

Antibodies to Tumor Necrosis Factors in the Treatment of Rheumatoid Arthritis and Spondyloarthritis: The Basic Science, Clinical Science and Unmet Needs; Results from a Single Center

Sundeep Kumar Upadhyaya

Indraprastha-Apollo Hospitals (IAH), New Delhi, India
Email: sundeepupadhyaya@hotmail.com

Received 2 January 2014; revised 2 February 2014; accepted 10 February 2014

Copyright © 2014 by author and Scientific Research Publishing Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY).
<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

Inflammatory rheumatological diseases like rheumatoid arthritis (RA) and ankylosing spondylitis/Spondyloarthritis (AS/SpA), have been treated with NSAIDs (non steroidal anti-inflammatory drugs), corticosteroids, and DMARDs (disease modifying anti-rheumatic drugs). These have been only partially effective for the management of symptoms, since they are rarely associated with the complete control of disease and rarely slow down radiological damage. Several cytokines have been implicated in the pathogenesis of the inflammation and tumor necrosis factor (TNF) is the most important. The last decade and a half has seen advances in the form of “anti-TNF” therapies for RA and AS/SpA patients which target and neutralize the TNF cytokines, and thus reduce the disease activity. Two anti-TNF therapies have been used in India for treating DMARD resistant RA and AS/SpA for the last 13 years; Infliximab and Etanercept respectively. This paper is a description of the clinical outcomes and unmet needs/toxicities associated with the treatment of RA and AS/SpA with anti-TNF therapies (Infliximab, Etanercept), at a single rheumatology center (tertiary care, super-specialty hospital, Indraprastha Apollo Hospitals, New Delhi) in north India.

Keywords

Anti-TNF Antibodies, Biologic Agents, Rheumatoid Arthritis, Ankylosing Spondylitis, Biologic Treatment, Spondyloarthritis, Infliximab, Etanercept, DMARD

1. Introduction

“Biologic therapies” for the treatment of arthritis and spondylitis have become a reality after the discovery of the role of various cytokines in the pathogenesis of these auto-immune diseases. These “biologic therapies” for arthritic disorders are mostly anti-cytokine antibodies, antibodies to other cell surface antigens, etc. These therapies are directed against TNF alpha (Anti-TNF Biologics), IL-6 (Tocilizumab), and against the CD 20 antigen of B-cells (Rituximab). While many of these are monoclonal antibodies, some exceptions to the “antibody” structure of biologics commonly in use for the same diseases, are the fusion proteins Etanercept (anti-TNF biologic) and Abatacept (co-stimulatory modulator). Abatacept is a “co-stimulatory blocker”—it blocks the T-B cell interaction.

Currently two anti-TNF biologics are available for clinical use in India and these are Infliximab (“Remicade”) and Etanercept (“Enbrel”) and have been in use in my clinic at IAH (Indraprastha-Apollo Hospitals) for 10 years. Infliximab is a molecule constructed by linking the Fc portion of the human Immunoglobulin molecule to the variable region of the mouse anti-TNF antibody. The molecule is approximately 70% human and 30% mouse. It is used for the treatment of Methotrexate (MTX) failed rheumatoid arthritis (RA) patients and for severe active Ankylosing Spondylitis (AS), not responding to NSAIDs. The doses are 3mg/kg infused at 0, 2, 6 weeks and then 8 weekly thereafter for RA, and 5mg/kg infused at 0, 2, 6 weeks and then 8 weekly for AS/SpA. In both diseases, and especially nearly always in RA patients, Methotrexate (MTX) is used as a DMARD along with the Anti-TNF therapy. Etanercept is a fusion protein: two p-75 extracellular receptor domains of the TNF are linked to the Fc portion of the human IgG1. Although not strictly a monoclonal antibody, its role in treating RA and AS/SpA is similar to the role of Infliximab, and is used at 50 mg subcutaneous weekly with MTX (in nearly all RA patients) or 50 mg subcutaneous weekly, without MTX (in most AS/SpA patients).

