Targeting Immunity in End-Stage Renal Disease

Ivano Baragetti[a]   Basset El Essawy[c]   Paolo Fiorina[b, d]

[a]Nephrology Division, Bassini Hospital; [b]International Center for T1D, Pediatric Clinical Research Center Fondazione Romeo ed Enrica Invernizzi, Department of Biomedical and Clinical Science L. Sacco, University of Milan, Milan, Italy; [c]Medicine, Al-Azhar University, Cairo, Egypt; [d]Nephrology Division, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Abstract

Background: Despite the stable incidence of end-stage renal disease (ESRD), it continues to be associated with an unacceptably high cardiovascular risk. ***Summary:*** ESRD is characterized by enhanced oxidative stress and severe inflammation, which boost cardiovascular risk, thus increasing cardiovascular-associated mortality rate. While substantial effort has been made in the technological innovation of dialytic techniques, few significant advances have been made to reduce inflammation in patients with ESRD. Indeed, this contrasts with the extensive scientific breakthroughs made in the basic field of science in targeting inflammation. There is thus a pressing need for clinical trials to test the effect of reducing inflammation in patients with ESRD. Here, we will revisit the negative effect of ESRD on inflammation and explore the impact of enhanced inflammation on cardiovascular outcomes and survival in patients with ESRD. Finally, we will discuss the need for clinical trials that target inflammation in ESRD, as well as weigh potential disadvantages and offer novel innovative approaches. ***Key Message:*** We will try to understand why the issue of inflammation has not been successfully addressed thus far in patients with ESRD, while at the same time weighing the potential disadvantages and offering novel innovative approaches for targeting inflammation in patients with ESRD.

© 2017 S. Karger AG, Basel

Introduction

Despite the fact that end-stage renal disease (ESRD) is stable in its incidence, suggesting some efficacy of preventive approaches (ERA/EDA Registry: www.era-edta-reg. org), ESRD remains associated with higher cardiovascular risk compared to normal individuals [1] and carries a mortality rate higher than in other chronic diseases (ERA/EDA Registry: www.era-edta-reg.org). Enhanced oxidative stress and severe inflammation boost cardiovascular risk, particularly in diabetic patients [2]. While an association between inflammation and cardiovascular risk has been established [3], little progress has been made in targeting elevated inflammation in ESRD. Here, we will revisit the negative effect of ESRD on inflammation, and explore its impact on cardiovascular outcomes and survival in dialyzed patients. Finally, we will also discuss possible clinical

Paolo Fiorina, MD, PhD
Nephrology Division, Boston Children's Hospital
Harvard Medical School, Enders Building 5th Floor Room EN511
300 Longwood Ave, Boston, MA 02115 (USA)
E-Mail paolo.fiorina @ childrens.harvard.edu

trials that target inflammation in patients with failing kidneys, while weighing the potential disadvantages and offering novel innovative approaches. We used the key words "inflammation," "ESRD," and "cardiovascular risk" in searches of the PubMed, Embase, and Cochrane databases and then selected literature from the last 10 years.

Causes of Increased Inflammation in ESRD

The incidence of high levels of inflammation in ESRD is not surprising, given that high-sensitivity C-reactive protein (hs-CRP) is elevated in the course of metabolic syndrome, diabetes, and smoking, all of which are prevalent in ESRD patients [4]. In this disease setting, a combination of oxidative burst [5], uremic toxicity, dyslipidemia, and oxidative stress resulting from dysfunctional mitochondrial electron transfer [6] generates free reactive species. These compounds induce oxidative modifications of carbohydrates such as advanced glycation end products (AGEs), advanced oxidation protein products (AOPPs), advanced lipoxidation end products (ALEs), oxidized low density lipoproteins (oxLDLs) and DNA, in turn recognized as damage-associated molecular patterns (DAMPs) by Toll-like receptors (TLRs), which are upregulated in many cell types in ESRD, including macrophages and neutrophils [7]. TLRs and nucleotide binding oligomerization domain-like receptors (NODs), particularly NOD2, recognize oxidized products, priming a deleterious cascade of proinflammatory signaling [8]. Inflammation is further worsened by the same blood–dialyzer contact, water impurities, anemia, and antioxidant loss during dialysis [9, 10], all of which activate the complement cascade and neutrophil granulocytes. Furthermore, iron administration, which is essential for anemia management, exerts direct mitochondrial toxicity [11], reacting with H_2O_2 and producing OH and AOPPs [12]. These effects are mitigated in part by neutrophil gelatinase-associated lipocalin (NGAL), a marker of iron status that also functions as a free iron scavenger [13]. Heparin, which may induce the release of myeloperoxidase from endothelial cells, has pro-oxidant and pro-inflammatory effects as well [10]. Among circulating factors involved in worsening inflammation in ESRD, the following should also be noted.

Advanced Glycation End Products
AGEs are augmented in ESRD and interact with their receptor (RAGE), thus enhancing NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells)-mediated production of cytokines (interleukin [IL]-1, IL-6, monocyte chemoattractant protein-1 [MCP-1], tumor necrosis factor-α [TNF-α]) and cell adhesion molecules on T-cells [14].

Homocysteine
Hyperhomocysteinemia has been observed in ESRD patients associated with impaired methyltransferase activity, which is essential to revert homocysteine to methionine and adenosyl methionine. The latter is mandatory for DNA and protein methylation, and a lack of this molecule may lead to DNA hypermethylation and inflammation [15, 16].

Indoxyl Sulfate and P-Cresyl Sulfate
These uremic toxins are increased in the advanced stages of renal disease and induce intercellular adhesion molecule-1 (ICAM-1) expression, activating NF-κB and reactive species production by endothelial cells [17], increasing leukocyte endothelial adhesion [18], endothelial E-selectin, MCP-1, and tissue factor expression [19].

Uremic Dyslipidemia
The association of uremic dyslipidemia with inflammation [20] is related to cellular expression of the receptors involved in immune response (TLRs, major histocompatibility complex-II [MHC-II], cluster of differentiation [CD]40, CD40 ligand, CD80, CD28, apoptosis antigen 1 [FAS], and FAS ligand), which may be influenced by fluidity of membrane structures called lipid rafts. Thus, the expression of the aforementioned receptors can be modulated by membrane cholesterol content, and it can be impaired by dysfunctional high density lipoprotein [HDL] reverse cholesterol transport [21]. This leads to enhanced membrane expression of MHC-II, CD80, CD86, and TLR4 [22] and inflammation. Low density lipoproteins (LDLs) are also oxidized to oxLDLs, largely because of lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$) [23], which produces highly proinflammatory lysophosphatidylcholine and oxidized free fatty acids [24].

Adaptive and Innate Immunity Abnormalities in ESRD

Oxidative stress, dialysis, and uremic dyslipidemia induce immune incompetence in ESRD, causing detrimental and aimless hyperactivation of the immune system. The proof of this phenomenon is found in evidence of elevated levels of peripheral markers of immune activation (e.g., cytokines and chemokines) [25–32]. Other pro-

inflammatory cell products, like NGAL [13], galectin-3 (GAL-3) [33], and Lp-PLA$_2$ [34], the first released by polymorphonuclear leukocytes and the others by macrophages, have been shown to be augmented as well.

