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Immunoregulatory role of TNFα in inflammatory kidney diseases

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Tumor necrosis factor alpha (TNFα), a pleiotropic cytokine, plays important inflammatory roles in renal diseases such as lupus nephritis, anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis and renal allograft rejection. However, TNFα also plays critical immunoregulatory roles that are required to maintain immune homeostasis. These complex biological functions of TNFα are orchestrated by its two receptors, TNFR1 and TNFR2. For example, TNFR2 promotes leukocyte infiltration and tissue injury in an animal model of immune complex–mediated glomerulonephritis. On the other hand, TNFR1 plays an immunoregulatory function in a murine lupus model with a deficiency in this receptor that leads to more severe autoimmune symptoms. In humans, proinflammatory and immunoregulatory roles for TNFα are strikingly illustrated in patients on anti-TNFα medications: These treatments are greatly beneficial in certain inflammatory diseases such as rheumatoid arthritis but, on the other hand, are also associated with the induction of autoimmune lupus-like syndromes and enhanced autoimmunity in multiple sclerosis patients. The indication for anti-TNFα treatments in renal inflammatory diseases is still under discussion. Ongoing clinical trials may help to clarify the potential benefit of such treatments in lupus nephritis and ANCA-associated glomerulonephritis. Overall, the complex biology of TNFα is not fully understood. A greater understanding of the function of its receptors may provide a framework to understand its contrasting proinflammatory and immunoregulatory functions. This may lead the development of new, more specific anti-inflammatory drugs.

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Tumor necrosis factor alpha (TNFα) is a pleiotropic cytokine widely implicated in immune regulation. Mainly produced by activated macrophages, it is most often associated with proinflammatory properties and plays a pivotal role in innate and adaptive immunity, especially in host defense mechanisms against intracellular bacteria.[1–3]

First described for its capacity to induce hemorrhagic necrosis in mouse tumor,[4,5] TNFα is now more recognized for its role in inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel diseases, psoriasis, and multiple sclerosis. The development of TNFα neutralizing treatments remarkably improved the prognosis of patients with rheumatoid arthritis,[6,7] severe Crohn's disease,[8] psoriasis, and psoriatic arthritis[9–11] or ankylosing spondylitis[12,13] and has rapidly become a first choice for treatment of many severe cases of these diseases.

More recently, accumulating evidence suggests that TNFα also plays an important immunoregulatory role and directly participates in the maintenance of immune homeostasis. It is thus not surprising that anti-TNFα treatments are not the panacea for inflammatory conditions, as it may be associated with the emergence of autoimmune symptoms such as the induction of autoantibodies (for example anti-dsDNA antibodies in up to 14% of rheumatoid arthritis patients treated with infliximab[14,15]), inflammatory neurological events,[15] and lupus syndromes.[14,16,17] Moreover, different clinical trials have failed to report a beneficial effect in patients with sepsis, a condition also directly related to TNFα.[18–21] Indeed, increased mortality in a subgroup of patients suffering from gram-positive sepsis has even raised concerns about the safety of these medications.[22] In addition, a controlled clinical trial of TNFα blockade in multiple sclerosis has shown a worsening of the symptoms in many patients receiving the anti-TNFα treatment associated with a non-significant trend of increased magnetic resonance imaging lesions[23] also reported in another study.[24] This underscores the complexity of TNFα biology in inflammatory diseases and emphasizes the need to better understand the role of TNFα and its receptors in different inflammatory conditions. The net effect of TNFα is a balance between its proinflammatory and immunosuppressive function, which is determined by the cellular microenvironment and differs, for instance, between the early and late phases of inflammation.

TNFα biology thus needs to be considered in the specific context of each inflammatory disease and involved tissue. Indeed, such dualistic immunosuppressive-proinflammatory roles have been described for other cytokines such as IL-12 and INFγ.[25–27]

The kidney is frequently affected in inflammatory and autoimmune diseases, and TNFα has been largely implicated in the inflammatory cascade leading to renal injury. The contrasting proinflammatory and immunosuppressive roles of TNFα in the kidney are evident in experimental models of lupus nephritis,[25,28–30] and anti-TNFα treatments have shown promising results in animal models of glomerulonephritis. However, their efficiency in human immune complex-mediated renal diseases is currently still in question. For instance, small open-label clinical trials[31–33] have shown promising results in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis nephritis contrasting with the failure of etanercept, a TNFα decoy receptor, in a recent larger randomized controlled trial in Wegener granulomatosis.[34] In lupus nephritis, infliximab, an anti-TNFα antibody, may also have some beneficial effects, and the results of an ongoing controlled clinical trial are forthcoming.[32,35–37] The effect of etanercept in the treatment of lupus nephritis is also underway.[38] In this review, we will describe the basic biology underlying the antagonistic effects of TNFα and discuss the role of TNFα and its receptors, as well as the future potential of anti-TNFα treatments, in renal inflammatory diseases.

TNFα AND ITS RECEPTORS

TNFα is initially expressed as a functional 26-kDa homotrimer transmembrane protein.[39–42] It may be cleaved by a metalloproteinase, the TNFα-converting enzyme (also named ADAM-17), and is released into the circulation as a functional 17-kDa soluble form.[43,44] Although TNFα is mostly expressed and secreted by hematopoietic cells, it may be expressed by tissue resident cells. In normal kidney, TNFα is usually not detected,[45,46] despite some data to the contrary.[47] However, most renal cells produce TNFα after stimulation. *In vitro* stimulation of mesangial cells with lipopolysaccharide (LPS)[48,49] or soluble aggregates of IgG[50] upregulates TNFα. Tubular epithelial cells also express TNFα after treatment with IL-1α or LPS.[51,52] *In vivo* epithelial cells generate TNFα after LPS exposure[49,52] and podocytes express TNFα during membranous nephropathy.[53]

In vivo, the TNFα expression pattern in the kidney seems to be related to the primary compartment injured. For instance, in renal ischemia-reperfusion injury,[54] renal obstruction,[55] or acute renal allograft rejection,[45] TNFα is mostly produced by tubular cells. On the other hand, TNFα expression is preferentially localized in glomerular cells in IgA nephropathy,[46] minimal change disease,[46] idiopathic membranous nephropathy,[46,53] or proliferative and membranous lupus nephropathy.[56,57] In vasculitis-associated nephritis, in which inflammation involves several kidney compartments, TNFα is expressed in resident glomerular cells, endothelial cells, interstitia and, to a lesser extent, tubular cells.[58]