2. Methods

The patients with RA and AS/SpA who were treated with anti-TNF therapies at Indraprastha Apollo Hospitals New Delhi, at the Rheumatology out-patient, the Rheumatology in-patient wards and the Rheumatology day care facility, from 2003 to 2013 were analyzed prospectively and retrospectively. Data were captured by a review of case records, a review of in-patient files and by telephonic interviews (wherever possible), primarily for the safety and efficacy of anti-cytokine therapies (Anti-TNF). “Treatment failures/inefficacies” were defined as high DAS 28 scores, or any two of the following: 6 or more active joints, night pains waking up patient, early morning stiffness of >one hour (joint or spine), pain on VAS > 6 on a scale of 0 - 10 (joint or spine), while continuing anti-TNF treatment. “Relapses” were defined as a similar high disease activity score, after discontinuation of anti-cytokine treatment in remitted patients. All patients with a diagnosis of RA and AS/SpA and who received at-least 6 months of therapy with Etanercept, or at-least 4 doses of Infliximab were included in the study. All patients with RA fulfilled the 1987 classification criterion for RA, and all patients with AS/SpA fulfilled the 1991 European Spondyloarthritis Study Group criteria (“ESSG criteria”). As for AS/SpA patients; a few had early disease and were categorized as (a) severe undifferentiated spondyloarthritis (UspA) with spinal ankylosis or (b) severe psoriatic spondyloarthritis with spinal ankylosis or (c) severe enthesitis related arthritis (juvenile ERA) or (d) NSAID and DMARD resistant reactive arthritis (ReA) with spinal ankylosis. The data have been compiled without reference to patient-years’ of exposure, except with the mandate that either at-least six months’ of etanercept treatment, or at-least 4 doses of Infliximab treatment, was mandatory for inclusion. For AS/SpA patients the definition of response was the attainment of BASDAI scores of less than 4 while on treatment. The relapses of disease after discontinuation of anti-cytokine treatment, both for RA and AS/SpA patients has not been described and discussed in detail.

3. Results

A total of 77 patients with RA were treated for at-least 6 months with etanercept or at-least 4 doses of Infliximab and all of them achieved low disease activity (see [Table 1](#)). One patient suffered from pulmonary tuberculosis (TB), one suffered upper left limb Herpes Zoster infection, and 2 patients had bronchopneumonia. UTI (urinary tract infections) and cellulitis was also reported and successfully managed (see [Table 1](#)). No deaths were reported while on treatment and none fulfilled criteria for serious adverse event except the one patient with bronchopneumonia, and three patients with cellulitis, who required par-enteral antibiotics. No cases of non respond-

ers were found, but most would have relapsed after 2 - 3 years (or less) and would have continued with low disease activity either with MTX, and or other DMARDs (see **Table 1**).

In another group of 202 AS/SpA patients, where both Etanercept and Infliximab were administered for 6 months to 8 yrs (a large majority for 6 - 9 months, exceptional cases for 2 - 8 years); 3 patients were reported with tuberculosis, 2 patients with soft tissue infections of the skin, 10 patients with UTI (culture positive: 7 E-Coli, 3 with Klebsiella), one with pneumonia (off anti-TNF for several months) (see **Table 2**). There were 6 patients (not included in this total number) who gave up therapy during this period (logistical reasons rather than inefficacy or toxicity). There were 6 primary non-responders (see **Table 2**).

4. Discussion

Efficacy of Infliximab and Etanercept in RA and AS: The anti-TNF biologics have been in clinical use for over a decade in the treatment of inflammatory arthritis and spondylitis. Several double-blind, placebo-controlled trials have established the efficacy of Infliximab in controlling inflammation in RA [1]. This was achieved both in terms of clinical improvement at 1 year and joint damage scores [2]. Other trials (“ASPIRE”) have established the role of Infliximab in early disease [3]. Similarly, the disease activity scores (“BASDAI”) improved significantly in AS patients [4]. Functional and metrology indices also improved as did the extra-articular manifestations (enthesitis and uveitis) over a period of three years in patients with AS [5].

Table 1. 77 patients with RA were treated for at-least 6 months with etanercept or at-least 4 doses of Infliximab and all of them achieved low disease activity.

