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Anti-Tumour Necrosis Factor-α Induced Systemic Lupus Erythematosus

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1. Introduction

There are new drugs in medicine represent a revolution in therapeutics in the current era. These drugs are produced by different molecular biological techniques. Anti-tumor necrosis factor- α (anti-TNF-α) agents are important new class of the biological therapy of disease modifying antirheumatic drugs (DMARD). They target specific proteins of tumor necrosis factor- α (TNF-α) in the immune systems known to increase the inflammatory processes. Anti-TNF–α agents are increasingly used for a rapidly expanding number of rheumatic autoimmune diseases including rheumatoid arthritis (RA), ankylosing spondylitis (AS), crohn's disease (CD), ulcerative colitis (UC), psoriasis, and psoriatic arthritis (PsA). They can increase odds of remission in both randomized controlled trials and clinical practice in early and established rheumatoid arthritis. They can withhold the radiological progression of certain diseases like RA. They can produce a dramatic normalization of acute phase reactants. Due to prolonged follow up periods, side effects profile for these agents is growing. This is in addition to their ability to neutralize specific immune pathways resulting in many adverse events. Autoimmune syndromes with cutaneous and systemic manifestations including systemic lupus erythematosus may occur in patients receiving anti-TNF-α therapies (Ramos-Casals, Brito-Zeron et al. 2007). These agents represent a challenge for the practicing clinician with a range of judgments for optimal use and management of adverse events. In this chapter an overview of TNF-α will be demonstrated including its wide use in clinical practice. A more focus on anti-TNF-α agents side effects profile will be presented particularly anti-TNF-α induced lupus erythematosus (ATIL). The chapter will address the various aspects related to ATIL including clinical manifestations, autoantibodies profile, management, prognosis and preventive strategies.

2. Tumor necrosis factor-α (TNF-α)

TNF and TNF receptors are members of a family of molecules (including Fas-ligand/fas, CD40 ligand/CD40) possessing crucial regulatory functions that include activation and apoptosis. TNF-α is an attractive therapeutic target owing to its abundant expression in the rheumatoid joint and plethora of proinflammatory effects that include regulation of

other proinflammatory mediators. TNF-α is a cytokine produced primarily by monocytes and macrophages but may also be produced by other cell types (e.g., B cells, T cells, mast cells, fibroblasts). TNF-α may further contribute to the pathogenesis of RA by induction of proinflammatory cytokines such as interleukin (IL)-1 and IL-6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophils and eosinophils, induction of the synthesis of acute-phase reactants, and the induction of tissue-degrading enzymes (matrix metalloproteinase enzymes) produced by synoviocytes and/or chondrocytes (Cush, Kavanaugh et al. 2011). It is expected then to have numerous biological effects in vivo with agents that inhibit the production or function of this cytokine.

3. Anti-tumor necrosis factor-α (TNF-α) agents

There are two strategies for inhibition of TNF-α which can be achieved either with monoclonal antibody such as infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), and golimumab (Simponi), or with a circulating receptor fusion protein such as etanercept (Enbrel) (Fig 1).

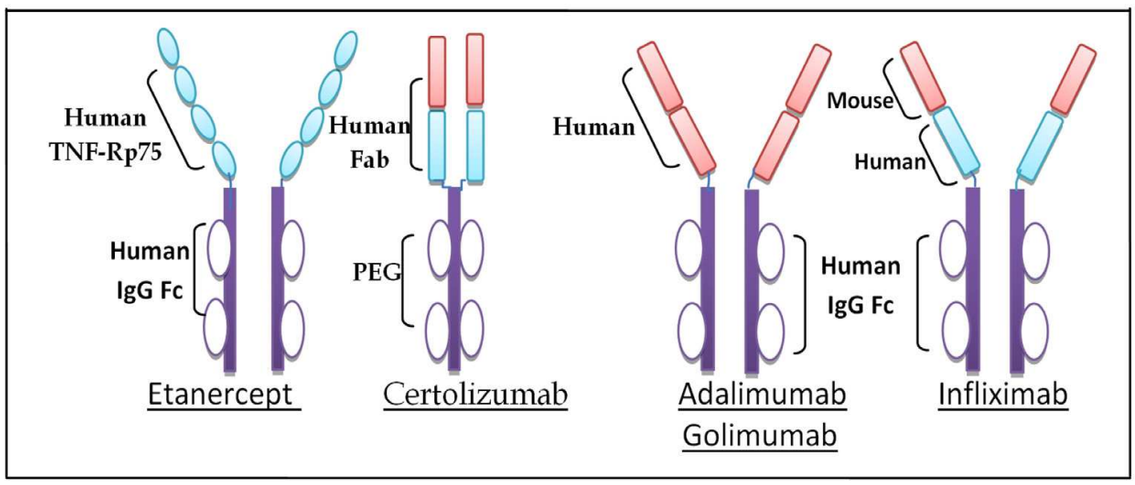

Fig. 1. Structure of anti- TNF-α agents.

3.1 Infliximab (Remicade)

Infliximab (Remicade) is a human/mouse chimeric monoclonal antibody against TNF-α and it was the first anti-TNF-α agent used to treat inflammatory disease. It was initially approved by the U.S. Food and Drug Administration (FDA) for the treatment of Crohn's disease in August 1998. Later on, it was approved by the FDA for the treatment of ulcerative colitis. Infliximab works by blocking the action of TNF-α by preventing it from binding to its receptor in the cell and neutralizing its action. However, the powerful action of infliximab that it causes programmed cell death of TNF-α expressing activated T lymphocytes, a cell type mediating inflammation, which explains its efficacy in Crohn's disease.(Van den Brande, Braat et al. 2003). This is in contrast to another TNF-α neutralizing medication, etanercept, which is worse than a placebo in Crohn's disease.(Van Den Brande,

Peppelenbosch et al. 2002) Infliximab is administered as an intravenous infusion, on a 2-4 weekly initially and then on a 6-8 weekly basis.

3.2 Etanercept (Enbrel)

Etanercept (Enbrel) is a p75 TNF--α receptor fusion protein produced through expression of recombinant DNA and conjugated to the Fc region of human immunoglobulin G (IgG1) which inhibits the binding of TNF to its cell surface receptor. Etanercept was developed by researchers at Immunex, and was released for commercial use in late 1998, soon after the release of infliximab. There are two types of TNF receptors: those found embedded in white blood cells that respond to TNF by releasing other cytokines, and soluble TNF receptors which are used to deactivate TNF and blunt the immune response. Etanercept mimics the inhibitory effects of naturally occurring soluble TNF receptors, the difference being that etanercept, because it is a fusion protein rather than a simple TNF receptor, has a greatly extended half-life in the bloodstream, and therefore a more profound and long-lasting biologic effect than a naturally occurring soluble TNF receptor. (Madhusudan, Muthuramalingam et al. 2005) The FDA has licensed etanercept for moderate to severe rheumatoid arthritis, moderate to severe polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and moderate to severe plaque psoriasis. Etanercept is administered as a subcutaneous injection with a dose of 25 mg twice weekly or 50 mg once weekly.

3.3 Adalimumab (Humira)

Adalimumab (Humira), the third approved TNF-α inhibitor after infliximab and etanercept, is a human anti-TNF-α monoclonal antibody. It binds to TNF-α preventing the activation of TNF receptors; adalimumab was constructed from a fully human monoclonal antibody, while infliximab is a mouse/human chimeric antibody. In 2008, adalimumab has been approved by the FDA for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and crohn's disease. It is administered subcutaneously bi-weekly as preloaded 0.8 mL syringes or preloaded pen devices.