Inflammation is pivotally driven by TLRs and NODs on polymorphonuclear leukocytes (chronically activated and degranulated) [35], which release reactive species and myeloperoxidase (MPO) [10, 36]. The latter phenomenon is linked to leukocyte apoptosis and impaired phagocytosis [37], impaired antigen presentation function [38, 39], and increased cytokine production [7]. Dialytic treatment may activate antibodies and complements; indeed, dialyzers absorb albumin, complement component 3 (C3), C1q, immunoglobulin G and ficolin, leading to activation of the alternative [9, 40], classical, and lectin [41] pathways of complement. All these alterations in innate immunity unavoidably have affects in adaptive immunity as well, inducing elevated number of high IL-2-producing T-cells [27], low number of B-lymphocytes (due to apoptosis) [42], dysfunctional memory CD4$^+$ T-cells [43], reduced CD4/CD8 ratio, increased Th1/Th2 ratio, and depletion of memory CD4 and CD8 T-cells and regulatory T-cells (Tregs; more likely to exhibit an IL-17 pro-inflammatory phenotype) [44].

Mechanisms by Which Inflammation May Increase Cardiovascular and Mortality Risk in ESRD

In patients with ESRD, several mediators of inflammation share a link with cardiovascular disease [34, 45–63] (Table 1). Indeed, this is quite dubious for C reactive protein (CRP), either in terms of mere association or from a pathogenic perspective. In fact, while in some trials CRP did not merge as a strong independent cardiovascular risk factor (instead of IL-1, IL-6, TNF-α, albumin, and body mass index) [52, 53, 55, 60], the genetic analysis of polymorphisms leading to a gain of function of gene transcription of CRP failed to demonstrate a dose-dependent effect of this marker [64] and a possible causal role. Other biomarkers (sTWEAK, MIC-1, CD4$^+$CD28-null T-cells, RANKL, pentraxin3, CCR5, GAL-3, myeloperoxidase, Lp-PLA$_2$, and sCD14), have also been linked to cardiovascular risk in ESRD [32, 34, 45–48, 51, 57, 61–63]. Besides studies of association, there are evidences that uremic serum directly causes vascular damage [65] via activation of pro-inflammatory endothelial pathways (e.g., TLR4, NF-κB, NALP3 [NACHT, LRR and PYD domains-containing protein 3] and p38 MAPK [p38 mitogen-activated protein kinase]),

which induce increased endothelial expression of ICAM-1, VCAM-1 (vascular cell adhesion molecule-1), von Willebrand factor [66, 67], reduced nitric oxide availability, generating endothelial dysfunction [68].

Though the association between inflammation and cardiovascular disease is undeniable and while there is some evidence of a possible pathophysiological role, a sure causal relationship can not be stated so far, given the lack of intervention trials with this end point.

Targeting Inflammation in ESRD: Preclinical Studies

Indirect Strategies

Oxidative stress drives inflammation in ESRD, and not surprisingly, targeting oxidative stress is associated with improved outcomes in preclinical models (Table 2). Wistar rats treated with antioxidants such as L-arginine [69], tocotrienol, or α-tocopherol [70] showed a decrease in plasmatic concentrations of endothelial and cardiovascular stress markers including sICAM-1, TNF-α, NF-κB, VCAM-1, MCP-1, and TGF-β. Similar results have been obtained with LF-4 (an ApoA-1 mimetic peptide) [71], telmisartan [72], the oral sorbent AST-120, by improving the uremic milieu in ApoE-deficient mice [73]. However, the lack of reliable ESRD murine models makes these results difficult to interpret or translate to humans.

Direct Strategies

Several strategies aimed at reducing inflammation directly were tested including the following: (i) the C3 antagonist Cp40, which blunts complement activation and increases IL-10 concentrations in Cynomolgus monkeys [74]; (ii) the proteasome inhibitor MG132 and the NF-κB inhibitor PDTC, which reduced the binding of NF-κB to DNA and TNF-α levels in New Zealand white rabbits [75]; (iii) thalidomide, which induced decreased expression of NF-κB in C57BL/6 mice [76]; (iv) IL-10, which reduced MCP-1 and RANTES (regulated on activation, normal T-cell expressed and secreted) in Sprague–Dawley rats [77]; and (v) ablation of chemokine receptors in inbred C57BL/6 mice, which prevented renal ischemia/reperfusion injury [78].

Targeting Inflammation in ESRD Clinical Trials

Indirect Strategies

Antioxidant therapies have been tested in human clinical trials as well to reduce cardiovascular risk. In the SPACE

Table 1. Evidence of a relationship between inflammation markers and cardiovascular risk

Patients	Pivotal findings
Dialysis patients ($n = 176$)	IL-6 independently predicts mortality (OD [95% CI] 2.7 [1.1–6.6]) [52]
Dialysis patients ($n = 1,228$)	CRP predicts mortality (HRs [95% CI] 1st tertile 2.2 [0.96–5.16], 2nd tertile 3.3 [1.49–7.33], 3rd tertile 4.19 [1.93–9.06]) [60]
Dialysis patients ($n = 231$)	High vs low IL-1, IL-6, and TNF-α levels predict mortality (HR [95% CI] 2.62 [1.44–3.69]) [53]
Dialysis patients ($n = 218$)	sTWEAK alone and with IL-6 predicts cardiovascular mortality (respective HRs [95% CI] 2.66 [1.24–5.62] each pg/mL and 7.45 [1.98–27.9] each pg/mL) [46]
Dialysis patients ($n = 1,041$)	Hs-CRP and IL-6 predict cardiac death (respective adjusted HRs [95% CI] 1.22 [0.96–1.55] each mg/dL and 1.21 [0.96–1.53] each pg/mL) [55]
Dialysis patients ($n = 54$)	Hs-CRP predicts silent cerebral infarction (HR [95% CI] 1.61 [1.17–2.85] each mg/dL) [56]
Dialysis patients ($n = 470$)	MIC-1 predicts mortality (OD [95% CI] 4.84 [1.09–21.62]) [45]
Dialysis patients	CRP and CD4 + CD28-null T-cells correlate with impaired flow-mediated vasodilatation and increased carotid intima-media thickness [57]
Dialysis patients ($n = 68$)	Inverse relationship between RANKL and vascular calcifications [47]
Dialysis patients ($n = 105$)	Hs-CRP, PTX3, IL-6/IL-10 ratio correlate with systolic dysfunction [62]
Dialysis and control patients	Inflammation correlates with endothelial glycocalyx damage [65]
Dialysis, CKD and control patients	VCAM-1, ICAM-1, vWF, and circulating endothelial cells correlate with p38 MAPK and NF-κB in ESRD [67]
Dialysis patients ($n = 413$)	CCR5 delta 32 and hs-CRP >10 mg/L predict mortality (HR [95% CI] 1.82 [1.29–2.58]) [61]
Dialysis patients ($n = 1,168$), patients submitted to coronary angiography ($n = 2,579$)	GAL-3 predicts cadiovascular mortality in LURIC and 4D studies (respective HRs [95% CI] 1.21 [1.01–1.44] and 1.12 [1.01–1.24] each SD) [48]
Dialysis patients ($n = 102$)	Lp-PLA$_2$ >194 nmol/min/mL predicts cardiovascular outcome (OD [95% CI] 2.54 [1.09–5.95]) [34]
Dialysis patients ($n = 236$)	Doubled MPO levels predict cardiovascular risk (HR [95% CI] 1.60 [1.17–2.18]) [51]
Dialysis patients ($n = 211$)	sCD14 predicts mortality (HR [95% CI] 3.11 [1.49–6.36] for 3rd tertile) [32]
Dialysis patients ($n = 310$)	sCD14 predicts mortality (HR [95% CI] 1.94 [1.01–3.75] for 3rd tertile [63]