	Total RA Patients	RA Patients Efficacy/failures	RA Patients Toxicity/Unmet needs
Etanercept (Anti-TNF)	50	All achieved LDA (ACR 50 DAS 28 < 3.2* (last assessment) Relapse rates uncertain**	1 patient-pulm. TB, 2 patients-UTI, 2 patients-folliculitis and abscess 1 patient-lower limb vasculitis (palpable purpura) 1 patient-H. Zoster
Infliximab (Anti-TNF)	27	All achieved LDA (ACR 50 DAS 28 < 3.2* (last assessment) Relapse rates uncertain**	2 patients-broncho-pneumonia, 1 patient-UTI, 1 patient-cellulitis

*Some patients even while on anti TNF therapy had moderate to high disease activity. Their DMARD and steroid use was subsequently modified to achieve low disease activity (LDA). The numbers of such Etanercept patients were 13, and for Infliximab patients, 7. **Many patients (approximately 25% of those who followed up post anti-cytokine treatment) had relapsed after 2-5 years of regular/ irregular DMARD therapy. After relapse seven patients of Etanercept therapy and who had discontinued Etanercept restarted etanercept and attained LDA. After relapse three patients on Etanercept therapy, but who had discontinued Etanercept, switched to Infliximab therapy and attained LDA. 4 Infliximab treated patients relapsed on discontinuation of Infliximab (variable times, 6 months to 2 years post treatment), but re-treatment with Infliximab, achieved LDA in 2 patients, and 2 patients switched over to Etanercept and attained LDA.

Table 2. 202 AS/SpA patients were administered for 6 months to 8 yrs.

	Total AS/SpA Patients	AS/SpA Patients Efficacy/failures	AS/SpA Patients Toxicity/Unmet needs
Etanercept	62	BASDAI < 4 achieved in nearly all patients 3 patients-inefficacy*	1 patient-cellulitis 6 patients-UTI 1 patient-folliculitis and multiple abscesses
Infliximab	140	BASDAI < 4 achieved in nearly all patients 3 patients-inefficacy*	3 patients-pulm. TB** 4 patients-UTI 1 patient – pneumonia 1 patient- “Conjunctival tumour” (dysplastic growth)

*Many or most patients would have relapsed after their 6 months of Etanercept therapy or 4 doses of Infliximab therapy, but since the follow-up data is incomplete, the numbers are not specified. The three patients, who had active disease in each of the etanercept and Infliximab groups even while continuing therapy with the respective anti-TNF products, had severe axial and peripheral disease. They did not attain a low BASDAI < 4 even after adjustments/changes of NSAIDs, intra-articular corticosteroids etc, and were lost to follow-up. **One patient developed pulmonary TB after the second dose of Infliximab, but successfully completed anti-TB treatment. Subsequently, this patient has been administered Infliximab intermittently, for the next 8 years. Two patients developed pulmonary TB after 5 doses of Infliximab and both were successfully treated with anti-TB treatment; one of these two patients has subsequently been treated successfully with etanercept.

In this cohort of patients seen at IAH New Delhi, the efficacy of Infliximab was similar. A few patients who had close clinical and radiological follow-ups, there was slowing down of erosive changes and a reduced joint space narrowing, associated with a reduction of DAS-28 changes. A few patients who started Infliximab therapy early in the AS disease process, had reduced functional deterioration, similar to the international studies.

Etanercept also achieved similar clinical success in RA and AS patients. In RA patients, the combination of Etanercept and MTX was superior to MTX alone in both early and advanced disease [6] [7]. The open label extension phase of Etanercept drug trials has established both the efficacy and safety of this agent in RA patients over a period of 10 years [8]. Etanercept was also very successful in randomized, placebo controlled trials for treatment of severe AS patients, first studied over a 24 week period [9] and then followed through an open label extension of 96 weeks [10]. In other multi-center studies, the disease activity, functional and metrology indices all improved in AS patients¹¹ similar to the Infliximab effect in AS patients. However, the stopping of Etanercept led to a relapse of AS features after a mean of 6 weeks [11] as compared to the relapse of AS features in Infliximab treated patients after a mean of 17.5 weeks [12].

As seen in **Table 1** and **Table 2**, the outcomes were similar for anti-TNF agents in this cohort of RA and AS patients. Given the cost of the anti-TNF agents and the very little medical insurance cover in India, the treatment with these agents for individual patients has been limited from a period of a few months to a few years, and there is a predictable relapse after discontinuation of therapy. There is extensive use of many biologic agents as “bridge therapy” (unpublished data) for bringing down the disease activity in both RA and AS patients to attain low disease states, and then following up with regular DMARDs and NSAIDs (unpublished data from India).