3.4 Other anti- TNF-α agents

Other two monoclonal antibodies targeting TNF-α are golimumab (Simponi), and certolizumab pegol (Cimzia); which is a Fab fragment of human anti-TNF-α antibody attached to a polyethylene glycol (PEG) moiety. In 2008, the FDA approved Cimzia for use in the treatment of crohn's disease in people who did not respond sufficiently or adequately to standard therapy. Large, randomized, double-blind trials in patients with rheumatoid arthritis have shown that golimumab in combination with methotrexate was more effective than methotrexate alone.(Oldfield and Plosker 2009).

4. Indications

The introduction of the TNF- α blocking therapies (anti-TNF) in 1998 marked the beginning of a new era in the treatment of chronic inflammatory human diseases, including RA, AS, psoriasis and PsA, and inflammatory bowel diseases. Infliximab, Etanercept, and adalimumab are the most common anti- TNF-α agents to be used with great response and disease control in the treated patients. The U.S FDA has approved the indications of anti TNF-α therapy (table 1).

Indication	Etanercept	Infliximab	Adalimumab
Rheumatoid arthritis (RA)	Yes [1]	Yes [1R]	Yes [1]
Early RA	Yes	Yes	Yes
Polyarticular juvenile arthritis	Yes [2]	--	--
Psoriatic arthritis	Yes [3E]	Yes [3]	Yes [3]
Ankylosing spondylitis	Yes [4]	Yes [4]	Yes [4]
Psoriasis	Yes [5]	Yes	--
Crohn disease	--	Yes [6]	Yes 6
Ulcerative colitis	--	Yes [7]	--

1- Indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function for patients with moderately to severely active rheumatoid arthritis. It can be initiated alone or in combination with methotrexate.

1R- Infliximab is approved for use in combination with methotrexate only.

2- Indicated for reducing signs and symptoms of moderately to severely active polyarticular course juvenile rheumatoid arthritis patients who have had an inadequate response to one or more DMARDs.

3- Indicated for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis.

3E- Only etanercept is indicated to inhibit the progression of structural damage and improve physical function for patients with moderately to severely active psoriatic arthritis. It can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

4- Indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

5- Indicated for the treatment of adult patients (>18 years) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

6- Indicated for reducing signs and symptoms and inducing or maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Infliximab is also indicated for reducing the number of enterocutaneous and rectovaginal fistulas and maintaining fistula closure in fistulizing Crohn disease.

7- Only infliximab is indicated for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

Table 1. U.S. Food and Drug administration-approved indications for anti-TNF-α therapy (Cush, Kavanaugh et al. 2011).

4.1 Rheumatoid Arthritis (RA)

RA is a chronic inflammatory autoimmune disease associated with debilitating and destructive polyarthritis and other systemic manifestations. DMARDs are used for treatment of patient with well-established RA and ongoing inflammation like methotrexate, sulfasalazine or hydroxychloroquine. If a patient had an inadequate response or intolerance to the usual treatment, biological therapy of anti-TNF-α can be used as monotherapy or in combination with other DMARDs. These recommendations have recently been modified because large controlled trials in early RA patients now allow their use as the initial DMARDs in RA.

4.2 Ankylosing Spondylitis (AS)

AS is a chronic inflammatory disease, that affect young males. It is characterized by its association with HLA B27 antigen and spinal inflammation mainly in form of sacroilitis. Patients with active AS who did not respond to conventional therapies can be managed with anti -TNF-α therapy.

4.3 Psoriasis and psoriatic arthritis

Psoriatic arthritis is a potentially debilitating disease that may affect small and large peripheral joints, and the axial skeleton, seen in more than 10% of patients with plaque psoriasis. Arthritis may precede onset of skin disease. The conventional therapy of psoriatic arthritis includes non-steroidal anti-inflammatory drugs (NSAID), systemic and intra-articular corticosteroids, and disease-modifying anti rheumatic drugs (DMARD) such as sulfasalazine or methotrexate. Recent trials in Psoriatic arthritis have shown excellent results with anti TNF-α therapy which have positive effects not only on joints, but also on the skin lesions.

4.4 Inflammatory Bowel Diseases (IBD)

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal tract. Although the primary etiological defect still remains unknown, genetic, environmental and microbial factors have been reported in activation of the mucosal immune response. TNF-α is one of the central cytokines in the underlying pathogenesis of mucosal inflammation which is responsible for the effectiveness of anti -TNF-α therapy. Infliximab, adalimumab and certolizumab all seems to be effective in CD. Infliximab is the only anti-TNF agent currently approved for UC. Although etanercept is a TNF-α blocker, it is not approved and marketed for IBD. A randomized, controlled trial showed that etanercept was no better than placebo in IBD (Sandborn, Hanauer et al. 2001). Both etanercept and infliximab neutralized TNF-α, but only infliximab bounds to T lymphocytes and induces apoptosis of these cells (Van den Brande, Braat et al. 2003).

4.5 Relative contraindications

Due to the accumulative experience developing from the worldwide use of these drugs, certain conditions considered relative contraindications for the use of anti-TNF-α agents. Most of these conditions were obtained mainly from observations in randomized controlled trials and post-marketing phase IV trials. These conditions include systemic lupus erythematosus, lupus overlap syndrome, a history of demyelinating disorder (multiple sclerosis, optic neuritis), untreated active or latent tuberculosis, congestive heart failure, and pregnancy. The use of a TNF-α inhibitor in these conditions is currently experimental in terms of risks and benefits.

5. Side effects

Short- and long-term therapy with anti-TNF-α agents is well tolerated; however, the increased risk of infrequent but serious complications warrant sustained vigilance on the part of physicians and patients alike.

5.1 Injection site reaction

Administration of anti -TNF-α either by intravenous infusion or subcutaneous injection may result in site reactions including development of redness, swelling, itching or even skin rash. Some patients report an allergic response to infliximab, possible reason may be due to its chimeric monoclonal antibody that has human part and mouse part.

5.2 Infections

TNF-α is a cytokine that plays a crucial role in the body's immune defense against bacterial infections. Infections are mainly consisting of upper respiratory tract infections, bronchitis and urinary tract infections. A systematic review of adverse effects of anti- TNF-α therapies as they were used in rheumatoid arthritis concluded that patients taking these agents are at 2.0 time higher risk for serious infections. Serious infections that were observed, included pneumonia, sepsis and pyelonephritis (Leombruno, Einarson et al. 2009).

It has been documented well in the literature that treatment with anti-TNF-α agents is associated with increased rate of tuberculosis, in form of miliary, lymphatic, peritoneal, as well as pulmonary tuberculosis. Most of the cases of tuberculosis occurred within the first eight months after initiation of anti -TNF-α therapy.(Gomez-Reino, Carmona et al. 2003) As a result, it is recommended that patients should be screened with a TB skin test prior to starting these medications. If there is evidence of prior exposure with positive skin test, treatment for TB can be given in combination with the anti-TNF-α agents. Other reported infections in patients on TNF-α inhibitors are fungal infections, such as pulmonary and disseminated histoplasmosis, coccidioidomycosis, and blastomycosis. It is recommended that patients with active infections should not be started on anti -TNF-α agents until their infection resolve. Furthermore, these agents should be temporarily discontinued in those patients who develop an infection while on therapy.

