**IS THERE A ROLE FOR TNFα BLOCKADE IN ANCA-ASSOCIATED VASCULITIS AND GLOMERULONEPHRITIS?**

**Stephen P McAdoo, Charles D Pusey**

**Department of Medicine, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN**

***Correspondence to: Professor Charles Pusey, Renal and Vascular Inflammation Section, Department of Medicine, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK. Tel: +44 20 8383 3152. Email: c.pusey@imperial.ac.uk.***

**Abstract**

Tumour necrosis factor alpha (TNFα) is a cytokine which is pivotal in the inflammatory response. Blockade of TNFα has been shown to be effective in a number of human autoimmune diseases, including rheumatoid arthritis, raising the question whether this approach may be effective in inflammatory kidney disease, such as ANCA-associated vasculitis (AAV). In AAV, there is considerable evidence for the role of TNFα in the pathophysiology of disease, including increased expression of TNFα mRNA in leucocytes and in renal tissue. Importantly, TNFα can induce leucocyte cell membrane expression of the autoantigens involved in vasculitis (proteinase 3 [PR3] and myeloperoxidase [MPO]), thus priming cells for the effects of ANCA. In rodent models of anti-GBM disease (nephrotoxic nephritis), TNF enhances glomerular injury and TNF blockade using soluble TNFαreceptor or anti-TNFα antibody ameliorates disease. Mice deficient in TNFα are protected from nephrotoxic nephritis and this effect is dependent mainly on intrinsic renal cells. A mouse model of anti-MPO antibody induced glomerulonephritis is enhanced by LPS, and this effect is blocked by anti-TNFα antibody. In a rat model of AAV induced by MPO (experimental autoimmune vasculitis) anti-TNFα antibody improves renal pathology and also reduces leucocyte transmigration, as shown by intravital microscopy. In clinical studies, the Wegener’s Granulomatosis Etanercept Trial (WGET) showed no benefit of additional etanercept versus standard therapy. However, there are several reasons why the results of the WGET study do not rule out the use of anti-TNFα antibody in acute renal AAV, including the study design and the considerable biological differences between the effects of etanercept and anti-TNFα antibody. There are several clinical studies demonstrating a response to anti-TNFα antibody in patients with AAV refractory to conventional treatment, and in some of these, the addition of anti-TNFα antibody was the only change in treatment. We suggest that further investigation of TNFα blockade in AAV is warranted.

**Keywords:** TNFα, ANCA, vasculitis, glomerulonephritis, TNFα blockade, inflammation

**Introduction**

Tumour necrosis factor alpha (TNFα) is a pleiotropic cytokine which plays a central role in inflammation and leads to the production of a wide range of other pro-inflammatory cytokines and chemokines. It also has important immune regulatory functions and can induce a number of anti-inflammatory and regulatory cytokines. TNFα is a 26 KDA transmembrane protein which can be cleaved by TNFαconverting enzyme into a soluble 17 KDA form. TNFbinds to two cell surface receptors, TNFR1 (CD120A, P55) and TNFR2 (CD120B, P75). These receptors engage different signalling pathways, with TNFR1 having a death domain on its intracellular region, whereas TNFR2 does not. Both receptors can also be cleaved from the cell surface and may circulate on their own or bound to TNFα. It has been suggested that they might act as decoys for TNFα, although they might have their own immunomodulatory functions. Binding of TNFα to its receptors can be inhibited by either monoclonal antibodies or soluble forms of the receptor (Figure 1). Early clinical and experimental studies in rheumatoid arthritis (RA) led to the identification of the TNFα dependent cytokine cascade and subsequent trials of TNFα blockade in patients with treatment resistant disease. This approach rapidly proved effective, and since then TNFα blockade has been approved in RA and a wide range of other chronic inflammatory diseases([1](#_ENREF_1)). Several studies have implicated TNFα or TNFRs in a range of different kidney diseases, and this topic has been previously reviewed([2](#_ENREF_2), [3](#_ENREF_3)).

There has been particular interest in the possible role of TNFα blockade in ANCA-associated vasculitis (AAV) and other forms of rapidly progressive glomerulonephritis (RPGN)([4](#_ENREF_4), [5](#_ENREF_5)). There is considerable evidence for the role of TNFα in pathogenesis of AAV from both clinical and experimental studies. For example, it has been shown that TNFα mRNA is upregulated in both peripheral blood mononuclear cells and in renal tissue from patients with granulomatosis with polyangiitis (GPA)([6](#_ENREF_6), [7](#_ENREF_7)). In particular, CD4 T cells in the granulomas found in GPA secrete large amounts of Th1 cytokines, including TNFα([8](#_ENREF_8)). *In vitro* studies have shown that TNFα is important in sensitising neutrophils and monocytes to the effects of ANCA. Priming these cells with TNFα induces cell membrane expression of PR3 and MPO where they are accessible to binding with ANCA([9](#_ENREF_9)). This subsequently leads to proinflammatory consequences, including neutrophil degranulation and production of reactive oxygen species, and also dysregulation of apoptosis and the development of netosis, which contributes to tissue damage and perpetuation of the autoimmune response([10](#_ENREF_10)). TNFα primes endothelial cells and promotes leucocyte endothelial adhesion by inducing expression of selectins and integrins([11](#_ENREF_11)). TNFα therefore plays a part in the endothelial damage induced by ANCA activated neutrophils. The TNFRs are also over-expressed at sites of inflammation in AAV([12](#_ENREF_12)) and increased levels of TNFRs have been associated with progression of other types of glomerulonephritis([13](#_ENREF_13), [14](#_ENREF_14)) . Although both types of TNFR contribute to glomerular injury, studies in knockout mice suggest that TNFR1 is more important in activation of intrinsic renal cells by soluble TNFα([15](#_ENREF_15)). We will consider whether TNFα blockade might be an effective approach in AAV and glomerulonephritis (GN) by reviewing its role in experimental models and clinical studies.

