Review Article

Anti-TNF-α Therapies in Systemic Lupus Erythematosus

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Tumor necrosis factor (TNF)-α is not just a proinflammatory cytokine. It has also been proposed to be an immunoregulatory molecule that can alter the balance of T regulatory cells. Anti-TNF-α therapies have been provided clinical benefit to many patients and introduced for treating moderate to severe rheumatoid arthritis, Crohn's disease, and other chronic inflammatory disorders. However, their use also is accompanied by new or aggravated forms of autoimmunity, such as formation of autoantibodies, including antinuclear antibodies (ANAs), antidouble-stranded DNA (dsDNA) antibodies, and anticardiolipin antibodies (ACL). Systemic lupus erythematosus (SLE) is a disease with autoimmune disturbance and inflammatory damage. The role of TNF-α in human SLE is controversial. Here we review the role of TNF-α in the pathophysiological processes of SLE and the likely effects of blocking TNF-α in treatment of SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease characterized by breakdown of selftolerance, B cell hyperactivity, autoantibody production, aberrant formation of immune complexes (ICs), and inflammation of multiple organs [1]. As a pleiotropic cytokine that has both immunoregulatory and proinflammatory effects [2, 3], Tumor necrosis factor (TNF)-α was reported to be increased in SLE and correlated with disease activity [4], and it has been proposed to contribute to the immunopathogenesis of SLE [5]. Recently an open-label study showed that anti-TNF therapy could suppress the local tissue destruction in SLE, but at the same time, use of anti-TNF-α agent leads to formation of autoantibodies, including autoantibodies to double-stranded DNA (ds-DNA) and cardiolipin increased [6]. As a consequent it was inferred that TNF blockade in SLE could pose dangers. This paper will focus on the role of TNF-α in the pathophysiological processes of SLE and the likely effects of blocking TNF-α in treatment of SLE.

2. Biology of TNF-α

TNF-α is a pleiotropic cytokine produced by many cell types, including macrophages, monocytes, lymphocytes, keratinocytes, and fibroblasts, in response to inflammation, infection, injury, and other environmental challenges [7]. TNF-α is not only a potent proinflammatory cytokine but also plays an important role in lymphocyte and leukocyte activation and migration, fever, acute-phase response, cell proliferation, differentiation, and apoptosis [8]. TNF-α exerts its effects through two distinct receptors: TNF receptor 1 (TNFR1) and TNFR2 [9]. Binding of the inherently trimeric TNF-α to TNFR1 and TNFR2 induces receptor trimerization and recruitment of several signaling proteins to the cytoplasmic domains of the receptors. The first protein recruited to TNFR1 is TNFR associated death domain (TRADD), which serves as a platform to recruit at least three additional mediators, Fas-associated death domain (FADD), receptor-interacting protein 1 (RIP-1), and TNF receptor-associated factor 2 (TRAF-2) [9–13]. TNFR1 transduces apoptotic and anti-inflammatory signals through the recruitment of FADD and subsequent recruitment and activation of Caspase 8 then leading to the activation of caspase cascade; the activation of Caspase 3 executes apoptosis [13]. TNFR1 also mediates antiapoptotic and inflammatory responses through the recruitment of TRAF-2 and RIP-1, which are critical in the activation of nuclear factor-kappa B (NF-κB), c-Jun NH2-terminal kinase (JNK), and mitogen-activated protein kinase (MAPK) [14]. On the other hand, it is known that the occupancy of TNFR2 by TNF-α leads to the recruitment of TRAF-1 and TRAF-2 [15].

TRAF-2 is essential for the process of activation of NF-κB, JNK, and MAPK, and mediates antiapoptotic and proinflammatory effects [16]. Therefore, TNFR2 is involved in the antiapoptotic and inflammatory effect of TNF-α whereas TNFR1 is involved in both apoptotic/anti-inflammatory and antiapoptotic/inflammatory signaling. The adapter proteins such as TRADD, FADD, RIP-1, and TRAF-2 are pivotal molecules in the apoptosis and inflammatory signal pathway of TNF-α, they play as 'bifurcations' and are indispensable [17].

