Asian Journal of Immunology

3(1): 208-222, 2020; Article no.AJI.57464

TNF-α, TNF Receptors and Their Complex Implications in Therapy

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Authors' contributions

This work was carried out in collaboration among all authors. Author BMC conceptualized and designed the review paper, performed the literature search, wrote the paper and wrote the first draft of the manuscript, collected feedback, incorporated the changes, prepared subsequent drafts and then the final manuscript. Authors PP, RC and JKI reviewed the manuscript and helped in shaping it. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Cynthia Aracely Alvizo Báez, Autonomous University of Nuevo Leon, Mexico.
Reviewers:
(1) Joseli Lannes Vieira, Brazil.
(2) Juei-Tang Cheng, Christian University, Taiwan.
Complete Peer review History: http://www.sdiarticle4.com/review-history/57464

Review Article

Received 10 May 2020
Accepted 02 June 2020
Published 10 June 2020

ABSTRACT

Tumor necrosis factor alpha (TNF-α), also called cachectin or cachexin, is a naturally occurring cytokine produced by activated macrophages and monocytes, and to a smaller scale by T-lymphocytes, B-lymphocytes, fibroblasts and astrocytes. It has both inflammatory and immunomodulatory roles effectuated through its action on tumor necrosis factor receptor-1 (TNFR1) and tumor necrosis factor receptor-2 (TNFR2). TNF-α overexpression (especially of TNFR1 mediated actions) or under expression (especially of TNFR2 mediated actions) may

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contribute to several diseases including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and juvenile inflammatory arthritis. Several anti-TNF therapies are proven to be beneficial in these diseases, including etanercept, infliximab, adalimumab, certolizumab and golimumab.
Biological responses of TNF-α include inflammation, apoptosis, immunomodulation, tissue repair, antiviral and antitumor activity and mediation of endotoxin-induced septic shock, recruitment of inflammatory cells including neutrophils, monocytes and lymphocytes to sites of infection; and cell activation through action on different receptors (TNFR1 and TNFR2).
Low grade chronic inflammation occurs in several other diseases including atherosclerosis, hypertension, chronic kidney disease, Alzheimer's disease, Parkinson's disease and multiple sclerosis. Researchers have explored whether anti-TNF therapies can be helpful in these diseases too. Both positive and negative effects of anti-TNF therapies have been observed in these diseases. These observations suggest that TNF-α and TNF receptors system have an incredibly complex pathophysiologic role, and hence blockade of this pathway results in complex effects on different organ systems. In this review we have explored the myriad effects on various organ systems due to TNF blockade, including COVID-19.

Keywords: Tumor necrosis factor alpha (TNF-α); rheumatoid arthritis; COVID-19; TNFR1; TNFR2.

1. INTRODUCTION

Tumor Necrosis Factor (TNF) is a naturally occurring inflammatory cytokine the TNF superfamily that consists of 19 members (ligands) [1]. They are type II transmembrane proteins that can bind to 29 receptors of the TNF receptor superfamily including FAS, CD40, CD27 and RANK [2].

TNF-α, also called cachectin or cachexin, is produced by activated macrophages and monocytes, and to a smaller scale by T-lymphocytes, B-lymphocytes, fibroblasts, and astrocytes [3]. It can bind to TNFR1 (tumor necrosis factor receptor-1) and TNFR2 (tumor necrosis factor receptor-2), and has both inflammatory and immunomodulatory roles [4]. It has been implicated in pathogenesis of several diseases including rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis and Crohn's disease [1,3].

TNF-α and TNF receptors system is complex and has complicated implications in therapy [5]. Anti-TNF agents including etanercept, infliximab and adalimumab are helpful in treatment of many diseases where chronic inflammation is involved-for example, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and Crohn's disease [5-8]. These therapies may predispose patients to increased risk of infections (including reactivation of tuberculosis), cardiovascular events, autoimmune diseases, malignancy, hepatitis, nephritis and tubulointerstitial diseases, as has been discussed later in this paper.

Several other diseases including atherosclerosis, hypertension, chronic kidney disease, Alzheimer's disease, Parkinson's disease and multiple sclerosis also show evidence of low-grade chronic inflammation. Researchers have explored whether anti-TNF therapies can be helpful in these diseases too. Both positive and negative effects of anti-TNF therapies have been observed in these diseases. These observations suggest that TNF-α and TNF receptors system have a complex pathophysiologic role, and hence blockade of this pathway results in complex effects on different organ systems. In this review we have explored the effects of TNF blockade on various organ systems.