The function of TNFα is relayed by two structurally distinct receptors, tumor necrosis factor receptor (TNFR)1 (TNFRSF1A, p55, CD120a) and TNFR2 (TNFRSF1B, p75, CD120b). They belong to the TNFα receptor superfamily, a group of type I transmembrane glycoprotein, characterized by a conserved homologous cysteine-rich domain in their extracellular region. Similar to TNFα, they form non-covalently bound homotrimers at the surface.[59,60] TNFR1 and TNFR2 are only 28% homologous mostly in their extracellular domain and share no homology in their intracellular regions. The cytoplasmic domains in both receptors are devoid of intrinsic enzyme activity and need to recruit cytosolic intermediate proteins to transduce signals.[60]

The two TNFRs have different affinity for the soluble and membrane-bound forms of TNFα. TNFR1 binds equally well to both forms of TNFα, whereas TNFR2 has a higher affinity for the membrane-bound form and a low-binding capacity for the soluble form of TNFα.[60] Interestingly, although soluble murine TNFα binds equally well to both human TNFRs, the human soluble TNFα can bind only to mouse TNFR1.[61]

The physiological relevance of the different affinities of TNFR2 for membranous versus soluble TNFα remains largely unclear. As the transmembrane form of TNFα is biologically active,[40] this may suggest a preferential role for TNFR2 during cell–cell interactions.[62] For instance, TNFα–TNFR2 interactions seem to be critical in the generation of FasL-dependent cytolytic T-cell effector pathways in murine hepatic viral infection.[63] TNFα–TNFR2 interactions also play a prominent role in the priming of CD4 + T cells in a murine model of intestinal graft-versus-host disease.[64] The specific cell–cell TNFα–TNFR2 interaction has also a pivotal function in the maturation of dendritic cells mediated by natural killer cells in mice.[65] In humans, $CD8^+$ T-cell apoptosis seems to be mediated specifically by the interaction between membranous TNFα and TNFR2, independently of TNFR1.[66]

Tumor necrosis factor receptor 1 is located mostly intracellularly in the *trans*-Golgi network with a smaller subset located at the cell surface.[67,68] The specific function of the Golgi location of the TNFR1 remains unresolved, but it may serve as a reservoir to reconstitute the plasma membrane TNFR1 pool, which is shed and internalized after binding its ligand.[67] The possibility that endogenously synthesized intracellular TNFα interacts with Golgi-associated TNFR1 has also been suggested.[68–70] Nevertheless, the interaction of TNFR1 with TRADD (TNF receptor-associated death domain protein), a proximal adapter molecule essential for transduction of TNFR1 signals, occurs only at the plasma membrane level, suggesting that surface TNFR1 is functionally more significant than the Golgi pool of the receptor.[68]

Both TNFRs are regulated differently and show different expression patterns. TNFR1 is widely expressed in many different cell types, whereas TNFR2 is preferentially expressed

in hematopoietic cells.[71] TNFR1 expression is under the control of a 'housekeeping'-type promoter,[72–74] which is consistent with the finding that its expression is less modulated than TNFR2. In the normal kidney, TNFR1 is expressed in the glomeruli, but not in the tubular compartment.[45] Its expression is increased in inflammatory kidney diseases such as human lupus nephritis (WHO class III/IV), but not in purely mesangial or membranous lupus nephritis (WHO class II and V) or in idiopathic membranous nephropathy.[47] In acute allograft rejection, TNFR1 expression in glomeruli is lost; however, infiltrating leukocytes in the interstitium, such as lymphocytes and macrophages, express TNFR1 highly.[45]

By contrast, TNFR2 is usually not expressed in normal kidney,[45,75] although it is present at low levels in isolated glomerular cells of normal kidney biopsies.[47,76] In response to renal injury, TNFR2 expression is induced both in interstitial post-capillary venules and in glomeruli in murine nephrotoxic serum nephritis and a model of immunecomplex-mediated glomerulonephritis.[75] It is upregulated in tubular cells in acute renal allograft rejection,[45,76] acute tubular necrosis,[76] and renal obstruction.[75] Interestingly, TNFR2 expression is increased in renal inflammation in a pattern that is similar to TNFα, which suggests a regulation of TNFR2 by its ligand, possibly through an autocrine or paracrine pathway. This is supported by experimental data: in a murine model of cisplatin-induced renal injury, TNFR2 mRNA upregulation observed in a renal tissue sample in a wild-type mouse was blunted in TNFα-deficient mice.[77] Another report described increased TNFR2 mRNA level in tubular cells (but not in glomerular cells) of human kidney culture samples after TNFR2 activation through a specific protein agonist (mutein).[76] The transcriptional regulation of TNFR2 can be attributed to its large promoter, which contains a variety of transcriptional factor-binding sites, including those for NFκB, AP-1, IRF-1, and GAS,[71] suggesting that the expression of TNFR2 may be finely regulated and highly variable depending on the microenvironment. Moreover, similar to TNFα mRNA,[78,79] TNFR2 mRNA contains a large 3′ untranslated region (more than 2000 bp in both humans and mice), which may play a role in post-transcriptional regulation of TNFR2 protein.[80]

Similar to TNFα, both TNFRs can be cleaved to a functional soluble form[59,60] by the common metalloproteinase TNFα-converting enzyme. The soluble receptors may also be produced from a spliced mRNA variant devoid of the transmembrane domain.[81] Soluble TNFRs may play a critical role in regulating the inflammatory response by binding and eventually neutralizing free TNFα.[82–85] Experimentally, administration of a soluble form of TNFR1 protects rats against glomerular injury in heterologous nephrotoxic nephritis, an animal model of immunecomplex-mediated glomerulonephritis.[86,87] In humans, the clinical significance of receptor cleavage is underscored by the existence of the TNFα receptor-1-associated periodic syndrome caused by an autosomal dominant genetic defect in the extracellular domain of TNFR1 that prevents its cleavage.[88] TNFα receptor-1-associated periodic syndrome patients develop a fluctuating autoinflammatory disease associated with recurrent periodic fever episodes over months or years without apparent infections, skin inflammatory lesions, and occasionally secondary amyloidosis without apparent infections.[43]

