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Anti-Tumor Necrosis Factor-α Induced Systemic Lupus Erythematosus[§]

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Abstract: Anti-tumor necrosis factor-alpha induced lupus (ATIL) represents a major diagnostic and therapeutic challenge. Most cases of ATIL are caused by infliximab, followed by etanercept and adalimumab. Symptoms can range from common, mild cutaneous lesions to rare, serious pleural or pericardial effusions, deep venous thrombosis, life-threatening pneumonitis, and neuritis. Constitutional symptoms often present in association with positive autoantibody serology. Diagnosis can be considered if there is a temporal relationship between symptoms and anti-tumor necrosis factor-α (TNF-α) therapy and at least one serologic and one non-serologic American College of Rheumatology criteria. Since it is contraindicated to use anti-TNF-α drugs in patients with systemic lupus erythematosus, it is recommended to perform a thorough immunological screening in any patient with polyarthritis to assure accurate diagnosis. In addition, prior to anti-TNF therapy, baseline immunological investigations (including antinuclear antibodies) should be performed, and there should be close follow up to assess the development of lupus manifestations. The main approach in the treatment of ATIL is withdrawal of the offending drug. Traditional therapy with corticosteroids and immunosuppressive agents may be required to achieve full resolution of lupus symptoms. In this review, we discuss the pathogenesis, clinical manifestations, and management of ATIL.

Keywords: Anti-tumour necrosis factor alpha, disease modifying anti-rheumatic drugs, drug-induced lupus, rheumatoid arthritis, systemic lupus erythematosus.

INTRODUCTION

The introduction of tumor necrosis factor-alpha (TNF-α) blocking therapies in 1998 marked the beginning of a new era in the treatment of chronic inflammatory human diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis and psoriatic arthritis (PsA), and inflammatory bowel diseases (IBD). Conventional therapy included disease modifying anti rheumatic drugs (DMARDs), namely methotrexate, sulfasalazine, and hydroxychloroquine. These recommendations have been modified because large controlled trials in patients with early RA now allow the use of anti-TNF-α therapy as the initial DMARDs in RA. Similarly, patients with active AS who do not respond to conventional therapy can be managed with anti-TNF-α therapy. Recent trials in psoriatic arthritis have shown excellent results with anti-TNF-α therapy, which has positive effects on joint as well as skin lesions. Until recently, infliximab was the only anti-TNF agent approved for the treatment of ulcerative colitis; adalimumab is now also used in the treatment of ulcerative colitis [1].

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Drug-induced lupus is a syndrome with symptoms, signs, and laboratory findings similar to idiopathic systemic lupus erythematous (SLE). More than 80 drugs have been implicated in the onset of drug-induced lupus. Of these, sulfadiazine was the first medication reported to cause drug-induced lupus [2]. The relationship between anti-TNF-α agents and induced lupus was confirmed by the disappearance of symptoms after withdrawal of the implicated drugs. Treatment with infliximab and etanercept has been commonly associated with drug-induced lupus erythematosus, but it is rarely related to adalimumab [3, 4] as infliximab and etanercept have been widely used for relatively longer periods.

Lupus-like syndrome and anti-TNF-*α* induced lupus erythematosus (ATIL) were the most common in a registry of autoimmune diseases associated with anti-TNF-*α* agents [5]. In the current review, we discuss the pathogenesis, clinical manifestations, and management of ATIL with the aim of increasing awareness of this condition among physicians managing patients on anti-TNF-α.