**Role of TNFα in experimental glomerulonephritis and vasculitis**

Investigation of the effects of TNFα in experimental glomerulonephritis was originally prompted by clinical observations that intercurrent infection exaggerated renal injury in several types of glomerulonephritis, including IgA nephropathy and ANCA-associated vasculitis. In one early study, it was shown that the administration of even small doses of TNFα increased glomerular damage in the heterologous phase of nephrotoxic nephritis (NTN) in the Sprague Dawley (SD) rat([16](#_ENREF_16)), a model that is not dependent on the development of ANCA, but that may be used to study the mechanisms of renal inflammation in crescentic nephritis. In subsequent experiments, it was shown that treatment with soluble TNF receptor (sTNFr p55) reduced glomerular injury in LPS enhanced NTN. This was accompanied by a reduction in glomerular IL-1β expression([17](#_ENREF_17)). In another early study, TNF binding protein, a dimeric form of the soluble receptor, was found to reduce glomerular injury in accelerated NTN in the SD rat, and decreased glomerular expression and circulating levels of macrophage migration inhibitory factor (MIF)([18](#_ENREF_18)). TNFα blockade can therefore reduce acute glomerular inflammation and also modulate production of other pro-inflammatory cytokines.

The role of TNFα was subsequently investigated in a more robust model of crescentic nephritis induced by nephrotoxic serum in the Wistar Kyoto (WKY) rat. In this model, preventive treatment with sTNFr p55 significantly improved glomerular disease and completely prevented crescent formation. If treatment was delayed until 4 days after induction of nephritis, when hypercellularity is well established, there was still a marked reduction in albuminuria and crescent formation. This was again accompanied by reduced glomerular expression of IL-1β([19](#_ENREF_19)). A blocking monoclonal antibody to rat TNFα has also been investigated in the same model. When given from day 0 or day 4 to day 14, there was improved renal function together with a significant reduction in crescents. When treatment was extended from day 4 to day 28, there was preservation of renal function and significantly less glomerular and tubulointerstitial scarring. Even when treatment was delayed until day 14, the time of peak crescent formation, there was still preserved renal function and reduced interstitial scarring by day 28. This was accompanied throughout by a reduction in urinary MCP-1([20](#_ENREF_20)). This work demonstrated the benefit of blocking endogenous TNFα in severe crescentic glomerulonephritis and, importantly, in the subsequent development of interstitial fibrosis.

Although nephrotoxic nephritis in mice does not produce such robust crescent formation, it does allow investigation of knockout strains. In an early study, accelerated NTN was induced in TNFα knockout and wild type mice. The TNFα knockout mice developed significantly less glomerular pathology and in particular showed less T cell infiltration and significantly fewer crescents([21](#_ENREF_21)). In subsequent work, bone marrow transplantation was used to investigate the importance of circulating leucocytes versus intrinsic renal cells. In accelerated NTN, TNFα knockout animals showed greatest protection from disease, whilst wild type to knockout chimeras showed less disease than knockout to wild type chimeras([22](#_ENREF_22)). This study suggests that intrinsic renal cells are the major cellular source of TNFα in this model, although circulating leucocytes also contribute.

More recently, the role of TNFα blockade has been investigated in rodent models of ANCA-associated vasculitis that may more accurately reproduce the biology of human disease. Experimental autoimmune vasculitis (EAV) can be induced by immunising WKY rats with human MPO in adjuvant. Animals develop circulating anti-MPO antibodies reactive with rat neutrophils, together with pauci-immune focal crescentic glomerulonephritis and alveolar haemorrhage. Using intravital microscopy of mesenteric vessels, we showed that anti-MPO antibodies in EAV enhanced leucocyte adhesion and transmigration *in vivo* in response to the chemokine CXCL1. A blocking monoclonal antibody to rat TNFα significantly reduced leucocyte transmigration and this was accompanied by abrogation of crescent formation and reduction in lung haemorrhage([23](#_ENREF_23)). This work demonstrates one possible mechanism of action of TNFα blockade in systemic vasculitis.

A model of anti-MPO antibody induced glomerulonephritis has been developed in mice. In this model, anti-MPO antibodies raised in MPO knockout mice are transferred to naïve recipients, which go on to develop pauciimmune necrotising glomerulonephritis. The severity of renal injury in this model can be enhanced by LPS and the severity of glomerular injury in the enhanced model can be reduced by administration of an anti-TNFα monoclonal antibody([24](#_ENREF_24)). In attempts to induce a similar model using anti-PR3 antibodies, although there was no glomerular injury, the intradermal injection of TNFα triggered local inflammation in these animals([25](#_ENREF_25)). These studies further support the role of TNFα in ANCA-associated inflammation.

The role of TNFα in murine models of systemic lupus erythematosus (SLE) is more complicated. In NZB /W mice, which show reduced production of TNFα, administration of recombinant TNFα early in life has a protective effect against lupus nephritis([26](#_ENREF_26)). It is likely that this is due to regulatory effects on the autoimmune response. However, later in the disease course in NZB/W mice, TNFα has the effect of worsening the renal disease, presumably due to its proinflammatory effects([27](#_ENREF_27)). In the MRL/lpr mouse, TNFα is overexpressed and levels of TNFα correlate with the degree of renal injury([28](#_ENREF_28)). Anti-TNFα antibody was shown to be of benefit in several clinical features of this model. It also reduces the severity of nephritis in the C3H.SW mouse model of SLE induced by injection of anti-DNA antibody([29](#_ENREF_29)).

**Clinical studies of anti-TNFα therapies in ANCA-associated vasculitis and glomerulonephritis**

***ANCA-associated vasculitis (AAV)***

A number of anti-TNFα therapies are now approved for clinical use in non-renal autoimmune and inflammatory conditions, such as rheumatoid arthritis (RA), the seronegative arthritides, and inflammatory bowel disease (IBD) (Table 2). The use of three agents – adalimumab, etanercept and infliximab – has been reported in AAV, the latter drug being most commonly employed (Table 3). The majority of reports are of compassionate, off-label use in resistant or refractory disease, where anti-TNFα therapy has been added to conventional treatment with corticosteroids and immunosuppression. Whilst these small series have clear limitations, being uncontrolled, including a diverse case mix, and employing variable definitions of refractory disease and remission, many appeared to suggest that anti-TNFα therapy has biological activity and potential clinical benefit in AAV. One of the largest prospective cohort studies, for example, showed that introduction of infliximab was associated with attaining disease remission in 88% of patients with severe disease, or who had previously shown an incomplete response to steroids and cytotoxic treatment([30](#_ENREF_30)). In the latter group, addition of infliximab was the only change in therapy prior to improvement. A parallel mechanistic study suggested infliximab treatment was associated with improvements in vascular endothelial dysfunction and circulating markers of disease activity([31](#_ENREF_31)). Similarly, the use of adalimumab, as adjuvant therapy with cyclophosphamide and corticosteroids, was associated with high rates of early remission (approximately 80% at 3 months) and the ability to significantly reduce steroid dose during induction treatment([32](#_ENREF_32)). Infectious episodes, occasionally severe, were observed in these series, though in patients with a burden of disease-related damage and previous immunosuppressive exposure, these cannot be wholly attributed to anti-TNFα treatment.