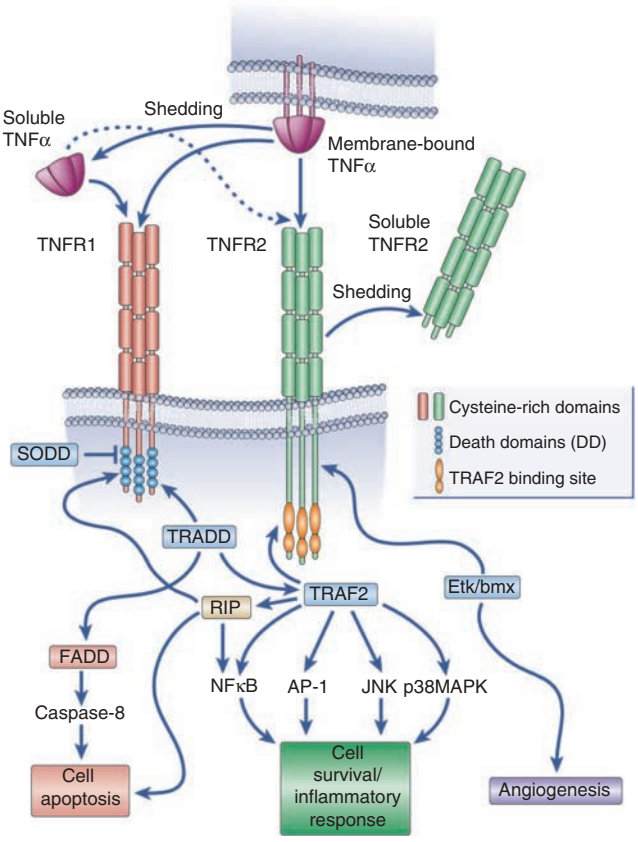

Figure 1 | TNFα receptor-signaling pathways. SODD, silencer of death domain protein; TRADD, TNF receptor-associated death domain protein; TRAF2, TNF receptor-associated factor 2 protein; Etk/bmx, endothelial/epithelial tyrosine kinase; FADD, Fas-associated death domain protein; RIP, receptor interacting protein; JNK, c-Jun N-terminal kinase.

SIGNALING PATHWAYS OF TNFR1 AND TNFR2

The main structural difference between TNFR1 and TNFR2 is the presence of a death domain (DD) in the cytoplasmic domain of TNFR1 (Figure 1).[89,90] In unactivated TNFR1, the DD is occupied by the SODD (silencer of DD protein), which prevents ligand-independent activation of the receptor. The binding of TNFα on TNFR1 induces the release of SODD and allows the TRADD to interact with the DD.[60] TRADD is an essential partner of TNFR1 for signal transduction[91] and can recruit the downstream adapter molecule FADD (fas-associated death domain), which initiates the caspase pathway responsible for apoptotic cell death. On the other hand, TRADD is also able to interact directly with the TNF receptor-associated factor 2 protein (TRAF2), which in turn

can trigger the activation of pathways, such as NFκB,[92] AP-1, c-Jun N-terminal kinase stress kinases, and p38MAPK, mostly implicated in cell survival signaling and inflammatory responses (reviewed in[3,60]). The receptor-interacting protein (RIP) is another important signaling intermediate interacting with TRAF2 and plays, for instance, a critical role in TNFα mediated lymphocyte apoptosis (cf below). Many other intermediate proteins, including inhibitory adapter proteins such as inhibitors of apoptosis protein family, also finely modulate the signaling of both TNFα receptors[3,60] and set the balance between apoptosis induction and cell proliferation signal. More details of these pathways can be found in the recent review of MacEwan.[60]

The signaling pathway engaged by TNFR2 is much less well understood. The cytosolic tail of TNFR2 directly bind TRAF2, which in turn mediates most of the signaling events induced by this receptor. For instance, the *in vitro* overexpression of TNFR2 activates NFκB through a TRAF2-dependent mechanism,[93] but through a signaling mechanism distinct from those involved in TNFR1–NFκB activation.[94] However, endogenous TNFR2 in cell types such as endothelial cells was not able to engage this pathway alone,[95] and may require co-activator signals. TNFR2 is also able to induce c-Jun N-terminal kinase and p38MAPK pathways and to interact with RIP through TRAF2.[3,60] Interestingly, a secondary indirect TRAF2-binding site in the TNFR2 cytoplasmic domain has been recently described. This novel interaction seems to regulate the capacity of TNFR2 to engage TRAF2, and thereby modulate its signaling capacity.[96] As shown for TNFR1, TNFR2 is able to induce apoptosis, possibly through a TNFR2–TRAF2–FADD interaction.[97]

A specific novel TNFR2-signaling pathway has been recently implicated in angiogenesis regulation.[98,99] TNFR2 interacts directly with the endothelial/epithelial tyrosine kinase (Etk/bmx) independently of TRAF2[100] and plays a critical role in VEGFR2 signal transduction in endothelial cells.[101] Etk then activates the phosphatidylinositol 3 kinase-Akt pathway,[100] which may contribute to the TNFα-induced cell proliferation and possibly tissue repair mechanisms. It is noteworthy that phosphorylation of Etk is a specific indicator of TNFR2 signaling.[76] Despite these *in vitro* data, the significance of TNFR2 signaling *in vivo* remains to be clarified.

Although TNFR1 signaling is widely implicated in inflammatory responses and is the hallmark of sepsis,[1,102] the role of TNFR2 and its signaling partners in inflammation is unclear. There is, however, accumulating experimental evidence suggesting that TNFR2 plays a role in inflammatory responses, independently of TNFR1. For instance, overexpression of human TNFR2 in transgenic mice is associated with increased lethality in the context of LPS exposure and these mice develop a spontaneous diffuse inflammatory phenotype independently of TNFR1 expression.[103] More recently, our group has shown a critical role for this receptor in renal injury in a murine model of immune complex glomerulonephritis.[75]

GENERIC ROLES OF TNFα IN INFLAMMATION

Proinflammatory roles

TNFα is a key player in innate and adaptive immunity. Its proinflammatory properties are well described and mainly lead to the activation and recruitment of inflammatory cells to the site of injury (Table 1). TNFα induces, for instance, the local activation of vascular endothelium, the release of nitric oxide and thereby local vasodilation, an increase of vascular permeability, the expression of adhesion molecules on the endothelial cells (ICAM-1, VCAM-1, E-Selectin), the release of other cytokines and chemokines (MCP-1, RANTES, IL-1, IL-6, IL-8), and the expression of class I and II major histocompatibility molecules.[1,2,104,105]