PATHOGENESIS OF ANTI-TUMOR NECROSIS FACTOR-A INDUCED LUPUS

The pathogenesis of anti- TNF-α in the development of SLE has not been yet clarified; however, several mechanisms have been proposed to explain the incidence of lupus or lupus-like syndromes in patients treated with anti-TNF-α therapy. For instance, anti-TNF-α suppresses the production of Th1 cytokines, thereby driving the immune response towards Th2 cytokine production, IL-10, and IFN-α, a hypothesis called 'cytokine shift". This leads to the production of autoantibodies and a lupus-like syndrome [6-

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10]. Another hypothesis is based on the assumption that systemic inhibition of TNF-α could interfere with apoptosis by decreasing CD44 expression. This affects the clearance of nuclear debris and apoptotic neutrophils by phagocytes and thus promotes autoantibody production against DNA and other nuclear antigens [11-16]. In addition, anti-TNF-α therapy may inhibit cytotoxic T-cells, leading to reduction of the elimination of autoantibody-producing B-cells [17].

The induction of autoantibodies by anti-TNF-α therapy has been widely documented [5]. Most patients who were treated with anti-TNF-α agents developed antibodies that were normally found almost exclusively in patients with SLE; however, these patients did not have any of the clinical features suggestive of SLE (5). The administration of TNF-α antagonists causes elevated titers of antinuclear antibodies (ANA) with a homogeneous pattern in patients who already started treatment with positive ANA serology. In addition, new-onset positive ANA may develop in previously negative ANA patients who were treated with TNF-α inhibitors [5]. The appearance of new anti-double-stranded DNA (anti-dsDNA) antibodies was reported during anti-TNF-α therapy, thus constituting strong evidence for the diagnosis of TNF-α antagonist-induced lupus-like syndrome. It has been reported that patients on anti-TNF-α agents have serum anti-dsDNA antibodies of IgG, IgM, and IgA subtypes. The most common induced antibodies were solely of the IgM subtype. This finding is in marked contrast to that seen in patients with idiopathic SLE in whom it is extremely rare to find elevated IgM antibodies without accompanying IgG anti-dsDNA antibodies [5]. While it was reported that anti-histone antibodies were detected in 57% of the patients with ATIL in one study [18], other authors reported that only 17% of the patients in their study were positive for anti-histone antibodies [19]. Anti-histone antibodies are not pathognomonic for drug-induced SLE, and they occur in more than 95% of cases of drug-induced SLE; they are also found in 75% of patients with idiopathic SLE [20]. The occurrence of anticardiolipin antibodies was detected in up to 25% of patients on anti-TNF-α agents who were treated for RA [21]. The presence of anti-Smith antibodies is almost exclusive of idiopathic SLE and rarely found in drug-induced SLE. Positive extractable nuclear antigens also may develop in patients on anti-TNF-α agents [5].

It has been confirmed that the induction of ANA and anti-dsDNA antibodies occur in patients who started treatment with anti-TNF-α agents. The development of only anti-dsDNA antibodies in the absence of other lupus-specific antibodies in the course of anti-TNF-α therapy is reassuring in terms of safety; however, long-term observation is mandatory. A comparison of different autoantibodies produced in ATIL as reported in three different studies is presented in (Table **1**) [6].

CLINICAL MANIFESTATIONS OF ANTI-TUMOR NECROSIS FACTOR-A-INDUCED LUPUS

The true incidence of ATIL is difficult to establish because of the paucity of data and lack of double-blinded placebo-controlled prospective studies, difficulties in establishing causality, and lack of universal recognition of this relatively new entity [20]. Post marketing studies on the three licensed anti-TNF-α agents have suggested that the estimated incidence of ATIL is 0.19%–0.22% for infliximab, 0.18% for etanercept, and 0.10% for adalimumab [19, 22]. The onset of symptoms ranges from less than one month to more than 4 years [23]. The most common anti-TNF-α agent in use currently is infliximab as it was the first drug 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 [5, 18].