Basic Biology of the mechanism of the Anti-TNF: The role of TNF- α has been established as significant in the patho-physiology of inflammatory arthritis and spondylitis [13] [14]. TNF mediates its action through two receptors, the TNF RI (CD120a) and TNF RII (CD120b) [15] Several signaling pathways are activated and several transcription factors, one of which is the NF κ B (Nuclear Factor kappa B) and protein kinases like the C-JunN-terminal kinase (JNK) and the P38 mitogen activated protein kinase (MAP) [15] Other cytokines like IL-1 and IL-6 are also impacted directly through TNF modulation.

Unmet needs Anti TNF therapy: Infusion reactions like nausea and headaches are very common, but mostly benign [16], and rarely require discontinuation of therapy [17]. Minor transfusion reactions like urticarial reactions, low grade fever, body pain and arthralgias are also reported, but can be treated with the use of medications (paracetamol, anti-histaminics). Therapy is rarely discontinued because of these reactions. Injection-site reactions are also common and affect areas of skin currently or previously injected subcutaneously (Etanercept). These reactions are as follows: urticarial rash, erythematous rash, or both, but rarely is discontinuation of therapy required because of this complication [18] [19].

Neutralizing antibodies are formed in patients treated with Infliximab therapy and these anti-bodies are directed against epitopes found on the mouse part of the antibody. These lead to allergic reactions as also to the reduced efficacy of the medication. Since, Etanercept is a humanized construct, only 3% of the patients treated with it develop antibodies to its molecular structure. Patients treated with Infliximab may develop antibodies to its molecular structure in as high as 53% of the patients [17]. Concomitant use of Methotrexate (MTX) reduces the antigenic potential of Infliximab, since MTX increases the half life of Infliximab [17].

A few patients both in the RA and AS/SpA group of patients, developed hypersensitivity and urticarial reactions (see **Table 1** and **Table 2**), but this did not require discontinuation. No scientific or biochemical analysis was done to determine whether these were related to antibody formation against the Infliximab molecule, nor was it possible to detect a difference in the efficacy of the treatments post-development of the skin allergies (given the small numbers of patients), but at-least three patients had urticarial rashes beginning with the first infusion of Infliximab, and were conservatively managed. A change or increase of doses was not done for any patient. As with the use of anti-TNF agents in other centers, headaches and arthralgias were reported during Infliximab infusions and these were managed by reducing the rate of infusion, and the use of analgesics. Predictably, the skin reactions were lesser in the Etanercept treated patients than the Infliximab treated patients (see **Table 1** and **Table 2**).

When used in animals anti TNF therapy increases the susceptibility to infections with intracellular organisms, but the incidence of other pathogens remains unchanged. The pathogens involved in human clinical trials are mycobacterium tuberculosis [20] [21], listeria monocytogenes [22], legionella [23], pneumocystis carinii [24] and fungi [25]. Tuberculosis is the most common clinically and in countries endemic for tuberculosis; the rates at which the patients develop tuberculosis when on anti-TNF therapy are higher in both RA and AS patients, as compared to western non endemic populations [26]. Of the two anti-TNF agents, Infliximab is associated with a

higher risk of tuberculosis.

Skin and soft tissue infections were commonest in the patients treated at IAH for both AS and RA (see **Table 1** and **Table 2**). Tuberculosis (TB) was also encountered despite the screening procedure adopted to rule out latent TB, and was more common for Infliximab treated patients compared to Etanercept treated patients. All patients who developed TB had the likelihood of reactivation of pulmonary TB rather than a new infection (all had clear results on Chest-Xray and Mantoux/ TB Quantiferon test), since they all developed the disease within 6 months of starting therapy, underscoring the point that an ongoing vigil for symptoms of fever, cough, night sweats and weight loss in anti-TNF treated patients, can be the one other important step in preventing full blown or disseminated TB in these patients. This also underscores the point that regular screening of these patients for latent TB by a Chest-X Ray and a Mantoux test/ TB Quantiferon Gold test, although mandatory and accurate in preventing latent TB, may not be a hundred percent accurate. No patients with Listeriosis or Legionella pneumonia were encountered, although this was a relatively new black box warning for patients on anti-TNF therapy.