5.3 Malignancy

The use of anti-TNF-α agents is accompanied by some worries about their long-term safety. Thus, it seems important to investigate whether blocking the action of this TNF-α cytokine might lead to an increased risk of malignancy. The particular worry concerns of lymphoproliferative malignancies, because these malignancies occur at an increased rate in immunosuppressed patients. There are concomitant risk factors that may predispose to lymphoma in patients with RA who are using anti-TNF-α therapy. Patients with RA per se have an increased risk for developing lymphoma(Van den Brande, Braat et al. 2003). Patients specifically treated with anti -TNF-α agents are likely to have more severe disease regarding both disease duration and disease severity, which may increase the risk of malignant transformation. The accompanying use of medication, especially cyclophosphamide and azathioprine may increase the risk of developing malignancy (Van den Brande, Braat et al. 2003). In one study, it has been observed that there is an increased risk of lymphoproliferative malignancies in patients with RA who were treated with high-dose azathioprine compared with non– azathioprine-treated RA controls (Silman, Petrie et al. 1988). In another study, an increased risk of bladder and skin cancer was observed in patients with RA who were treated with cyclophosphamide (Radis, Kahl et al. 1995). Most of the reported cases of lymphoma in patients with RA who were treated with methotrexate are related to Epstein-Barr virus (EBV) (Georgescu and Paget 1999). Methotrexate exposure is almost a universal practice in anti -TNF-α treated patients and could be an important

confounder of the subsequent risk for lymphoproliferative malignancies. In response to this risk of lymphoma, the US Food and Drug Administration (FDA) convened a meeting in March 2003 to review the safety data on TNF-α antagonists, focusing on the risk of malignancy in general and lymphoproliferative malignancies in particular(Kovacs, Vassilopoulos et al. 1996; Cush JJ 2003). Six lymphomas were found among 6303 RA patients treated with TNF-α inhibitors in controlled clinical trials, but none were observed in placebo-treated patients. A total of 23 lymphomas were observed (9 etanercept, 4 infliximab, 10 adalimumab) during drug treatment, with an increased standardized incidence ratio (SIR, relative risk) of 3.47, 6.35, and 5.42, respectively (Cush JJ 2003). However, the 95% confidence intervals for these SIRs were particularly wide and overlapping, thus not permitting any separation of lymphoma risk due to drug or active RA alone. Rates of solid tumors were not increased when anti-TNF-α agents associated malignancies were compared with population expectations at an FDA meeting in 2003. Similarly, in registry studies, no overall increase in risk has been reported in RA patients whether or not exposed to TNF inhibitors (Cush JJ 2003). For all this evidence, there is no clear answer regarding the risk of developing lymphoma in patients with RA and on anti -TNF-α therapy, either if it is related to anti-TNF-α therapy or to RA itself and other confounding factors.

5.4 Autoimmune diseases

Anti-TNF-α agents are widely being used for a large number of patients with different rheumatic and systemic autoimmune diseases. As a result of this use, these agents have been associated with an increasing incidence of autoimmune diseases as adverse effects, principally vasculitis, lupus like syndrome, antiphospholipid-like features, and interstitial lung disease. Other autoimmune diseases have been described, such as sarcoidosis, autoimmune hepatitis, uveitis, and thyroiditis (Ramos-Casals, Brito-Zeron et al. 2008). The clinical characteristics, outcome and pattern of autoimmune diseases following TNF-α targeted therapies have been analyzed through a baseline Medline search of articles published between January 1990 and May 2008. A total of 379 cases have been reported with drug induced autoimmune diseases (table 2) (Ramos-Casals, Brito-Zeron et al. 2008).

The reported cases of vasculitis have been classified into cutaneous vasculitis and visceral vasculitis (table 3) (Ramos-Casals, Brito-Zeron et al. 2008). Most of these cases of vasculitis overwhelmingly presented as cutaneous lesions, in form of purpura, ulcerative lesions, nodules or digital vasculitis. Regarding the biopsy, 75% of specimens were leukocytoclastic vasculitis, 15% necrotizing vasculitis, 5% lymphocytic vasculitis, and 2% urticarial vasculitis(Ramos-Casals, Brito-Zeron et al. 2008). Other patients may develop visceral vasculitis including peripheral nerve, renal, lung, and CNS involvements. Peripheral neuropathy may present in a form of axonal peripheral neuropathy, mononeuropathy multiplex, multifocal motor neuropathy with conduction block, or chronic inflammatory demyelinating polyradiculoneuropathy (Ramos-Casals, Brito-Zeron et al. 2008). Patients on anti -TNF-α agents may develop glomerulonephritis (GN) with a biopsy of pauci-immune GN, crescenting necrotizing GN or IgA GN (Ramos-Casals, Brito-Zeron et al. 2008). Pulmonary involvement has been described in association with patients who are having perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) focal segmental necrotizing GN and crescentic GN. Rare cases have been reported with CNS involvement presented as central retinal artery occlusion, confusion of unclear origin and seizure(Ramos-Casals, Brito-Zeron et al. 2008). Systemic vaculitis has been reported in a form of temporal arteritis, Henoch-Schonlein purpura, and polyarteritis nodosa (Ramos-Casals, Brito-Zeron et al. 2008).

Interstitial lung disease (ILD) has been developed after starting anti -TNF-α therapy in a form of interstitial pneumonitis, pulmonary hemorrhage and bronchiolitis obliterans organizing pneumonia. The specific feature of the ILD associated with anti-TNF-α therapy is the poor prognosis in spite of cessation of these agents. Therefore initiation of corticosteroids and immunosuppressive agents is mandatory (Ramos-Casals, Brito-Zeron et al. 2008).

	Reported cases (*n*)	Mean age ± SEM (years)	Female (%)	Underlying disease: RA, Sp, IBD (%)	Biological agent: INF, ETA, ADA, other (%)
a) Systemic autoimmune diseases					
• DIL	**140**	**49.51 ± 1.68**	**77**	**72, 7, 11**	**37, 33, 25, 6**
• Vasculitis	**139**	**51.55 ± 2.68**	**79**	**92, 7, 8**	**43, 42, 7, 7**
• APS/APS-like disease	**42**	**50.00 ± 3.79**	**70**	**26, 11, 26**	**45, 41, 5, 9**
• Sarcoidosis	**38**	**49.41 ± 2.05**	**65**	**60, 37, 0**	**26, 61, 10, 3**
b) Organ-specific autoimmune diseases					
• Optical neuritis[a]	**123**	**43.47 ± 3.29**	**63**	**37, 17, 25**	**43, 49, 7, 1**
• Interstitial lung disease	**118**	**62.79 ± 1.98**	**77**	**77, 6, 4**	**43, 47, 3, 7**
• Inflammatory ocular disease	**87**	**45.96 ± 2.16**	**81**	**41, 48, 0**	**18, 79, 2, 0**
• MS/MS-like[a]	**55**	**42.83 ± 1.99**	**70**	**59, 17, 12**	**20, 51, 27, 2**
• Peripheral neuropathies[b]	**44**	**52.47 ± 2.16**	**66**	**61, 16, 16**	**74, 12, 14, 0**
• Autoimmune hepatitis	**19**	**45.24 ± 2.83**	**76**	**32, 47, 21**	**79, 10, 10, 0**

DIL: drug-induced lupus; APS: antiphospholipid syndrome; MS: multiple sclerosis; RA: rheumatoid arthritis; Sp: spondyloarthropathies; IBD: inflammatory bowel disease; INF: infliximab; ETA: etanercept; ADA: adalimumab; SEM: standard error of the mean.
a Eight patients had the two processes.
b Excluding those appearing in patients with vasculitis.

Table 2. Characteristic of main autoimmune diseases associated with biological agents (BIOGEAS Registry, last update July 15, 2009)(Ramos-Casals, Roberto Perez et al.).

Clinical characteristics of Vasculitis	Number of cases
Cutaneous vasculitis	96
Leukocytoclastic	44
Necrotic	8
Lymphocytic	5
Urticaria	2
Not biopsied	37
Peripheral neuropathy	18
Glomerulonephritis	17
Central nervous system	6
Pulmonary involvement	3
Systemic vasculitis	5

Table 3. Clinical characteristics of 145 patients with vasculitis related to TNF-α targeted therapy.