sTWEAK, serum TNF-related weak inducer of apoptosis; MIC-1, macrophage inhibitory cytokine-1; RANKL, receptor activator of nuclear factor kappa-B ligand; CCR5, C-C chemokine receptor type 5.

study, a reduction of 64% for overall end points and of 70% for myocardial infarction was observed with vitamin E in ESRD patients [79]. The study by Jun et al. [80], in which 10 trials pooling nearly 2,000 patients with altered kidney function who were treated with several antioxidants (e.g., vitamin E, co-enzyme Q, acetylcysteine, bardoxolone methyl and human recombinant superoxide dismutase) were analyzed, showed a 43% reduction in cardiovascular end points (RR = 0.57), but only in dialysis patients. Disappointingly, anti-hypertensives, statins, and lifestyle changes failed to reduce cardiovascular risk in ESRD patients [81]. In particular, the efficacy of renin–angiotensin sys-

tem inhibitors is far from being demonstrated. With regard to homocysteine-lowering treatments, while showing conflicting results on endothelial function [82, 83], results did not suggest improved prevention of cardiovascular events either in ESRD [84] or kidney transplanted patients [85]. However, it is possible that lowering hyperhomocysteinemia may be of value in diabetic patients [86, 87].

Targeting Complement

Pharmacological complement inhibition by anti-C1 and anti-C5a compounds may abrogate intradialytic inflammation, due to blood–dialyzer contact. However, the

Table 2. Experimental therapies aimed at reducing inflammation in preclinical models of CKD and ESRD

| Experimental model	Study design	Results
Cynomolgus hemodialysis model	Complement activation treated with the C3 inhibitor Cp40	Reduced complement activation and increased levels of IL-10 [74]
Adenine-induced CKD in C57BL/6 mice ($n = 30$)	3 Groups: (a) Control group (b) Adenine diet group (c) Adenine + thalidomide group	Reduced expression of cytokines and activation of NK-kB in the kidney [76]
Subtotal nephrectomized rats	3 Groups: (a) Untreated group (b) Telmisartan group (c) Telmisartan antagonist GW9662 group	Telmisartan antagonized macrophage infiltration, osteopontin, and VCAM-1 expression, all blunted by GW9662 [72]
5/6 nephrectomy rats receiving the ApoA1 mimetic drug L4F	3 Groups: (a) Control sham operated rats (b) Placebo group (c) L4F group	L4F reduced MCP-1 and NF-κB expression [71]
Extensive renal mass reduction in rats	4 Groups: (a) CKD rats (b) L-arginine group (c) L-carnitine, catechin, vitamins E and C (d) group (e) L-carnitine, catechin, vitamins E and C + L-arginine group	L-arginine decreased cytokines Antioxidants decreased cytokines and sICAM-1, increasing IL-4 levels L-arginine + antioxidants recovered normal cytokines and sICAM-1 [69]
New Zealand white rabbits submitted to 5/6 nephrectomy or sham operation ($n = 24$)	3 Groups: (a) CKD untreated rabbits (b) Proteasome inhibitor MG132 group (c) NF-κB inhibitor PDTC group	Reduced NF-κB DNA binding capacity and reduction of TNF-α levels in the MG132 group, similarly to PDTC [75]
Streptozotocin-induced diabetic rats with CKD	2 Groups: (a) Tocotrienol and α-tocopherol group (b) Control group	Tocotrienol, associated with α-tocopherol, prevented the elevation of TNF-α, TGF-β, and the activation of NF-κB [70]
Rats	2 Groups: (a) IL-10-transfected group (b) Control group	IL-10 reduced the expression of MCP-1, IFN-γ, IL-2, and RANTES [77]
ApoE-deficient mice treated with AST-120	3 Groups: (a) Uninephrectomy (b) Subtotal nephrectomy (c) Sham operation	Reduced aortic expression of MCP-1, TNF-α, and IL-1β [73]

IFN-γ, interferon-γ; NTGF-β, transforming growth factor-β.

high costs of these drugs are a major concern for healthcare providers. Conversely, 5C6 peptide (binding to factor H coated to polystyrene materials) [88], PMX-53 (which bind to C5aR) [89], Compstatin and POT-4 (which antagonize C3) [90], may represent promising alternatives.

Targeting Cytokines

Few trials evaluating cytokine targeting in ESRD can be found. One is based on the administration of a recombinant human IL-1 receptor antagonist (Anakinra) [91].