The risk of lymphoma and lung cancer in patients with RA is higher than the background rate, and theoretically, this rate may be further enhanced by anti-TNF treatments. The severity and duration of RA and the concomitant use of immune modulators like MTX further increases the risk [27]. In a scientific analysis the risk of lymphoma in RA patients treated with anti-TNF agents compared with other RA patients treated with other therapies was no different [28]. This was perhaps because after age, sex, and disease modulation adjustments were made, the risk of lymphoma with anti-TNF use seemed to be comparable to the control group [29]. Although only a few patients treated with anti-TNF agents actually develop the full blown syndrome of drug induced lupus, the development of anti-nuclear and anti ds-DNA (double stranded DNA) anti-bodies is fairly common [29]. Severe lupus manifestations like lupus nephritis and neuropsychiatric lupus are even rarer in this subset of patients [30]. Multiple sclerosis like illnesses have been reported in patients with RA on anti TNF therapy [31], and patients who had pre-existing multiple sclerosis had worsening of their symptoms when they were on anti-TNF therapy [32] [33]. Congestive heart failure (CHF) is another risk with anti-TNF therapy and worsening of congestive heart failure and higher mortality was found in clinical studies assessing the efficacy of anti-TNF therapy for treating class III/class IV CHF and those studies were abandoned midway. In patients with RA, anti-TNF therapy is contraindicated in patients with class III/class IV CHF, although the TNF inhibitors do not appear to increase the incidence of CHF per se [34]. More recent data from several registries indicate that overall cardiac mortality in treated patients is expected to be lesser due to reduced coronary inflammation.

From the available data it appears that only one patient from the entire set of anti-TNF patients treated at IAH, developed a tumor; this was a conjunctival growth with dysplasia and was successfully treated. No patient had an overt drug induced lupus in the anti-TNF treated patients, but a formal evaluation of Anti-Nuclear antibodies (ANA) was done only in 7 patients for various reasons (fever, skin rash, serositis etc), and all were reported negative. No patients with de-myelination or worsening of CHF were reported from this cohort. From the available information on all patients, both on follow-up and from case records and telephonic interviews, the incidence and prevalence of unmet needs and toxicities, is similar to larger international studies, but the data is incomplete given the long interval of inclusion (2003 - 2013), the very high rate of treatment discontinuations and poor follow-ups.

5. Conclusion

To conclude, the era of biologic therapy has truly arrived and the treatment of inflammatory-rheumatic disorders has seen a paradigm shift. There are many agents for the treatment of RA and AS/SpA, including many biologic agents, so the current treatment strategies differ from country to country and from center to center. High costs, TB and infections are some of the unmet needs related to the use of anti-cytokine biologics. Moreover which biologic is to be used in which patient and when this has to be discontinued (if at all), are also some of the unanswered questions related to the use of anti-cytokine biologics. “Treat to target” and low disease activity achievement are the goals of therapy. Recommendations on the use of anti-cytokine biologic antibodies and non cytokine biologics have been published in the past [35], and similar recommendations have also been proposed from India; for RA [36] and for AS [37]. Treatment algorithms for early [38] and established RA [39], both in separate formats, with the emphasis on early diagnosis and treatment of RA, have also been published and are widely accepted and followed all over India.

Disclosures

Dr. Sundeep Upadhyay has received educational and travel grants from Johnson and Johnson (Janssen), and

Pfizer, and has also served on advisory boards of these companies.