6. Anti-TNF-α Induced Lupus Erythematosus (ATIL)

Drug induced lupus is a syndrome with symptoms, signs, and laboratory findings similar to idiopathic SLE. The diagnosis requires a temporal relationship between symptoms and therapy for at least four American Congress of Rheumatology criteria for SLE (Ramos-Casals, Brito-Zeron et al. 2007). More than 80 drugs have been implicated in drug-induced lupus, with sulfadiazine being the first reported in 1945 (Vasoo 2006). The relationship between drugs and induced lupus was confirmed by the disappearance of symptoms with drugs withdrawal.

Treatment with anti-TNF-α agents have been reported to be associated with drug-induced lupus erythematosus, most commonly with infliximab and etanercept, and rarely related to adalimumab (Haraoui and Keystone 2006; van Rijthoven, Bijlsma et al. 2006), as infliximab and etanercept have been used wider and for longer period than adalimumab. Lupus-like syndrome and ATIL were the most common in a registry of autoimmune diseases associated with anti-TNF-α agents (Ramos-Casals, Brito-Zeron et al. 2007). In this study, analysis of 92 cases with ATIL revealed that all had clinical and immunological features suggestive of SLE, 94% had positive autoantibodies, 89% had cutaneous features, 39% had musculoskeletal manifestations and general symptoms were presented in 29% (Ramos-Casals, Brito-Zeron et al. 2007).

Majority of patients with ATIL were diagnosed with RA as it will be shown below. It can be argued that the development of ATIL was actually due to a change induced by anti-TNF-α agents from RA to SLE? It is well recognized clinically that patients may evolve from one disease to another. It can be argued as well that those RA patients who developed ATIL were actually carrying the diagnosis of SLE but with a predominant presentation of polyarthritis and the use of anti-TNF-α agents had just triggered other lupus manifestations? This notion is supported, as it will be shown below by the fact that some patients with ATIL had positive ANA prior to initiation of Anti-TNF-α agents. All these arguments remain areas for ongoing research to help clinicians learn more about Anti-TNF-α agents and the actual pathogenesis of ATIL. It has to be noted that ATIL developed not only in RA patients but in patients with PsA, CD, and AS as well. The abundance of case reports and case series support the notion that anti-TNF-α therapy can induce a lupus-like syndrome as a separate and well recognized clinical entity. Rigorous exclusion of SLE prior to initiation of Anti-TNF-α agents is extremely important as a preventive action (see below).

6.1 Role of TNF-α in the pathogenesis of SLE

TNF-α is pleiotropism cytokine that has both immunoregulatory and proinflammatory effects, and its blockage has been proposed to be beneficial for the majority of patients with rheumatoid arthritis or inflammatory bowel disease. However, anti-TNF-α therapy has led in some cases to a significant incidence of drug-induced autoantibodies production and ATIL. TNF-*a* blocking could relieve the inflammation induced by TNF-*a*, at the same time the immunoregulatory and antiapoptotic effects of TNF-*a* could also be blocked which may lead to autoimmunity (Ramos-Casals, Brito-Zeron et al. 2007).

6.1.1 Immunoregulatory effects and apoptosis of TNF-α in SLE

In an experimental study, a heterozygous mice was generated which has reduced TNF-*a* production, by crossing NZB mice with TNF-*a* deficient mice. These mice developed

enhanced autoimmunity and severe renal disease similar to the classic mice model of SLE. Autoimmune responses were associated with an early spontaneous increase in serum levels of antinuclear antibodies (ANA) and hyperproliferating B cells which readily express anti-double stranded DNA antibodies (anti-ds DNA) antibodies specificities in response to polyclonal and T helper stimuli. These findings demonstrate a physiological role for TNF-*a* in suppressing the emergence of autoreactive lymphocytes in the NZB model and indicate that defective TNF-*a* function may be causative of the autoimmune and pathological phenomena in lupus. Loss of physiological TNF-*a* production in an autoimmunity prone background suffices to exacerbate antinuclear autoimmunity and the development of disease (Kontoyiannis and Kollias 2000).

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 release of nuclear autoantigens in patients with SLE (Gergely, Grossman et al. 2002). 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 (Emlen, Niebur et al. 1994). It has been showed that permeabilitized lupus T cells displayed significantly lower amounts of TNF-*a*, a functional Fas/Fas-ligand path and adequate amounts of intracellular TNF-*a* 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 blockage (Kovacs, Vassilopoulos et al. 1996).

The clinical reports about the levels of TNF-*a* in SLE patients' were controversial. In most studies, TNF-*a* is found to be increased and appeared to be bioactive in the sera of patients with active SLE, and levels of TNF-*a* have been shown to correlate with SLE disease activity (Aringer, Feierl et al. 2002; Aringer and Smolen 2003). In another study, it has been found that SLE patients had elevated plasma levels of TNF-*a* with no correlation of disease activity (Zhu, Landolt-Marticorena et al. 2010). Furthermore, in a third study, it has been demonstrated that TNF-*a* levels were higher in patients with inactive disease compared with patients with very active disease, suggesting that TNF-*a* could be a protective factor in SLE patients (Gomez, Correa et al. 2004).

HLA-DR2 and DQwl positive subjects frequently exhibit low production of TNF-*a* whereas DR3 and DR4 positive subjects show high levels of TNF-*a* production. DR2 and DQwl positive SLE patients show low levels of TNF-*a* inducibility; this genotype is also associated with an increased incidence of lupus nephritis (LN). DR3 positive SLE patients, on the other hand, are not predisposed to nephritis, and these patients have high TNF-*a* production. DR4 haplotype is associated with high TNF-*a* inducibility and is negatively correlated with LN. These data suggested that low TNF-*a* production may be involved in the genetic predisposition to LN, and may help explain the association between HLADR2/DQwl and susceptibility to LN (Jacob, Fronek et al. 1990).

As TNF receptor1 (TNFR1)—TNFR associated death domain (TRADD)--Fas-associated death domain (FADD) system leading to apoptotic signaling, the down regulation of TRADD, FADD in 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. 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 pro survival agenda that increases the likelihood of autoimmune diseases (Rosen and Casciola-Rosen 2001), (Balomenos and Martinez 2000).
The dysregulation of programmed cell death is suggested to be involved in the generation of autoantibodies. The low expression of TRADD, receptor-interacting protein 1 (RIP-1), and TNF receptor associated factor 2 (TRAF-2) might be one of the etiopathogeneses leading to redundant apoptotic death in SLE patients. It has been indicated that decreased expression of TRADD, RIP-1, and TRAF-2 and restrained pathogenesis for the loss of immune tolerance and redundant apoptotic cell death, leading to massive production of autoantibodies in SLE patients (Zhu, Yang et al. 2007).

6.1.2 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. It has been 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, with WHO class III and IV LN, while no TNF-α is detected in healthy kidney tissues. Most of the conducted studies have demonstrated that TNF-α is expressed in LN of all WHO classes and high TNF-α expression is associated with high histological disease activity. Also, it has been found that upregulation of renal expression of TNF-α in class III and class IV LN by immunohistochemical studies, and the upregulation 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 (Aringer and Smolen 2004).

6.2 Clinical trials of anti- TNF-α therapy in SLE

SLE is a multifactorial autoimmune disease characterized by breakdown of self-tolerance, B cell hyperactivity, autoantibody production, aberrant formation of immune complexes, and inflammation of multiple organs. As TNF-α is a proinflammatory cytokine, participate in inflammatory tissue damage and in SLE pathogenesis, few clinical trials have been conducted regarding the use of anti TNF-α agents in patients with active SLE.
In 2008, an open-label study was reported about the safety and efficacy of TNF-blockade in SLE. Seven 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 levels were increased in 4 of 7 patients, and IgM anti-cardiolipin antibodies were also increased in 4 of 7 patients, peaking 4–10 weeks after the last infliximab infusion. This trial suggested that while anti-TNF-*a* agent 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 (Aringer and Smolen 2008). A long-term follow up study was conducted of 13 patients about the adverse events and efficacy of TNF-*a* blockade with infliximab in SLE patients. It 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(Aringer, Houssiau et al. 2009).

