF-alpha converting enzyme (TACE)/matrix metalloproteinase inhibitor that is under investigation in RA.[47] Theoretically, while this agent may reduce secretion of TNF-alfa, it could allow membrane expression of it, which could be pathogenically important. Clinical trial data should answer such concerns; to date TMI-1 has not been studied in CKD.

3.2. IL-1 inhibition

IL-1 is another multifunctional cytokine that plays a central role in the inflammatory reaction.[26] A variety of approaches to IL-1 inhibition have been employed.

3.2.1. IL-1 receptor antagonist (IL-1Ra)—The agonist effects of IL-1 are partially regulated by IL-1Ra, a naturally occurring glycoprotein inhibitor that binds the high affinity cell surface IL-1 receptor without activating it, and thus competes with the active IL-1 molecule for binding sites.[48] The effects of IL-1Ra include decreased prostaglandin production, decreased matrix metalloproteinase production, and reduction in the infiltration of tissues by mononuclear cells.[49–51] Anakinra is a human recombinant IL-1Ra that is available for treatment of rheumatoid arthritis and it may also be useful in treating other rheumatic disorders such as Still's disease. It differs from the native human protein in that it is not glycosylated and it has an additional N-terminal methionine. Anakinra may also show promise in the treatment of inflammation in patients with CKD. To date, a single study has been conducted regarding the pharmacokinetics of this drug in patients with impaired renal function.[52] Anakinra (1 mg/kg IV) was given to twelve patients with normal renal function, and twenty patients on hemodialysis. Another arm of this study evaluated subcutaneous (SQ) administration of 100mg of anakinra to 5 groups of patients stratified according to varying degrees of renal function ranging from normal to ESRD. This study demonstrated that the main route of elimination for Anakinra is renal clearance, and that hemodialysis has a very small effect on clearance. As a result of this study, thrice weekly dosing of anakinra may be possible.

3.2.2. IL-1 "trap"—Cytokine traps are high-affinity blockers of cytokine action that may be more potent inhibitors than other agents.[53] IL-1 is among the first cytokines targeted by this approach. Rilonacept is an IL-1 trap that incorporates two signaling chains of the cell surface IL-1 receptor linked by the Fc portion of IgG1 to form a soluble IL-1 binding protein with high affinity.[54] This agent is in clinical trials in children with juvenile idiopathic arthritis and in adults with RA. It has not yet been studied in patients with CKD.

3.2.3. IL-1 beta converting enzyme (ICE) inhibition—Inhibition of the IL-1 beta converting enzyme (ICE) reduces cytokine production by inhibiting posttranslational protein processing.[26] ICE cleaves the inactive precursor of IL-1 beta into an active molecule, and ICE inhibition could decrease the release of biologically active IL-1. This approach could also reduce the synthesis of interleukin-18 (IL-18) a cytokine that is part of the IL-1 superfamily and that also has pleiotropic effects. TNF is also produced though a pathway that may be amenable to a similar approach. An oral ICE inhibitor, pralnacasan was studied in animal models.[55;55] In preliminary human studies antiinflammatory effects were present; diarrhea and nausea were the most frequently reported adverse effects. A phase IIB clinical trial of pralnacasan in rheumatoid arthritis was suspended due to hepatotoxic effects in animals that received the drug for several months. It is unlikely that this agent will be tested in CKD.

3.3. IL-6 inhibition

Interleukin-6 (IL-6) has both proinflammatory and antiinflammatory effects.[57] Its roles are also multiple: it can activate T cells, B cells, macrophages, and osteoclasts, and it is a pivotal mediator of the hepatic acute-phase response. IL-6 binds to both soluble and membrane-bound receptors and leads to the transduction of intracellular signals, mediating gene activation and a wide variety of biologic activities.[58] Tocilizumab is a humanized anti-human IL-6 receptor antibody of the IgG1 subclass made by grafting a mouse anti-human IL-6 receptor monoclonal antibody onto human IgG1. Tocilizumab competes for both the membrane-bound and soluble forms of human IL-6 receptor, thus inhibiting the binding of the native cytokine to its receptor and interfering with the cytokine's effects. Clinical trials with tocilizumab indicate that this medication could be a an effective agent for the treatment of both RA and juvenile RA.[59;60] We are not aware of plans to use this medication in CKD.