As most of these mechanisms may be triggered by the soluble form of TNFα, the specific role of its transmembrane form remains unclear. However, experiments with engineered transgenic mice offer some clues. Mice expressing only a mutated non-cleavable transmembrane form of the TNFα are fully protected against endotoxic shock,[41] but retain cell-mediated immunity against *Mycobacterium bovis* bacillus Calmette-Guerin infection.[106] On the other hand, overexpression of a non-cleavable form of TNFα in mice induces an inflammatory phenotype characterized mainly by severe arthritis.[107,108] Moreover, the constitutive endothelial-specific overexpression of this non-cleavable form of TNFα in mice induces a diffuse inflammatory phenotype with chronic leukocyte infiltration in the kidneys, liver, and lungs, together

Table 1 | Proinflammatory versus immunoregulatory properties of TNFα

Proinflammatory	Immunoregulatory
Blood vessels activation	*Organogenesis of secondary lymphoid organs*
• Vasodilation • Increase of vascular permeability • Expression of adhesion molecules: ICAM-1, VCAM-1, E-Selectin	• Formation and maturation of germinal centers • Maturation of follicular dendritic cells
Cell activation	*Maintenance of central and peripheral tolerance*
• Activation/priming of leukocytes • Induction of expression of MHC I and II • Proliferation of fibroblasts and mesangial cells	• Thymocyte apoptosis • Activation induced T cell apoptosis • Induction of C1q and serum amyloid P components
Induction of chemokines, cytokines, and other inflammatory mediators	*Immunosuppression*
• Release of cytokines and chemokines: MCP-1, RANTES, IL-1, IL-6, IL-8, complement component C3 • Release of prostaglandins, leukotrienes, nitric oxide, and reactive oxygen species • Upregulation of matrix metalloproteinases	• Downregulation of TCR-signaling and T-cell responsiveness • B-cell sensitization to FAS-mediated apoptosis

ICAM-1, intercellular adhesion molecule 1; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; RANTES, regulated upon activation, normal T-cell expressed, and secreted (CCL5); TCR, T-cell receptor; VCAM-1, vascular cell adhesion molecule-1.

with an upregulation of the adhesion molecules ICAM-1 and VCAM-1 in the endothelium of the liver and the kidneys.[109] Although the underlying mechanisms for these phenotypes remain unclear, these data do suggest that TNFα cleavage may be important in downregulating local TNFα-induced inflammatory events.

In the kidney, TNFα may be directly involved in renal injury. Although monocytes/macrophages remain the main source of TNFα, the local production of TNFα by stimulated intrinsic renal cells seems to be functionally more relevant in renal inflammation.[110] This is supported by the observation that these cells may be the source and target of TNF. TNFα expression, induced in human intrinsic renal cells or tubular cells in different inflammatory conditions,[45,46,56,57] preferentially target mesangial cells to produce inflammatory mediators implicated in renal injury, such as M-CSF, MCP1, GM-CSF, IL-6, prostaglandins E2, platelet-activating factor, reactive oxygen metabolites, tissue factor, and TNFα itself through an autocrine pathway.[111–115] Glomerular endothelial cells are also a target of TNFα, which induces the expression of endothelial VCAM-1 and E-Selectin.[115] Moreover, TNFα amplifies the production of the third component of the complement cascade by endothelial cells,[116] which plays a critical role in the pathogenesis of murine immune complex-mediated glomerulonephritis.[117,118]

Immunoregulatory roles

TNFα also shows critical immunoregulatory functions in both innate and adaptive immunity (Table 1). It is, for instance, an important mediator of lymphoid organogenesis.[2,3] TNFα-deficient mice form lymphoid nodes, but with an aberrant architecture devoid of a germinal center and follicular dendritic cells.[119] This seems to be mediated mostly by TNFR1,[120] as TNFR2-deficient mice present with normal lymphoid tissue. It is thus not surprising that TNFα possesses immunoregulatory functions, which may be critical in the maintenance of immune tolerance. As already mentioned, the importance of its immunosuppressive role is strikingly underscored by the autoimmune syndromes observed in patients treated with anti-TNFα medications,[14–17] and particularly by the failure of the TNFα blockade in multiple sclerosis with a higher number and rate of clinical exacerbations of disease observed in some treated patients.[23,24]

In animal models, diminished expression of TNFα has been associated with the emergence of autoimmune diseases.[78] For example, in experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis, TNFα-deficient mice develop more severe disease than wild-type or TNFα-heterozygous animals.[121] In a specific mouse strain (129/SV) usually resistant to this model, TNFα deficiency leads to the development of neurological symptoms. Administration of recombinant human TNFα in TNFα-deficient mice prevents the occurrence of the disease or reverses symptoms when administered 10 days after the induction of the disease.[121] These observations are supported by two other publications showing exacerbated disease in TNFR2-deficient mice, suggesting a pivotal role for TNFα–TNFR2 in controlling the emergence of central nervous system autoreactivity.[122,123] Finally, a third report emphasizes the immunosuppressor role of TNFα–TNFR2 in this model: in the absence of TNFα, but independently of TNFR1, myelin-specific T-cell autoreactivity fails to regress as normally observed in wild-type mice, and memory T cells expansion is prolonged.[124]

Besides brain inflammation, this immunoregulatory role of TNFα is observed in other animal inflammatory models, suggesting a generic immunoregulatory function for TNFα. For instance, nonobese diabetic mice, which spontaneously develop diabetes and are used as a model of human autoimmune insulin-dependent diabetes mellitus, present three to five times lower TNFα production capacity compared with another close mouse strain (SWR), suggesting that lower production of TNFα may trigger autoimmunity emergence.[125] Indeed, they show significant improvement in disease indices after intraperitoneal injections of recombinant murine TNFα.[125] A similar effect of exogenous administration of TNFα in New Zealand lupus-prone mice has been observed.[30] This immunoregulatory role of TNFα in the lupus model will be discussed in detail below.