The promising observations of these early series, however, were not fully borne out in the two randomised trials of anti-TNFα therapy in AAV that have been conducted to date. A small randomised study compared the use of infliximab and rituximab in refractory GPA. Approximately one third of patients had a treatment response to infliximab, although response rates to rituximab were higher (50%), and thus this study is regarded as having negative outcome for the use of infliximab([33](#_ENREF_33)). A much larger randomised, placebo controlled study examined the use of etanercept as add-on therapy to conventional treatment with corticosteroids and either methotrexate or cyclophosphamide, for maintenance of remission, in a large cohort of patients with GPA (the Wegener’s Granulomatosis Etanercept Study, WGET)([34](#_ENREF_34)). This study found no benefit of etanercept in this context. Reassuringly, there was no difference in the rate of infectious complications between the intervention and placebo groups, though of concern when the study was first reported, an excess of solid cancers was observed in the etanercept treated group.

Based on the findings of these studies, and in particular the WGET trial, many now regard anti-TNFα therapy as a failed strategy in AAV. The important limitations of these trials should, however, be considered before abandoning this therapeutic approach. Since the publication of the former study([33](#_ENREF_33)), rituximab has gone on to become an established and effective treatment in AAV, for both remission-induction and remission-maintenance. Failure to demonstrate superiority to rituximab, therefore, may not necessarily imply an absence of any biologic or therapeutic effect. In the WGET study([34](#_ENREF_34)), etanercept was used as ‘add-on’ therapy, along with standard treatment, in a cohort of patients with moderately severe disease (only 50% had renal involvement and BVAS scores were relatively low at enrolment). Thus the potential effect of anti-TNFα treatment may not have been apparent in a group of patients that was likely to respond well to conventional therapy. In addition, differences in disease response have been observed with different anti-TNFα agents in other conditions – it is recognised, for example, that etanercept is less effective than infliximab in granulomatous diseases, including Crohn’s disease([35](#_ENREF_35)), and WGET enrolled only patients with GPA and none with MPA. This variation in disease response may be due to differences in pharmacokinetics and dynamics between the different drugs. For example, etanercept can only interact with soluble TNFα, whereas infliximab may interact with cell membrane-bound forms, and other functional binding differences are described([36](#_ENREF_36)). Thus, the efficacy, or lack thereof, of etanercept should not be used to determine the validity of this general approach with other agents, and it is notable that the uncontrolled studies which suggested benefit of anti-TNFα treatment in refractory disease all employed monoclonal antibody preparations rather than the soluble fusion protein. Finally, concerns regarding the risk of malignancy with anti-TNFα treatment in AAV may have been overstated – a subsequent analysis of the WGET study, with an extended period of follow up([37](#_ENREF_37)), suggested that the increased risk of cancer was not different between the intervention and placebo groups when compared to the general population, and that this risk could not be attributed solely to etanerept treatment, as overall duration of disease, past history of malignancy prior to trial enrolment, and previous cyclophosphamide exposure also played a significant role. In addition, there is conflicting evidence regarding the increased risk of malignancy following anti-TNFα therapy in much larger cohorts of patients with rheumatoid arthritis([38](#_ENREF_38), [39](#_ENREF_39)).

For these reasons, it remains possible that anti-TNFα therapy has a role in the management of AAV, potentially for refractory disease, or as a steroid sparing agent during the induction phase of treatment. An ongoing trial, for example, is studying the use of a C5a receptor antagonist as a substitute for corticosteroids, rather than as ‘add-on’ therapy, and a similar approach could be employed using anti-TNFα treatment. Alternatively, it may be that specific disease manifestations should be considered for anti-TNFα therapy. Recent reviews of the ophthalmology literature, for example, indicate that anti-TNFα treatment may be of particular benefit in scleritis and retinal vasculitis([40](#_ENREF_40), [41](#_ENREF_41)), and experience at our centre suggests that anti-TNFα may be a useful strategy for resistant ocular manifestations in AAV (manuscript in preparation). In the future, well-designed clinical studies, along with identification of biomarkers or other disease features that predict response to targeted anti-TNFα therapy, may allow us to better define how these agents could be used in the management of AAV.

***Anti-TNFα therapy in other glomerulonephritides***

***Systemic lupus erythematosus (SLE)***: Whilst preclinical data strongly implicate TNFα in the pathogenesis of crescentic glomerulonephritis and AAV, the rationale for targeting TNFα in SLE is less clear, given the protective role for TNFα described in some murine models of lupus, and the reported development of lupus-like serology, sometimes associated with clinical manifestations, in large cohorts of patients treated with anti-TNFα drugs for other indications (discussed further below). Taken together, these studies suggest that TNFα may have a role in suppressing the development of autoimmunity. Conversely, circulating TNFα levels are increased in patients with SLE and levels correlate with disease activity, and intra-renal TNFα expression appears to correlate with the severity of lupus nephritis (reviewed in([42](#_ENREF_42))), suggesting that it may have a role in mediating end-organ damage once autoimmunity is established, and on which basis it may represent a therapeutic target. Three small, uncontrolled, open-label, prospective studies of anti-TNFα treatment in SLE have been published([43-45](#_ENREF_43)). All employed infliximab in addition to conventional therapy, and all reported moderate clinical responses following short-term treatment, including in patients with active lupus nephritis. Notably, increases in anti-dsDNA and anti-cardiolipin antibody levels were seen in some patients. They did not appear to correlate with disease activity or relapse risk, although thrombotic events were reported. Two randomised controlled trials of anti-TNFα treatment for lupus nephritis were initiated in 2006/7, although both were terminated before completion: one study failed to recruit well (NCT00368264) and the other was terminated due to concerns regarding risk-benefit ratio of treatment (NCT00447265). Given the number of other biologic targets currently under investigation in SLE, and concerns regarding the potential for anti-TNFα to exacerbate or trigger disease flares, it seems unlikely that anti-TNFα agents will be extensively investigated for the treatment of lupus in the future.