3.4. Costimulation blockade

The activation of T cells by antigen presenting cells requires two signals: binding of the T cell receptor-peptide-MHC II complex and binding of cell surface costimulatory molecules that provide the essential "second signal".[61–63] Two major costimulatory systems are described: CD28 and/or cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) that can bind to one of two other proteins, CD80 or CD86 (often referred to as B7–1/B7–2),[62] and CD40, which binds to CD154 (also known as CD40 ligand, CD40L, or gp39).[61]

Abatacept (also called CTLA4-Ig) is a soluble fusion protein comprising CTLA-4 and the Fc portion of IgG1. It prevents CD28 from binding to CD80/CD86, due to its higher affinity for CD28. Administration of CTLA4-Ig prevents or ameliorates collagen-induced arthritis in mice and is beneficial in transplantation models.[64;65] Abatacept is approved for use in RA. It is unclear if there are plans for its use in CKD.

3.5. B cell depletion

B cell depletion is emerging as a new therapeutic approach in a variety of inflammatory conditions. Lymphocytes of the B cell lineage express on their surface CD20, a B lymphocyte-specific molecule; this is lost as B cells differentiate into plasma cells. Rituximab is a B cell depleting monoclonal anti-CD20 antibody, made up of both mouse and human parts. Rituximab causes B cell depletion and may do so through a variety of antibody-dependent mechanisms.[66] By virtue of the absence of CD20 protein expression on their surface, plasma cells are resistant to rituximab. As a consequence of this, immunoglobulin levels remain within the normal range, despite profound B cell depletion that persists for several months following a single course of treatment. Levels of autoantibodies with important roles in the pathophysiology of specific diseases such as rheumatoid factor in RA,[67;68] anti-dsDNA antibodies in systemic lupus erythematosus, [69] and antineutrophil cytoplasmic antibodies (ANCA) in ANCA-associated vasculitis [70–72] are, however, affected by B cell depletion. Rituximab may thus hold promise as a therapeutic agent in several immune-mediated conditions, and it has been examined for the treatment of various glomerular diseases.[73–77] It is unclear if this agent will be employed

for the treatment of chronic inflammation in CKD, since the autoantibody depletion resultant after B cell depletion may be more specific to certain types of diseases.

3.6. Interleukin-15 (IL-15) inhibition

IL-15 is an innate response cytokine that mediates a broad range of effects including activation of T cells, B cells, natural killer (NK) cells and neutrophils. It also regulates cell survival and protects various cell types from apoptosis and it may facilitate angiogenesis. [78]

HuMax-IL15 is a fully human antibody that is capable of binding both soluble and membrane bound IL-15. HuMax-IL15 is currently in phase I/II clinical trials in patients with RA. This agent appears to be well tolerated, and it produced encouraging responses after four or eight weeks of therapy in RA.[79] Adverse events reported were flu-like symptoms, transient fever, myalgia, upper respiratory tract infection, herpes simplex viral infection, and aphthous stomatitis. Larger studies are awaited; it is unclear if this agent will be used in CKD.

3.7. Interleukin-18 (IL-18) inhibition

IL-18 has multiple roles, including mediation of interferon-gamma production, IL-8 release, and NF-kappaB mediated transcription of inflammatory cytokines. A recombinant human IL-18 binding protein was identified that effectively blocked these effects of IL-18 in vitro. [80] Recombinant human IL-18 binding protein is being studied for potential efficacy and safety in the treatment of RA;[81] it is unclear if this agent has the potential to be used in CKD in the future.

3.8. Agents with complex or unclear mechanisms of action

Opposite to the previously described “designer” agents, several medications have been found to have antiinflammatory properties while being used for different primary indications.