Clinically, ATIL may present in the form of isolated cutaneous or systemic manifestations. Most of the reported clinical features of anti-TNF-α-induced SLE present as cutaneous lesions, which in most cases are similar to those present in idiopathic SLE. The cutaneous features of ATIL are most commonly malar rash, pruritic rash, photosensitive rash, or purpura [24]. Other cutaneous features are discoid rash, mucosal ulcers, and alopecia [24]. The diagnosis of these cutaneous symptoms is based on clinical features in combination with the concurrent use of an implicated drug. Many of the reported cases, therefore, did not have skin lesions biopsied for diagnosis [25]. When described, the pathological changes of ATIL are similar to those observed in patients with non-drug-associated idiopathic SLE [18, 19].

Patients on anti-TNF-α therapy may develop systemic features of SLE, which 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 autoantibody serology. Other systemic symptoms that have been reported are the induction of new-onset polyarthritis or progressive, worsening symptoms of arthritis in the form of joint tenderness, swelling, and effusion; some patients develop arthralgia without evidence of arthritis [19]. Arthritis was the first sign

Table 1. Comparison of Antibodies in Anti-Tumor Necrosis Factor-*α* Induced Lupus Erythematosus as Reported in Three Different Studies[a]

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)

Abbreviations: ANA, antinuclear antibodies; dsDNA, double-stranded DNA; aPL, antiphospholipid antibodies; ENAs, extractable nuclear antigens.
[a]Adapted with permission from Williams *et al.* [6].

observed (in 71% of cases) in a cohort of patients in one center [25]. It was also the most debilitating sign. Other rare and serious clinical characteristics may develop as adverse effects in patients on anti-TNF-α agents. These include serositis with pleurisy or pericarditis, pleural or pericardial effusions, deep venous thrombosis, life-threating pneumonitis, and neuritis (Table **2**) [18].

Table 2. Clinical Features of 33 Reported Cases with Anti-Tumor Necrosis Factor-*α* Induced Lupus Erythematosus[a]

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%

[a]Adapted with permission from Costa *et al.* [18].

Patients with ATIL may present with unusual manifestations that are even uncommon in idiopathic SLE. This requires clinical suspicion of ATIL in any patient presenting with unusual clinical findings, and invasive methods may be required to confirm the diagnosis. The prevalence of clinical manifestations and laboratory features in ATIL, drug-induced lupus erythematosus, and SLE as reported in three different studies is shown in Table **3** [5].

DIAGNOSIS OF ANTI-TUMOR NECROSIS FACTOR-A-INDUCED LUPUS

The clinical presentation of ATIL can vary. More so, specific diagnostic criteria have not yet been established. However, in most reported cases, the diagnosis was made based on the development of one or more symptoms consistent with SLE, ongoing exposure to an anti-TNF-α agent, no prior history of SLE, and resolution of symptoms when the offending drug was discontinued. The strict application of the American College of Rheumatology (ACR) criteria for idiopathic SLE would probably lead to the exclusion of ATIL in many patients receiving anti-TNF-α therapy. Therefore, for the purpose of early diagnosis, the following criteria can be considered [19]: (1) a temporal relationship between symptoms and anti-TNF-α therapy; (2) at least one serologic ACR criteria of SLE, for example, ANA, anti-dsDNA antibodies; and (3) at least one non-serologic ACR criteria, such as arthritis, serositis, hematologic disorder, or malar rash. Musculoskeletal symptoms are taken into account only if they reappear with other lupus symptoms in a patient in whom they had previously disappeared while receiving anti- TNF-α therapy. Isolated positive results for ANAs or anti-dsDNA antibodies are not considered diagnostic, given their high frequency in patients receiving this therapy.