***Focal segmental glomerulosclerosis (FSGS):*** TNFα has been implicated in the pathogenesis of FSGS since the description of elevated plasma and urine levels of TNFα in patients with nephrotic syndrome secondary to FSGS and minimal change disease in the 1990s([46](#_ENREF_46)). In a subsequent study, spontaneous TNFα production by cultured peripheral blood mononuclear cells isolated from patients with FSGS correlated with the severity of proteinuria and the degree of glomerulosclerosis observed on renal biopsy([47](#_ENREF_47)). Successful treatment, using infliximab and etanercept, of recurrent FSGS in a paediatric renal transplant recipient has been described in an isolated case report([48](#_ENREF_48)), and long-term follow-up of a phase I study of adalimumab in resistant FGSG suggested attenuation of renal function decline in a proportion of patients([49](#_ENREF_49)). However, a subsequent phase 2 study failed to recruit well, or to identify any benefit in those patients analysed([50](#_ENREF_50)). To the best of our knowledge, there are no ongoing studies of anti-TNFα therapy in FSGS.

***Safety of anti-TNFα therapy***

The development of circulating autoantibodies after anti-TNFα therapy is a well-recognised occurrence. The detection of antinuclear antibodies, for example, in patients treated with anti-TNFα therapy for RA or IBD in clinical trials, has been reported at rates of 29-77% after infliximab, 11-36% with etanercept, and 13% with adalinumab([51](#_ENREF_51)). Anti-double stranded DNA and anti-phospholipid antibodies are also reported, but at lower frequencies. It has been suggested that TNFα inhibition skews the immune response towards a Th2 response that favours IL-10, IFNg and autoantibody production. In addition, anti-TNFα therapy may induce apoptosis and the release of autoantigens from inflammatory cells, thus promoting autoantibody production([52](#_ENREF_52)). Reliable data on the frequency of clinical manifestations associated with these autoantibodies is scarce, however, mostly being limited to anecdotal case reports and series. A registry-initiated study identified 22 cases of drug-associated lupus syndromes in an estimated population of 10,000 patients treated with either infliximab or etanercept for inflammatory arthritis in France until 2003, though as a retrospective, survey-based analysis, it may under-estimate the true incidence of this phenomenon([53](#_ENREF_53)). In this cohort, cutaneous disease manifestations predominated (no patients had lupus nephritis), developing on average nine months into anti-TNFα therapy, and resolving in almost all cases with cessation of treatment. A subsequent literature review identified 105 cases of anti-TNFα therapy associated lupus, with a similar time and pattern of clinical presentation, and low rates of renal involvement (approximately 5%)([54](#_ENREF_54)). In both studies, both monoclonal antibody and soluble receptor therapies were equally implicated in the development of lupus-like disease. The latter review also identified several other autoimmune conditions associated with anti-TNFα therapy, including cutaneous vasculitis, interstitial lung disease, and psoriasis. There are also cases of various other renal and glomerular disorders associated with anti-TNFα therapy, including minimal change disease, membranous nephropathy, IgA nephropathy and pauci-immune necrotizing GN([55](#_ENREF_55)). It may be difficult to confirm causality in these cases, since many of the underlying inflammatory diseases for which anti-TNFα therapy is prescribed are themselves associated with other autoimmune and glomerular disorders. We suggest that patients should be carefully monitored for the development of new autoimmune phenomena and renal disease after initiating anti-TNFα therapy, particularly in the first 12 months, and that treatment should be withdrawn should these develop. In the future, systematic, prospective, registry-based studies may define the true extent of autoimmune syndromes associated with anti-TNFα therapy.

The risk of infectious complications, particularly mycobacterial infection([56](#_ENREF_56)), following anti-TNFα therapy in non-renal disorders is well recognised, and should not be forgotten when adopting this approach in AAV. Such patients are increasingly likely to have been exposed to prior immunosuppressive therapy, including biologic agents, and a significant proportion will have additional, functional immune-paresis related to chronic kidney disease, and already heightened risk of mycobacterial infection([57](#_ENREF_57)). However, as discussed above, concerns about the development of malignancy have probably been overstated.

~~Concerns regarding the induction of autoimmunity, and in particular lupus-like syndromes, with the use of these agents have already been discussed, and it should be noted that a variety of other renal and glomerular disorders have been associated with anti-TNFα treatment, including minimal change disease, membranous nephropathy, ANCA-associated pauci-immune necrotizing GN(~~[~~58~~](#_ENREF_58)~~,~~ [~~59~~](#_ENREF_59)~~), and other systemic vasculitides. The use of these agents in patients with a pre-existing tendency to autoimmunity clearly requires careful monitoring and follow up. However, as discussed above, concerns about the development of solid cancers have probably been overstated.~~

**Conclusions**

The available experimental and clinical data provide strong evidence that TNFα contributes to the pathogenesis of various forms of GN, and AAV in particular. Despite demonstrating remarkable efficacy in non-renal diseases such as rheumatoid arthritis and inflammatory bowel disease, anti-TNFα therapies have not found an established role in the treatment of glomerular disease or vasculitis. Uncontrolled studies suggest that anti-TNFα agents have biological activity and potential therapeutic benefit in AAV (and lupus nephritis and FSGS) though the only large randomised, controlled trial to date (WGET) failed to show any benefit in preventing disease relapse in AAV. This negative outcome, the subsequent explosion in other drug targets and biologic therapies, and potential concerns about their role in inducing autoimmunity, have meant that anti-TNFα agents are now largely discounted as a therapeutic option in AAV. This conclusion, however, may have been premature: limitations in trial design, differences in bio-activity of individual drugs, and failure to consider specific diseases or disease phenotypes that are most likely to respond to therapy, may mean that we have not yet identified how best to use these agents. A clearer understanding of the role of TNFα in the pathogenesis of the spectrum of glomerulonephritis may, in the future, open new avenues for clinical studies and prospective trials. Within the field of AAV in particular, future studies might also address whether anti-TNFα drugs have a role in treating refractory disease, as steroid or cytotoxic sparing agents, or in managing specific disease manifestations. Pending such studies, we highlight the published experience of anti-TNFα use in refractory disease, and remind clinicians that this remains a possible approach in the management of critical disease unresponsive to the conventional repertoire of immunosuppressant treatment.

**Acknowledgements**

We would like to acknowledge support from the NIHR Imperial Biomedical Research Centre.

**Conflict of interest**

The authors declare no conflicts of interest.

**Figure legend**

Inhibition of binding of TNFα to its receptors by monoclonal anti-TNFα antibody or soluble recombinant receptor.