3.8.1. Peroxisome proliferator activated receptor gamma (PPAR-gamma) agonists—PPAR-gamma, a member of the nuclear receptor superfamily of ligand-activated transcription factors, is highly expressed in atherosclerotic plaques.[82;83] The agonists of this receptor in clinical use are the thiazolidinediones rosiglitazone and pioglitazone. These agents have insulin-sensitizing actions and are used in the treatment of type 2 diabetes. Accumulating evidence suggests that PPAR-gamma agonists may have inhibitory effects on inflammatory processes in atherosclerotic plaques through indirect (insulin-sensitizing) and direct mechanisms.

One important molecular target of PPAR-gamma agonism is the transcription factor called nuclear factor-kappa-B (NF-kappa-B), which controls the synthesis of many pro-inflammatory genes.[84–87] Rosiglitazone has been shown to possess an antiinflammatory effect in vitro [88;89] and in animal models.[90] An antiinflammatory and antioxidant effect of rosiglitazone would be of potential benefit in conditions such as atherosclerosis, which is characterized by a chronic inflammation of the arterial wall.[34] Troglitazone,[91] an agent that was withdrawn from the market due to hepatotoxicity, and pioglitazone [92] have also

been shown to reduce carotid arterial intimal-medial thickness; this phenomenon could be causally related to an antiinflammatory effect of thiazolidinediones. Rosiglitazone caused suppression of intranuclear content of NF-kappa-B in mononuclear cells and the plasma concentrations of CRP and MCP-1 in a non-randomized study of both nondiabetic and diabetic subjects,[93] and reduced serum CRP levels in randomized, double-blind, placebo-controlled studies of diabetic [94] and non-diabetic [95] patients. Rosiglitazone also reduced insulin requirements and CRP levels in diabetic patients with ESRD on peritoneal dialysis. [96] There are no studies a priori examining the effect of PPAR-gamma agonists on hard clinical end points such as mortality in patients with CKD. A recent meta-analysis showed a significant increase in the risk of myocardial infarction in patients with type 2 diabetes treated with rosiglitazone, leading to a heated debate about the risks and benefits of using this agent.[97] Similar findings were reported in an observational study of diabetic patients on MHD,[98] suggesting that the future application of PPAR-gamma agonists in patients with CKD will have to be re-evaluated.

3.8.2. Non-steroidal antiinflammatory drugs (NSAID)—NSAIDs are one of the most commonly used drug classes worldwide, used by over 17 million Americans on a daily basis. The main mechanism of action of NSAIDs is the inhibition of cyclooxygenase, whereby they impair the transformation of arachidonic acid to prostaglandins, prostacyclin and thromboxanes.[99] Non-prostaglandin effects have been postulated to explain certain effects seen with NSAIDs; these include a decrease in the expression of L-selectin and thus an inhibition of neutrophil-endothelial adherence,[100] and the in vitro inhibition of NF-kappa-B dependent transcription with consequent inhibition of inducible nitric oxide synthetase.[101] The latter effect is characteristic of aspirin at therapeutic doses; other NSAIDs require supra-therapeutic doses to achieve the same.[101] A novel prostaglandin-mediated effect of NSAIDs is the inhibition of apoptosis; this may explain observations finding an association between aspirin use and a lower incidence of colorectal cancer.[102] It is unclear if NSAIDs will ever be explored in CKD for the alleviation of chronic inflammation with the goal of improving mortality. The adverse impact on kidney function in patients with CKD who are not on dialysis makes this very unlikely. Furthermore, the recent withdrawal of rofecoxib, a selective COX-2 inhibitor due to increased risk of cardiovascular events highlights the potential pitfalls of such an approach.