TNF-α is both a proinflammatory cytokine and an immunoregulatory cytokine. TNF-α has differential effects on B cells, T cells, and dendritic cells, as well as on the process of programmed cell death. During the (auto)immune response, TNF-α acts as a growth factor for B cells and may promote dendritic cell (DC) maturation but leads to T cell hyporesponsiveness and to the expression of antiapoptotic molecules. The latter is very important in the immune homeostasis: on one hand, TNF-α restrains autoreactive T cells through the negative regulation of T cell receptor (TCR) signal transduction and the induction of T cell apoptosis in the peripheral blood [18]; on another hand, TNF-α counteracts Fas-mediated apoptosis through the activation of NF-κB and the induction of antiapoptotic molecules, then decreases the stimulation to immune system caused by apoptosis-derived nucleosome, and inhibits the production of autoantibody [19]. From the aspect of inflammation, TNF is induced by IC and promotes inflammation and secondary tissue destruction; liberation of autoantigens during necrosis could fuel autoimmunity [19].

By directing its two transmembrane receptors to deliver signals of cellular proliferation, differentiation, or apoptosis, TNF-α appears not only to orchestrate acute responses to infection and immunological injury but also to act as a balancing factor required for the re-establishment of physiological homeostasis and immune regulation [20]. The level, timing, and duration of TNF-α activity are of pivotal regulatory significance in immune physiology. Aberrations in any of these factors result in perturbed phenotypes that depend on a multitude of TNFR-mediated activities, be it pro-inflammatory, immune activating, or even immunosuppresive [20].

Within such pleiotropism of functions, blockade of TNF-α in recent clinical trials of rheumatoid arthritis or inflammatory bowel disease, although so far impressively beneficial for the majority of patients, has also led in some cases to a significant incidence of drug-induced anti-dsDNA production and lupus and in manifestations of neuroinflammatory disease [21–23]. TNF-α blocking could relieve the inflammation induced by TNF-α, at the same time the immunoregulatory and antiapoptotic effects of TNF-α could also be blockade which may lead to autoimmunity [24].

3. TNF-α Participates in SLE Pathologic Changes

Disregulated TNF-α production, be it low or high, characterizes many autoimmune diseases. Recent evidence supports a dualistic, pro-inflammatory, and immune- or disease-suppressive role for TNF-α in these conditions [20]. Because of the complex genetics of SLE and the tight linkage of the *Tnf* gene with the MHC locus, the physiological role of TNF-α and its adaptors in the pathogenesis of lupus has remained uncertain [25].

3.1. Aberrant Immunoregulatory Effects of TNF-α in SLE. In the classic animal model of SLE, the (NZB×NZW)F1 mouse, initial studies demonstrated the benefit of early recombinant TNF-α (rTNF-α) administration, or TNF-α boosting reagents, towards the onset of lupus nephritis but not on B cell hyperactivity and autoantibody responses [26–28].

Kontoyiannis and Kollias generated heterozygous (NZB × B6, 129 Tnf^0)F1 mice, which have reduced TNF-α production, by crossing NZB mice with TNF-α deficient mice [25]. (NZB × Tnf^0)F1 hemizygous mice developed enhanced autoimmunity and severe renal disease similar to the (NZB × NZW)F1 mice. Autoimmune responses were associated with an early spontaneous increase in serum levels of antinuclear autoantibodies and hyperproliferating B cells which readily express anti-dsDNA specificities in response to polyclonal and T helper stimuli. These findings demonstrate a physiological role for TNF-α in suppressing the emergence of autoreactive lymphocytes in the NZB model and indicate that defective TNF-α function may be causative of the autoimmune and pathological phenomena in lupus [25]. Loss of physiological TNF-α production in an autoimmunity prone background suffices to exacerbate anti-nuclear autoimmunity and the development of disease [25]. To that end TNF-α dysfunction may appear epistatic to the dominance of MHC heterozygosity associated with lupus autoimmunity [29, 30]. Genetic studies have indicated that the hypoproducing Tnf^Z allele derived by the NZW parent and the H-2d/z heterozygosity of the MHC locus are dominant contributors to the susceptibility of this model to autoimmunity [31, 32].