Fourteen subjects were randomized to receive 100 mg Anakinra or placebo subcutaneously for 4 weeks. The trial was biased by the presence of more severe inflammation in the placebo arm. Treated patients exhibited 53 and 40% reduction in hs-CRP and IL-6 levels, respectively, as compared to 1% reduction and 20% increase in the placebo group [91]. In another trial, the TNF-α antagonist, etanercept, tested with 10 dialyzed patients treated for 44 weeks failed to produce any effect on inflammation [92].
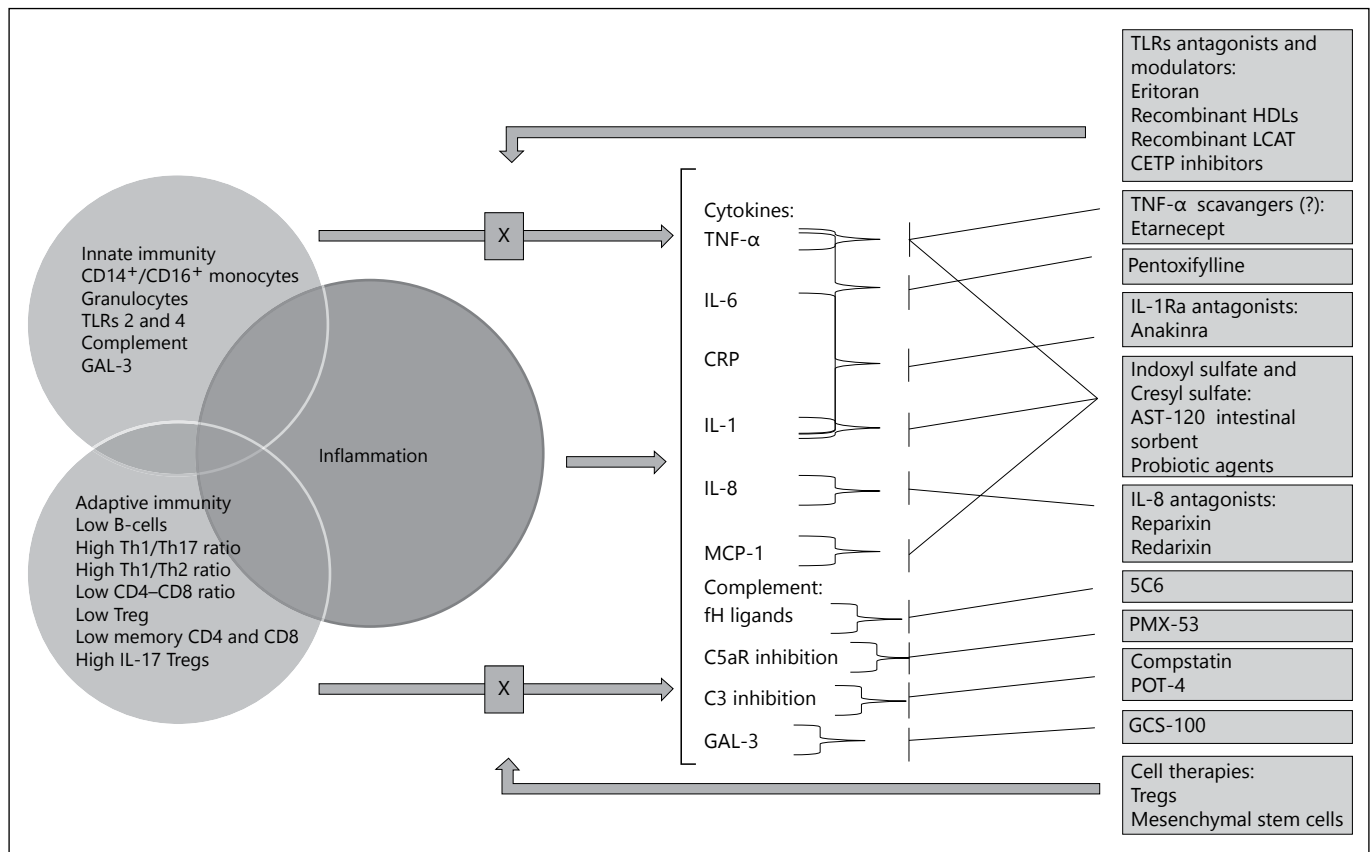
Fig. 1. Schematic attempt to show pathways that may be targeted or are currently being targeted in ESRD.

Lessons Learned from Trials and the Next Immunological/Anti-Inflammatory Trial in ESRD

The goal of improving cardiovascular risk in dialysis patients can be achieved with integrated management, ranging from strict blood pressure and glycemic control, through treatment with antioxidant compounds, to administration of novel anti-inflammatory molecules [93, 94]. Indeed, while an optimal blood pressure and glycemic control are difficult to achieve in real life, more anti-inflammatory treatments (Fig. 1) should be encouraged to confirm, for instance, the interesting results obtained with IL-1α receptor antagonists. The effect of novel TLR antagonists on the inflammatory response and cardiovascular risk in ESRD should be tested as well [95]. Likewise, therapies improving HDL concentrations (e.g., recombinant HDLs, recombinant lecithin-cholesterol acyltransferase [rLCAT], cholesteryl ester transfer protein [CETP] antagonists, torcetrapib, dalcetrapib and evacetrapib) should be evaluated. Strategies aiming at the lowering of uremic toxins, such

as indoxyl sulfate and p-cresyl sulfate, by using intestinal probiotics may also prove interesting [96]. No data on the effect of galectin targeting in dialysis are available. The only reported experience is a trial developed by La Jolla Pharmaceutical Company in patients with chronic kidney disease stage 3b, treated with a complex polysaccharide (GCS-100), which binds to GAL-3 inhibiting profibrotic effects. A reduction in GFR decline was observed (see ASN 2014 abstract book). Also rGAL-1 which, contrarily to GAL-3, may have immunomodulatory and anti-inflammatory properties may be considered for use in this context [97]. Cell therapy may play an important role in the next clinical trials. Tregs have a crucial role in maintaining immunological self-tolerance and in limiting the inflammatory response to immune reactions [98], possibly containing the aimless immunological activation in ESRD [98]. Finally, mesenchymal stem cells, which possess immunomodulatory properties, may be harnessed to reduce inflammation as shown in diabetes, transplantation, and diabetic nephropathy [99–103].

Conclusions

Inflammation is one of the pivotal causes of mortality and morbidity in ESRD patients. Targeting of inflammation will be necessary to reduce the devastating cardiovascular complications observed in ESRD patients. Unfortunately, this has not been adequately addressed thus far in this population, particularly in diabetic patients, who may benefit the most from these approaches [104].

Acknowledgments

Disclosure Statement

The authors have no conflicts of interests to declare.

References

1 Tonelli M, Karumanchi SA, Thadhani R: Epidemiology and mechanisms of uremia-related cardiovascular disease. Circulation 2016; 133:518–536.

2 La Rocca E, Fiorina P, Astorri E, Rossetti C, Lucignani G, Fazio F, Giudici D, Castoldi R, Bianchi G, Di Carlo V, Pozza G, Secchi A: Patient survival and cardiovascular events after kidney-pancreas transplantation: comparison with kidney transplantation alone in uremic IDDM patients. Cell Transplant 2000;9: 929–932.

3 Stenvinkel P: Inflammatory and atherosclerotic interactions in the depleted uremic patient. Blood Purif 2001;19:53–61.

4 Beddhu S, Kimmel PL, Ramkumar N, Cheung AK: Associations of metabolic syndrome with inflammation in CKD: results from the third national health and nutrition examination survey (NHANES III). Am J Kidney Dis 2005; 46:577–586.

5 Li N, Karin M: Is NF-kappaB the sensor of oxidative stress? FASEB J 1999;13:1137–1143.

6 Vaziri ND, Dicus M, Ho ND, Boroujerdi-Rad L, Sindhu RK: Oxidative stress and dysregulation of superoxide dismutase and NADPH oxidase in renal insufficiency. Kidney Int 2003;63:179–185.

7 Gollapudi P, Yoon JW, Gollapudi S, Pahl MV, Vaziri ND: Leukocyte toll-like receptor expression in end-stage kidney disease. Am J Nephrol 2010;31:247–254.

8 Anders HJ, Lech M: NOD-like and toll-like receptors or inflammasomes contribute to kidney disease in a canonical and a non-canonical manner. Kidney Int 2013;84:225–228.

9 Ekdahl KN, Lambris JD, Elwing H, Ricklin D, Nilsson PH, Teramura Y, Nicholls IA, Nilsson B: Innate immunity activation on biomaterial surfaces: a mechanistic model and coping strategies. Adv Drug Deliv Rev 2011;63:1042–1050.