3.8.3. Hydroxy-methylglutaryl-Coenzyme A inhibitors (statins)—Statins drugs are usually employed to lower blood cholesterol level, but their effects appear to go beyond cholesterol-lowering, and include an antiinflammatory mechanism. In studies of primary and secondary cardiovascular prevention statins were found to lower serum CRP concentration as early as 14 days into therapy, independent of their lipid-lowering effects.[103–106] Patients with RA who were given atorvastatin in a clinical trial experienced symptomatic improvement and the reduction of CRP.[107] At least some of the cardiovascular benefits seen with statin therapy are now being attributed to their antiinflammatory effect. Different statins may have different antiinflammatory potency.[108] The mechanism of action of the statins' antiinflammatory nature is not fully understood; it may involve the inhibition of the main beta-2 integrin LFA-1 and thus the impairment of inflammatory cell adhesion, [109;110] or reduced lipidation of intracellular proteins and reduced expression of major

histocompatibility complex II molecules on antigen presenting cells with subsequent decrease in T-lymphocyte activation.[111] The use of statins for antiinflammatory purposes in CKD is an intriguing possibility. The negative findings of the 4D study which examined the effect on mortality and cardiovascular events of atorvastatin vs. placebo in diabetic dialysis patients are disappointing from this standpoint.[5] Nevertheless, two large clinical trials examining statin therapy in patients with various stages of CKD are being conducted, [112;113] which should provide further evidence for or against the usefulness of statins in this patient population, including answers regarding the role of their antiinflammatory effects.

3.8.4. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB)—ACE inhibitor and ARB medications are used primarily for blood pressure lowering purposes, but they have been found to exert a beneficial impact on outcomes in pathologic states such as congestive heart failure and CKD. The benefits seen in such conditions may be related to mechanisms different from their antihypertensive effect. One such potential mechanism is an antiinflammatory effect. In one study of patients with CHF high dose enalapril reduced IL-6 levels, with a concomitant decrease in the thickness of the interventricular septum.[114] In another short term study of CHF patients the use of candesartan reduced plasma levels of TNF-alfa, IL-6 and vascular adhesion molecules.[115] ACE inhibitors have also shown anti-inflammatory properties in the general population and in patients with CKD.[116;117] These classes of medications could thus be used as an a priori therapy against chronic inflammation in CKD, especially since their well established benefits in other areas should mitigate fears about potential deleterious effects. We are unaware of any current clinical trials testing this hypothesis, though.

3.8.5. Sevelamer hydrochloride—Sevelamer hydrochloride is a cationic polymer that is currently being used in patients with ESRD as an intestinal phosphate binder. This agent also possesses several “pleiotropic” effects that are unrelated to its original clinical indication; one such effect may be the amelioration of inflammation. A lowering of CRP levels was seen with the use of sevelamer hydrochloride in some,[118;119] but not all studies.[120] One proposed mechanism of action for an antiinflammatory effect of sevelamer hydrochloride is the decrease in calcium phosphate microcrystal depositions in the vessel wall, which have been shown to promote macrophage activation and the production of pro-inflammatory cytokines.[121] While theoretically appealing, the practical utility of sevelamer hydrochloride as an effective treatment for chronic inflammation in CKD is questionable, based on the negative outcomes of a recently published clinical trial comparing sevelamer hydrochloride with calcium-based phosphate binders.[122]

3.8.6. Heparin—Heparin is a glucosoaminoglycan that has seen widespread use as an anticoagulant agent. It has been recognized recently that heparin also possesses antiinflammatory properties, which appear to be distinct from its anticoagulant activity.[123] Such effects were seen in patients with RA,[124] asthma [125] and ulcerative colitis.[126] A potential mechanism of action is inhibition of leukocyte extravasation through binding to the beta-2 integrin CD11b/CD18.[127;128] An intriguing possibility is the development of new agents that retain the antiinflammatory properties of heparin, but without the anticoagulant

effects.[123;128] How this will affect patients with CKD is yet unclear. The practical impact of a heparin-related antiinflammatory effect in this patient population is questionable, given that heparin is already routinely applied as an anticoagulant with hemodialysis, yet chronic inflammation remains very common in these patients.