6.3 Development of autoantibodies

The induction of autoantibodies and anti-TNF-α therapy has been widely documented (De Bandt, Sibilia et al. 2005). Most of patients who were treated with anti-TNF-α agents developed antibodies that normally found almost exclusively in patients with SLE, however, these patients do not have any clinical features suggestive of SLE (Charles, Smeenk et al. 2000). Therefore, discontinuation of these agents is not indicated but this evident do not exclude potential induction of clinical lupus signs or symptoms and patients need further close follow up and observation (Charles, Smeenk et al. 2000). TNF-α antagonists lead into an elevated titers of ANA with a homogeneous pattern in patients who already started treatment with positive serology of ANA. In addition, new onset of positive ANA may develop in previously negative ANA patients treated with TNF-α inhibitors (FDA 2008; Lin, Ziring et al. 2008). Development of new onset of anti-ds DNA antibodies, more specific antibodies of SLE, was reported during anti- TNF-α therapy which represents a strong evidence for diagnosis of induction of lupus-like syndrome following treatment with these agents. However, anti-ds DNA antibodies are found in 50-70% of patients with idiopathic SLE while their prevalence is from 9% to 33% in patients treated with anti- TNF-α (FDA 2008; Lin, Ziring et al. 2008). It has been reported that patients on anti-TNF-α agents had serum antibodies to ds DNA of IgG, IgM, and IgA subtypes. In all reported patients, most common induced antibodies were solely of the IgM subtype. This finding is in marked contrast to the patients with idiopathic SLE, in whom although IgM antibodies to ds DNA are fairly common, it is extremely rare to find this response without accompanying IgG anti-ds DNA antibodies (Charles, Smeenk et al. 2000). Anti-histone antibodies are detected in 57% among patients with ATIL in one study (Costa, Said et al. 2008) and only in 17% in another study (De Bandt, Sibilia et al. 2005). It should be noted that anti-histone antibodies are not pathognomonic for drug-induced SLE and occur in more than 95% of cases, they are also found in 75% of cases with idiopathic SLE (Katz and Zandman-Goddard 2010). Hypocomplementemia is found in up to 59% of patients with ATIL while this finding is extremely rare in other drug-induced lupus (Costa, Said et al. 2008). The occurrence of anticardiolipin (ACL) antibodies were detected in anti-TNF-α treated patient. Up to 25% of patients on anti- TNF-α agents for RA developed IgG or IgM ACL, but thrombosis is observed in much fewer patients (about 4%) (Cambien, Bergmeier et al. 2003). It is also known that TNF-α has potent antithrombotic properties. It is therefore conceivable that the association of ACL antibodies and inhibition of TNF-α could lead to an increase risk of thrombosis. The presence of anti-Smith antibodies is almost exclusive of idiopathic SLE and rarely found in drug-induced SLE. Anti-nucleosome antibodies of the IgG subtype are considered to be a more sensitive marker for SLE than anti-dsDNA and anti-histone antibodies (Amoura, Koutouzov et al. 2000). Although there are number of patients who develop anti-nucleosome antibodies during treatment with anti- TNF-α agents, this number is not statistically significant. Positive ENAs also may develop in patients on these agents (Costa, Said et al. 2008). A comparison of different autoantibodies produced in ATIL reported in three different studies is presented in (table 4) (Williams, Gadola et al. 2009).

It has been confirmed that the induction of ANA and anti-dsDNA antibodies occur in patients who started treatment with anti-TNF-α agents, and the presence of this serological

finding is unrelated to the genetic background or the underlying disease process. The development of only anti-dsDNA antibodies with absence of other lupus specific antibodies in the consequence of anti- TNF-α therapy is reassuring in terms of the safety of this treatment; however, long term observation is mandatory.
Among laboratory findings, the hematological results that have been reported secondary to anti-TNF-α agents that are typical of idiopathic SLE which include leukopenia, thrombocytopenia, and lymphopenia (Costa, Said et al. 2008).

Autoantibody	Costa et al., 2008, (Britain), (n=33)	Ramos et al., 2007, (Spain), (n=72)	De Bandt et al., 2005, (French), (n=12)
ANA, n (%)	**32/32 (100)**	**57 (79)**	**12 (100)**
dsDNA, n (%)	**29/32**	**52 (72)**	**11 (92)**
Histone, n (%)	**16/28 (57)**	**Not reported**	**2 (17)**
aPL, n (%)	**Not reported**	**8 (11)**	**6 (50)**
ENAs, n (%)	**10/19 (53)**	**Anti-Sm 7 (10)** **Anti-Ro/La 9 (12)** **Anti-RNP 5 (7)**	**5 (42)**

Table 4. Comparison of the developed antibodies in ATIL reported in three different studies (Williams, Gadola et al. 2009). ANA: antinuclear antibodies, dsDNA: double stranded DNA, aPL: antiphospholipid antibodies, ENAs: extractable nuclear antigens.

6.4 Clinical manifestations of anti-TNF-induced SLE (ATIL)

The true incidence of ATIL is difficult to establish due to the paucity of data and lack of double blind placebo-controlled prospective studies, difficulty to establish causality and lack of universal recognition of this relatively new entity (Katz and Zandman-Goddard). Post marketing studies on the three licensed anti-TNF-α agents have suggested an estimated incidence of ATIL of 0.19%–0.22% for infliximab, 0.18% for etanercept and 0.10% for adalimumab (De Bandt, Sibilia et al. 2005; Schiff, Burmester et al. 2006). However, the prevalence of ATIL in the main randomized controlled trials (RCTs) using anti-TNF agents is higher, with 14 (0.76%) cases in the 1842 patients included in 17 studies (Ramos-Casals, Roberto Perez et al.). It has to be realized that this is an accumulative figure and it does not represent the exact prevalence. The mean duration of disease before initiation of anti-TNF-α therapy was 13.5 years in one cohort (range, 1-35 years)(Wetter and Davis 2009). Onset of symptoms ranges from less than one month to more than 4 years (Williams and Cohen). In another larger report, the mean latency time until the manifestations of ATIL was 41 weeks (Ramos-Casals, Brito-Zeron et al. 2007). There was, in this series, a 5:1 female : male ratio. The most common disease for which anti-TNF-α was used for was RA (Ramos-Casals, Brito-Zeron et al. 2007; Costa, Said et al. 2008). Other diseases include but not limited to juvenile idiopathic arthritis, PsA, AS, CD. In one cohort, most patients who developed ATIL were having CD (Wetter and Davis 2009). The most common anti-TNF-α agent in use currently is infliximab as it is the first to be approved and introduced to clinical practice. Obviously, most of the cases of ATIL were due to infliximab use followed by etanercept and adalimumab respectively (Ramos-Casals, Brito-Zeron et al. 2007; Costa, Said et al. 2008). (Table 5) demonstrates the clinical characteristics of 92 patients with ATIL reported in the

literature up to December 2006 (Ramos-Casals, Brito-Zeron et al. 2007). (Table 6) demonstrates comparison of different features of ATIL reported in some studies (Williams, Gadola et al. 2009).