2. BIOLOGICAL PROPERTIES OF TNF-A AND TNF RECEPTORS

2.1 Tumor Necrosis Factor-α

Tumor necrosis factor-α (TNF-α) was discovered by Lloyd J Old together with Elizabeth Carswell in 1975 [6,9]. They discovered that TNF-α is produced by lymphocytes and macrophages that cause lysis of specific type of cells like tumor cells [6]. This discovery led to the discovery of a number of other cytokines including lymphotoxin alpha (TNF-β), CD40L, CD27L, and FASL [6,9].

Biological responses of TNF-α include inflammation, apoptosis, immunomodulation, tissue repair, antiviral and antitumor activity and mediation of endotoxin-induced septic shock. It is involved in recruitment of inflammatory cells including neutrophils, monocytes and

lymphocytes to sites of infection; and cell activation through its action on different receptors (TNFR1 and TNFR2) [3,4,10].

TNF-α exhibits both pro-inflammatory and immunoregulatory properties. In addition to its function as an endogenous pyrogen, TNF-α has been shown to initiate a powerful inflammatory response by stimulating the generation of other inflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10, corticosteroids, and metalloproteinases [3,10]. Once the triggering factor for the immune system activation is eliminated, TNF-α steps in again to control and resolve the inflammatory process [3].

The gene that codes for human TNF-α is located on short arm of chromosome 6, linked to human leucocyte antigen (HLA) B [11-13]. There are two forms of TNF-α: transmembrane TNF-α or membrane-associated TNF-α (mTNF-α) and soluble TNF-α (sTNF-α). Membrane-associated TNF-α (mTNF-α) is cleaved by metalloproteinases ADAM-17[TNF-α converting enzyme (TACE)] to soluble TNF-α [sTNF-α] that can subsequently be detected in blood plasma [4,6,11,14]. Please refer to Table 1 for an overview [4,6,11-14].

2.2 TNF Receptors

TNF-α acts through two cell-surface receptors- Tumor Necrosis Factor Receptor 1 (TNFR1), also known as p55, TNFRSF1A, CD120a; and Tumor Necrosis Factor Receptor 2 (TNFR2) also known as p75, TNFRSF1B, CD120b [15-17]. Although both TNFR1 and TNFR2 can bind with the soluble and transmembrane forms of TNF-α, TNFR2 has high affinity for the transmembrane form of TNF-α [16].

Jonathan Holbrook et al have described TNF-α and TNF receptors in detail [14]. TNFR1 is expressed on almost all cells [14]. It has 'death domain or DD' in its intracellular region. When TNF-α binds with TNFR1, it leads to recruitment of TNFR1-associated DD (TRADD) [14]. This triggers an inflammatory response or cell survival response through activation of NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), or cell death response depending on the physiological state of the cell [3,14,17].

TNFR2 is expressed in immune cells [predominantly in T regulatory cells (Tregs)], neurons and endothelial cells [3,14]. Besidesleading to direct actions after TNF-α binding occurs, TNFR2 may have a 'ligand-passing' role as well: soluble TNF-α may dissociate from TNFR2 rapidly and then bind with TNFR1 [16,17].

There is no death domain (DD) in TNFR2. After interacting with TNF-α, TNFR2 binds with the proteins TNFR-associated factors 1 and 2 (TRAF1 and TRAF2) activating NF-kB. NF-kB then triggers a cell survival response including immune modulation, inflammation and tissue regeneration depending on the conditions [3,14,17]. TNFR2 has an important role in pancreatic regeneration, protection of cardiomyocytes, remyelination, survival of some neuronal cells and in stem cell proliferation too [3]. Since TNFR2 does not bind with TRADD, it does not lead to cell death response. Please refer to Fig. 1. Please note that the figure is symbolic for easy understanding. It is not representative of true molecular structure of TNF or its receptors.