3.8.7. Megestrol acetate—Megestrol acetate is a synthetic derivate of progesterone that is primarily used as an appetite stimulant, but was also found to inhibit the activity of proinflammatory cytokines such as IL-1, IL-6, and TNF-alfa.[129–133] As an appetite stimulant in HD patients, megestrol acetate was found to improve appetite, increase energy and protein intake and increase dry weight and to improve quality of life.[134–136] The downside is that it can induce many side effects such as headaches, dizziness, confusion, diarrhea, hyperglycemia, thromboembolic phenomena, breakthrough uterine bleeding, peripheral edema, hypertension, adrenal suppression, and adrenal insufficiency.[129] Large, randomized, controlled trials will be needed to determine if the use of this agent in HD patients can be beneficial for the treatment of chronic inflammation.

3.8.8 Antioxidant therapies—One of the many potential causes of chronic inflammation is oxidative stress (Table 1). Therapeutic agents with anti-oxidant properties have been investigated and found to have the potential to lower the incidence of cardiovascular events in patients receiving MHD. High dose vitamin E supplementation was found to lower the risk of the composite outcome of myocardial infarction, stroke, peripheral vascular disease and angina in a small clinical trial in patients on MHD.[137] The use of vitamin C infusion and of vitamin E coated dialyzers in patients receiving MHD has also been shown to reduce oxidative stress;[138] no clinical trials have examined yet the impact of this strategy on mortality or other relevant clinical end points. Another small study in MHD patients found that treatment with acetylcysteine lowered the composite outcome of various cardiac events.[139] It is unclear to what extent the beneficial effects of the above antioxidants is related to an antiinflammatory effect, since the impact of oxidative stress on the vasculature is more complex in nature, and involves pathways that are not related to inflammation.[140;141] Furthermore, the feasibility and safety of these therapeutic regimens need to be tested in larger studies and in studies that include patients with CKD who are not yet on dialysis.

4. Conclusion

Chronic inflammation is very common in patients with CKD, especially in those who are on dialysis. The high burden of cardiovascular disease in this patient population, and the failure of several therapeutic interventions aimed at correcting traditional cardiovascular risk factors have lead to an increased focus on the role of non-traditional risk factors, of which chronic inflammation appears to be particularly important. Since many of the causes of chronic inflammation in CKD are non-modifiable, pharmacologic interventions aimed at correcting inflammation appear to be a promising new alternative strategy in the quest to improve the outcomes of this patient population. While the majority of the currently available antiinflammatory therapies have not yet been examined in patients with CKD, some of them have shown promise in reducing the levels of inflammatory markers. These preliminary benefits could translate into improved clinical outcomes, but well-powered clinical trials will be needed to prove the efficacy and the safety of any antiinflammatory agent in CKD.

5. Expert opinion

Chronic inflammation clearly represents an intriguing target in patients with CKD, especially those on chronic maintenance dialysis. At this point in time the level of evidence linking inflammation to increased mortality in this patient population is associative, but the consistency of the findings, the biologic plausibility of the process and the presence of similar findings in different patient populations all strengthen the possibility of a cause-effect relationship.[142] What are clearly missing are randomized controlled trials. This is not all that surprising, given that a beneficial effect in patients with CKD would have to be proven for hard clinical end points (such as mortality), which requires significantly larger resources compared to conditions where short term symptomatic improvement could be construed as a therapeutic success. The relative ease of proving success may be one reason why most antiinflammatory agents have been studied in rheumatologic conditions (the larger number of affected patients being another reason); relatively smaller numbers, more complicated pharmacokinetics and a higher degree of comorbidities may be reasons why the CKD population does not appear to be a desirable target to many pharmaceutical companies when thinking about new indications for their drugs. A few pharmacologic antiinflammatory interventions are being studied in CKD (such as etanercept and pentoxiphylline, see Table 3), albeit only for their effect on the surrogate end points of serum levels of inflammatory markers. We are hopeful that these pioneering trials will yield positive findings and will prompt larger clinical trials with more meaningful end points in the near future. Proof of clinical benefit may then lead to a treatment indication and this would almost certainly be followed by a proliferation of studies using similar or alternative agents. Unfortunately, the recent failure of several well-designed clinical trials in dialysis patients aimed at correcting a single metabolic abnormality [5;9] has dampened significantly the enthusiasm toward finding the “silver bullet” that would improve the high mortality seen in these patients.