Kollias and Kontoyiannis also showed that TNF-α deficient mice in a mixed B6,129 genetic background (H-2b/b) had a normal life span and appeared macroscopically healthy, but they developed mild anti-nuclear autoimmunity in the form of IgG2b and IgG3 anti-DNA antibodies [20]. In addition, 40% of female mice show mild IgG deposits on their glomeruli and alterations in glomerular structure resembling the initial stages of lupus nephritis (LN). In contrast, clinical symptoms and terminal glomerulonephritis do not develop [20]. The apparent lack of pathology in the presence of ensuing autoimmunity can be explained by the absence of the pro-inflammatory activities of TNF-α. TNF-α has been indicated to play a dominant role in mesangial macrophage activation, apoptosis of renal tubular epithelia, and antiglomerular antibody-induced kidney destruction [33–36]. Recently, it was demonstrated that anti-TNF administration suppressed experimental SLE induced by the injection of human anti-DNA autoantibodies in mice [37].

Apoptosis (programmed cell death (PCD)) plays an important role in the homeostasis of the immune response.

Peripheral blood lymphocytes (PBLs) from SLE patients exhibit increased spontaneous and diminished activation-induced apoptosis. Increased spontaneous apoptosis of PBLs has been linked to chronic lymphopenia and comparted-mentalized release of nuclear autoantigens in patients with SLE [38]. The appearance of high numbers of autoreactive lymphocytes in the peripheral blood of patients with SLE might be a consequence of defective activation-induced cell death (AICD) [39]. Kovacs B et al. [40] showed that permeabilitized lupus T cells displayed significantly lower amounts of TNF-α, a functional Fas/Fas-ligand path and adequate amounts of intracellular TNF-α were needed for the CD3-mediated T cell death. Prolonged survival of autoreactive T cells can lead to increased autoantibody production. Defective activation-induced apoptosis in lupus would worsen under TNF blockade.

The clinic reports about the levels of TNF-α in SLE patients were controversial [41, 42]. In most studies, TNF-α is found to be markedly increased and appears to be bioactive in the sera of patients with active SLE, and levels of TNF-α have been shown to correlate with SLE disease activity [4, 19]. Our previous study found that SLE patients had elevated plasma levels of TNF-α as compared to controls, however there was no correlation with disease activity [43]. Gómez D et al. have showed that TNF-α levels and the TNF/IL-10 ratio were higher in patients with inactive disease compared with patients with very active disease and controls, suggesting that TNF-α could be a protective factor in SLE patients [42].

HLA-DR2- and DQwl-positive donors frequently exhibit low production of TNF-α whereas DR3- and DR4-positive subjects show high levels of TNF-α production [44]. DR2, DQwl-positive SLE patients show low levels of TNF-α inducibility; this genotype is also associated with an increased incidence of LN [44]. DR3-positive SLE patients, on the other hand, are not predisposed to nephritis, and these patients have high TNF-α production. DR4 haplotype is associated with high TNF-α inducibility and is negatively correlated with LN [44]. These data suggested that low TNF-α production may be involved in the genetic predisposition to LN, similar to the $(NZB \times NZW)F1$ LN model system [45] and may help explain the association between HLA-DR2/DQwl and susceptibility to LN. However, a substantial portion of SLE patients are DR3 associated; clearly these patients do not have low TNF-α production, similar to MRL-lpr/lpr and BXSB mice, which also show high levels of TNF-α production [44]. This result suggests that SLE is not a single condition but rather can be subdivided into at least two subsets: one associated with DR2/DQwl increased susceptibility to LN and low TNF-α production; the other associated with DR3 and high TNF-α production associated with lupus without nephritis [44].

Although TNF signaling adaptors are quite important in the function of TNF-α, the roles they play in the pathogenesis of SLE are not clear by now. In our previous study, we demonstrated that the expression of TRADD, FADD, RIP-1, and TRAF-2 in PBMCs from SLE patients significantly decreased as compared with healthy control subjects [46]. These data pointed to that aberrant proapoptotic signals,