3. TNF-α POLYMORPHISM AND DISEASES

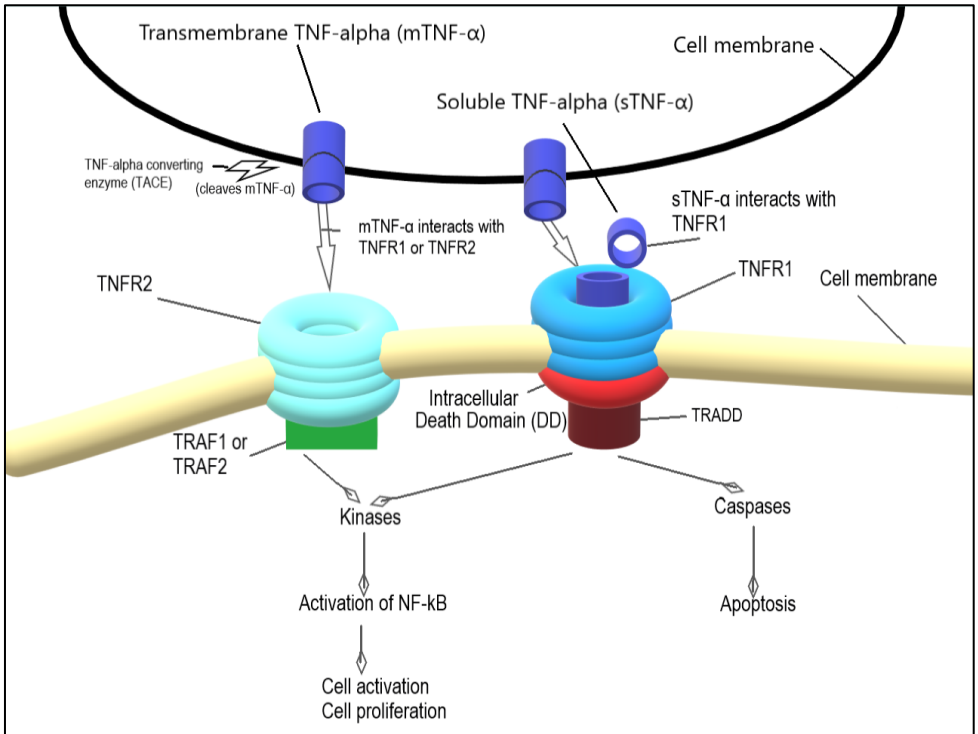
TNF-α polymorphisms may have an influence on susceptibility of diseases. A few examples are given below.

3.1 Rheumatoid Arthritis

Role of TNF-α -308G/A polymorphism and differential expression of TNF-α in pathogenesis

Table 1. The two forms of TNF-α

	Soluble TNF-α	Transmembrane TNF-α
Amino Acids	157 amino acid residues	233 amino acid residues
Molecular weight	17 kDa	26 kDa
Receptor Interaction	Attaches to Type 1 and Type 2 TNF receptors (TNF-R1 and TNF-R2); cellular actions mainly mediated through TNF-R1.	Attaches to TNF-R1 and TNF-R2; actions mainly mediated through TNF-R2.
Sites of action	Acts at sites distant from TNF-α producing cells.	Acts locally



Adapted image (with permission) from (1) Holbrook J, Lara-Reyna S, Jarosz-Griffiths H, McDermott M. Tumour necrosis factor signaling in health and disease. F1000Res. 2019;8:F1000 Faculty Rev-111. Published 2019 Jan 28. Doi:https://doi.org/10.12688/f1000research.17023.1; and (2) Yang S, Wang J, Brand DD, Zheng SG. Role of TNF-TNF Receptor 2 Signal in Regulatory T Cells and Its Therapeutic Implications. Front Immunol. 2018;9:784. Published 2018 Apr 19. doi:https://doi.org/10.3389/fimmu.2018.00784

Fig. 1. An overview of TNF-α signaling pathway

of rheumatoid arthritis was evaluated by Somdatta Das, et al. [18]. They conducted a case-control study, including 126 rheumatoid arthritis patients and160 community matched age and sex controls. The study duration was 3 years. They found that presence of TNF-α -308A allele and differential TNF-α expression are associated with increased risk susceptibility for rheumatoid arthritis [18]. This study suggests that polymorphism of TNF-α has a role in pathogenesis of rheumatoid arthritis.

3.2 Systemic Lupus Erythematosus

Y-J Lin, et al investigated the association of TNF-alpha genetic polymorphisms (-1031T/C, -863C/A, -857T/C, -308A/G and +489A/G) in SLE patients and controls in Taiwanese population [19].

Their observations included [19]:

- The frequency of the polymorphisms at -1031 and -857 were significantly different in patients with antinuclear antibodies and hematological disorders respectively.
- The frequency of a allele of the polymorphisms at -308 was significantly increased in patients with malar rash, discoid rash, photosensitivity, oral ulcers and serositis.
- The frequency of the polymorphisms at +489 was significantly different in patients with discoid rash and photosensitivity.

Julian Ramírez-Bello, et al investigated whether the TNF -238G/A, -308G/A, -376G/A (rs1800750), and -1031T/C (rs1799964) polymorphisms are associated with SLE or lupus nephritis susceptibility in a Mexican population [20]. The study included 442 patients with SLE and 495 controls. The investigators found that TNF -238G/A and -1031T/C polymorphisms were associated with SLE susceptibility [20].

These observations of different investigators suggest that TNF-alpha genetic polymorphisms contribute to increased SLE susceptibility.