An intriguing possibility is the application of one or more of the agents known to have pleiotropic effects beyond their primary mechanisms of action, such as statins or PPAR-gamma agonists (Table 3). Such agents could theoretically be effective through a wider range of mechanisms beside their antiinflammatory effects, which could make them more effective. Their side effect profiles may also be more tolerable (and more acceptable, both for patients and for regulatory authorities) compared to the more potent pure antiinflammatory agents that can increase the risk of serious infections and malignancies.

Given the current level of evidence it is too early to advocate any one antiinflammatory agent as a therapy for chronic inflammation in patients with CKD. Such medications have significant potential to become successful treatments in this patient population, but large and well designed randomized controlled trials will be needed before such an indication can be established.

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Table 1

Potential contributors of inflammation in chronic kidney disease

A. Causes of Inflammation in CKD Independent of Dialysis Treatment/Technique
1. Decreased clearance of pro-inflammatory cytokines
2. Volume overload
3. Oxidative stress
4. Carbonyl stress
5. Increased level of endotoxins
6. Decreased levels of antioxidants
7. Deteriorating protein-energy nutritional state and food intake
8. Increased susceptibility to infection in uremia
9. Genetic factors such as low production of anti-inflammatory cytokines
10. Inflammatory diseases with kidney involvement (SLE, HIV, etc.)
11. Increased prevalence of other comorbid conditions
12. Remnant (failed) kidney transplant
B. Additional Contributing Factors Related to Dialysis Treatment
I. Hemodialysis:
1. Exposure to dialysis tubing
2. Dialysis membranes with decreased biocompatiblility (eg, cuprophane)
3. Impurities in dialysis water and/or dialysate
4. Back-filtration or back-diffusion of contaminants
5. Foreign bodies, such as PTFE in current or remnant vascular access
6. Intravenous catheter
II. Peritoneal Dialysis:
1. Episodes of overt or latent peritonitis
2. PD-catheter as a foreign body and its related infections
3. Constant exposure to PD solution

CKD, chronic kidney disease; GFR, glomerular filtration rate; SLE, systemic lupus erythematosus; HIV, human immune-deficiency virus; PTFE, poly-tetra-fluoro-ethylene; PD, peritoneal dialysis.

Table 2

Inflammatory markers in CKD patients (adopted, with permission, from Kalantar-Zadeh K. Inflammatory marker-mania in chronic kidney disease: pentraxins at the crossroad of universal soldiers of inflammation. Clin J Am Soc Nephrol 2007; 2:872-5)

Category	Marker (and commonly used abbreviation)	Evidence for outcome predictability in CKD*
Short pentraxins	C-reactive protein (CRP) Serum amyloid P (SAP)	++++ ++
Long pentraxins	Pentraxin-3 (PTX3) neuronal pentraxins	++ ?
Pro-inflammatory cytokines	Interleukin-6 (IL-6) Interleukin-1 beta (IL-1β) Tumor necrosis factor alpha (TNF-α) Interleukin-8 (IL-8) Interleukin-18 (IL-18) Interleukin-12 (IL-12) interferon gamma (IFNγ)	++++ + +/− + ? ? +
Anti-inflammatory cytokines	Interleukin-10 (IL-10) IL-1 receptor antagonist (IL-1ra) Interleukin-4 (IL-4) transforming growth factor beta (TGF-β)	? + ? ?
Adipokines and related compounds	Adiponectin Visfatin Resistin Leptin CD163	++ + + + +
Adhesion molecules and endothelial markers	intercellular adhesion molecule-1 (ICAM-1) vascular cell adhesion molecule-1 (VCAM-1) E-selectin	++ ++ +
Coagulation markers	Fibrinogen Tissue plasminogen activator (t-PA) Plasminogen activator inhibitor-1 [PAI-1]), von Willebrand factor (vWF) & factor VII fibrin D-dimer	+ + + ? ?
Inflammatory molecules with negative acute phase reaction	Albumin (negative) Transferrin or TIBC Iron Fetuin	++++ ++ ++ +
Inflammatory lipoproteins	HDL inflammatory index (HII) Oxidized LDL (oxLDL)	++ +
inflammatory enzymes	Myeloperoxidase (MPO) matrix metalloproteinase (MMP-9)	+ +
Pro-inflammatory transcription factors	activator protein-1 (AP-1) nuclear factor-kappa B (NF-κB)	+ +
Other inflammatory markers	Serum ferritin Serum amyloid A (SAA) neopterin (monocyte/macrophage activator) Platelet count WBC count Neutrophil count Erythrocyte sedimentation rate (ESR)	+++ + + +++ ++ + +