At a cellular level, several mechanisms of the immunoregulatory effects of TNFα have been proposed, primarily related to T-cell homeostasis.[25] TNFα plays a critical role in T-cell regulation.[126] Activated T cells principally express TNFR2, which is mainly implicated in T cell TNFα-mediated apoptosis.[66,127] This process is directly regulated by the intermediate signaling protein kinase RIP, which acts as a 'molecular switch' between cell death and survival. Although RIP plays a protective role in TNFR2-mediated apoptosis of thymocytes,[128] the loss of expression of RIP by activated peripheral T cells sensitizes these cells to TNFR2-mediated apoptosis.[129] TNFR1 is, however, also able to induce apoptosis of activated T cells.[130,131] The role of TNFα in T-cell homeostasis has been convincingly shown *in vivo*: transgenic overexpression of TNFα specifically in pancreatic islet prevents diabetes in nonobese diabetic mice by inhibiting the development of auto-reactivity[132] through the induction of CD4+ T-cell peripheral tolerance.[133] By inducing apoptosis of thymocytes and mature T cells, TNFα is thus directly implicated in maintaining central as well as peripheral tolerance. Moreover, apoptosis of activated T cells mediated by TNFα may be a critical step in the termination of inflammatory processes.

TNFα may also modulate the level of T-cell responsiveness. In a murine model, chronic exposure to TNFα downregulates T-cell receptor signaling and lowers T-cell responsiveness to antigenic stimulation *in vitro* and *in vivo*.[134,135] Other data suggest that TNFα also plays a role in B-cell homeostasis. For instance, TNFα may prevent B-cell apoptosis in T cell areas, but it also sensitizes them to Fas-mediated apoptosis at a later stage of differentiation,

thereby offering another protective mechanism against autoimmunity emergence.[136] This is also illustrated by the impaired B-cell development and the striking absence of B220 + B cells in mice overexpressing human TNFR2.[103] An alternative mechanism indirectly mediated by TNFα for maintenance of central tolerance has also been proposed.[25] TNFα is important in the production of acute serum proteins in inflammation, such as C1q and serum amyloid P component, which have been implicated in the clearance of apoptotic cells and their potentially autoreactive contents. Indeed, C1q and serum amyloid P component-deficient mice develop autoantibodies and lupus nephritis.[137–139] Reduced production or function of TNFα may limit the release of these acute phase mediators and thereby facilitate autoimmunity.

TNFα IN INFLAMMATORY KIDNEY DISEASES

Immune complex-mediated glomerulonephritis

TNFα is largely implicated in renal inflammation and glomerular damage induced by immune complex deposition. Renal expression of TNFα is upregulated in both mice and human glomerulonephritis,[46,47,53,57] and correlates with an increase in serum and urine levels of TNFα.[57,140] The functional proinflammatory role of TNFα has been shown in experimental models of immune complex-mediated glomerulonephritis, in which TNFα deficiency or TNFα blockade treatments clearly offer protection against glomerular injury. For instance, in the well described accelerated nephrotoxic serum nephritis model, systemic administration of TNFα exacerbated glomerular injury in rats.[141] By contrast, pentoxifylline treatment in a similar model, which interferes with the endogenous production of TNFα, has beneficial effects. It limits renal injury if administered preventively or started at the peak of the disease, albeit to a lesser extent.[142] Anti-TNFα treatments also offer some protection against this model of glomerulonephritis in rats.[86,143,144] Similarly, TNFα-deficient mice are partially protected against glomerular injury (proteinuria and crescentic lesions) and present with lower renal infiltration of T cells and neutrophils.[145,146] Moreover, using bone marrow chimeric mice, it has been convincingly shown that intrinsic renal cells are the principal source of TNFα responsible for glomerular damage in this model.[110]

A recent publication by our group offers new insights on the respective role of each TNFR in immune complex-mediated glomerulonephritis.[75] When TNFR1- and TNFR2-deficient mice were subjected to the accelerated nephrotoxic nephritis model and renal damage was compared with wild-type animals, TNFR1-deficient mice presented with a delay in disease that was associated with a reduction in the adaptive humoral response (that is, lower circulating mouse anti-rabbit IgG after rabbit IgG immunization). This may be explained by impaired T-cell priming required for B-cell activation and proliferation, as earlier reports have shown that TNFR1 is required for T-cell priming[124] and the delayed type hypersensitivity response.[147] However, at a later time point, TNFR1-deficient mice presented with glomerular damage to a similar extent as did wild-type mice, but with a marked increase in lymphocytic infiltration in renal tissue, which may explain the development of glomerular damage despite the impaired adaptive immune response in these animals. This was linked to a decrease in T-cell apoptosis, which may be mediated by TNFR1 as shown by other groups.[130,131] More strikingly, TNFR2-deficient mice were completely protected against disease despite a proven preservation of their humoral response (circulating mouse anti-rabbit IgG comparable with wild-type mice) and an efficient delayed type hypersensitivity response as reported earlier.[147] The reduction in renal injury was associated with a marked decrease in C3 glomerular deposition as well as in nearly absent renal leukocyte infiltration. As complement activation is associated with glomerular damage in this model of glomerulonephritis,[148–150] a link between TNFR2 and complement activation may in part explain this phenotype. TNFR2-deficient mice also presented with a defect in renal leukocyte recruitment, which is supported by another report showing a decrease of renal leukocyte infiltration in TNFR2-deficient mice subjected to cisplatin-induced renal injury.[77] This is possibly related to a significantly lower expression of ICAM-1 in these mice compared with wild-type or TNFR1-deficient animals[77] or with a defect in the chemoattractant function of the complement cascade. Moreover, bone marrow chimeric experiments identified that TNFR2 specifically expressed on intrinsic renal cells, possibly glomerular endothelial cells, are the critical event leading to glomerular injury in this glomerulonephritis model.[75] Overall, our work shows the critical selective proinflammatory role of TNFR2 in mediating renal injury in glomerular disease.

Lupus nephritis

A large body of evidence implicates TNFα in systemic lupus nephritis. As reviewed recently,[36] the role of TNFα in this disease is ambiguous as it plays both proinflammatory and immunoregulatory roles. In lupus nephritis, the role of TNFα may be biphasic. In the initiation phase of autoimmune disease, it may have a critical immunosuppressive function, but later in the evolution of the disease, it may orchestrate the inflammatory process responsible for tissue injury. Indeed, in the classic animal models of systemic lupus erythematosus (SLE), (New Zealand black (NZB) × New Zealand white (NZW))F1 and MRL-*lpr/lpr*, TNFα plays an immunosuppressive role by inhibiting the emergence of autoreactivity, whereas in the latter phase, TNFα leads to end-organ damage, in particular lupus nephritis.