References

- [1] Maini, R., St. Clair, E.W., Breedveld, F., *et al.* (1999) Infliximab (Chimeric Anti-Tumour Necrosis Factor α Monoclonal Antibody) versus Placebo in Rheumatoid Arthritis Patients Receiving Concomitant Methotrexate: A Randomized Phase III Trial. *Lancet*, **354**, 1932-1939. [http://dx.doi.org/10.1016/S0140-6736\(99\)05246-0](http://dx.doi.org/10.1016/S0140-6736(99)05246-0)
- [2] Lipsky, P.E., Desiree, M.F.M., van der Heijde, D.M., *et al.* (2000) Infliximab and Methotrexate in the Treatment of Rheumatoid Arthritis. *The New England Journal of Medicine*, **343**, 1594-1602. <http://dx.doi.org/10.1056/NEJM200011303432202>
- [3] St. Clair, E.W., van der Heijde, D.M., Smolen, J.S., *et al.* (2004) Combination of Infliximab and Methotrexate Therapy for Early Rheumatoid Arthritis: A Randomized, Controlled Trial. *Arthritis & Rheumatology*, **50**, 3432-3443. <http://dx.doi.org/10.1002/art.20568>
- [4] Braun, J., Brandt, J., Listing, J., *et al.* (2002) Treatment of Active Ankylosing Spondylitis with Infliximab: A Randomised Controlled Multicentre Trial. *Lancet*, **359**, 1187-1193. [http://dx.doi.org/10.1016/S0140-6736\(02\)08215-6](http://dx.doi.org/10.1016/S0140-6736(02)08215-6)
- [5] Braun, J., Baraliakos, X., Brandt, J., *et al.* (2005) Persistent Clinical Response to the Anti-TNF- α Antibody Infliximab in Patients with Ankylosing Spondylitis over 3 Years. *Rheumatology*, **44**, 670-676. <http://dx.doi.org/10.1093/rheumatology/keh584>
- [6] Moreland, L.W., Schiff, M.H., Baumgartner, S.W., *et al.* (1999) Etanercept Therapy in Rheumatoid Arthritis: A Randomized, Controlled Trial. *Annals of Internal Medicine*, **130**, 478-486. <http://dx.doi.org/10.7326/0003-4819-130-6-199903160-00004>
- [7] Weinblatt, M.E., Kremer, K.M., Bankhurst, A.D., *et al.* (1999) A Trial of Etanercept, a Recombinant Tumor Necrosis Factor Receptor: Fc Fusion Protein in Patients with Rheumatoid Arthritis Receiving Methotrexate. *The New England Journal of Medicine*, **340**, 253-259. <http://dx.doi.org/10.1056/NEJM199901283400401>
- [8] Moreland, L.M., Cohen, S.B., Baumgartner, S.W., *et al.* (2001) Long-Term Safety and Efficacy of Etanercept in Patients with Rheumatoid Arthritis. *The Journal of Rheumatology*, **28**, 1238-1244.
- [9] Davis, J.C., Van der Heijde, D., Braun, J., *et al.* (2003) Recombinant Human Tumor Necrosis Factor Receptor (Etanercept) for Treating Ankylosing Spondylitis: A Randomized, Controlled Trial. *Arthritis & Rheumatology*, **48**, 3230-3236. <http://dx.doi.org/10.1002/art.11325>
- [10] Davis, J.C., van der Heijde, D., Braun, J., *et al.* (2005) Sustained Durability and Tolerability of Etanercept in Ankylosing Spondylitis for 96 Weeks. *Annals of the Rheumatic Diseases*, **64**, 1557-1562. <http://dx.doi.org/10.1136/ard.2004.035105>
- [11] Brandt, J., Khariouzov, A., Listing, J., *et al.* (2003) Six-Month Results of a Double-Blind, Placebo-Controlled Trial of Etanercept Treatment in Patients with Active Ankylosing Spondylitis. *Arthritis & Rheumatology*, **48**, 1667-1675. <http://dx.doi.org/10.1002/art.11017>
- [12] Baraliakos, X., Listing, J., Brandt, J., *et al.* (2005) Clinical Response to Discontinuation of Anti-TNF Therapy in Patients with Ankylosing Spondylitis after 3 Years of Continuous Treatment with Infliximab. *Arthritis Research & Therapy*, **7**, R439-R444. <http://dx.doi.org/10.1186/ar1693>
- [13] Koch, A.E., Kunkel, S.L. and Strieter, R.M. (1995) Cytokines in Rheumatoid Arthritis. *Journal of Investigative Medicine*, **43**, 28-38.
- [14] Feldman, M., Brennan, F.M. and Maini, R.N. (1996) Role of Cytokines in Rheumatoid Arthritis. *Annual Review of Immunology*, **43**, 28-38.
- [15] Bazzoni, F. and Beutler, B. (1996) The Tumor Necrosis Factor Ligand and Receptor Families. *The New England Journal of Medicine*, **334**, 1717-1725. <http://dx.doi.org/10.1056/NEJM199606273342607>
- [16] Lipsky, P.E., Desiree, M.F.M., van der Heijde, D.M., *et al.* (2000) Infliximab and Methotrexate in the Treatment of Rheumatoid Arthritis. *The New England Journal of Medicine*, **343**, 1594-1602. <http://dx.doi.org/10.1056/NEJM200011303432202>
- [17] Maini, R., St. Clair, E.W., Breedveld, F., *et al.* (1999) Infliximab (Chimeric Anti-Tumour Necrosis Factor α Monoclonal Antibody) versus Placebo in Rheumatoid Arthritis Patients Receiving Concomitant Methotrexate: A Randomized Phase III Trial. *Lancet*, **354**, 1932-1939. [http://dx.doi.org/10.1016/S0140-6736\(99\)05246-0](http://dx.doi.org/10.1016/S0140-6736(99)05246-0)
- [18] Smolen, J., Kay, J., Doyle, M.K., *et al.* (2009) Golimumab in Patients with Active Rheumatoid Arthritis after Treatment with Tumor Necrosis Alpha Inhibitors (GO-AFTER Study): A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Trial. *Lancet*, **374**, 210-221.
- [19] Kavanaugh, A., Smolen, J.S., Emery, P., *et al.* (2009) Effect of Certolizumab Pegol with Methotrexate on Home and Work Place Productivity and Social Activities in Patients with Active Rheumatoid Arthritis. *Arthritis & Rheumatology*,