antiapoptotic signals, and proinflammatory signals of TNF-α pathway may involve in the immunopathogenic injury in SLE. These findings are consistent with the studies done by K. Maas et al. in which they indicated that TRADD and TRAF-2 in PBMCs of patients were downregulated in SLE by gene assay analysis [47]. As TNFR1–TRADD–FADD system leading to apoptotic signaling, the downregulation of TRADD, FADD in PBMCs from patients with SLE may promote an anti-apoptotic effect. Defects in expression of these genes may increase the likelihood that lymphocytes avoid the normal processes used by the immune system to eliminate unwanted lymphocytes or to down-regulate an immune response [48, 49]. If patients carry this autoimmune gene expression signature, signaling pathways essential for the maintenance of tolerance may not function properly. This may permit lymphocytes to escape tolerance and adopt a prosurvival agenda that increases the likelihood of autoimmune diseases. TNFR1–TRADD–RIP-1–TRAF-2 system leads to the anti-apoptotic and inflammatory signaling [7]. In our previous study, it was showed that the more severity of the disease, the lower expression of the three adaptor proteins of TRADD, RIP-1, and TRAF-2, and it implied that there was less restraint of apoptotic death [46]. The expression of Caspase 3 was also significantly upregulated in SLE patients. Self-antigen exposure has been suggested to occur as a consequence of massive apoptotic death, this death is accompanied by delayed removal of apoptotic bodies due to defective phagocytosis of phagocytic cells [50–52]. These events gave rise to a large number of nucleosomes and intracellular proteins circulating in the SLE sera [33, 35], which indicate that there was massive apoptotic death. Development of autoantibodies and tissue damage are predominant in most SLE patients [53]. The dysregulation of programmed cell death is suggested to be involved in the generation of autoantibodies. The low expression of TRADD, RIP-1, and TRAF-2 in PBMCs might be one of the etiopathogeneses leading to redundant apoptotic death in SLE patients. Our study indicated that decreased expression of TRADD, RIP-1, and TRAF-2 mRNA by PBMCs and restrained TNF-α-induced anti-apoptosis, as well as advanced lymphocyte apoptosis, may play a role in the pathogenesis for the loss of immune tolerance and redundant apoptotic cell death, leading to massive production of autoantibodies in SLE patients [46]. These abnormalities may participate in the immunopathogenic injury mediated by the aberrant TNF-α signaling pathway in SLE.

3.2. Inflammatory Effects of TNF-α in the Pathogenesis of SLE.

TNF-α is the most important proinflammatory cytokine and a harbinger of tissue destruction, and it is at the top of a pro-inflammatory "cascade" leading to tissue damage. In contrast to the complex role of TNF-α in apoptosis and in immune regulation, its powerful proinflammatory effects are unequivocal. In the classic lupus model, the MRL/lpr mice, high TNF-α was found in their serum as well as in their nephritic kidneys, and both serum and renal TNF-α are correlated with disease activity [54–56]. Anti-TNF therapy in MRL/lpr mice is beneficial [57, 58]. In NZB/W mice, kidneys with glomerulonephritis contained remarkably high

amounts of TNF-α, and low dosages of TNF-α administered in late NZB/W disease accelerated renal damage [59, 60]. TNF-α can be induced by immune complexes and is locally produced in the immune complex glomerulonephritis lesions of patients with SLE kidney disease, as it is produced in the inflamed kidneys of lupus mice [61–64].

To determine whether administration of TNF-α would accelerate renal injury and mortality, D. C. Brennan et al. injected murine rTNF-α intraperitoneally into female NZB/W or C3H/FeJ mice at two doses, 2.0 micrograms or 0.2 micrograms, three times weekly for 2 or 4 months beginning at 2 or 4 months of age. Administration of the lower dose of rTNF-α accelerated renal disease and mortality rate when treatment was initiated at 4 months of age. At the higher dose, rTNF-α promoted disease. Treatment administered from 2–4 months of age did not accelerate renal disease [28]. Overall the data presented above indicate that on the one hand, early TNF-α is required to suppress autoimmunity but on the other hand, its presence may aid the development of renal pathology [20].