Main Characteristic	No. (%)
Underlying rheumatic disease (n=92)	
Rheumatoid arthritis	**77 (84%)**
Crohn disease	**8 (9%)**
Ankylosing spondylitis	**2 (2%)**
Psoriatic arthritis	**2 (2%)**
Other	**3 (3%)**
Anti-TNF agent (n=62)	
Infliximab	**40 (44%)**
Etanercept	**37 (40%)**
Adalimumab	**15 (16%)**
Demographic characteristics (n=62)	
Female/male	**52/10**
Mean age at diagnosis of vasculitis (yr±SEM)	**50.9 ± 2.3**
Length of anti-TNF treatment ± SEM (wk)	**41.2 ± 5.7**
SLE criteria (n=72)	
ANA	**57 (79%)**
Anti-dsDNA	**52 (72%)**
Cutaneous features	**48 (67%)**
Arthritis	**22 (31%)**
Cytopenia	**16 (22%)**
Serositis	**9 (12%)**
aPL	**8 (11%)**
Anti-Sm antibodies	**7 (10%)**
Nephropathy	**5 (7%)**
Oral ulcers	**3 (4%)**
CNS involvement	**2 (3%)**
Number of SLE criteria fulfilled (n=72)	
≥ 4 (defined SLE)	**37 (51%)**
3 (lupus-like syndrome)	**17 (24%)**
1-2 (isolated lupus features)	**18 (25%)**
Outcome (n=72)	
Improvement	**71**
Time of improvement (mo ± SEM)	**9.9 ± 1.4**
Rechallenge phenomenon	**2/8 (33%)**

Table 5. Clinical characteristics of 92 patients with lupus related to TNF-targeted therapy (Ramos-Casals, Brito-Zeron et al. 2007).

ACR diagnostic criteria for lupus	BSRBR data, (Britain), (n=41)	Coasta et al., 2008, (USA), (n=33)	Ramos-Casal et al., (Spain), (n=72)	De Bandt et al., 2005, (France), (n=12)
Malar rash. N (%)	**Not reported**	**Not reported**	**Not reported**	**5 (42)**
Discoid rash, n (%)	**25 (61)**	**24 (73)**	**48 (67)**	**0**
Photosensitivity, n (%)	**4 (10)**	**Not reported**	**Not reported**	**5 (42)**
Oral ulcer, n (%)	**5 (12)**	**1 (3)**	**3 (4)**	**0**
Arthritis, n (%)	**3 (7)**	**17 (52)**	**22 (31)**	**6 (50)**
Serositis, n (%)	**0**	**3 (18)**	**9 (12)**	**3 (25)**
Renal Disorder, n (%)	**0**	**3 (9)**	**5 (7)**	**0**
Neurological disorder, n (%)	**0**	**0**	**2 (3)**	**0**
Hematological disorder, n (%)	**1(2)**	**20 (61)**	**Cytopenia-16 (22)**	**6 (50)**
Immunological disorder, n (%)	**4 (10)**	**29 (88)**	**dsDNA-52 (72), anti-Sm-7 (10)**	**11 (92)**
Anti-nuclear antibodies, n (%)	**13 (32)**	**32 (97)**	**57 (79)**	**12 (100)**

Table 6. Features of patients with ATIL based on case reports and case series in some studies (Williams, Gadola et al. 2009).

6.4.1 Development of cutaneous manifestations

ATIL may present in variable forms of clinical features, either in form of isolated cutaneous manifestations or systemic manifestations. Most of the reported clinical features of anti-TNF-α-induced SLE are in form of cutaneous lesions **(**tables 5 and 6). Most of these symptoms are similar to that symptoms present with idiopathic SLE. The cutaneous features of ATIL are most commonly malar rash, pruritic rash, photosensitive rash or purpura (Ramos-Casals, Brito-Zeron et al. 2008). Other cutaneous features are discoid rash, mucosal ulcers, and alopecia (Ramos-Casals, Brito-Zeron et al. 2008). The diagnosis of these cutaneous symptoms is based upon the clinical features in combination with concurrent use of an implicated drug. Therefore, many of the reported cases did not have skin lesions biopsied for diagnosis (Wetter and Davis 2009). When described, the pathological changes of this adverse effect are similar to those observed in patients with non-drug-associated idiopathic SLE (De Bandt, Sibilia et al. 2005; Costa, Said et al. 2008).

6.4.2 Development of systemic manifestations

Patients on anti- TNF-α therapy may develop systemic features of SLE that usually resolve after discontinuation of the offending drug. The associated general features include constitutional symptoms of fever, malaise, and weight loss which are considered as common symptoms of SLE after anti- TNF-α therapy and they often present in association with positive serology of autoantibodies. Other systemic symptom that reported is induction of

new onset of polyarthritis or progression to worsening symptoms of presented arthritis in form of joint tenderness, swelling, and effusion, some other patients develop arthralgia without evidence of arthritis (De Bandt, Sibilia et al. 2005). Arthritis was the first sign to develop in 71% in a cohort of patients in one center (Wetter and Davis 2009). It was also the most debilitating sign. Other rare and serious clinical characteristics may develop as side effects in patients on anti-TNF-α agents include serositis with pleurisy or pericarditis, pleural or pericardial effusions, deep venous thrombosis, life-threating pneumonitis, and neuritis (Costa, Said et al. 2008) (Table 7). Two cases of biopsy-confirmed proliferative lupus nephritis were described in patients treated with etanercept for juvenile RA (Mor, Bingham et al. 2005; Stokes, Foster et al. 2005). Renal biopsies revealed severe hypercellularity, endocapillary proliferation, wire loops and intraluminal deposits. Immunofluoresence shared positive staining for all immunoglobulin isotypes as well as C3 and Clq. Extensive electron-dense deposits were visualized by electron microscopy. Of note, focal proliferative lupus nephritis (Class III) was described with adalimumab (Stokes, Foster et al. 2005).

Clinical manifestation	Number of reported cases	% of reported cases
Rash	24/33	73 %
Polysynovitis	17/33	52 %
Fever	17/33	52 %
Myalgias	8/33	24 %
Pericardial/pleural effusion	3/33	9 %
Nephritis	3/33	9 %
Valvulitis	1/33	3 %
Pneumonitis	1/33	3 %
Deep venous thrombosis	1/33	3 %
Oral ulcer	1/33	3 %

Table 7. Clinical features of 33 reported cases with ATIL (Costa, Said et al. 2008).

ATIL may present with unusual manifestation that is even uncommon feature of idiopathic SLE. This requires clinical suspension for ATIL in any patient presenting with unusual clinical findings. Invasive methods may be required to confirm the diagnosis. In a case that we reported (Almoallim 2011), adalimumab was initiated in a patient to control her symptoms of RA. She presented with prolonged morning stiffness and severe polyarthritis evident by swelling and tenderness in her metacarpophalangeal joints (MCPs), elbows, shoulders, knees and ankles. Serology for RF, anti-citrullinated protein antibodies (ACPA), and ANA (1:160) were all positive. While the patient was on adalimumab therapy, she showed significant improvement with complete remission of her disease. Within one year of this treatment, she developed diffuse muscle weakness mainly proximal rather than distal which made her unable to get up from the bed, climb stairs or even stand from sitting position. She had signs of active arthritis in two MCP joints in the right and bilateral wrist joints. She had mild hyperpigmented area around the mouth with no skin rashes elsewhere. She had a very high titer of ANA (1:1280) with emerging of a new onset of strongly positive

anti-ds DNA antibodies, her creatinine kinase was entirely normal. Electromyograghy (EMG) was suggestive of inflammatory myopathy. MRI deltoid and thigh showed mild edema involving the right triceps muscle with minimal enhancement in the post contrast sequence (Figure.2). Deltoid biopsy showed focal mild perivascular and endomysial lymphohistiocytic which revealed inflammatory myositis (Figure.3). Based on the clinical findings, the positive serology of ANA and anti-ds DNA, and the biopsy findings, the diagnosis of adalimumab induced lupus myositis was made. Given the profound muscle weakness that she had, she received 1 gm of pulse methylprednisolone intravenously daily for three days then she was maintained on 60 mg/day, in addition she received rituximab 1000 mg intravenously, two doses in two weeks. This regimen was well tolerated and she recovered fully. Ten months later, she was asymptomatic with normal power, negative serology for anti-dsDNA antibodies and off treatment. In another case report, the patient developed severe myositis as a part of complex overlap syndrome following treatment with adalimumab, with positive serology for ANA and anti-dsDNA antibodies (Liozon, Ouattara et al. 2007).