- 15, 1592-1600.
- [20] Bean, A.G., Roach, D.R., Briscoe, H., *et al.* (1999) Structural Deficiencies in Granuloma Formation in TNF Gene-Targeted Mice Underlie the Heightened Susceptibility to Aerosol Mycobacterium Tuberculosis Infection. *Journal of Immunology*, **162**, 3504-3511.
- [21] Ehlers, S., Benini, J., Kutsch, S., *et al.* (1999) Fatal Granuloma Necrosis Despite Intact Antibacterial Functions in TNFRp55-Deficient Mice Chronically Infected with *M. Avium*. *Infection and Immunity*, **67**, 3571-3579.
- [22] Rothe, J., Lesslauer, W., Lötscher, H., *et al.* (1993) Mice Lacking the Tumour Necrosis Factor Receptor 1 Are Resistant to TNF-Mediated Toxicity but Highly Susceptible to Infection by *Listeria Monocytogenes*. *Nature*, **364**, 798-802. <http://dx.doi.org/10.1038/364798a0>
- [23] Skerret, S.J., Bagby, G.J., Schmidt, R.A. and Nelson, S. (1997) Antibody-Mediated Depletion of Tumour Necrosis Factor- α Impairs Pulmonary Host Defenses to *Legionella pneumophila*. *Journal of Infectious Diseases*, **176**, 1019-1028. <http://dx.doi.org/10.1086/516530>
- [24] Chen, W., Havell, E.A. and Harmsen, A.G. (1992) Importance of Endogenous Tumor Necrosis Factor and Gamma Interferon in Host Resistance Against *Pneumocystis carinii* Infection. *Infection and Immunity*, **60**, 1279-1284.
- [25] Allendoerfer, R. and Deepe, G.S. (1998) Blockade of Endogenous TNF- α Exacerbates Primary and Secondary Pulmonary Histoplasmosis by Differential Mechanisms. *Journal of Immunology*, **160**, 6072-6082.
- [26] Wolfe, F., Michaud, K., Anderson, J. and Urbansky, K. (2004) Tuberculosis Infection in Patients with Rheumatoid Arthritis and the Effect of Infliximab Therapy. *Arthritis & Rheumatology*, **50**, 372-379. <http://dx.doi.org/10.1002/art.20009>
- [27] Wolfe, F. and Michaud, K. (2004) Lymphoma in Rheumatoid Arthritis: The Effect of Methotrexate and Anti-Tumor Necrosis Factor Therapy in 18,572 Patients. *Arthritis & Rheumatology*, **50**, 1740-1751. <http://dx.doi.org/10.1002/art.20311>
- [28] Askling, J., Fored, C.M., Baeklung, E., *et al.* (2005) Haematopoietic Malignancies in Rheumatoid Arthritis: Lymphoma Risk and Characteristics after Exposure to Tumour Necrosis Factor Antagonists. *Annals of the Rheumatic Diseases*, **64**, 1414-1420. <http://dx.doi.org/10.1136/ard.2004.033241>
- [29] Olsen, N.J. and Stein, C.M. (2004) New Drugs for Rheumatoid Arthritis. *The New England Journal of Medicine*, **350**, 2167-2179. <http://dx.doi.org/10.1056/NEJMr032906>