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 1: Tumour necrosis factor alpha (TNFαblockade in experimental glomerulonephritis and vasculitis** | | | |
| **Author** | **Model** | **Agent** | **Outcome** |
| Karkar ([17](#_ENREF_17)) | SD rat NTN | STNFr p55 | Reduced glomerular inflammation and IL1 expression |
| Lan ([18](#_ENREF_18)) | SD rat NTN | TNF binding protein | Reduced glomerular inflammation and MIF expression |
| Karkar ([19](#_ENREF_19)) | WKY rat NTN | STNFr p55 | Prevention: abrogation of crescents  Treatment: reduced crescents and IL1 |
| Khan ([20](#_ENREF_20)) | WKY rat NTN | Anti-TNFα mAb | Prevention: reduced crescents and urine MCP-1  Treatment: reduced glomerular injury and interstitial scarring |
| Le Hir ([21](#_ENREF_21)) | TNF -/- mouse NTN | - | Knockout protected from crescents |
| Timoshanko ([22](#_ENREF_22)) | TNF -/- chimeric mice NTN | - | Intrinsic renal cells major source of TNF with contribution from leucocytes |
| Little ([23](#_ENREF_23)) | WKY rat EAV | Anti-TNFα mAb | Abrogation of crescents  Improvement lung haemorrhage  Inhibition leucocyte transmigration |
| Huugen ([24](#_ENREF_24)) | Mouse anti-MPO GN | Anti-TNFα mAb | Reduced glomerular inflammation |
| Abbreviations: SD –Sprague Dawley; WKY – Wister Kyoto; NTN – nephrotoxic nephritis; EAV – experimental autoimmune vasculitis; MPO - myeloperoxidase | | | |

|  |  |  |
| --- | --- | --- |
| **Table 2: Anti-tumour necrosis factor alpha (TNFα) therapies in current clinical use** | | |
| **Agent** | **Description** | **EMA Licenced Indications** |
| Infliximab  (Remicade®) | * Mouse-human chimeric monoclonal antibody | * Rheumatoid arthritis * Ankylosing spondylitis * Psoriatic arthritis * Psoriasis * Inflammatory bowel disease |
| Adalimumab  (Humira®) | * Human monoclonal antibody | * Rheumatoid arthritis * Juvenile idiopathic arthritis * Ankylosing spondylitis * Psoriatic arthritis * Psoriasis * Inflammatory bowel disease * Hidradenitis suppurativa |
| Etanercept  (Enbrel®) | * Soluble TNFα-receptor-Fc’ fusion protein | * Rheumatoid arthritis * Juvenile idiopathic arthritis * Ankylosing spondylitis * Psoriatic arthritis * Psoriasis |
| Golimumab  (Simponi®) | * Human monoclonal antibody | * Rheumatoid arthritis * Ankylosing spondylitis * Psoriatic arthritis * Ulcerative colitis |
| Certolizumab  (Cimzia®) | * Humanised mouse monoclonal Fab’ fragment; polyethylene-glycolated | * Rheumatoid arthritis |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 3: Clinical studies of anti-tumour necrosis factor alphas (TNFα) therapies in ANCA-associated vasculitis (AAV)** | | | | | |
| **Study, Year, Design** | **Agent, Dose, Duration** | **N** | **Indication** | **Key Outcomes** | **Adverse Events & Other Comments** |
| Stone, 2001([60](#_ENREF_60))  Open label, prospective cohort study | ETN  25mg  Twice per week for 6 months | 20  All GPA  Renal involvement in 4/20 | Active (n=6) or persistent disease (n=14)  ETN added to CS and other IS | * 16/20 achieved BVAS/WG scores of 0 at some point during the 6 month study, though intermittent disease activity was common | * Injection site reactions were common, but treatment was otherwise well tolerated * One patient developed pneumococcal tracheobronchitis * No deaths |
| Booth, 2002([61](#_ENREF_61))  Case series | IFX  200mg  Monthly for 3 months | 6  3 GPA, 3 MPA  Proportion with renal involvement not reported | Refractory disease  IFX added to CS and other IS (not specified) | * Remission achieved in 83% * Early response; four patients remitted within 2 weeks * Allowed steroid taper or withdrawal in 5 cases | * One patient relapsed when treatment period extended to 2 months * No adverse events reported |
| Bartolucci, 2002([62](#_ENREF_62))  Open-label, uncontrolled pilot study | IFX  5mg/kg  Weeks 0, 2, 6  Then every 8 weeks | 10  2 RA, 7 GPA, 1 MC  No GPA with renal involvement | Refractory disease  IFX added to CS for first 6w, then added other IS (included CYC/AZA/MTX/MMF) | * Remission in 100% (50% partial or 50% complete) at 6 months * Symptom attenuation by 2 weeks in 4/10 cases * Allowed steroid taper or withdrawal in 7 cases at 6 months | * No infections * Cutaneous eruptions following IFX infusions in two patients * Two relapses whilst on treatment (GPA and MC) |
| Lamprecht 2002([63](#_ENREF_63))  Cases series | IFX  3-5mg/kg  Weeks 0, 2, 6  Then every 4 weeks | 6  All GPA  Renal involvement in 4/6 | Refractory disease  IFX added to CS and CYC | * Remission 83% at 6 months. * Allowed steroid taper in all responders | * Higher dose of IFX (5mg/kg) possibly more effective * One patient withdrawn due to suspected systemic infection * No relapses reported |
| Zaenker, 2004([64](#_ENREF_64))  Case report | IFX  4mg/kg  Weeks 0, 2, 6 & 10 | 1 MPA  With renal involvement | Active disease  IFX added to iv and oral CS only; AZA for maintenance | * Biopsy-proven resolution of glomerulonephritis by 12 weeks | * No relapse during 1 year follow up |
| Kleinert, 2004([65](#_ENREF_65))  Case report | IFX  3mg/kg  6 doses in 6 months | 1 GPA  With renal involvement | Refractory disease  IFX added to CS and CYC/AZA | * Achieved clinical and renal remission following six month treatment | * Minor flare responded to increased AZA only * No significant adverse events reported |
| Booth, 2004([30](#_ENREF_30))  Open label, prospective cohort study | IFX  5mg/kg  Weeks 0, 2, 6 & 10 | Study 1: 16  7 GPA, 9 MPA  13/16 with renal involvement  Study 2: 16  12 GPA, 4 MPA  Proportion with renal involvement not stated | Study 1: Adjuvant therapy (with CYC and CS) for remission induction in new or relapsing active disease  Study 2: Additional therapy for persistent disease despite 3 month therapy with CS and CYC/AZA/MTX/MMF | * Overall 88% remission, at mean time 6 weeks, in both studies * Steroid sparing compared to published protocols in Study 1, and allowed steroid reduction in Study 2 | * In total 5 relapses (2 in Study 1, 3 in Study 2) * 6 patients with severe infections (2 in Study 1 and 4 in Study 2), though a heavily pre-treated cohort. * A patient in Study 2 developed lymphoma * 2 deaths (both in Study 1) due to pneumonia and active vasculitis * Parallel mechanistic study suggest IFX improves endothelial dysfunction and circulating markers of disease activity([30](#_ENREF_30)) |
| WGET, 2005([34](#_ENREF_34))  Prospective, randomised, placebo-controlled trial | ETN  25mg  Twice per week for study duration | 89 (vs 92 in control group)  All GPA  53% with renal involvement | Remission maintenance  ETN as adjuvant therapy with CS and CYC/MTX | * No difference in primary endpoint between groups: 69.7% etanercept vs 75.3% placebo, p=0.39. * No significant difference in the risk of disease flares between groups (0.89 flares per 100 person-years follow up; p=0.54). | * No difference in overall rate of severe adverse events/deaths (56.2% vs 57.1%; p=0.9) during mean follow up of 27 months. * There was a significantly increased rate of solid cancers in the ETN group (6 vs 0 cases in placebo group; p=0.01), although long-term follow up suggests this cannot be attributed solely to ETN exposure([37](#_ENREF_37)). |
| Josselin, 2008([66](#_ENREF_66))  Case series | IFX  5mg/kg  Weeks 0, 2 & 6  Then 4-6 weekly | 15  10 GPA, 1 MPA  3 RA, 1 MC  (Includes nine patients previously reported by Bartolucci)  No AAV cases had renal involvement | Refractory disease  IFX added to CS and other IS | * 11/15 in remission by week 6 * Remaining 4/15 showed improvement (BVAS reduction ≥50%) | * 10 relapses at a median of 13 months (7 after stopping IFX, 3 whiles still receiving treatment) * 1 case of severe pneumonia reported * No malignancies |
| Laurino, 2010([32](#_ENREF_32))  Open label, prospective cohort study | ADA  40mg  Every 2 weeks for 3 months | 14  9 GPA, 5 MPA  All had renal involvement | Active disease  ADA as adjuvant therapy with with CS and conventional IS | * Remission 79% within 14 weeks * Steroid sparing compared to conventional published regimens | * 5 patients experienced relapse during mean follow up of 40 months * Three patients experienced infectious episodes * One death on dialysis |
| Morgan, 2011([67](#_ENREF_67))  Open label, non-randomised prospective cohort study | IFX  5mg/kg  Weeks 0, 2, 6 & 10 | 16  11 GPA, 5 MPA  11/16 with renal involvement | Active disease  IFX with CS and CYC/ MMF | * No difference in rates or remission, adverse events, damage, or relapses, compared to parallel standard IS group (CS, CYC ± PEX; n=17) | * Standard IS group had more severe disease; 7/17 required additional PEX * IFX group had higher proportion of patients with relapsing disease (7/16 vs 0/17). * Three deaths in IFX group (pancreatic cancer, acute MI, pneumonia) during long-term follow up |
| De Menthon, 2011([33](#_ENREF_33))  Open label, prospective, randomised trial of IFX vs RTX | IFX  3-5mg/kg  Weeks 0, 2, 6  Then every 4 weeks | 9  All GPA  3/9 with renal involvement  (8 GPA with RTX) | Refractory disease  IFX added to CS and other IS (including CYC/AZA/MTX/CMX) | * Remission 33% at 12 months (2 complete, 1 partial) * Less effective than RTX group (50% remission 12 months) | * One death from invasive aspergillosis at day 60 * Five remaining patients had progressive or relapsing disease |
| IFX, infliximab; ETN, etanercept; ADA, adalimumab; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; RA, rheumatoid arthritis; MC, mixed essential cryoglobulinaemia; CYC, cyclophosphamide; AZA, azathioprine; MTX, methotrexate; MMF, mycophenolate mofetil; RTX, rituximab; PEX, plasma exchange; CS, corticosteroids; CMX, co-trimoxazole; BVAS, Birmingham Vasculitis Activity Score. | | | | | |