3.3 Crohn's Disease

Genoile Santana, et al conducted a case-control and cross-sectional study to analyze whether TNF-α -308 polymorphism is associated with Crohn's disease and its clinical features [21]. They enrolled 91 patients with Crohn's disease and 91 controls (either with gastroesophageal reflux disease or functional dyspepsia) in Salvador [21]. The investigators observed that high TNF-α producing predicted phenotype was associated with the penetrating form of Crohn's disease and colectomy. They found that the TNF-α -308 polymorphism was not associated with the perianal disease [21].

4. TNFR1 GENE POLYMORPHISM AND DISEASES

4.1 Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

Missense mutations of TNFR1 gene results in development of Tumor Necrosis Factor receptor-associated periodic syndrome (TRAPS), an autosomal dominant disease [22]. The gene mutation results in structural alteration of TNFR1 receptor rendering it nonfunctional and its retention in endoplasmic reticulum [23]. The disease is associated with unprovoked prolonged periodic or episodic fever (fever lasting from a few days to months, average duration 21 days), severe abdominal pain, localized inflammation affecting multiple organs, and migrating rash on the limbs [23]. Since these inflammatory episodes are unprovoked, they are described as 'autoinflammation' [14]. There is an elevation of cytokines IL-6 and TNF-α in this disease [23].

There is a paradox in the pathogenesis of TRAPS: as TNFR1 is associated with inflammation, nonfunctional TNFR1 should not lead to inflammation, contrary to the observation of inflammation affecting multiple organs in this disease [23]. This suggests that mechanism of action of the TNF-α and TNF receptors is complex, and further studies are needed to elucidate these mechanisms.

Treatment modalities include high doses of prednisolone, high dose non-steroidal anti-inflammatory drugs, colchicine, etanercept, anakinra (IL-1 receptor antagonist), canakinumab (anti-IL-1β), and tocilizumab (anti-IL-6) but each have variable success [14,23]. Presently, anti-interleukin- 1β therapy is the standard to treat more severe cases of TRAPS [14].

4.2 Susceptibility to Develop Invasive Pulmonary Aspergillosis

Investigators have found that polymorphism of both TNFR1 and TNFR2 is associated with increased susceptibility to invasive pulmonary aspergillosis. Sainz et al found that TNFR1 gene polymorphism results in greater susceptibility to invasive pulmonary aspergillosis [24]. The group had found in an earlier study that TNF-α gene polymorphism or TNF-α levels had no correlation with susceptibility to invasive pulmonary aspergillosis, while polymorphism in TNFR2 gene was strongly associated with susceptibility to the infection [25].

5. TNFR2 GENE POLYMORPHISM AND DISEASES

TNFR2 gene polymorphism may affect susceptibility and/or severity of some diseases. A few examples are given below. In all these examples, the sample size is small. More studies are needed to evaluate this area.

5.1 Schizophrenia

Renata Suchanek-Raif, et al conducted a case control study involving 401 patients and 657 controls to study whether the three single nucleotide polymorphisms (rs3397, rs1061622, and rs1061624) in *TNFR2* gene were associated with a predisposition to paranoid schizophrenia in Caucasian population [26]. They observed that *TNFR2* gene polymorphism of rs3397, rs1061622, and rs1061624 are associated with a higher risk of developing schizophrenia and a more severe course of progression in males [26]. In this study, the rs3397 single nucleotide polymorphisms were found to be protective for women [26]. These observations suggest that TNFR2 gene polymorphisms

Table 2. Anti-TNF therapeutic agents

TNF Inhibitor	Mechanism of action	Specificity	Dosage schedule	Approved Indications
Etanercept	Fully human soluble TNF receptor inhibitor	sol TNF, tmTNF, lymphotoxin A	Subcutaneous injection weekly	RA, PA, JIA, AS
Infliximab	Mouse Chimeric monoclonal antibody to TNF-α	sol TNF, tmTNF	Intravenous injection every 6-8 weeks	RA, PA, JIA, AS, CD, UC
Adalimumab	Fully human monoclonal antibody against TNF-α	sol TNF, tmTNF	Subcutaneous injection every 2 weeks	RA, PA, JIA, AS, UC, CD
Certolizumab	Human Fab fragment against TNF attached to 2 polyethylene glycol molecules	sol TNF, tmTNF	Subcutaneous injection every 4 weeks	RA, PA, AS, CD
Golimumab	Fully human monoclonal antibody against TNF-α	sol TNF, tmTNF	Subcutaneous injection every month	RA, AS, PA, UC

RA-rheumatoid arthritis; PA-psoriatic arthritis; AS- ankylosing spondylitis; JIA-juvenile inflammatory arthritis; UC-ulcerative colitis; CD- Crohn's disease; sol TNF- soluble tumor necrosis factor; tm TNF- transmembrane tumor necrosis factor

have a role in determining severity of schizophrenia.