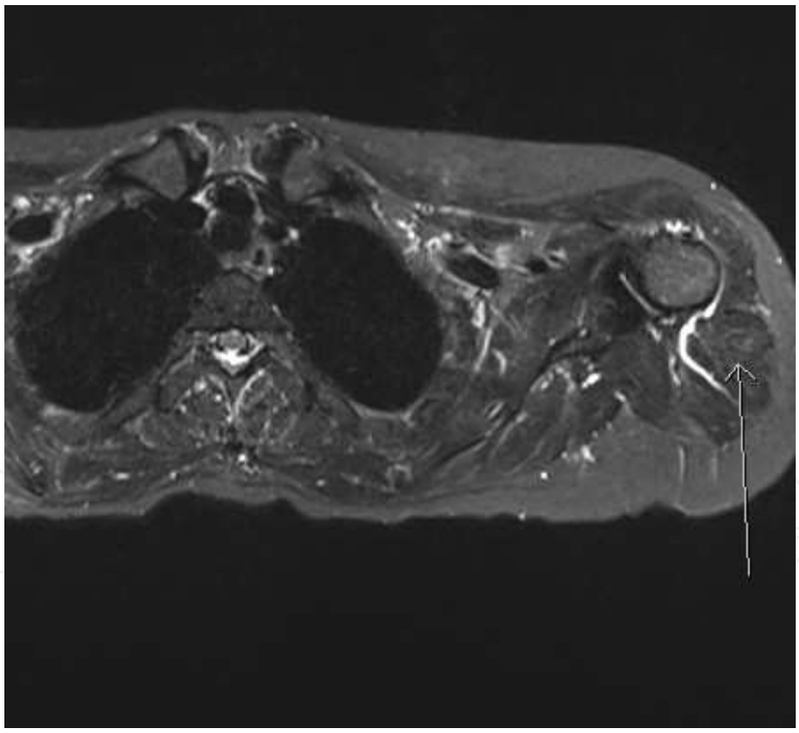

Fig. 2. MRI right arm showed mild edema involving the right triceps muscle with minimal enhancement in the post contrast sequence in comparison to other muscles which appeared mildly atrophied.

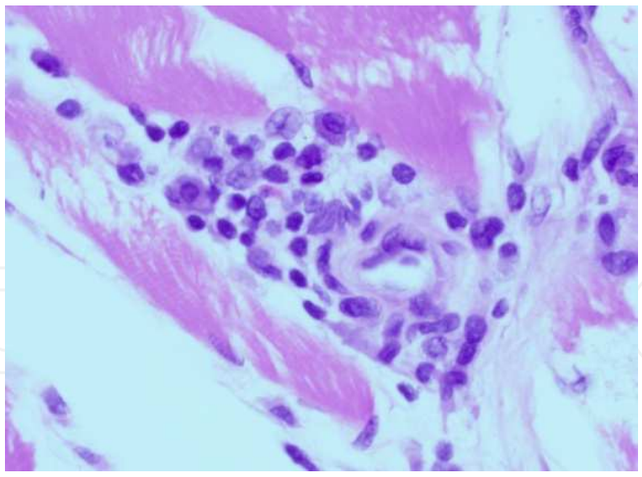

Fig. 3. Biopsy from right arm (triceps muscle) using Hematoxylin and Eosin stain, original magnification 400, which revealed inflammatory myositis (focal mild perivascular and endomysial lymphohistiocytic inflammation).

6.5 Differences between ATIL and classic Drug Induced Lupus Erythematosus (DILE)

These comparisons are observations based on the abundance of case reports in the literature. Skin rashes for example are thought to be more common in ATIL in comparison to DILE (Costa, Said et al. 2008). It is noticed that the classical cutaneous features of SLE is rare in DILE (Katz and Zandman-Goddard). While myalgias is more common in DILE (Yung and Richardson 1994) in comparison to ATIL. The incidence of fever is similar in both diseases in one series (Costa, Said et al. 2008). (Table 8) represents the prevalence of clinical manifestations and laboratory features in ATIL, DILE and SLE as reported in three different studies (Ramos-Casals, Brito-Zeron et al. 2007).

Feature	Anti-TNF-related lupus (%)	Procainamide-realted lupus (%)	Idiopathic SLE (%)
ANA	**79**	**>95**	**99**
Anti-dsDNA	**72**	**<5**	**90**
Rash/cutaneous involvement	**67**	**<5**	**54-70**
Arthritis	**31**	**20**	**83**
Fever/general symptoms	**23**	**45**	**42**
Hypocomplementemia	**17**	**<5**	**48**
Leukopenia	**14**	**15**	**66**
Serositis	**12**	**50**	**28**
Anticardiolipin antibodies	**11**	**5-20**	**15**
Glomerulonephritis	**7**	**<5**	**34**
Thrombocytopenia	**6**	**<5**	**31**
Neuropsychiatric	**3**	**<5**	**12**
Anti-histone antibodies	**Not reported**	**>95**	**50-60**

Table 8. Prevalence of clinical manifestations and laboratory features in lupus related to anti-TNF agents compared with idiopathic SLE (Ramos-Casals, Brito-Zeron et al. 2007).

6.5 Diagnosis of Anti-TNF-α-induced lupus erythematosus

Development of SLE in patients who is being treated with anti-TNF-α agents is well documented throughout the literature and the diagnosis of this side effect is crucial. The clinical presentation of ATIL can vary, and specific diagnostic criteria have not been established. However, in the most reported cases, the diagnosis was made on the basis of the development of one or more symptoms compatible with SLE, ongoing exposure to an anti--TNF-α agent, no prior history of SLE, and resolution of symptoms when the offending drug is discontinued. The strict application of the American College of Rheumatology criteria for idiopathic SLE (ACR criteria) would probably exclude the diagnosis of ATIL in many patients receiving anti-TNF-α therapy. Therefore, for the purpose of early diagnosis; the following criteria can be considered (De Bandt, Sibilia et al. 2005): (1) a temporal relationship between symptoms and anti-TNF-α-therapy; (2) at least 1 serologic finding that compatible with ACR criteria eg, ANA, anti-dsDNA antibodies, and (3) at least 1 non serologic finding that compatible with ACR criteria eg, arthritis, serositis, hematologic disorder, malar rash. The musculoskeletal symptoms were taken into account only if they reappeared with other lupus symptoms in a patient in whom they had previously disappeared while receiving anti- TNF-α therapy as in the case reported above in section 6.4.2. Isolated positive results for ANAs or anti-dsDNA antibodies were not considered for diagnosis, given their high frequency in patients receiving this therapy (De Bandt, Sibilia et al. 2005).