TNFα levels are very variable in SLE patients and in different animal models. The role of TNFα in SLE is difficult to study because of the complex genetics of this disease and the tight linkage between the TNFα gene and the major histocompatibility complex locus.[151] A case in point is that different HLA genotypes in patients associated with both low and high levels of circulating TNFα have an increase in incidence of SLE.[25,152] Consistent with these findings, the two principal experimental models of SLE in mice,

(NZB × NZW)F1 and MRL-*lpr/lpr*, have low and high levels of the cytokine, respectively.

Aside from the major histocompatibility complex genetic susceptibility to autoimmune disease of NZB mice, NZW mice in the (NZB × NZW)F1 model have genetic aberrations in the untranslated region of the TNFα mRNA that reduce its stability and thus the translation efficiency of the protein.[29] NZW mice therefore show a reduction of 50–60% of TNFα production under stimulated conditions (that is, *in vitro* LPS treatment of peritoneal macrophages).[25,30] Thus, a reduction of TNFα production may be linked to the emergence of autoimmunity in susceptible genetic backgrounds. This is supported by earlier studies showing that replacement therapy of exogenous recombinant TNFα to (NZB × NZW)F1 mice delayed the development of lupus nephritis without affecting B cell and autoantibody responses.[28,30]

Kontoyiannis *et al.*[25] specifically evaluated the role of TNFα reduction in the (NZB × NZW)F1 lupus model. They showed that first generation offspring of NZB mice crossed with TNFα-deficient mice show an autoimmune phenotype similar to the (NZB × NZW)F1 mice. That is, NZB-TNFα^{null} mice present with autoantibodies and spontaneous glomerulonephritis, however, with a delay and a milder phenotype compared with (NZB × NZW)F1 mice, suggesting an additional contribution of the NZW background. The authors speculate that the low TNFα production in these mice may facilitate the switch from IgM to pathogenic IgG anti-dsDNA antibody production and significantly increase the proliferative response of B cells. In the MRL-*lpr/lpr* SLE murine model, TNFα may also have an initial immunosuppressive role. When these mice are crossed with TNFR1-deficient mice, they present with much more severe autoimmune disease and glomerulonephritis, possibly because of a compensatory decrease in activation-induced T-cell apoptosis.[131] Thus, TNFα plays an important immunomodulating role in the initiation phase of the two models of lupus nephritis with lower production of TNFα triggering a breakage of tolerance in genetically susceptible animals.

In humans, TNFα may also play an initial immunomodulatory role. TNFα and its receptor polymorphisms in SLE patients may give some insights into the role of TNFα in lupus nephritis. For instance, HLA-DR2-positive individuals are prone to autoimmune diseases and, in particular, lupus nephritis. This HLA genotype is correlated with lupus nephritis development, which in turn is associated with a lower production of TNFα.[153] The most frequently reported polymorphism of TNFα is -308 A/G, which is associated with an increase in susceptibility to SLE, in particular in Caucasians, as shown in a recent meta-analysis.[154] This polymorphism may be functionally associated with a slight increase in the promoter activity and thus TNFα production, which may explain the enhanced end-organ damage observed in these patients. By contrast, another polymorphism of TNFα promoter (−863 C/A) is associated with protection from SLE,[152] despite the fact that it too induces an increase in activity of the promoter. In this case, it may be speculated that it is linked to the immunosuppressive role of TNFα in the early phase of SLE. Another frequently reported polymorphism is the TNFR2 M196R, which is associated with chronic inflammatory disorders, such as familial rheumatoid arthritis and ulcerative colitis.[155] This functional polymorphism modulates the signaling properties of TNFR2 by decreasing its ability to recruit TRAF2 and activate the NFκB pathway; this subsequently enhances TNFR1-induced apoptosis.[156] TNFR2 M196R has been recently associated with SLE in the Japanese patients,[155,157] but this association was not confirmed in two transmission disequilibrium test studies that included mainly Caucasian families.[158,159] The TNFR2 M196R polymorphism functional significance may thereby be specific to ethnicity.

In addition to its immunosuppressive roles, TNFα is clearly implicated in end-organ tissue injury in SLE patients and, in particular, lupus nephritis. In both mice[160–162] and humans,[56,57,163] TNFα is highly expressed in the kidney during lupus nephritis and SLE patients typically present with high serum levels of TNFα and soluble TNFRs that correlate with disease activity.[36,164–166] Moreover, recombinant TNFα administration in MRL-*lpr/lpr* mice[167] after the onset of the nephritis in (NZB × NZW)F1 mice[161] is associated with increased renal damage. Similarly, TNFα blockade suppresses SLE induced experimentally in mice by the injection of a human DNA autoantibody,[168] as well as lung inflammation or arthritis induced in lupus-prone mice.[169,170]

A few case reports and one small open-label study have shown promising clinical improvement in lupus nephritis in about two-third of the patients treated with infliximab, a commercial chimeric monoclonal anti-TNFα antibody.[36,37] Infliximab treatment was, however, associated with increased autoantibody titer, but was not coupled with SLE flares and resolved after interruption of the treatment.[37,171] The clinical improvement can be easily explained by the quick potent inhibition of the proinflammatory properties of TNFα leading to renal tissue injury. To avoid emergence of clinically significant autoimmune disorders induced by anti-TNFα treatments, Aringer *et al.*[36] propose a short four dose-inducing treatment of TNFα blockade associated with azathioprine. They have recently started the first double-blind placebo-controlled trial evaluating this protocol in patients with corticosteroid-resistant membranous lupus nephritis.[172]

ANCA-associated vasculitis nephritis

TNFα is largely implicated in ANCA-associated vasculitis nephritis. Its expression is upregulated in the glomeruli, interstitia and, to a lesser extent, in tubular cells in renal biopsies of patients with Wegener's granulomatosis or microscopic polyangiitis.[58] In vasculitis, expression of TNFα is also increased in peripheral blood mononuclear cells,[173] and circulating levels of soluble TNFR1 and TNFR2 are highly increased in MPO-ANCA-associated vasculitis

patients.[174] Their peripheral blood neutrophils also express higher amounts of both membranous receptors.[174] A polymorphism of the promoter of TNFα (−238 G/A), which is associated with a higher cytokine level, is more frequent in Wegener's granulomatosis patients and may contribute to disease susceptibility,[175] thus providing a clue to the functional relevance of TNFα in this disease.