5.2 Coronary Artery Disease

V.H Sankar, et al conducted a study to evaluate whether polymorphism at position 196 in exon 6 of tumor necrosis factor 2 (TNFR2) gene is associated with coronary artery disease [27]. The investigators found that the incidence of coronary artery disease in patients with MM genotype was 65% and in those with RM genotype was 42% [27]. The investigators concluded that MM genotype of TNFR2 increases the risk of developing coronary artery disease, and the RM genotype has a protective role [27].

5.3 Chagas Disease

Libeth Criado, et al included 313 Chagas disease patients from Colombia who were serologically positive for Trypanosoma cruzi [28]. Out of these 313 patients, 159 had cardiomyopathy, and 154 were asymptomatic [28]. The investigators found that distribution of the TNFA -1031C and -308A alleles between cardiomyopathic and asymptomatic subjects was significantly different [28]. The investigators suggested that TNFA -1031C and -308A gene polymorphisms may influence susceptibility to develop cardiomyopathy in Chagas disease [28].

6. ANTI-TUMOR NECROSIS FACTOR THERAPEUTIC AGENTS

TNF-α is involved in pathogenesis of several diseases including rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis and Crohn's disease [1,3]. Anti-TNF therapeutic agents are used for several therapeutic indications including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PA), juvenile inflammatory arthritis (JIA), Crohn's disease (CD) and ulcerative colitis (UC) [5-8]. Table 2 depicts a brief overview of these agents [5-8,29].

7. IMPACT OF TNF BLOCKADE ON DIFFERENT ORGAN SYSTEMS

7.1 Immune System and Infections

The pro-inflammatory role of TNF-α is a vital component of host defense against infections [10]. TNF-α blockers increase the risk of infections (bacterial, viral, and mycotic), including tuberculosis, histoplasmosis, candidiasis, aspergillosis, listeriosis, infection with atypical mycobacterium, pneumocystis carinii [30,31]. Lymphoma, neuropathy and bowel obstruction have also been noted with the use of anti TNF-α therapeutic agents [31].

TNF-α together with other cytokines including interferon-delta (IFN-δ), generates a cell-mediated immune response to intracellular pathogens including mycobacterium tuberculosis, listeria and histoplasma species leading to granuloma formation [10]. Granuloma formation is required to contain the growth of and for the resolution of these infections [10]. Use of ant-TNF-α therapeutic agents inhibits this cell

mediated immune response and granuloma formation, hence increasing the risk of granulomatous diseases including tuberculosis.

Reactivation of infections may also occur, including reactivation of latent tuberculosis and hepatitis B virus [30,31]. Use of live vaccines during anti-TNF therapy is not recommended, as this may cause vaccine associated disease, including disseminated infection [32].

The risk of serious infections in highest in the first few months. The incidence of infection declines over time. Galloway et al evaluated and compared data of 11,798 anti-TNF treated patients and 3,598 non biologic disease-modifying antirheumatic drugs (nbDMARD) treated rheumatoid arthritis patients. They observed that the incidence rate of serious infections was 42 per 1000 patient-years in anti-TNF treated patients, and 32 per 1000 patient-years in nbDMARD treated patients indicating a significant increase in serious infection risk with the use of anti-TNF therapy [33]. The adjusted serious infection rate was 20% higher in anti-TNF treated individuals than nbDMARD treated subjects [33]. This risk was highest in the first six months of therapy, and then started to decline [33].

Liao et al conducted a meta-analysis and found that the risk of serious infections defined as those that were life-threatening, requiring hospitalization and/or intravenous antibiotic therapy, or leading to significant disability/death, and general infections (infections regardless of severity and microorganisms) were lower in etanercept (soluble receptor) treated individuals, as compared with the monoclonal antibodies (adalimumab and infliximab) [34]. The risk of tuberculosis was also lower in Etanercept treated individuals as compared to the individuals treated with adalimumab or infliximab [34].

7.1.1 Leprosy

TNF plays an important role in pathogenesis of nerve lesions in leprosy. High levels of TNF have been detected in reactional skin lesions in leprosy [35]. TNF may be involved in early stages of Schwann cell infection by mycobacterium leprae [35]. TNF induces IL-6 and IL-8 production that contribute to neuroinflammation [35]. Mycobacterium leprae also induces IL-23 production in Schwann cells that contributes to demyelination [35]. More studies are required to evaluate the effect of anti-TNF therapy in patients with leprosy.