10 Honda H, Ueda M, Kojima S, Mashiba S, Hirai Y, Hosaka N, Suzuki H, Mukai M, Watanabe M, Takahashi K, Shishido K, Akizawa T: Assessment of myeloperoxidase and oxidative alpha1-antitrypsin in patients on hemodialysis. Clin J Am Soc Nephrol 2009;4:142–151.

11 Zager RA: Parenteral iron compounds: potent oxidants but mainstays of anemia management in chronic renal disease. Clin J Am Soc Nephrol 2006;1(suppl 1):S24–S31.

12 Tovbin D, Mazor D, Vorobiov M, Chaimovitz C, Meyerstein N: Induction of protein oxidation by intravenous iron in hemodialysis patients: role of inflammation. Am J Kidney Dis 2002;40:1005–1012.

13 Bolignano D, Coppolino G, Romeo A, De Paola L, Buemi A, Lacquaniti A, Nicocia G, Lombardi L, Buemi M: Neutrophil gelatinase-associated lipocalin (NGAL) reflects iron status in haemodialysis patients. Nephrol Dial Transplant 2009;24:3398–3403.

14 Yamagishi S, Nakamura K, Matsui T, Noda Y, Imaizumi T: Receptor for advanced glycation end products (RAGE): a novel therapeutic target for diabetic vascular complication. Curr Pharm Des 2008;14:487–495.

15 Pfalzer AC, Choi SW, Tammen SA, Park LK, Bottiglieri T, Parnell LD, Lamon-Fava S: S-adenosylmethionine mediates inhibition of inflammatory response and changes in DNA methylation in human macrophages. Physiol Genomics 2014;46:617–623.

16 Perna AF, Acanfora F, Satta E, Lombardi C, Ingrosso D, De Santo NG: Hyperhomocysteinemia and cardiovascular disease in uremia: the newest evidence in epidemiology and mechanisms of action. Semin Nephrol 2004; 24:426–430.

17 Tumur Z, Shimizu H, Enomoto A, Miyazaki H, Niwa T: Indoxyl sulfate upregulates expression of ICAM-1 and MCP-1 by oxidative stress-induced NF-kappaB activation. Am J Nephrol 2010;31:435–441.

18 Pletinck A, Glorieux G, Schepers E, Cohen G, Gondouin B, Van Landschoot M, Eloot S, Rops A, Van de Voorde J, De Vriese A, van der Vlag J, Brunet P, Van Biesen W, Vanholder R: Protein-bound uremic toxins stimulate crosstalk between leukocytes and vessel wall. J Am Soc Nephrol 2013;24:1981–1994.

19 Gondouin B, Cerini C, Dou L, Sallee M, Duval-Sabatier A, Pletinck A, Calaf R, Lacroix R, Jourde-Chiche N, Poitevin S, Arnaud L, Vanholder R, Brunet P, Dignat-George F, Burtey S: Indolic uremic solutes increase tissue factor production in endothelial cells by the aryl hydrocarbon receptor pathway. Kidney Int 2013;84:733–744.

20 Kaysen GA, Dalrymple LS, Grimes B, Chertow GM, Kornak J, Johansen KL: Changes in serum inflammatory markers are associated with changes in apolipoprotein A1 but not B after the initiation of dialysis. Nephrol Dial Transplant 2014;29:430–437.

21 Kaseda R, Jabs K, Hunley TE, Jones D, Bian A, Allen RM, Vickers KC, Yancey PG, Linton MF, Fazio S, Kon V: Dysfunctional high-density lipoproteins in children with chronic kidney disease. Metabolism 2015;64:263–273.

22 Norata GD, Pirillo A, Ammirati E, Catapano AL: Emerging role of high density lipoproteins as a player in the immune system. Atherosclerosis 2012;220:11–21.

23 Delporte C, Van Antwerpen P, Vanhamme L, Roumeguere T, Zouaoui Boudjeltia K: Low-density lipoprotein modified by myeloperoxidase in inflammatory pathways and clinical studies. Mediators Inflamm 2013;2013: 971579.

24 Zalewski A, Macphee C: Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. Arterioscler Thromb Vasc Biol 2005;25:923–931.

25 Rysz J, Banach M, Cialkowska-Rysz A, Stolarek R, Barylski M, Drozdz J, Okonski P: Blood serum levels of IL-2, IL-6, IL-8, TNF-alpha and IL-1beta in patients on maintenance hemodialysis. Cell Mol Immunol 2006; 3:151–154.

26 Wong CK, Szeto CC, Chan MH, Leung CB, Li PK, Lam CW: Elevation of pro-inflammatory cytokines, C-reactive protein and cardiac troponin T in chronic renal failure patients on dialysis. Immunol Invest 2007;36:47–57.

27 Bohler T, Canivet C, Nguyen PN, Galvani S, Thomsen M, Durand D, Salvayre R, Negre-Salvayre A, Rostaing L, Kamar N: Cytokines correlate with age in healthy volunteers, dialysis patients and kidney-transplant patients. Cytokine 2009;45:169–173.

28 Rysz J, Majewska E, Stolarek RA, Banach M, Cialkowska-Rysz A, Baj Z: Increased levels of soluble TNF-alpha receptors and cellular adhesion molecules in patients undergoing bioincompatible hemodialysis. Am J Nephrol 2006;26:437–444.

29 Lin Z, Gong Q, Zhou Z, Zhang W, Liao S, Liu Y, Yan X, Pan X, Lin S, Li X: Increased plasma CXCL16 levels in patients with chronic kidney diseases. Eur J Clin Invest 2011;41:836–845.

30 Richter R, Forssmann U, Henschler R, Escher S, Frimpong-Boateng A, Forssmann WG: Increase of expression and activation of chemokine CCL15 in chronic renal failure. Biochem Biophys Res Commun 2006;345:1504–1512.

31 Caballero A, Ruiz-Esteban P, Palma E, Ramirez P, Fuentes L, Sola E, Rudas E, Alonso A, Hernandez D: Decrease in the percentage of peripheral blood CXCR3highCD4+ lymphocytes after renal transplantation. Transpl Immunol 2014;31:7–10.

32 Raj DS, Carrero JJ, Shah VO, Qureshi AR, Barany P, Heimburger O, Lindholm B, Ferguson J, Moseley PL, Stenvinkel P: Soluble CD14 levels, interleukin 6, and mortality among prevalent hemodialysis patients. Am J Kidney Dis 2009;54:1072–1080.

33 Meijers WC, van der Velde AR, Ruifrok WP, Schroten NF, Dokter MM, Damman K, Assa S, Franssen CF, Gansevoort RT, van Gilst WH, Sillje HH, de Boer RA: Renal handling of galectin-3 in the general population, chronic heart failure, and hemodialysis. J Am Heart Assoc 2014;3:e000962.

34 Rolla R, De Mauri A, Valsesia A, Vidali M, Chiarinotti D, Bellomo G: Lipoprotein profile, lipoprotein-associated phospholipase A2 and cardiovascular risk in hemodialysis patients. J Nephrol 2015;28:749–755.