T.Takemura et al. have found that TNF-α is clearly expressed in glomeruli of LN patients, mainly by infiltrating macrophages but also by endothelial cells, glomerular visceral epithelium, and mesangial cells (MCs) of all eight samples with WHO class III and IV LN, while no TNF-α is detected in healthy kidney tissues [61]. TNF-α is also found in the interstitium. R. Herrera-Esparza et al. have analyzed 19 kidney biopsies with class III or IV LN and demonstrated TNF-α expression in 10 of these biopsies [62]. TNF-α was seen along the interstitial space of the glomerular loops and in tubular epithelium. TNF-α mRNA was detected in six biopsies and seen in tubular epithelium and in mononuclear cells infiltrating the glomerular loops [62]. It is interesting that TNF-α was mostly found in samples with high histological activity indices. M.Aringer and J.S. Smolen showed that glomerular TNF-α expression was correlated with histological activity but was largely independent of the WHO class [19]. The involvement of TNF-α in LN is further supported by the improvement of LN under TNF-α blocking therapy (e.g., infliximab) [63, 64]. All these studies indicate that TNF-α is expressed in LN of all WHO classes and high TNF-α expression is associated with high histological disease activity. In our previous study, we found markedly up-regulated renal expression of TNF-α in class III and class IV LN by immunohistochemical studies, and the up-regulation of TNF-α was correlated with increased number of proliferating cell nuclear antigen (PCNA-)positive cells, CD68-positive cells and the activity index of renal pathologic changes [65].

The up-regulated renal TNF-α expression is considered to play an important role in the activation of local inflammation and formation of tissue damage. TNF-α is at the top of inflammation cascade, and the activation of TNF-α signaling pathway could transmit inflammatory signaling by activation of NF-κB, which enters the nucleus and activates transcription of proinflammatory gene targets such as interleukin-1β (IL-1β), IL-6, and IL-8 [66]. In inflamed kidneys of SLE, TNF-α is induced by IC and promotes inflammation and secondary tissue destruction; liberation of autoantigens during necrosis could fuel autoimmunity [19]. The findings from our previous study are consistent with previous reports where TNF-α is found to be highly expressed in glomeruli in all forms of LN [62, 67], and the degree of TNF-α expression correlates with renal inflammatory activity, as measured by a histological activity index. In our previous immunohistochemical study, we also found that the renal expression of TNF-α, TRADD, RIP, and TRAF-2 was markedly up-regulated in class III and class IV LN, these results suggested that the proinflammatory effect mediated by TNF-α signaling was facilitated in local tissue [65]. Our study showed the number of PCNA-positive cells increased markedly in glomerular endothelial cells, glomerular mesangial cells, and parietal epithelial cells lining Bowman's capsule, endothelial cells in renal interstitial capillaries and larger vessels, and tubular epithelium in specimens from patients with class III and IV LN as well. This suggested that there is considerable cell proliferation in these tissues. The increase in the number of PCNA-positive cells was consistent with the up-regulation of TNF-α, TRADD, RIP, and TRAF-2, suggesting that the TNF-α–TRADD–RIP–TRAF-2 signaling could mediate cell proliferation in LN. We also found that CD68-positive macrophages were markedly increased in class III and IV LN, and the up-regulation of TNF-α, TRADD, RIP, and TRAF-2 correlated with increased number of CD68-positive cells and the activity index of renal pathologic changes. CD68 plays a critical role of macrophage maturation and thus its increase would facilitate the enhancement of macrophage-mediated immune responses such as TNF-α release. The WHO classification of LN (class I-VI) does not equally distribute disease activity. For example, when renal sclerosis occurs in class VI, local inflammatory activity may be less severe under microscope. Our previous study has apparently demonstrated that the expression of TNF-α and TNF-α adapter proteins is independent of the WHO class of LN [65]. By in vitro study we showed knockdown TRAF-2 by siRNA significantly suppressed soluble aggregated IgG (AIgG)-induced up-regulation of TRAF-2, IL-1β, and IL-6. Meanwhile the cell proliferation was inhibited, and apoptotic cells were increased. From these results we concluded that TRAF-2 could induce the proinflammatory and proliferative effects of soluble AIgG on rat MCs. Thus, TRAF-2 may represent a future target for therapy of IC-mediated GN [68].