7.1.2 Chagas disease

Chagas disease is caused by protozoan parasite Trypanosoma cruzi [36]. Chronic Chagas disease cardiomyopathy (chronic Chagasic cardiomyopathy), the main manifestation of Chagas disease, is associated with heart failure [36,37]. Elevated levels of TNF-α occur in chronic Chagas disease cardiomyopathy and are related to the severity of left ventricular dysfunction [36,37]. Low grade inflammation occurs in cardiac tissue in presence of elevated TNF and interferon-γ levels. Pereira I.R found in their experimental studies in mice that short term anti-TNF therapy together with trypanocidal treatment may have beneficial effect in chronic Chagasic cardiomyopathy [36]. However other investigators have observed conflicting results in animal studies, and have noticed that anti-TNF therapy may actually aggravate the cardiomyopathy [37]. More studies are required to evaluate the effect of anti-TNF therapy in chronic Chagasic cardiomyopathy.

7.1.3 COVID-19

High mortality associated with coronavirus disease 2019 (COVID-19) has prompted researchers worldwide to accelerate the research activities to find possible safe and effective treatment options and preventive measures including vaccines [38]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19, enters the host cells through angiotensin converting enzyme-2 expressed by type II surfactant-secreting alveolar cells in the lungs [38]. The most important mediators that drive inflammatory response to COVID-19 are not completely known. Upregulation of different cytokines including interleukin-1 (IL-1), interleukin-6 (IL-6), TNF, and interferon-γ occurs in COVID-19 [38]. ‘Cytokine storm’, in which too many cytokines are suddenly released into circulation, can cause severe inflammatory response that causes more harm than good. Marc Feldmann, et al have discussed this topic in detail and have proposed that clinical trials are needed to evaluate safety and effectiveness of anti-TNF therapies, particularly infliximab and adalimumab [38]. They speculate that these anti-TNF agents may be beneficial in decreasing the intensity of the ‘cytokine storm’, reduce inflammation, and help in severe COVID-19 [38].

7.2 Autoimmune Disorders

The mechanisms leading to disease through TNF-α and TNF receptors pathway are complex showing both positive and negative effects on autoimmune disorders. A few cases have been reported of etanercept and adalimumab inducing systemic lupus erythematosus and lupus serositis [39-43]. But there are other reports favoring anti-TNF therapeutic agents having beneficial effect on these autoimmune diseases. Uppal, et al investigated the effect of infliximab in active systemic lupus erythematosus subjects and found that the drug significantly decreases the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). They concluded that anti-TNF therapeutic agents are interesting candidates that can be explored further for treatment of active SLE [44]. There are conflicting experiences with other anti-TNF therapies and autoimmune diseases too.

It is known that there is deficiency of TNFR2 in several autoimmune diseases that could result in uncontrolled inflammatory activity through soluble TNF-α, TNFR1 pathway. Instead of using non-specific anti-TNF-α therapeutic agents that cause varying impact on both TNFR1 and TNFR2 pathways resulting in unpredictable consequences, using specific agents to target TNFR1 or TNFR2 pathways may yield better and predictable results. Yang et al have proposed that either using agents that specifically block TNF-α or TNFR1 and preserve the available TNFR2; or using TNFR2 agonists to increase the number of TNFR2 and promote tissue regeneration may prove to be good therapeutic strategies in autoimmune diseases [3]. Further studies are required to evaluate whether these strategies are indeed beneficial and could be safely implemented.

7.3 Cardiovascular System

TNF-α levels have an important relationship with cardiovascular diseases and events including congestive heart failure [30,31]. The level of TNF-α has been shown to be predictive of recurrent myocardial infarction [43]. Also, TNF-α level may play a role in hypertension, dyslipidemia, and atherosclerosis [45-48].

Investigators have proposed that TNF-α induces atherogenesis by promoting induction of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) expression by endothelial cells and vascular smooth muscle cells, endothelial cell apoptosis, and smooth muscle cell migration and proliferation [45]. Interestingly, the cellular location of TNFR1 may have effects on atherogenesis. As an example, TNFR1 in macrophages may decrease atherogenesis, whereas the TNFR1 in the arterial walls may promote atherogenesis [45,48].

TNF-α might have a role in arterial inflammation and intimal hyperplasia [15]. Kitagaki et al showed that TNF-α is an important contributor to arterial inflammation in mice and that blockage of TNFR1 inhibits intimal hyperplasia following experimentally induced arterial inflammation (post injury) [15]. TNFR2 signaling mediates inhibition of neointimal formation by decreasing adherent cells and apoptosis of endothelial cells as well as the activation, proliferation and migration of endothelial cells [15].

7.4 Malignancy

TNF-α is an important cytokine that is involved in tumor surveillance and hence anti-TNF therapy theoretically poses a risk for developing malignancies. This has been substantiated in several studies indicating that anti-TNF therapeutic agents may be associated with an increased risk of malignancies including lymphoma, breast cancer, colorectal cancer, and melanoma [30,31,49].