- [30] Charles, P.J., Smeenk, R.J.T., De Jong, J., Feldmann, M. and Maini, R.N. (2000) Assessment of Antibodies to Double-Stranded DNA Induced in Rheumatoid Arthritis Patients Following Treatment with Infliximab, a Monoclonal Antibody to Tumor Necrosis Factor α : Findings in Open-Label and Randomized Placebo-Controlled Trials. *Arthritis & Rheumatology*, **43**, 2383-2390. [http://dx.doi.org/10.1002/1529-0131\(200011\)43:11<2383::AID-ANR2>3.0.CO;2-D](http://dx.doi.org/10.1002/1529-0131(200011)43:11<2383::AID-ANR2>3.0.CO;2-D)
- [31] Mohan, N., Edwards, E.T., Cupps, T.R., *et al.* (2001) Demyelination Occurring During Anti-Tumor Necrosis Factor Alpha Therapy for Inflammatory Arthritides. *Arthritis & Rheumatology*, **44**, 2862-2869. [http://dx.doi.org/10.1002/1529-0131\(200112\)44:12<2862::AID-ART474>3.0.CO;2-W](http://dx.doi.org/10.1002/1529-0131(200112)44:12<2862::AID-ART474>3.0.CO;2-W)
- [32] van Oosten, B.W., Barkhof, F., Truyen, L., *et al.* (1996) Increased MRI Activity and Immune Activation in Two Multiple Sclerosis Patients Treated with Monoclonal Anti-Tumor Necrosis Factor Antibody cA2. *Neurology*, **47**, 1531-1534. <http://dx.doi.org/10.1212/WNL.47.6.1531>
- [33] The Lenercept Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group (1999) TNF Neutralization in MS: Results of a Randomized, Placebo-Controlled Multicenter Study. *Neurology*, **53**, 457-465. <http://dx.doi.org/10.1212/WNL.53.3.457>
- [34] Wolfe, F. and Michaud, K. (2004) Heart Failure in Rheumatoid Arthritis: Rates, Predictors, and the Effect of Anti-TNF Therapy. *The American Journal of Medicine*, **116**, 305-311. <http://dx.doi.org/10.1016/j.amjmed.2003.09.039>
- [35] Singh, J.A., Furst, D.E., Bharat, A., *et al.* (2012) 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Anti-Rheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis. *Arthritis Care & Research*, **64**, 625-639. <http://dx.doi.org/10.1002/acr.21641>
- [36] Misra, R., Sharma, B.L., Gupta, R., *et al.* (2008) Indian Rheumatology Association Consensus Statement on the Management of Adults with Rheumatoid Arthritis. *Indian Journal of Rheumatology*, **3**, S1-S16. [http://dx.doi.org/10.1016/S0973-3698\(10\)60373-1](http://dx.doi.org/10.1016/S0973-3698(10)60373-1)
- [37] Malaviya, A.N., Shankar, S., Arya, V., *et al.* (2010) Indian Rheumatology Association Consensus Statement on the Diagnosis and the Treatment of Axial Spondyloarthropathies. *Indian Journal of Rheumatology*, **5**, 16-34. [http://dx.doi.org/10.1016/S0973-3698\(10\)60531-6](http://dx.doi.org/10.1016/S0973-3698(10)60531-6)
- [38] Upadhyaya, S. (2012) Treatment of Early RA. *Apollo Medicine*, **9**, 345-346. <http://dx.doi.org/10.1016/j.apme.2012.09.005>
- [39] Upadhyaya, S. (2012) Treatment of Established RA. *Apollo Medicine*, **9**, 347-348. <http://dx.doi.org/10.1016/j.apme.2012.09.006>