**References**

1. Feldmann M, Pusey CD. Is there a role for TNF-alpha in anti-neutrophil cytoplasmic antibody-associated vasculitis? Lessons from other chronic inflammatory diseases. Journal of the American Society of Nephrology : JASN. 2006;17(5):1243-52.

2. Speeckaert MM, Speeckaert R, Laute M, Vanholder R, Delanghe JR. Tumor necrosis factor receptors: biology and therapeutic potential in kidney diseases. American journal of nephrology. 2012;36(3):261-70.

3. Vielhauer V, Mayadas TN. Functions of TNF and its receptors in renal disease: distinct roles in inflammatory tissue injury and immune regulation. Seminars in nephrology. 2007;27(3):286-308.

4. Jarrot PA, Kaplanski G. Anti-TNF-alpha therapy and systemic vasculitis. Mediators of inflammation. 2014;2014:493593.

5. Mukhtyar C, Luqmani R. Current state of tumour necrosis factor {alpha} blockade in Wegener's granulomatosis. Annals of the rheumatic diseases. 2005;64 Suppl 4:iv31-6.

6. Deguchi Y, Shibata N, Kishimoto S. Enhanced expression of the tumour necrosis factor/cachectin gene in peripheral blood mononuclear cells from patients with systemic vasculitis. Clinical and experimental immunology. 1990;81(2):311-4.

7. Noronha IL, Kruger C, Andrassy K, Ritz E, Waldherr R. In situ production of TNF-alpha, IL-1 beta and IL-2R in ANCA-positive glomerulonephritis. Kidney international. 1993;43(3):682-92.

8. Komocsi A, Lamprecht P, Csernok E, Mueller A, Holl-Ulrich K, Seitzer U, et al. Peripheral blood and granuloma CD4(+)CD28(-) T cells are a major source of interferon-gamma and tumor necrosis factor-alpha in Wegener's granulomatosis. The American journal of pathology. 2002;160(5):1717-24.

9. Csernok E, Ernst M, Schmitt W, Bainton DF, Gross WL. Activated neutrophils express proteinase 3 on their plasma membrane in vitro and in vivo. Clinical and experimental immunology. 1994;95(2):244-50.

10. Kessenbrock K, Krumbholz M, Schonermarck U, Back W, Gross WL, Werb Z, et al. Netting neutrophils in autoimmune small-vessel vasculitis. Nature medicine. 2009;15(6):623-5.

11. Mackay F, Loetscher H, Stueber D, Gehr G, Lesslauer W. Tumor necrosis factor alpha (TNF-alpha)-induced cell adhesion to human endothelial cells is under dominant control of one TNF receptor type, TNF-R55. The Journal of experimental medicine. 1993;177(5):1277-86.