35 Cohen G, Raupachova J, Horl WH: The uraemic toxin phenylacetic acid contributes to inflammation by priming polymorphonuclear leucocytes. Nephrol Dial Transplant 2013;28:421–429.

36 Majewska E, Baj Z, Sulowska Z, Rysz J, Luciak M: Effects of uraemia and haemodialysis on neutrophil apoptosis and expression of apoptosis-related proteins. Nephrol Dial Transplant 2003;18:2582–2588.

37 Sardenberg C, Suassuna P, Andreoli MC, Watanabe R, Dalboni MA, Manfredi SR, dos Santos OP, Kallas EG, Draibe SA, Cendoroglo M: Effects of uraemia and dialysis modality on polymorphonuclear cell apoptosis and function. Nephrol Dial Transplant 2006;21:160–165.

38 Ramirez R, Carracedo J, Berdud I, Carretero D, Merino A, Rodriguez M, Tetta C, Martin-Malo A, Aljama P: Microinflammation in hemodialysis is related to a preactivated subset of monocytes. Hemodial Int 2006;10(suppl 1):S24–S27.

39 Yoon JW, Pahl MV, Vaziri ND: Spontaneous leukocyte activation and oxygen-free radical generation in end-stage renal disease. Kidney Int 2007;71:167–172.

40 Nilsson B, Ekdahl KN, Mollnes TE, Lambris JD: The role of complement in biomaterial-induced inflammation. Mol Immunol 2007; 44:82–94.

41 Mares J, Richtrova P, Hricinova A, Tuma Z, Moravec J, Lysak D, Matejovic M: Proteomic profiling of blood-dialyzer interactome reveals involvement of lectin complement pathway in hemodialysis-induced inflammatory response. Proteomics Clin Appl 2010;4:829–838.

42 Fernandez-Fresnedo G, Ramos MA, Gonzalez-Pardo MC, de Francisco AL, Lopez-Hoyos M, Arias M: B lymphopenia in uremia is related to an accelerated in vitro apoptosis and dysregulation of BCL-2. Nephrol Dial Transplant 2000;15:502–510.

43 Litjens NH, Huisman M, van den Dorpel M, Betjes MG: Impaired immune responses and antigen-specific memory CD4+ T cells in hemodialysis patients. J Am Soc Nephrol 2008; 19:1483–1490.

44 Afzali B, Edozie FC, Fazekasova H, Scotta C, Mitchell PJ, Canavan JB, Kordasti SY, Chana PS, Ellis R, Lord GM, John S, Hilton R, Lechler RI, Lombardi G: Comparison of regulatory T cells in hemodialysis patients and healthy controls: implications for cell therapy in transplantation. Clin J Am Soc Nephrol 2013; 8:1396–1405.

45 Breit SN, Carrero JJ, Tsai VW, Yagoutifam N, Luo W, Kuffner T, Bauskin AR, Wu L, Jiang L, Barany P, Heimburger O, Murikami MA, Apple FS, Marquis CP, Macia L, Lin S, Sainsbury A, Herzog H, Law M, Stenvinkel P, Brown DA: Macrophage inhibitory cytokine-1 (MIC-1/GDF15) and mortality in end-stage renal disease. Nephrol Dial Transplant 2012;27:70–75.

46 Carrero JJ, Ortiz A, Qureshi AR, Martin-Ventura JL, Barany P, Heimburger O, Marron B, Metry G, Snaedal S, Lindholm B, Egido J, Stenvinkel P, Blanco-Colio LM: Additive effects of soluble TWEAK and inflammation on mortality in hemodialysis patients. Clin J Am Soc Nephrol 2009;4:110–118.

47 Ozkok A, Caliskan Y, Sakaci T, Erten G, Karahan G, Ozel A, Unsal A, Yildiz A: Osteoprotegerin/RANKL axis and progression of coronary artery calcification in hemodialysis patients. Clin J Am Soc Nephrol 2012;7:965–973.

48 Drechsler C, Delgado G, Wanner C, Blouin K, Pilz S, Tomaschitz A, Kleber ME, Dressel A, Willmes C, Krane V, Kramer BK, Marz W, Ritz E, van Gilst WH, van der Harst P, de Boer RA: Galectin-3, renal function, and clinical outcomes: results from the LURIC and 4D studies. J Am Soc Nephrol 2015;26:2213–2221.

49 Hogas S, Schiller A, Voroneanu L, Constantinescu D, Timar R, Cianga P, Siriopol D, Bob F, Cianga C, Onofriescu M, Gadalean F, Hogas M, Mihaescu A, Bilha SC, Timar B, Kanbay M, Banach M, Covic A: Predictive value for galectin 3 and cardiotrophin 1 in hemodialysis patients. Angiology 2016;67:854–859.

50 McCullough PA, Agrawal V, Danielewicz E, Abela GS: Accelerated atherosclerotic calcification and monckeberg's sclerosis: a continuum of advanced vascular pathology in chronic kidney disease. Clin J Am Soc Nephrol 2008;3:1585–1598.

51 Wang AY, Lam CW, Chan IH, Wang M, Lui SF, Sanderson JE: Prognostic value of plasma myeloperoxidase in ESRD patients. Am J Kidney Dis 2010;56:937–946.

52 Honda H, Qureshi AR, Heimburger O, Barany P, Wang K, Pecoits-Filho R, Stenvinkel P, Lindholm B: Serum albumin, C-reactive protein, interleukin 6, and fetuin A as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. Am J Kidney Dis 2006;47:139–148.

53 Cohen SD, Phillips TM, Khetpal P, Kimmel PL: Cytokine patterns and survival in haemodialysis patients. Nephrol Dial Transplant 2010;25:1239–1243.

54 Beddhu S, Cheung AK, Larive B, Greene T, Kaysen GA, Levey AS, Rocco M, Sarnak M, Toto R, Eknoyan G; Hemodialysis (HEMO) Study Group: Inflammation and inverse associations of body mass index and serum creatinine with mortality in hemodialysis patients. J Ren Nutr 2007;17:372–380.

55 Parekh RS, Plantinga LC, Kao WH, Meoni LA, Jaar BG, Fink NE, Powe NR, Coresh J, Klag MJ: The association of sudden cardiac death with inflammation and other traditional risk factors. Kidney Int 2008;74:1335–1342.

56 Anan F, Shimomura T, Kaku T, Kaneda K, Imagawa M, Tsukagawa H, Masaki T, Nawata T, Yonemochi H, Eshima N, Saikawa T, Yoshimatsu H: High-sensitivity C-reactive protein level is a significant risk factor for silent cerebral infarction in patients on hemodialysis. Metabolism 2008;57:66–70.

57 Sun Z, Ye H, Tang B, Shen X, Wu X, Zhong H, Song W: Prevalence of circulating CD4+CD28null T cells is associated with early atherosclerotic damage in patients with end-stage renal disease undergoing hemodialysis. Hum Immunol 2013;74:6–13.