Our previous study has showed that the expression of mRNA for TNF-α adapter molecules, such as TRADD, RIP-1, and TRAF-2, decreased significantly in PBMCs from patients with SLE, and the expression of these adapters was negatively correlated with the SLE activity index [46]; but the expression of TNF-α, TRADD, RIP, and TRAF-2 in glomerular and tubular cells was increased in Class III and IV LN while the increased TNF-α, TRADD, RIP, and TRAF-2 levels also correlated with the number of CD68-positive or PCNA-positive cells and renal pathologic severity [65]. The reason for the remarkable discrepancy in the expression of TNF-α adapter proteins, TRADD, RIP, and TRAF-2 in various organic tissues is unknown but may be related to distinct role and regulating factors of TNF-α and its adapter proteins in different tissues [65]. This discrepancy
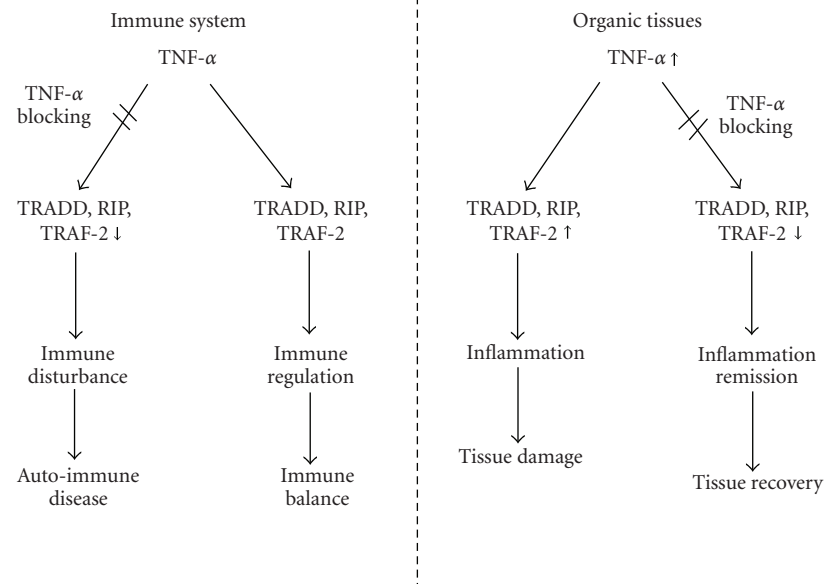
FIGURE 1: Distinct role and regulating factors of TNF-α and its adapter proteins immune system and organic tissues. TNF-α blocking in different tissues may lead to different consequences.

may indicate that TNF-α blocking in distinct tissue could lead to different consequences (Figure 1).

4. Clinic Trials of TNF-α Blockade in SLE

SLE is an autoimmune disease with inflammatory tissue damage and TNF-α participates in SLE pathogenesis. As "TNF is at the top of a pro-inflammatory "cascade". . . blocking just this one of the many pro-inflammatory cytokines might, by means of its downstream effects, have an important influence on the complex disease process. . ." [69], blocking TNF-α in SLE might be beneficial to SLE patients. There are several clinic trials about TNF-α blocking in SLE by now, and the results seem to be not so exciting [6, 70–72].

M.Aringer et al. reported an Open-Label Study in 2004 about the safety and efficacy of TNF-Blockade in SLE [6]. 6 patients with moderately active SLE (4 with nephritis and 3 with arthritis refractory to other therapies) were given 4 infusions of 300 mg doses of infliximab, a chimeric anti-TNF-α antibody, in addition to immunosuppression with azathioprine or methotrexate. The only significant adverse events observed were urinary tract infection in 3 patients, 1 of which was accompanied by Escherichia coli bacteremia, and a prolonged febrile episode of putatively viral origin in 1 of them. These patients had similar infectious conditions in the past. None of the patients need terminating the treatment prematurely. Levels of antibodies to ds-DNA and cardiolipin increased in 4 patients, but this was not associated with a decrease in serum complement levels, with vascular events or with flares. In contrast, disease activity declined during therapy. All 3 patients with joint involvement experienced remission of arthritis, which relapsed 8–11 weeks after the last infliximab infusion. In the 4 patients with lupus

nephritis, proteinuria decreased significantly within 1 week after initiation of therapy and was diminished by >60% within 8 weeks, remaining at low levels until the end of the observation period (at least several months). From these exciting results they concluded that Infliximab did not lead to adverse events related to increase of SLE activity although autoantibodies to ds-DNA and cardiolipin increased [6].