In vasculitis pathogenesis, TNFα is critically implicated in the priming of neutrophils and monocytes, inducing their expression of MPO and proteinase-3 at the surface through p38-MAPK- and ERK-dependent pathways.[176] ANCA then binds the exposed autoantigens and, after crosslinking with Fcγ receptors, triggers neutrophil oxidative burst, degranulation, cytokines production, and subsequent inflammatory events that eventually lead to endothelium injury and end-organ tissue damage, such as alveolar hemorrhage and pauci-immune crescentic glomerulonephritis (reviewed in[177]).

The proinflammatory role of TNFα in vasculitis *in vivo* has been explored in experimental models of ANCA. For instance, in an experimental autoimmune vasculitis model in rats,[178,179] the administration of anti-TNFα antibody dramatically reduced glomerular lesions (near absence of crescentic lesions in treated animals) as well as interstitial nephritis, hematuria, albuminuria, and alveolar hemorrhage.[178] Besides the role of TNFα on neutrophils, this beneficial effect of TNFα blockade may be also explained by the important role of TNFα in leukocyte–endothelial cell interactions leading to endothelial cell injury in vasculitis as shown by intravital microscopy in this model.[178,179] Another ANCA-associated vasculitis model has been developed in mice: splenocytes or anti-MPO antibodies raised in MPO-deficient mice are transferred to naive animals, which consequently develop pauci-immune necrotizing glomerulonephritis.[180] Concomitant administration of LPS in this model is associated with more severe glomerular injury that is counteracted by anti-TNFα treatment. This supports thereby an important role for TNFα in ANCA-associated vasculitis and suggests a potential benefit for TNFα blockade in treatment of these diseases.[181] Indeed, encouraging beneficial results of open-label administration of infliximab in ANCA-associated vasculitis patients have been reported.[31–33] However, a recent randomized controlled trial evaluating etanercept in Wegener's granulomatosis patients showed no benefit.[34] As discussed further, this last study does not rule out a potential benefit of TNFα blockade in vasculitis, but does indicate the need for more controlled trials.

Kidney allograft rejection

As allograft rejection is mediated by both innate and adaptive immune responses, it is not surprising that TNFα is largely implicated in graft failure (review in[182]). Indeed, TNFα has been implicated in kidney allograft rejection for many years, but its specific role in proinflammatory events leading to graft injury is not fully understood. In rat experimental models, TNFα mRNA expression is upregulated in tissue samples during both acute and chronic kidney allograft rejection.[183,184] In humans, TNFα expression is also increased in renal tissue during acute rejection.[185–187] Plasmatic and urinary TNFα levels are also significantly elevated,[188,189] as well as circulating soluble TNFR1 and TNFR2.[190] Interestingly, elevation of TNFα circulating level may be predictive of transplant rejection and was observed 2 days before the clinical manifestations in one report.[191] In chronic allograft nephropathy, TNFα is also upregulated[186,192] and may be specifically implicated in the intimal hyperplasia of arterial walls observed in late graft failure.[192,193]

In acute rejection, a prominent role of TNFα–TNFR2 is suggested by a detailed study in which expression of TNFα and its receptors in biopsy samples was compared between normal and acute rejected kidneys.[45] By immunofluorescence and *in situ* mRNA hybridization, TNFα and TNFR2 were found to be absent in normal kidney, but both were consistently upregulated in the tubular epithelial cells while remaining undetectable in glomeruli during acute rejection. Furthermore, their level of expression correlated with the severity of the rejection episode. By contrast, TNFR1 was expressed in normal glomeruli, predominantly in endothelial cells, but became virtually undetectable during acute renal rejection.[45]

A functional role for TNFα in kidney allograft acute rejection may be inferred from a nonhuman primate allograft model. Administration of recombinant human TNFR:Fc fusion protein significantly delayed the onset of rejection and prolonged the overall allograft survival.[194] Different polymorphisms of TNFα also suggest its proinflammatory role in graft rejection. Indeed, in kidney transplant recipients, the TNFα promoter polymorphism −308 G/A, associated with a high cytokine level,[195] is frequently reported to be correlated with an increased risk of acute renal allograft rejection.[196–203] There are, however, some reports failing to show such an association.[204,205] In chronic allograft nephropathy, this polymorphism has also been recently associated with an increased risk for disease,[206] although this has not been confirmed in other reports.[207,208] Most of these studies have, however, assessed the polymorphisms of the graft recipients, whereas the local production of TNFα by donor tissue may also play a role. Nevertheless, one recent report did assess the potential link between the TNFα −308 G/A polymorphism in both recipients and donors. Interestingly, an association was observed between allograft rejection and recipient high producer −308 A polymorphism, whereas no correlation was found with the donor genotype.[209] To date, there are no data on the efficacy of anti-TNFα treatments in kidney allograft recipients. One open-label single-center clinical trial has been recently initiated, but results have not yet been published.[182]

TNFα-NEUTRALIZING TREATMENTS IN KIDNEY DISEASES

Given that TNFα shows both proinflammatory and immunosuppressive properties, it is not simple to predict the

effect of anti-TNFα treatments. Such treatments show great benefit in inflammatory diseases such as rheumatoid arthritis[6,7] and Crohn's disease,[8] but autoimmunity has been observed in some of the treated patients, and in other cases, such as sepsis or multiple sclerosis, inefficiency and potential harmful effects have been noted, thus raising concerns about the safety of these treatments in general.

Moreover, the actual anti-TNFα treatments are not equivalent and may thus explain the different outcomes observed.[210] The chimeric monoclonal anti-TNFα antibody infliximab, as well as the newer humanized monoclonal anti-TNFα antibody adalimumab, is able to induce cell lysis when bound to membrane-bound TNFα, for example, in macrophages.[211,212] By contrast, etanercept, a recombinant protein of TNFR2 fused with the Fc domain of human immunoglobulin G1 (IgG1), primarily binds soluble TNFα versus membrane-bound TNFα and does not directly induce cell apoptosis. In contrast with infliximab, it is also able to bind lymphotoxin-α.[15,210] This biochemical difference may account for the variable efficiency of etanercept and infliximab observed in the clinic, especially in granulomatosis diseases: although both medications are efficient in rheumatoid arthritis patients, etanercept has no beneficial effect in Crohn's disease,[213] which is in contrast with the reported efficiency of both infliximab[8,214] and adalimumab[215] in treatment of Crohn's disease. Similarly, in the recent double-blind controlled study, Wegener's Granulomatosis Etanercept Trial (WGET), etanercept failed in the treatment of Wegener's disease,[34] which is in contrast with many reports and one small open-label study that observed a beneficial effect of infliximab in this disease.[31–33] These results highlight the need to evaluate the efficacy of each anti-TNFα regimen in each inflammatory disease.

