Review

Anti-TNF-induced lupus

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The use of protein-based anti-TNF-α therapies such as antibodies and soluble TNF-α receptors is commonly associated with the induction of autoantibodies, whereas anti-TNF-induced lupus (ATIL) is rare. ATIL can occur with any of the available TNF inhibitors, but the frequency and clinical characteristics of ATIL vary between different drugs. Cutaneous, renal and cerebral involvement as well as dsDNA antibodies are more common in ATIL compared to classical drug-induced lupus (DIL), suggesting different pathogenic mechanisms of ATIL and DIL. True ATIL must be clinically differentiated from mixed CTD, SLE or overlap syndromes unmasked, but not induced, by anti-TNF-α treatment of unclassified polyarthritis. The pathogenesis of ATIL is still unknown. Concomitant immunosuppression can reduce autoantibody formation in ATIL, and withdrawal of anti-TNF-α therapy usually leads to resolution of symptoms. Steroids and/or immunosuppressive therapy may be required in severe cases.

KEY WORDS: Drug-induced, Lupus, Anti-TNF, Arthritis.

Background

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, PsA, AS and Crohn's disease. All currently available TNF-α-blocking drugs are recombinant proteins. Infliximab and adalimumab are anti-TNF-α antibodies and etanercept is a fusion protein of TNF-α receptor p75 and the Fc portion of human IgG1. All of these have a range of adverse effects in common, including the formation of autoantibodies and the development of drug-induced lupus (DIL) [1].

DIL was first described in 1945 as a complication of sulfadiazine therapy [2]. Over 80 medications have since been associated with development of DIL. While there are no formal diagnostic criteria for DIL, it is characterized by a milder disease course compared with classical SLE and the fact that DIL resolves spontaneously after the offending drug has been stopped. Some groups use relatively broad criteria including: one or more symptoms compatible with SLE; adequate and ongoing exposure to a specific drug; no prior history of SLE; and resolution of symptoms on cessation of the suspected precipitating drug [3]. Others also require the presence of ANA or anti-histone antibodies [4]. The most rigorous definition requires patients to meet 4 out of 11 ACR diagnostic criteria for lupus while exposed to a drug known to cause DIL [5, 6].

Anti-TNF-α therapies are the latest class of medications found to be associated with a 'lupus-like' syndrome. It is unclear at this stage whether these cases are 'typical' DIL or represent a distinct syndrome of 'anti-TNF-induced lupus' (ATIL). However, the severity of disease suggests that ATIL is a distinct syndrome induced by immunomodulatory treatment. Making this distinction is complicated by the different criteria used to diagnose DIL, as described above.

Induction of autoantibodies

Induction of autoantibodies by anti-TNF treatment was observed in the first clinical trials of infliximab for RA [7–9]. Pooled analysis of these initial open-label and randomized placebo-controlled trials showed that ANA positivity increased from 29% pre-treatment to 53% post-treatment [10]. Amongst RA patients treated with infliximab, 22 out of 156 (14%) developed anti-dsDNA antibodies [10]. The majority of these were IgM antibodies. One of the patients developed a reversible lupus-like clinical syndrome (0.6%) associated with IgM, IgA and IgG anti-dsDNA antibodies [10]. The development of autoantibodies has also been reported in patients receiving anti-TNF therapy for spondyloarthropathies and Crohn's disease [11–18].

Several prospective studies of patients receiving anti-TNF therapy have been performed with the objective of estimating the incidence of autoantibodies (Table 1) [11–25]. Frequent induction of ANA and dsDNA was observed amongst infliximab-treated patients with AS in some studies [14, 15], but not in others [20]. The concomitant use of MTX might have suppressed the induction of ANA and dsDNA antibodies in the spondyloarthropathy patients of the latter studies. However, other studies have not replicated these findings [26]. Compared with infliximab, etanercept was less associated with induction of autoantibodies in AS patients [15]. While it remains contentious whether infliximab, adalimumab and etanercept differ in the frequency with which they induce ANA and dsDNA autoantibodies, it is generally accepted that all three can do so (Table 1). Furthermore, more recent studies indicate that the specificities of anti-TNF-α-induced autoantibodies are not related to the patient's underlying diagnosis and that the anti-dsDNA autoantibodies are largely restricted to IgM class of antibodies, which are short-term and probably non-pathogenic. Other serological features of lupus appear to be rare (Table 1) [27].

Attempts have been made to identify the specificity of anti-TNF-induced ANA using multiplexed fluorescent microsphere immunoassay (MFMI), IIF and ELISA methods [28]. These studies revealed the presence of autoantibodies against SSB, RNP, Sm, Jo-1 and histones in some patients with RA and AS, with anti-SSB antibodies being slightly more common. Interestingly, all patients were negative for anti-ENA antibodies by the ELISA method and for anti-dsDNA by both IIF and MFMI [28].