In 2008, M.Aringer and J.S. Smolen published another paper about the changes in autoantibodies occurring in SLE patients treated with 4 infusions of the chimeric anti-TNF-α antibody infliximab [70]. In the open-label safety study, 7 patients with SLE were treated with infliximab at weeks 0, 2, 6, and 10 in combination with azathioprine or methotrexate. Autoantibodies to ds-DNA increased in 5 of 7 patients. Histone, chromatin, and IgM anti-cardiolipin levels were increased in 4 of 7, 6 of 7, and 4 of 7 patients, respectively, peaking 4–10 weeks after the last infliximab infusion, but falling to baseline levels or lower thereafter. In the in vitro experiments, TNF-α withdrawal after long-term incubation with recombinant human TNF-α led to increased percentages of apoptotic cells. These results suggested that while TNF-α blockade was clinically effective, the majority of SLE patients treated with infliximab showed an increase in autoantibodies to nuclear antigens and phospholipids. These increases were transient and were not associated with disease flares. These results indicated that increased availability of apoptotic antigens after TNF-α blockade may play a role in the autoantibody formation induced by TNF-α blockade [70].

In 2009, Uppal et al. reported a pilot study for the efficacy and safety of infliximab in active SLE [71]. A total of 46 individuals (27 patients with active SLE and 19 healthy control volunteers) were studied. Nine patients with SLE

were allocated to treatment arm and 18 were allocated to control arm. In addition to conventional treatment, treatment arm received infliximab infusions 3 mg/kg body weight at 0, 2, and 6 weeks and then q 8 weeks for a total of 24 weeks, that is, a total of five doses. Four patients from treatment arm dropped out due to infliximab infusion reaction and 12 patients dropped out from the control arm. The treatment group showed significantly greater improvement in SLE Disease Activity Index (SLEDAI). Improvements in several Health status (SF-36) subscales, patient global assessment (PGA) of disease activity and Visual Analogue Scale-(VAS-) Fatigue, were also greater in the treatment group but did not achieve statistical significance. The mean levels of TNF-α, soluble TNFR-1 (p55 srTNF-α), and TNFR-2 (p75 srTNF-α) were higher in the SLE group compared with the healthy controls but did not change significantly over the study period. No safety issues with infliximab were seen in this study. In view of improvement in several SLE parameters and good safety profile of infliximab, they thought anti-TNF-α therapy was an interesting candidate approach for treating SLE [71].

Recently Aringer M. et al. reported a long-term follow-up study of 13 patients about the adverse events and efficacy of TNF-α blockade with infliximab in SLE patients [72]. Out of nine patients with LN, six had a long-term response after four infusions of infliximab in combination with azathioprine, lasting for up to 5 years. All five patients with lupus arthritis responded, but this response did not last for >2 months after the last infusion. One additional patient had a long-lasting improvement in SLE interstitial lung disease. No symptoms suggestive of infliximab-induced SLE flares occurred in any patients. Short-term treatment appeared relatively safe, but one patient developed deep-vein thrombosis and several infections. Under long-term therapy, two patients had life-threatening or fatal events, namely, central nervous system lymphoma and Legionella pneumonia. Retreatment and treatment without concomitant immunosuppression led to drug reactions. Their study indicated that short-term therapy with four infusions of infliximab in combination with azathioprine was relatively safe and had remarkable long-term efficacy for LN and, potentially, also interstitial lung disease. Long-term therapy with infliximab, however, was associated with severe adverse events in two out of three SLE patients, which may have been provoked by infliximab and/or by their long-standing refractory SLE and previous therapies [72].

Recently E. Soforo et al. have reported 6 women who developed active SLE satisfying American College of Rheumatology diagnostic criteria with life-threatening manifestations after receiving TNF blockade for treatment of rheumatoid arthritis or psoriatic arthritis [73]. They thought the mechanism of TNF blocker-induced lupus may be related to a shift from death by apoptosis to necrosis, the latter resulting in the release of nuclear debris, a trigger of ANA production and lupus. They concluded that patients treated with TNF blockers, especially those with positive ANA, should be closely monitored for development of SLE [73]. These data indicated that induction of ANA or pre-existing high-titer ANA in TNF-treated patients is associated

with the development of lupus and therefore TNF blockade is ill-advised in this group of patients.

In summary, TNF-α exerts both deleterious tissue-damaging effects mainly through its pro-inflammatory activities and beneficial activities by dampening aggressive autoimmune responses. SLE is a disease with autoimmune disturbance and inflammatory damage, so blocking TNF-α in this autoimmune-prone chronic inflammatory disease may lead to different outcomes, depending on timing and duration of treatment.

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