12. Hasegawa M, Nishii C, Ohashi A, Tomita M, Nakai S, Murakami K, et al. Expression of tumor necrosis factor receptors on granulocytes in patients with myeloperoxidase anti-neutrophil cytoplasmic autoantibody-associated vasculitis. Nephron Clinical practice. 2009;113(3):c222-33.

13. Sonoda Y, Gohda T, Suzuki Y, Omote K, Ishizaka M, Matsuoka J, et al. Circulating TNF receptors 1 and 2 are associated with the severity of renal interstitial fibrosis in IgA nephropathy. PloS one. 2015;10(4):e0122212.

14. Lee SM, Yang S, Cha RH, Kim M, An JN, Paik JH, et al. Circulating TNF receptors are significant prognostic biomarkers for idiopathic membranous nephropathy. PloS one. 2014;9(8):e104354.

15. Taubitz A, Schwarz M, Eltrich N, Lindenmeyer MT, Vielhauer V. Distinct contributions of TNF receptor 1 and 2 to TNF-induced glomerular inflammation in mice. PloS one. 2013;8(7):e68167.

16. Tomosugi NI, Cashman SJ, Hay H, Pusey CD, Evans DJ, Shaw A, et al. Modulation of antibody-mediated glomerular injury in vivo by bacterial lipopolysaccharide, tumor necrosis factor, and IL-1. J Immunol. 1989;142(9):3083-90.

17. Karkar AM, Tam FW, Steinkasserer A, Kurrle R, Langner K, Scallon BJ, et al. Modulation of antibody-mediated glomerular injury in vivo by IL-1ra, soluble IL-1 receptor, and soluble TNF receptor. Kidney international. 1995;48(6):1738-46.

18. Lan HY, Yang N, Metz C, Mu W, Song Q, Nikolic-Paterson DJ, et al. TNF-alpha up-regulates renal MIF expression in rat crescentic glomerulonephritis. Mol Med. 1997;3(2):136-44.

19. Karkar AM, Smith J, Pusey CD. Prevention and treatment of experimental crescentic glomerulonephritis by blocking tumour necrosis factor-alpha. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2001;16(3):518-24.

20. Khan SB, Cook HT, Bhangal G, Smith J, Tam FW, Pusey CD. Antibody blockade of TNF-alpha reduces inflammation and scarring in experimental crescentic glomerulonephritis. Kidney international. 2005;67(5):1812-20.

21. Le Hir M, Haas C, Marino M, Ryffel B. Prevention of crescentic glomerulonephritis induced by anti-glomerular membrane antibody in tumor necrosis factor-deficient mice. Laboratory investigation; a journal of technical methods and pathology. 1998;78(12):1625-31.

22. Timoshanko JR, Sedgwick JD, Holdsworth SR, Tipping PG. Intrinsic renal cells are the major source of tumor necrosis factor contributing to renal injury in murine crescentic glomerulonephritis. Journal of the American Society of Nephrology : JASN. 2003;14(7):1785-93.

23. Little MA, Bhangal G, Smyth CL, Nakada MT, Cook HT, Nourshargh S, et al. Therapeutic effect of anti-TNF-alpha antibodies in an experimental model of anti-neutrophil cytoplasm antibody-associated systemic vasculitis. Journal of the American Society of Nephrology : JASN. 2006;17(1):160-9.

24. Huugen D, Xiao H, van Esch A, Falk RJ, Peutz-Kootstra CJ, Buurman WA, et al. Aggravation of anti-myeloperoxidase antibody-induced glomerulonephritis by bacterial lipopolysaccharide: role of tumor necrosis factor-alpha. The American journal of pathology. 2005;167(1):47-58.

25. Pfister H, Ollert M, Frohlich LF, Quintanilla-Martinez L, Colby TV, Specks U, et al. Antineutrophil cytoplasmic autoantibodies against the murine homolog of proteinase 3 (Wegener autoantigen) are pathogenic in vivo. Blood. 2004;104(5):1411-8.

26. Jacob CO, McDevitt HO. Tumour necrosis factor-alpha in murine autoimmune 'lupus' nephritis. Nature. 1988;331(6154):356-8.

27. Brennan DC, Yui MA, Wuthrich RP, Kelley VE. Tumor necrosis factor and IL-1 in New Zealand Black/White mice. Enhanced gene expression and acceleration of renal injury. J Immunol. 1989;143(11):3470-5.

28. Yokoyama H, Kreft B, Kelley VR. Biphasic increase in circulating and renal TNF-alpha in MRL-lpr mice with differing regulatory mechanisms. Kidney international. 1995;47(1):122-30.

29. Segal R, Dayan M, Zinger H, Mozes E. Suppression of experimental systemic lupus erythematosus (SLE) in mice via TNF inhibition by an anti-TNFalpha monoclonal antibody and by pentoxiphylline. Lupus. 2001;10(1):23-31.

30. Booth A, Harper L, Hammad T, Bacon P, Griffith M, Levy J, et al. Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. Journal of the American Society of Nephrology : JASN. 2004;15(3):717-21.

31. Booth AD, Jayne DR, Kharbanda RK, McEniery CM, Mackenzie IS, Brown J, et al. Infliximab improves endothelial dysfunction in systemic vasculitis: a model of vascular inflammation. Circulation. 2004;109(14):1718-23.

32. Laurino S, Chaudhry A, Booth A, Conte G, Jayne D. Prospective study of TNFalpha blockade with adalimumab in ANCA-associated systemic vasculitis with renal involvement. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2010;25(10):3307-14.

33. de Menthon M, Cohen P, Pagnoux C, Buchler M, Sibilia J, Detree F, et al. Infliximab or rituximab for refractory Wegener's granulomatosis: long-term follow up. A prospective randomised multicentre study on 17 patients. Clinical and experimental rheumatology. 2011;29(1 Suppl 64):S63-71.

34. Wegener's Granulomatosis Etanercept Trial Research G. Etanercept plus standard therapy for Wegener's granulomatosis. The New England journal of medicine. 2005;352(4):351-61.

35. Sandborn WJ, Hanauer SB, Katz S, Safdi M, Wolf DG, Baerg RD, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2001;121(5):1088-94.

36. Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. The Journal of pharmacology and experimental therapeutics. 2002;301(2):418-26.