Berghen et al observed incidence of malignancy in 365 rheumatoid arthritis patients receiving anti-TNF therapy at a single center from January 2000 until January 2012 that received anti-TNF therapy [49]. They observed occurrence of 34 malignancies in 30 patients after the start of anti-TNF treatment. Among these, 20 patients developed a solid malignancy, 6 a hematologic, 2 a solid and a hematologic malignancy, and 2 patients developed multiple (2 solid) malignancies. They also observed that some immune modulation-related lymphoproliferative disorders regressed spontaneously after stopping anti-TNF therapy. They concluded that the malignancy risk in rheumatoid arthritis patients treated with anti-TNF therapy was slightly higher than in the normal population [49].

However, there are other studies that have shown conflicting results. Mercer et al compared the rates of solid tumors in 11,767 anti-TNF treated patients with 3,249 non-biologic or synthetic disease modifying anti-rheumatic drugs (s-DMARDs- including methotrexate, azathioprine and cyclophosphamide) in 5-year data was obtained from British Society for

Rheumatology Biologics Register [50]. None of these patients had prior history of cancer. They observed that solid tumors developed in 81 per 10,000 patient-years in anti-TNF treated patients, and 117 per 10,000 patient-years in s-DMARDs treated patients. There was no statistically significant difference in risk of solid cancer for anti-TNF treated versus sDMARD treated patients [50]. Another study by Min Jung et al also showed similar results [51]. The investigators collected information of 45,423 seropositive rheumatoid arthritis patients from Korean Nationwide Health Insurance claims data. They compared incidence of tumor in patients receiving anti-TNF therapy (2,337 patients), and those receiving conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs- including methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, cyclosporine, tacrolimus, azathioprine, mizoribine, and bucillamine) (43,086 patients) from the 5 years of data. They found that 1732 patients in csDMARD group and 49 patients in anti-TNF group developed malignancy. On statistical analysis, the investigators found that incidence of cancer was similar in RA patients treated with anti-TNF and csDMARDs [51].

7.5 Nervous System

Increased production of TNF-α has been noticed in several central nervous system disorders including multiple sclerosis, Alzheimer's disease, Parkinson's disease, HIV encephalopathy, meningitis, stroke, demyelinating disorders, neuropathy, and myelosuppression [30,31,52-56]. High levels of TNF in nervous system disorders promote demyelination, axonal degeneration and increased permeability of blood brain barrier [35].

TNFR2 has a neuroprotective role and serves an important role in oligodendrocyte regeneration and remyelination [3,53]. Fischer et al synthesized a soluble, human TNFR2 agonist (TNC-scTNFR2) by genetic fusion of tenascin C to a TNFR2-selective single-chain TNF molecule and showed that TNC-scTNFR2 rescues human differentiated neurons from oxidative stress induced cell death [57]. They speculated that TNFR2 agonists may be good therapeutic options in several diseases, including neurodegenerative, cardiac and autoimmune and diseases [57].

Alzheimer's disease: TNF-α and TNFR1 levels are increased, and TNFR2 levels are decreased in human Alzheimer's disease brain tissues [30,53]. Though theoretically it appears that anti-TNF therapy should be helpful in Alzheimer's disease, investigators have observed conflicting results. As an example, experimental studies in animals have shown that infliximab that binds TNF-α (anti-TNF-α therapy) reduced amyloid plaques and tau phosphorylation in Alzheimer's disease in mice as early as 3 days after the intracerebroventricular injection; and improves object recognition memory impairment [58,59]. Shi et al reported that intrathecal injection of infliximab improved cognition significantly in a female suffering from Alzheimer's disease [60]. Peri-spinal injection of etanercept has been shown to improve cognitive impairment within minutes of administering the injection [61].

It is generally accepted that total inhibition of TNF (especially inhibition of the neuroprotective TNFR2) may nullify the positive effects of anti-TNF therapies [53]. Though there are case reports and experimental data supporting a beneficial role [58-61], more studies (large scale, randomized controlled trials) are needed to explore the safety and efficacy of anti-TNF therapies in Alzheimer's disease.

Multiple sclerosis: Experimental studies in animals with multiple sclerosis has shown beneficial effect of anti-TNF therapies. However, investigators have also reported conflicting evidence: several cases of development of multiple sclerosis after initiating anti-TNF therapy [54-56]. Titelbaum et al. reported new onset multiple sclerosis in a rheumatoid arthritis patient who was on etanercept therapy for two years. On stopping etanercept, there was radiological resolution of lesions. However, after 6 months, new lesions developed [62]. These conflicting evidences suggest that more studies are required in this therapeutic area to get a clearer picture regarding whether anti-TNF therapy is beneficial in multiple sclerosis.