Compared with traditional immunosuppressive drugs, anti-TNFα treatments are generally safe. Therefore, it is tempting to apply these treatments in many inflammatory conditions, including kidney diseases. However, some serious side effects of anti-TNFα treatment should be considered. For example, aside from the autoimmune responses as detailed in this review and the increased incidence of bacterial infections and activation of latent tuberculosis infection in anti-TNFα-treated patients,[15,216] another concerning safety issue is the higher incidence of lymphomas[217,218] and potentially solid tumors during anti-TNFα treatment, which has been attributed to a possible decrease in immunosurveillance. For instance, in a *post hoc* analysis of Wegener's Granulomatosis Etanercept Trial (see further), six cases of solid malignancies among 89 treated patients (7%) have been reported.[219] Moreover, co-treatment with cyclophosphamide may increase this risk, as well as the underlying disease, such as rheumatoid arthritis, which may itself confer a higher malignancy risk. This increased frequency of tumors is however controversial[35] and a large cohort study of 4160 rheumatoid arthritis patients treated with TNFα antagonists did not show any increased risk of lymphomas after adjustment for age, sex, and disease duration.[220]

There is currently no validated indication of anti-TNFα treatments in kidney diseases. However, as mentioned above, there are growing emerging data suggesting a potential benefit of infliximab in lupus nephritis. Moreover, despite the negative results of the etanercept in the WGET trial, open label studies and case reports consistently suggest a beneficial effect of infliximab in Wegener's granulomatosis. Given the known differences in the mechanisms of action between etanercept and anti-TNFα monoclonal antibody, beneficial effects of anti-TNFα antibodies in vasculitis may still be expected. Controlled trials evaluating the efficiency of infliximab and adalimumab in both vasculitis-associated nephritis and lupus nephritis are urgently required. At least two clinical trials are ongoing in patients with lupus nephritis, and the results of a recent randomized clinical trial in ANCA-associated vasculitis are expected (Table 2).[38,172,221]

SUMMARY

TNFα biology in inflammatory diseases is complex as TNFα shows both proinflammatory and immunoregulatory properties. Therefore, its contribution to each inflammatory condition may differ, as illustrated by anti-TNFα treatments, which provide great benefits for rheumatoid arthritis patients, but in contrast enhance autoimmunity in patients with multiple sclerosis. In kidney diseases, experimental data suggest that TNFα also exhibits both proinflammatory and immunosuppressive functions. Nonetheless, some studies have suggested benefits of anti-TNFα treatments in renal inflammation, although this needs to be convincingly shown in randomized controlled trials. This may not be an easy task because of the limited and heterogeneous patient population for diseases such as ANCA-associated vasculitis or SLE and the variable involvement of the kidney in some of these cases. Paradoxically, as anti-TNFα may lead to the induction in autoimmunity, including lupus syndrome and glomerulonephritis in a subset of patients, new approaches for treatment of renal inflammatory and autoimmune diseases may be required. We postulate that new strategies should focus on its two receptors, which relay the multiple functions of TNFα through distinct intracellular signals. For example, in kidney diseases, TNFR2 may be the preferred target, as its expression is induced during renal inflammation in a renal compartment-specific manner and its deficiency in mice confers significant protection from renal tissue injury in autoimmune disease models.[75,103,157,222] Moreover, its immunosuppressive functions may be redundant with TNFR1. It is noted that TNFR1 deficiency enhances disease in the MRL-*lpr/lpr* SLE model.[131] Thus, the specific blockade of TNFR2, which preserves TNFR1 function, may aid in balancing the proinflammatory and immunosuppressive functions of TNFα in renal diseases. Along these lines, identifying key signaling events downstream specifically of TNFR2 may reveal additional therapeutic targets for modulating TNFR2 function.

Table 2 | Anti-TNFα treatments in inflammatory kidney diseases, ongoing clinical trials[a]

Title (ClinicalTrials.gov Identifier)	Intervention	Study design	Inclusion criteria	Outcome measures	Status
'A double-blind, randomized, placebo-controlled, multi-center trial of anti-TNF-α chimeric monoclonal antibody (Infliximab) and Azathioprine in patients suffering from systemic lupus erythematosus (SLE) with WHO Class V glomerulonephritis' (NCT00368264)	Infliximab (5 mg/kg, 4 infusions)	Randomized, double-blind, placebo controlled, multi-center	SLE with American College of Rheumatology criteria fulfilled Biopsy-proven membranous glomerulonephritis (WHO class V) with Proteinuria >3 g/day despite adequate ACE inhibitors and/or AT II antagonists and steroids treatment	Time needed to reduce proteinuria to <1.5 g/day	Ongoing, recruiting participants, estimated enrollment = 44
'A randomized, double-blind, placebo-controlled, phase II, multi-center study for treatment of lupus nephritis by inhibition of tumor necrosis factor-α using Etanercept' (NCT00447265)	Etanercept (50 mg, 1 × /week)	Randomized, double-blind, placebo controlled, multi-center	SLE with 4/11 American College of Rheumatology criteria fulfilled Active lupus nephritis Detectable levels of double-stranded DNA Receiving mycophenolate mofetil or azathioprin treatments for lupus nephritis	*Safety analysis:* Incidence of severe adverse events (NCI CTCAE grade III or greater) *Efficacy analysis:* Renal response, time to and duration of renal response	Ongoing, recruiting participants, estimated enrollment = 28
'Infliximab versus Rituximab in systemic necrotizing vasculitides with positive ANCA after relapse or resistant immunosuppressant therapies' (NCT00307593)	Inflximab, Rituximab	Randomized, open label	Systemic ANCA-positive vasculitis Relapsing or refractory vasculitis resistant to corticosteroids and conventional immunosuppressant therapies	Partial or complete remission of vasculitis	Completed (June 2007), enrollment = 20

ANCA, anti-neutrophil cytoplasmic antibody; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SLE, systemic lupus erythematosus; WHO, World Health Organization;
[a]Referenced in http://www.ClinicalTrials.gov

DISCLOSURE

The authors declare no competing interests.

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