37. Silva F, Seo P, Schroeder DR, Stone JH, Merkel PA, Hoffman GS, et al. Solid malignancies among etanercept-treated patients with granulomatosis with polyangiitis (Wegener's): long-term followup of a multicenter longitudinal cohort. Arthritis and rheumatism. 2011;63(8):2495-503.

38. Thompson AE, Rieder SW, Pope JE. Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis and rheumatism. 2011;63(6):1479-85.

39. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295(19):2275-85.

40. de Fidelix TS, Vieira LA, de Freitas D, Trevisani VF. Biologic therapy for refractory scleritis: a new treatment perspective. Int Ophthalmol. 2015;35(6):903-12.

41. Rosenbaum JT, Sibley CH, Lin P. Retinal vasculitis. Current opinion in rheumatology. 2016;28(3):228-35.

42. Aringer M, Smolen JS. Therapeutic blockade of TNF in patients with SLE-promising or crazy? Autoimmun Rev. 2012;11(5):321-5.

43. Aringer M, Graninger WB, Steiner G, Smolen JS. Safety and efficacy of tumor necrosis factor alpha blockade in systemic lupus erythematosus: an open-label study. Arthritis and rheumatism. 2004;50(10):3161-9.

44. Uppal SS, Hayat SJ, Raghupathy R. Efficacy and safety of infliximab in active SLE: a pilot study. Lupus. 2009;18(8):690-7.

45. Matsumura R, Umemiya K, Sugiyama T, Sueishi M, Umibe T, Ichikawa K, et al. Anti-tumor necrosis factor therapy in patients with difficult-to-treat lupus nephritis: a prospective series of nine patients. Clinical and experimental rheumatology. 2009;27(3):416-21.

46. Suranyi MG, Guasch A, Hall BM, Myers BD. Elevated levels of tumor necrosis factor-alpha in the nephrotic syndrome in humans. American journal of kidney diseases : the official journal of the National Kidney Foundation. 1993;21(3):251-9.

47. Bakr A, Shokeir M, El-Chenawi F, El-Husseni F, Abdel-Rahman A, El-Ashry R. Tumor necrosis factor-alpha production from mononuclear cells in nephrotic syndrome. Pediatr Nephrol. 2003;18(6):516-20.

48. Leroy S, Guigonis V, Bruckner D, Emal-Aglae V, Deschenes G, Bensman A, et al. Successful anti-TNFalpha treatment in a child with posttransplant recurrent focal segmental glomerulosclerosis. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2009;9(4):858-61.

49. Peyser A, Machardy N, Tarapore F, Machardy J, Powell L, Gipson DS, et al. Follow-up of phase I trial of adalimumab and rosiglitazone in FSGS: III. Report of the FONT study group. BMC Nephrol. 2010;11:2.

50. Trachtman H, Vento S, Herreshoff E, Radeva M, Gassman J, Stein DT, et al. Efficacy of galactose and adalimumab in patients with resistant focal segmental glomerulosclerosis: report of the font clinical trial group. BMC Nephrol. 2015;16:111.

51. Atzeni F, Sarzi-Puttini P. Autoantibody production in patients treated with anti-TNF-alpha. Expert Rev Clin Immunol. 2008;4(2):275-80.

52. Atzeni F, Talotta R, Salaffi F, Cassinotti A, Varisco V, Battellino M, et al. Immunogenicity and autoimmunity during anti-TNF therapy. Autoimmun Rev. 2013;12(7):703-8.

53. De Bandt M, Sibilia J, Le Loet X, Prouzeau S, Fautrel B, Marcelli C, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis research & therapy. 2005;7(3):R545-51.

54. Ramos-Casals M, Brito-Zeron P, Soto MJ, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies. Best Pract Res Clin Rheumatol. 2008;22(5):847-61.

55. Piga M, Chessa E, Ibba V, Mura V, Floris A, Cauli A, et al. Biologics-induced autoimmune renal disorders in chronic inflammatory rheumatic diseases: systematic literature review and analysis of a monocentric cohort. Autoimmun Rev. 2014;13(8):873-9.

56. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. The New England journal of medicine. 2001;345(15):1098-104.

57. British Thoracic Society Standards of Care C, Joint Tuberculosis C, Milburn H, Ashman N, Davies P, Doffman S, et al. Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease. Thorax. 2010;65(6):557-70.

58. Stokes MB, Foster K, Markowitz GS, Ebrahimi F, Hines W, Kaufman D, et al. Development of glomerulonephritis during anti-TNF-alpha therapy for rheumatoid arthritis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2005;20(7):1400-6.

59. Doulton TW, Tucker B, Reardon J, Velasco N. Antineutrophil cytoplasmic antibody-associated necrotizing crescentic glomerulonephritis in a patient receiving treatment with etanercept for severe rheumatoid arthritis. Clinical nephrology. 2004;62(3):234-8.

60. Stone JH, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, Hoffman GS. Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety. Arthritis and rheumatism. 2001;44(5):1149-54.

61. Booth AD, Jefferson HJ, Ayliffe W, Andrews PA, Jayne DR. Safety and efficacy of TNFalpha blockade in relapsing vasculitis. Annals of the rheumatic diseases. 2002;61(6):559.

62. Bartolucci P, Ramanoelina J, Cohen P, Mahr A, Godmer P, Le Hello C, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. Rheumatology. 2002;41(10):1126-32.

63. Lamprecht P, Voswinkel J, Lilienthal T, Nolle B, Heller M, Gross WL, et al. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. Rheumatology. 2002;41(11):1303-7.

64. Zaenker M, Arbach O, Helmchen U, Glorius P, Ludewig S, Braasch E. Crescentic glomerulonephritis associated with myeloperoxidase-antineutrophil-cytoplasmic antibodies: first report on the efficacy of primary anti-TNF-alpha treatment. Int J Tissue React. 2004;26(3-4):85-92.

65. Kleinert J, Lorenz M, Kostler W, Horl W, Sunder-Plassmann G, Soleiman A. Refractory Wegener's granulomatosis responds to tumor necrosis factor blockade. Wien Klin Wochenschr. 2004;116(9-10):334-8.

66. Josselin L, Mahr A, Cohen P, Pagnoux C, Guaydier-Souquieres G, Hayem G, et al. Infliximab efficacy and safety against refractory systemic necrotising vasculitides: long-term follow-up of 15 patients. Annals of the rheumatic diseases. 2008;67(9):1343-6.

67. Morgan MD, Drayson MT, Savage CO, Harper L. Addition of infliximab to standard therapy for ANCA-associated vasculitis. Nephron Clinical practice. 2011;117(2):c89-97.