Table 3

Antiinflammatory pharmacologic therapies.

Target	Agent	Structure	Mechanism of action	Approved indications	Anti-inflammatory use in CKD
TNF	Etanercept (Enbrel®, Amgen, Inc. and Wyeth Pharmaceuticals)	Two p75 TNF receptors bound to the Fc portion of IgG (soluble TNF receptor).	Binds TNF.	Rheumatoid arthritis, ankylosing spondylitis, psoriasis.	Phase II trial in ESRD underway.
	Onercept (Serono)	p55 soluble TNF receptor.	Binds TNF.	None yet; Phase III clinical trial for psoriasis discontinued for safety reasons.	None.
	Infliximab (Remicade®, Centocor, Inc.)	Chimeric monoclonal antibody.	Binds TNF.	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, inflammatory bowel disease.	None.
	Adalimumab (Humira®, Abbott Laboratories)	Humanized monoclonal antibody.	Binds TNF.	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn's disease.	None.
	Certolizumab (UCB Pharma Ltd.)	Pegylated Fab fragment of a humanized monoclonal antibody.	Binds TNF.	None yet; tested in Crohn's disease, psoriasis.	None.
	Thalidomide (Thalidomid®, Celgene Corp.)	Alpha- (N-phthalimido) glutaramide	Decreases the transcription of TNF (immunomodulatory)	Chemotherapy, erythema nodosum leprosum, HIV wasting	None.
	Lenalidomide (Revlimid®, Celgene Corp.)	Thalidomide analogue	Immunomodulator	Chemotherapy	None.
	Pentoxifylline (Trental®, Sanofi-Aventis)	1- (5-oxohexyl)-3, 7-dimethylxanthine	Non-specific phosphodiesterase inhibitor; inhibits TNF transcription.	No antiinflammatory indication.	None; tested in clinical trials.*
	CF101 (Can-Fite BioPharma)	?	A3 Adenosine receptor agonist; inhibits TNF transcription.	None yet, tested in Phase I and II trials for rheumatoid arthritis and cancer.	None.
	TMI-1	4-[[4-(2-butynyloxy)phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-(3S) thiomorpho linecarboxamide	Dual TNF-converting enzyme/matrix metalloprotease inhibitor.	None yet; studied in rheumatoid arthritis.	None.
IL-1β	Anakinra (Kineret®, Amgen, Inc.)	Human recombinant IL-1 receptor antagonist	Competitively inhibits IL-1 binding to IL-1 receptor.	Rheumatoid arthritis.	None.**
	Rilonacept (Regeron Pharmaceuticals, Inc.)	Fusion protein of human cytokine receptor extracellular domains and the Fc portion of human IgG1.	IL-1 trap.	None yet; pending indication for cryopirin-associated periodic syndromes.	None.