58 Uchida E, Anan F, Masaki T, Kaneda K, Nawata T, Eshima N, Saikawa T, Yoshimatsu H: Monocyte chemoattractant protein-1 is associated with silent cerebral infarction in patients on haemodialysis. Intern Med J 2012; 42:29–34.

59 Winkler K, Hoffmann MM, Krane V, Drechsler C, Wanner C; German Diabetes and Dialysis Study Investigators: Lipoprotein-associated phospholipase A2 and outcome in patients with type 2 diabetes on haemodialysis. Eur J Clin Invest 2012;42:693–701.

60 Takahashi R, Ito Y, Takahashi H, Ishii H, Kasuga H, Mizuno M, Suzuki Y, Yuzawa Y, Maruyama S, Murohara T, Imai E, Matsuo S: Combined values of serum albumin, C-reactive protein and body mass index at dialysis initiation accurately predicts long-term mortality. Am J Nephrol 2012;36:136–143.

61 Muntinghe FL, Verduijn M, Zuurman MW, Grootendorst DC, Carrero JJ, Qureshi AR, Luttropp K, Nordfors L, Lindholm B, Brandenburg V, Schalling M, Stenvinkel P, Boeschoten EW, Krediet RT, Navis G, Dekker FW: CCR5 deletion protects against inflammation-associated mortality in dialysis patients. J Am Soc Nephrol 2009;20:1641–1649.

62 Assa S, Hummel YM, Voors AA, Kuipers J, Westerhuis R, Groen H, Bakker SJ, Muller Kobold AC, van Oeveren W, Struck J, de Jong PE, Franssen CF: Hemodialysis-induced regional left ventricular systolic dysfunction and inflammation: a cross-sectional study. Am J Kidney Dis 2014;64:265–273.

63 Raj DS, Shah VO, Rambod M, Kovesdy CP, Kalantar-Zadeh K: Association of soluble endotoxin receptor CD14 and mortality among patients undergoing hemodialysis. Am J Kidney Dis 2009;54:1062–1071.

64 Zhang L, Kao WH, Berthier-Schaad Y, Plantinga L, Fink N, Smith MW, Coresh J: C-reactive protein haplotype predicts serum C-reactive protein levels but not cardiovascular disease risk in a dialysis cohort. Am J Kidney Dis 2007;49:118–126.

65 Vlahu CA, Lemkes BA, Struijk DG, Koopman MG, Krediet RT, Vink H: Damage of the endothelial glycocalyx in dialysis patients. J Am Soc Nephrol 2012;23:1900–1908.

66 Martin-Rodriguez S, Caballo C, Gutierrez G, Vera M, Cruzado JM, Cases A, Escolar G, Diaz-Ricart M: TLR4 and NALP3 inflammasome in the development of endothelial dysfunction in uraemia. Eur J Clin Invest 2015; 45:160–169.

67 Caballo C, Palomo M, Cases A, Galan AM, Molina P, Vera M, Bosch X, Escolar G, Diaz-Ricart M: NFκB in the development of endothelial activation and damage in uremia: an in vitro approach. PLoS One 2012;7:e43374.

68 Jia P, Jin W, Teng J, Zhang H, Zou J, Liu Z, Shen B, Cao X, Ding X: Acute effects of hemodiafiltration versus conventional hemodialysis on endothelial function and inflammation: a randomized crossover study. Medicine (Baltimore) 2016;95:e3440.

69 Korish AA: Multiple antioxidants and L-arginine modulate inflammation and dyslipidemia in chronic renal failure rats. Ren Fail 2010;32:203–213.

70 Kuhad A, Chopra K: Attenuation of diabetic nephropathy by tocotrienol: involvement of NFkB signaling pathway. Life Sci 2009;84: 296–301.

71 Vaziri ND, Bai Y, Yuan J, Said HL, Sigala W, Ni Z: ApoA-1 mimetic peptide reverses uremia-induced upregulation of pro-atherogenic pathways in the aorta. Am J Nephrol 2010;32: 201–211.

72 Toba H, Tojo C, Wang J, Noda K, Kobara M, Nakata T: Telmisartan inhibits vascular dysfunction and inflammation via activation of peroxisome proliferator-activated receptor-γ in subtotal nephrectomized rat. Eur J Pharmacol 2012;685:91–98.

73 Yamamoto S, Zuo Y, Ma J, Yancey PG, Hunley TE, Motojima M, Fogo AB, Linton MF, Fazio S, Ichikawa I, Kon V: Oral activated charcoal adsorbent (AST-120) ameliorates extent and instability of atherosclerosis accelerated by kidney disease in apolipoprotein E-deficient mice. Nephrol Dial Transplant 2011; 26:2491–2497.

74 Reis ES, DeAngelis RA, Chen H, Resuello RR, Ricklin D, Lambris JD: Therapeutic C3 inhibitor Cp40 abrogates complement activation induced by modern hemodialysis filters. Immunobiology 2015;220:476–482.

75 Feng B, Zhang Y, Mu J, Ye Z, Zeng W, Qi W, Luo Z, Guo Y, Yang X, Yuan F: Preventive effect of a proteasome inhibitor on the formation of accelerated atherosclerosis in rabbits with uremia. J Cardiovasc Pharmacol 2010; 55:129–138.

76 Santana AC, Degaspari S, Catanozi S, Delle H, de Sa Lima L, Silva C, Blanco P, Solez K, Scavone C, Noronha IL: Thalidomide suppresses inflammation in adenine-induced CKD with uraemia in mice. Nephrol Dial Transplant 2013;28:1140–1149.

77 Mu W, Ouyang X, Agarwal A, Zhang L, Long DA, Cruz PE, Roncal CA, Glushakova OY, Chiodo VA, Atkinson MA, Hauswirth WW, Flotte TR, Rodriguez-Iturbe B, Johnson RJ: IL-10 suppresses chemokines, inflammation, and fibrosis in a model of chronic renal disease. J Am Soc Nephrol 2005;16:3651–3660.

78 Fiorina P, Ansari MJ, Jurewicz M, Barry M, Ricchiuti V, Smith RN, Shea S, Means TK, Auchincloss H Jr, Luster AD, Sayegh MH, Abdi R: Role of CXC chemokine receptor 3 pathway in renal ischemic injury. J Am Soc Nephrol 2006;17:716–723.

79 Boaz M, Smetana S, Weinstein T, Matas Z, Gafter U, Iaina A, Knecht A, Weissgarten Y, Brunner D, Fainaru M, Green MS: Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): Randomised placebo-controlled trial. Lancet 2000;356:1213–1218.

80 Jun M, Venkataraman V, Razavian M, Cooper B, Zoungas S, Ninomiya T, Webster AC, Perkovic V: Antioxidants for chronic kidney disease. Cochrane Database Syst Rev 2012; 10:CD008176.

81 Cice G, Di Benedetto A, D'Isa S, D'Andrea A, Marcelli D, Gatti E, Calabro R: Effects of telmisartan added to angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure a double-blind, placebo-controlled trial. J Am Coll Cardiol 2010;56:1701–1708.