6.6 Treatment of Anti-TNF-α-induced Lupus Erythematosus (ATIL)

The main approach regarding the treatment of ATIL is the withdrawal of offending drug. The time until symptoms resolution ranges from three weeks to six months (De Bandt, Sibilia et al. 2005; Wetter and Davis 2009). The level of autoantibodies have been either normalized or decreased in response to drug withdrawal (De Bandt, Sibilia et al. 2005; Wetter and Davis 2009). However, some investigators have suggested that TNF-α antagonists do not need to be discontinued if the patient has isolated induction of autoantibodies without any clinical manifestations of lupus (Ramos-Casals, Brito-Zeron et al. 2007; Kerbleski and Gottlieb 2009). It has to be realized that autoimmune diseases may coexist and there is always the possibility of latent idiopathic SLE triggered by anti-TNF-α agents. Strongly positive autoantibodies should raise the suspicion for ATIL. In addition to discontinuing of anti- TNF-α therapy, many patients required to be treated by the traditional therapy for idiopathic SLE to achieve full resolution of their lupus symptoms. The Spanish Study Group of Biological Agents in Autoimmune Diseases (BIOGEAS) classified all patients with autoimmune diseases secondary to the use of biologic agents into two groups, i.e. mild (with cutaneous, articular or general features) and severe (with pulmonary, renal or neurological involvement) disease (Ramos-Casals, Brito-Zeron et al. 2007). For mild disease, it has been suggested to withdraw TNF-α antagonists and for severe disease, immediate cessation of the offending drug and addition of corticosteroids and other immunosuppressive agents. The British Society for Rheumatology's (BSR) guidance for suspected ATIL recommends withdrawal of anti-TNF- α therapy, but does not specify additional treatment measures (Ledingham, Wilkinson et al. 2005). It has been reported that lupus-like symptoms in patients receiving anti-TNF-α therapy disappeared in most of the cases after withdrawal of the anti- TNF-α therapy (Ramos-Casals, Brito-Zeron et al. 2007). Forty per cent of the patients also received corticosteroids, while 12% required additional immunosuppression with azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate or cyclophosphamide in one of the largest series of ATIL (Ramos-Casals,

Brito-Zeron et al. 2007). In a reported case of a patient who developed ATIL in a form of a pruritic photo-distributed skin rash after initiation of etanercept therapy, patient has been treated with hydroxychloroquine beside drug discontinuation and systemic corticosteroids(Williams and Cohen 2011). We reported case of a patient who developed lupus myositis after treatment with adalimumab for rheumatoid arthritis. She received pulse steroid therapy and two doses of rituximab. The treatment was well tolerated with complete recovery. The patient was then maintained on hydroxychloroquine and azothioprine. She remained asymptomatic for 10 months of follow up (Almoallim 2011). An important question is whether patients with ATIL can safely receive an alternative anti–TNF-α agent? There are limited evidences that support the safety of re-challenging with alternative anti-TNF-α agents. Reports regarding this issue are scarce, but one author described 4 patients who were re-challenged with the same or different agents and had no recurrence of lupus symptoms (3 received etanercept and 1 received adalimumab)(Cush 2004). In another study, 4 of 5 patients tolerated an alternative TNF inhibitor (adalimumab for 3 patients, etanercept for 1) without recurrence of ATIL after discontinuation of infliximab (Wetter and Davis 2009). Nevertheless, these findings should be interpreted cautiously, given the small number of patients who were re-challenged. In addition, some of these reports were conducted on patients with ATIL with mild disease and few clinical findings. The successful continued therapy with an alternative anti-TNF-α agent reported for one patient (Williams and Cohen), was actually manifested with only cutaneous findings. The clinical decision to continue an alternative anti-TNF-α agent in ATIL patients with severe and systemic involvement is really hard to make. Exposing patients to the risk of developing another serious complication from an offending drug, even if it were another drug in the same class is against the basic principles of safe practice.

6.7 Prognosis of Anti-TNF-α -induced Lupus Erythematosus (ATIL)

Most patients who developed ATIL had a good prognosis upon discontinuation of these agents. Normalization of the emerged autoantibodies and resolution of lupus symptoms occur when the offending drugs is stopped without recurrence. Some patients might need to be started on corticosteroids and immunosuppressive agents for full recovery as described above. However, patients who developed serious side effects in form of renal or neurological involvements may have residual effects (Ramos-Casals, Brito-Zeron et al. 2007).

6.8 Prevention of Anti-TNF-α-induced Lupus Erythematosus (ATIL)

ATIL is a well documented entity. Physicians need to use these biological agents in caution with close follow up. It is not known whether ATIL and other autoimmune phenomena are a contributing factor for the high rate of long-term drug failure/discontinuation of anti-TNF-α therapy(Papagoras, Voulgari et al.) Rigorous follow up and early recognition of any complication developing while patients receiving anti-TNF-α agents, are essential to assure patients safety on the long term. This should help clinicians to learn more about these agents and identify appropriate approaches in different clinical settings encountered. As the use of anti-TNF-α agents has become more widely spread, the incidence of ATIL will likely also increase. There are currently no recommendations for prevention of ATIL. It has been suggested that concurrent use of immunosuppressive agents may reduce the incidence of autoantibody formation and thereby reduce the incidence of ATIL (Eriksson, Engstrand et al. 2005). Indeed, methotrexate can exert a suppressive effect on the production of autoantibodies in patients with isolated cutaneous lupus (Boehm, Boehm et al. 1998).

Although direct comparison between studies is difficult, as the majority of patients on anti-TNF will also be taking MTX, data from clinical trials of infliximab in patients with RA suggest that concurrent therapy with DMARDs is not protective (Charles, Smeenk et al. 2000; Eriksson, Engstrand et al. 2005). It has to be noted also that some RA patients had lupus features before the initiation of anti-TNF-α agents (Ramos-Casals, Brito-Zeron et al. 2007). Use of anti-TNF-α agents may have triggered or unmasked the symptoms of SLE in some patients. For this reason, assuring the diagnosis of RA prior to initiation of anti-TNF-α therapy is an extremely important aspect in the prevention process. Presence of SLE is considered a contraindication to the use of anti-TNF-α therapy. Therefore, it is recommended to perform a thorough baseline immunological screening for any patient with definite polyarthritis to assure accurate diagnosis. It is recommended to perform a detailed immunological screening for any patient whom you are considering anti-TNF-α therapy for. Some recommendations have been suggested for each patient upon starting anti-TNF-α therapy which will help in the therapeutic approach for autoimmune diseases induced by these biological agents (Ramos-Casals, Brito-Zeron et al. 2007). First, perform baseline immunological analysis and chest X-ray before treatment. Second, maintain specific follow up centered on the possible development of cutaneous, articular, or pulmonary manifestations. Third, evaluate adverse effects related to anti-TNF-α accurately, discarding the existence of undiagnosed autoimmune diseases (mainly systemic vasculitis). Fourth, preexisting SLE, especially in the presence of sever organ involvement (renal, pulmonary, or neurogical), should be considered as a precautionary scenario for the use of anti-TNF-α therapy. Finally, anti-TNF-α agents should not be used in patients with preexisting interstitial lung disease (table 9).

1.	Perform baseline immunological analysis and chest X-ray before treatment.
2.	Maintain specific follow up centered on the possible development of cutaneous, articular, or pulmonary manifestations.
3.	Evaluate adverse effects related to anti-TNF-α accurately, discarding the existence of undiagnosed autoimmune diseases (mainly systemic vasculitis).
4.	Preexisting SLE, especially in the presence of sever organ involvement (renal, pulmonary, or neurogical), should be considered as a precautionary scenario for the use of anti-TNF-α therapy.
5.	Anti-TNF-α agents should not be used in patients with preexisting interstitial lung disease.

Table 9. Some recommendations for each patient upon starting anti-TNF-α therapy. Adopted with modifications from (Ramos-Casals, Brito-Zeron et al. 2007).

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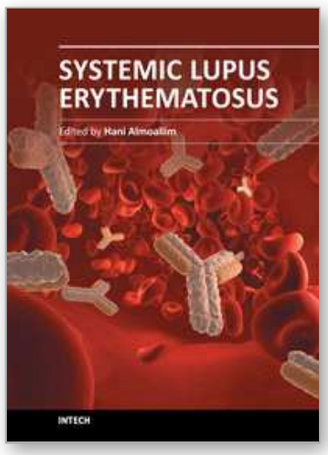

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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

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