Target	Agent	Structure	Mechanism of action	Approved indications	Anti-inflammatory use in CKD
	Pralnacasan (Vertex Pahrmaceuticals)	Ethyl-hemiacetal prodrug.	IL-1 converting enzyme inhibitor. May also inhibit production of IL-18.	None; Phase IIB trial in rheumatoid arthritis suspended due to toxicity.	None.
IL-6	Tocilizumab (Actemra®, Roche/Chugai)	Humanized monoclonal antibody.	Blocks IL-6.	None in the US; approved in Japan for Castleman's disease; Phase III trials completed in rheumatoid arthritis.	None.
CTLA-4	Abatacept (Orencia®, Bristol-Myers Squibb)	Soluble fusion protein comprising CTLA-4 and the Fc portion of IgG1.	Prevents CD28 from binding to CD80/ CD86 (costimulatory blocker)	Rheumatoid arthritis.	None.
CD20	Rituximab (Rituxan®, Genetech, Inc. and Biogen Idec Inc.)	Monoclonal anti-CD20 antibody (both mouse and human portions).	B cell depletion through multiple antibody-dependent mechanisms.	Non-Hodgkin lymphoma, rheumatoid arthritis.	Studied in various glomerular diseases.
IL-15	HuMax-IL 15 (Genmab A/S)	Recombinant human antibody against IL-15.	Binds IL-15.	None; studied in Phase I/II trials for rheumatoid arthritis.	None.
IL-18	rhIL-18	Recombinant human antibody against IL-18.	Binds IL-18 and blocks induction of IFN-gamma and other cytokines.	None; studied in rheumatoid arthritis.	None.
NF-kappa-B	Pioglitazone (Actos®, Takeda Pharmaceuticals America Inc.) and Rosiglitazone (Avandia®, GlaxoSmithKline)	Thiazolidinediones.	PPAR-gamma agonists; decrease production of NF-kappa-B and increases inhibitor-kappa-B levels. May also have other mechanisms of action.	Diabetes mellitus; no anti-inflammatory indication.	None. Reduced CRP levels in a study of patients on peritoneal dialysis.
COX	NSAIDs (multiple)	various	Inhibition of cyclooxygenase and lipoxygenase and reduction of prostaglandin synthesis.	Various acute and chronic conditions associated with inflammation.	None.
Uncertain	Statins (multiple)	various	Hydroxy-methylglutaryl-Coenzyme A inhibitors. But anti-inflammatory effect may be unrelated to cholesterol lowering.	Cholesterol lowering; no anti-inflammatory indication.	None; effect on outcomes tested in clinical trials.

Target	Agent	Structure	Mechanism of action	Approved indications	Anti-inflammatory use in CKD
Uncertain	ACE-inhibitors/Angiotensin receptor blockers (multiple)	various	Decrease lipopolysaccharide-stimulated production of multiple cytokines	Anti-hypertensive; no anti-inflammatory indication.	Anti-hypertensive; no anti-inflammatory indication.
Uncertain	Sevelamer hydrochloride (Renagel®, Genzyme Corp.)	Cationic polymer.	Binds phosphorus and other molecules in the intestinal tract. Potentially anti-inflammatory mechanisms include the reduction of low molecular weight uremic toxin levels or a direct effect on arterial wall calcification.	Phosphate binder; no anti-inflammatory indication.	Phosphate binder in ESRD.
Uncertain	Heparin (generic)	Glucoseaminoglycan formed by repeated sulphated oligosaccharide units	Possible anti-inflammatory mechanism involves attenuation of CD11b dependent leukocyte adherence. Other mechanisms possible.	Anticoagulant; no anti-inflammatory indication.	Anticoagulant; no anti-inflammatory indication.
Uncertain	Megestrol acetate (Megace®, Bristol-Myers Squibb and Par Pharmaceuticals Inc.)	Synthetic derivative of progesterone.	Downregulation of IL-1, IL-6 and TNF.	Appetite stimulant; no anti-inflammatory indication.	None; studied in trials of nutritional status in ESRD.
Uncertain	Vitamin E (generic)	Alfa-tocopherol.	Anti-oxidant effect.	Replacement in vitamin E deficiency.	None.
Uncertain	Acetylcystein (Acetadote®, Cumberland Pharmaceuticals)	Acetylcystein.	Anti-oxidant effect.	Acetaminophen overdose, mucolytic use, prevention of contrast nephropathy.	None.

* At least one clinical trial is currently in process and registered at ClinicalTrial.gov

** Phase II clinical trial in progress