82 Buccianti G, Raselli S, Baragetti I, Bamonti F, Corghi E, Novembrino C, Patrosso C, Maggi FM, Catapano AL: 5-methyltetrahydrofolate restores endothelial function in uraemic patients on convective haemodialysis. Nephrol Dial Transplant 2002;17:857–864.

83 van Guldener C, Janssen MJ, Lambert J, ter Wee PM, Jakobs C, Donker AJ, Stehouwer CD: No change in impaired endothelial function after long-term folic acid therapy of hyperhomocysteinaemia in haemodialysis patients. Nephrol Dial Transplant 1998;13:106–112.

84 Nigwekar SU, Kang A, Zoungas S, Cass A, Gallagher MP, Kulshrestha S, Navaneethan SD, Perkovic V, Strippoli GF, Jardine MJ: Interventions for lowering plasma homocysteine levels in dialysis patients. Cochrane Database Syst Rev 2016;5:CD004683.

85 Bostom AG, Carpenter MA, Kusek JW, Levey AS, Hunsicker L, Pfeffer MA, Selhub J, Jacques PF, Cole E, Gravens-Mueller L, House AA, Kew C, McKenney JL, Pacheco-Silva A, Pesavento T, Pirsch J, Smith S, Solomon S, Weir M: Homocysteine-lowering and cardiovascular disease outcomes in kidney transplant recipients: primary results from the folic acid for vascular outcome reduction in transplantation trial. Circulation 2011;123: 1763–1770.

86 Paroni R, Fermo I, Fiorina P, Cighetti G: Determination of asymmetric and symmetric dimethylarginines in plasma of hyperhomocysteinemic subjects. Amino Acids 2005;28:389–394.

87 Fiorina P, Lanfredini M, Montanari A, Peca MG, Veronelli A, Mello A, Astorri E, Craveri A: Plasma homocysteine and folate are related to arterial blood pressure in type 2 diabetes mellitus. Am J Hypertens 1998;11:1100–1107.

88 Wu YQ, Qu H, Sfyroera G, Tzekou A, Kay BK, Nilsson B, Nilsson Ekdahl K, Ricklin D, Lambris JD: Protection of nonself surfaces from complement attack by factor H-binding peptides: implications for therapeutic medicine. J Immunol 2011;186:4269–4277.

89 Hezmee MN, Shiels IA, Rolfe BE, Mills PC: Complement C5a: impact on the field of veterinary medicine. Vet J 2012;192:264–271.

90 Kourtzelis I, Markiewski MM, Doumas M, Rafail S, Kambas K, Mitroulis I, Panagoutsos S, Passadakis P, Vargemezis V, Magotti P, Qu H, Mollnes TE, Ritis K, Lambris JD: Complement anaphylatoxin C5a contributes to hemodialysis-associated thrombosis. Blood 2010;116:631–639.

91 Hung AM, Ellis CD, Shintani A, Booker C, Ikizler TA: IL-1β receptor antagonist reduces inflammation in hemodialysis patients. J Am Soc Nephrol 2011;22:437–442.

92 Don BR, Kim K, Li J, Dwyer T, Alexander F, Kaysen GA: The effect of etanercept on suppression of the systemic inflammatory response in chronic hemodialysis patients. Clin Nephrol 2010;73:431–438.

93 Fiorina P, Vergani A, Bassi R, Niewczas MA, Altintas MM, Pezzolesi MG, D'Addio F, Chin M, Tezza S, Ben Nasr M, Mattinzoli D, Ikehata M, Corradi D, Schumacher V, Buvall L, Yu CC, Chang JM, La Rosa S, Finzi G, Solini A, Vincenti F, Rastaldi MP, Reiser J, Krolewski AS, Mundel PH, Sayegh MH: Role of podocyte B7-1 in diabetic nephropathy. J Am Soc Nephrol 2014;25:1415–1429.

94 Yu CC, Fornoni A, Weins A, Hakroush S, Maiguel D, Sageshima J, Chen L, Ciancio G, Faridi MH, Behr D, Campbell KN, Chang JM, Chen HC, Oh J, Faul C, Arnaout MA, Fiorina P, Gupta V, Greka A, Burke GW 3rd, Mundel P: Abatacept in B7-1-positive proteinuric kidney disease. N Engl J Med 2013;369:2416–2423.

95 Kay E, Scotland RS, Whiteford JR: Toll-like receptors: role in inflammation and therapeutic potential. Biofactors 2014;40:284–294.

96 Taki K, Takayama F, Niwa T: Beneficial effects of bifidobacteria in a gastroresistant seamless capsule on hyperhomocysteinemia in hemodialysis patients. J Ren Nutr 2005;15: 77–80.

97 Cedeno-Laurent F, Dimitroff CJ: Galectin-1 research in T cell immunity: past, present and future. Clin Immunol 2012;142:107–116.

98 Hendrikx TK, van Gurp EA, Mol WM, Schoordijk W, Sewgobind VD, Ijzermans JN, Weimar W, Baan CC: End-stage renal failure and regulatory activities of CD4+CD25 bright+FoxP3+ T-cells. Nephrol Dial Transplant 2009;24:1969–1978.

99 Fiorina P, Voltarelli J, Zavazava N: Immunological applications of stem cells in type 1 diabetes. Endocr Rev 2011;32:725–754.

100 Ben Nasr M, Vergani A, Avruch J, Liu L, Kefaloyianni E, D'Addio F, Tezza S, Corradi D, Bassi R, Valderrama-Vasquez A, Usuelli V, Kim J, Azzi J, El Essawy B, Markmann J, Abdi R, Fiorina P: Co-transplantation of autologous MSCs delays islet allograft rejection and generates a local immunoprivileged site. Acta Diabetol 2015;52:917–927.

101 D'Addio F, Trevisani A, Ben Nasr M, Bassi R, El Essawy B, Abdi R, Secchi A, Fiorina P: Harnessing the immunological properties of stem cells as a therapeutic option for diabetic nephropathy. Acta Diabetol 2014;51:897–904.

102 Fiorina P, Jurewicz M, Vergani A, Petrelli A, Carvello M, D'Addio F, Godwin JG, Law K, Wu E, Tian Z, Thoma G, Kovarik J, La Rosa S, Capella C, Rodig S, Zerwes HG, Sayegh MH, Abdi R: Targeting the CXCR4-CXCL12 axis mobilizes autologous hematopoietic stem cells and prolongs islet allograft survival via programmed death ligand 1. J Immunol 2011;186:121–131.

103 D'Addio F, Valderrama Vasquez A, Ben Nasr M, Franek E, Zhu D, Li L, Ning G, Snarski E, Fiorina P: Autologous nonmyeloablative hematopoietic stem cell transplantation in new-onset type 1 diabetes: a multicenter analysis. Diabetes 2014;63:3041–3046.

104 Doria A, Niewczas MA, Fiorina P: Can existing drugs approved for other indications retard renal function decline in patients with type 1 diabetes and nephropathy? Semin Nephrol 2012;32:437–444.