7.6 Kidneys

TNF-α blockers used in rheumatoid arthritis and Crohn's disease occasionally result in the development of autoantibodies, lupus-like syndrome, and glomerulonephritis [63]. This has raised a concern regarding the use of TNF-α blocking agents in patients who are at risk of developing renal disease or who have underlying renal disease [63].

TNF-α may be produced in inflamed kidneys from infiltrating monocytes and macrophages, and intrinsically by renal tissue including podocytes, mesangial cells, proximal tubules, thick ascending limb of loop of Henle, and the collecting ducts [16,64]. TNF-α is cytotoxic to renal cells and is involved in renal scarring [65-67]. TNF-α induces the production of reactive oxygen species including superoxide. Superoxide increases glomerular permeability to albumin [68]. Animal studies have shown that nitric oxide is also produced in several glomerular diseases. Nitric oxide has a protective effect and protects the kidneys from the injurious effect of superoxide, and even reverses the damage [68].

In kidneys, TNFR1 is primarily present in glomeruli and peritubular endothelial cells [16]. TNFR2 is usually absent in the kidneys in normal state [16]. In several renal diseases, TNFR2 levels increase in the kidneys especially at the site of injury [16].

TNF-α has been implicated in acute kidney injury (AKI) and chronic kidney disease (CKD) [69]. Studies in animal models have shown that inflammatory cytokines like TNF-α play a role in development of AKI and its inhibition may protect kidneys from the damage [70,71]. However, anti-TNF therapy may also result in acute kidney injury. Michael B Stokes et al reported 5 cases of rheumatoid arthritis who developed acute kidney injury possibly due to anti-TNF therapy [72]. TNF-α and TNFR1 and TNFR2 are higher in chronic kidney disease [65,73]. Richard et al found that higher levels of TNF-α are associated with more rapid worsening of renal functions over time in patients with chronic kidney disease [65]. It has also been observed that high levels of TNFR 1 and TNFR2 in diabetes are associated with progression of diabetic kidney disease, and higher mortality [74].

TNF-α may play a role in renal ischemia-reperfusion injury post kidney transplantation [69]. In the pathogenesis of renal ischemia-reperfusion injury, TNF-α induces fibrin deposition, cellular infiltration, vasoconstriction and apoptosis [69].

Investigators have found that inhibition of TNFR2 pathway may be helpful in decreasing incidence of glomerulonephritis. The possible underlying mechanisms that are involved in this are not completely understood. TNFR2 (but not TNFR1) is found in high concentration in renal tubular epithelial cells in renal tubulointerstitial nephritis and interacts with 'sef' or IL-17RD, causing activation of NF-kB pathway and inflammation [16,17]. TNF-α may enhance the interaction of TNFR2 and IL-17RD, but the presence of TNF-α is not absolutely necessary for the interaction to occur (upregulated TNFR2 may trigger interaction with IL-17RD independent of TNF-α) [17]. This may be one of the pathogenic mechanisms explaining the role of upregulated TNFR2 contributing to nephritis and tubulointerstitial renal diseases [17]. The evidence is helpful, but more studies are needed to understand the role of TNF-α and TNF receptors in renal diseases.

Kidney transplant recipients are on immunosuppressive medications and are already at an increased risk of infections [75]. Anti-TNF therapy may increase this risk of infections and malignancy in kidney transplant recipients and should be used with caution [76].

8. CONCLUSION

TNF-α, TNFR1 and TNFR2 systems are complex. Increased concentration of TNF-α is a prominent feature of many diseases including rheumatoid arthritis, ankylosing spondylitis, juvenile inflammatory arthritis, Crohn's disease, ulcerative colitis and psoriatic arthritis. The beneficial effects of anti-TNF therapies in these diseases led to the speculation that these therapeutic agents may be helpful in other ailments that have abnormalities in concentration of TNF-α and TNF receptors- for example, in Alzheimer's disease, Parkinson's disease, systemic lupus erythematosus, tubulointerstitial nephritis, diabetic nephropathy, chronic kidney disease, and cardiovascular diseases including hypertension and atherosclerosis. However, investigators have found that this is not entirely true. While some studies have shown beneficial effects of anti-TNF therapy, other studies have shown conflicting results that point towards the complex nature of TNF-α and TNF receptors pathway. More extensive research is needed to understand this system, so that better and more selective anti-TNF therapeutic agents may be developed to help in diseases including Alzheimer's disease, multiple sclerosis, Parkinson's disease, renal and cardiovascular diseases.

DECLARATION

We thank IQVIA (communications, branding, and legal units) for giving us permission, and 'no

objection' note for publication of this paper. We thank IQVIA for providing us the support and infrastructure needed to complete this paper, including giving us the opportunity to form this great team that was instrumental in bringing this paper to conclusion.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/57464