APPROACH AND MANAGEMENT OF ANTI-TUMOR NECROSIS FACTOR-A-INDUCED LUPUS

The main approach in the treatment of ATIL is withdrawal of the offending drug. Symptoms resolve within three weeks to six months after withdrawal of the implicated drug [19, 25]. In addition to discontinuing anti- TNF-α therapy, many patients require traditional therapy for idiopathic SLE to achieve full resolution of their lupus symptoms. In one of the largest series of patients with ATIL, it was been reported that lupus-like symptoms disappeared in most of the cases after withdrawal of the drug [5]. Forty

Table 3. Prevalence of Clinical Manifestations and Laboratory Features in Drug-Induced Lupus Compared with Idiopathic SLE[a]

Feature	Anti-TNF-Related Lupus (%)	Procainamide-Related 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

Abbreviations: ANA, antinuclear antibodies; dsDNA, double-stranded DNA; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.
[a]Adapted from Ramos-Casals *et al.* [5].

percent of the patients also received corticosteroids, while 12% required additional immunosuppression with azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate or cyclophosphamide. One report describes the case of a patient with RA who developed lupus myositis after treatment with adalimumab. Treatment with pulse steroid therapy and two doses of rituximab resulted in complete remission of her symptoms, and she remained asymptomatic for 10 months on maintenance therapy, comprising hydroxychloroquine and azathioprine [26].

There is limited evidence that supports the safety of re-challenging patients who developed ATIL with alternative anti-TNF-α agents. There are several reported cases of ATIL that were re-challenged with the same or different agents, who had no recurrence [23, 25, 27]. Nevertheless, these findings should be interpreted cautiously, given the small number of patients who were re-challenged. In addition, some of these studies were conducted on patients with ATIL who had mild disease and few clinical findings. Consequently, the clinical decision to continue an alternative anti-TNF-α agent in patients who develop ATIL is hard to make, especially if there is severe and systemic involvement. More so, it is against the basic principles of safe practice to expose patients to the risk of developing another serious complication.

Most patients who develop ATIL have a good prognosis after discontinuation of the causative agent. Normalization of autoantibodies and resolution of lupus symptoms occur when the offending drug is discontinued, and there is no recurrence thereafter. In some patients, corticosteroids and immunosuppressive agents might be required to achieve full recovery as described above. However, patients who develop serious renal or neurological adverse events may have residual effects [5].

Physicians need to use biological agents known to cause ATIL with caution. It is not known whether ATIL and other autoimmune phenomena are contributing factors to the high rate of long-term drug failure or discontinuation of anti-TNF-α therapy [28]. Rigorous follow up and early recognition of any complication that develops while patients are receiving anti-TNF-α agents are essential to assure patient safety on the long-term. This should help clinicians learn more about these agents and identify appropriate approaches in the different clinical settings encountered. As the use of anti-TNF-α agents has become more widespread, the incidence of ATIL will likely also increase. There are currently no recommendations for the prevention of ATIL. It has been suggested that the concurrent use of immunosuppressive agents may reduce the incidence of autoantibody formation and thereby reduce the incidence of ATIL [14]. The 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 initiating anti-TNF-α therapy is an important aspect in the prevention process. The presence of SLE is considered a contraindication to the use of anti-TNF-α therapy. It is thus recommended to perform a thorough immunological screening for any patient with polyarthritis to assure accurate diagnosis. It is also recommended to perform a detailed immunological screening for any patient whom the physician is considering anti-TNF-α therapy for. Some recommendations have been suggested for each patient upon initiation of anti-TNF-α therapy. These recommendations will help in the therapeutic approach of autoimmune diseases induced by these biological agents [5]. 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 severe organ involvement (renal, pulmonary, or neurological), 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.

CONCLUSION

Anti-TNF-α agents are an important addition to treatment options for RA and other autoimmune disorders. Unfortunately, these agents have been documented to cause lupus-like syndrome with the appearance of new onset ANA and anti-dsDNA. Although it is unclear whether anti-TNF-α agents serve as an exacerbating factor of an underlying lupus or as a triggering factor of SLE, withdrawal of the offending drug remains the mainstay of therapy. Prognosis is good, with normalization of autoantibodies and resolution of the symptoms within a few months after cessation of the offending drug; however, the safety of re-challenging patients who develop ATIL with alternative anti-TNF-α agents deserves further exploration, as there is currently not enough evidence to support this fact.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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