A retrospective study of RA patients receiving infliximab or etanercept over a 3-year period found significant increases in

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TABLE 1. Occurrence of autoantibodies and ATIL in studies of the patients with RA, AS, PsA or Crohn's disease

Disease	Study	Anti-TNF given	ANA antibodies present, %	dsDNA antibodies present, %	Other antibodies, %	Number of patients with lupus features
RA	Erikkson et al., 2005 [19]	Infliximab	24 (baseline) 77 (30 weeks)	IgG antibodies: 2 (baseline), 66 (30 weeks)	10% anti-nucleosome (baseline); 24% at 30 weeks	2 (1—myalgia, arthritis, leucopenia, hypocomplementaemia, anti-histone; 1—rash, arthralgia, vasculitis, leucopenia, dsDNA, anti-nucleosome antibodies)
RA	De Rycke et al., 2003 [14]	Infliximab	51.6 (baseline) 82.3 (end)	0 (baseline) 11.3 (end)	1.6 anti-nucleosome (baseline), 8.1 (30 weeks); 6.5 ENAs (baseline), 12.9 (30 weeks)	0
RA	De Rycke et al., 2005 [15]	Infliximab	40.7 (1 year)	49.2 (1 year)	Anti-nucleosome antibodies in one patient; IgM aCL titres increased significantly	0
RA	Gonnet-Gracia et al., 2008 [16]	Infliximab/etanercept	Infliximab—43.6 (baseline), 73 (1 year); etanercept—58.5 (baseline), 53.3 (1 year)	Infliximab—0 (baseline) 9.5 (1 year); etanercept—20.7 (baseline) 5.1 (1 year)	NS	3 (2—infliximab given for chilblain lupus, 1—patient given etanercept)
RA	Fusconi et al., 2007 [21]	Infliximab/etanercept	Infliximab/etanercept—up to 100	Infliximab—78; etanercept—50	0	Not given. Switching anti-TNF, still similar results
RA	Atzeni et al., 2005 [18]	Infliximab	63.8	13	NS	NS
RA	Atzeni et al., 2005 [18]	Etanercept/ adalimumab	Etanercept—11; adalimumab—increased titres in 5.3	Etanercept—15; adalimumab—increased titres in 12.9	NS	NS
RA	Weinblatt et al., 2003 [22]	Adalimumab	11.1 (positive by week 24)	3.9 (positive by week 24)	NS	0
RA	Moreland et al., 1999 [23]	Etanercept	11	5 (> 6 months)	NS	0
RA	Weinblatt et al., 1999 [24]	Etanercept	NS	15	NS	NS
RA	Benucci et al., 2008 [25]	Infliximab/etanercept/ adalimumab	Infliximab—63.1; etanercept—51.1; adalimumab—44.8 (at 24 weeks)	Infliximab—10.5; etanercept—4.65; adalimumab—3.4 (at 24 weeks)	Anti-nucleosome/ANA 85.5% concordance	NS
AS	Gonnet-Gracia et al., 2008 [16]	Infliximab/etanercept	Infliximab—27.1 (baseline) 52% (1 year); etanercept—22.2 (baseline), NR at 1 year	Infliximab—0 (baseline), 2 (1 year); etanercept—22.2 (baseline), NR at 1 year	NS	0 0
AS	De Rycke et al., 2003 [14]	Infliximab	17.1 (baseline) 88.6 (end)	0 (baseline) 17.1 (end)	8.6 anti-nucleosome (baseline); 11.4 (34 weeks) 8.6 ENAs (baseline); 17.1 (34 weeks)	0
AS	De Rycke et al., 2005 [15]	Infliximab	61.8 (1 year)	70.6 (1 year)	Anti-nucleosome antibodies in 1 patient; IgM aCL titres increased significantly	0
AS	De Rycke et al., 2005 [15]	Etanercept	15 (1 year)	15 (1 year)	0	0
RA, AS and PsA	Bacquet-Deschryver et al., 2008 [17]	Infliximab/etanercept/ adalimumab	Infliximab—86.8; etanercept—6.2; adalimumab—50 (> 24 months)	Infliximab—1.8; etanercept—0; adalimumab—0 (> 24 months)	0	1 (rash, IgG dsDNA antibodies)
Crohn's	Vermeire et al., 2003 [11]	Infliximab	56.8 (24 months)	32 (24 months)	21% anti-histone positive (24 months)	2 (1.6%) developed DIL; no major organ involvement
Crohn's	Atzeni et al., 2005 [12]	Infliximab	8 (baseline) 42 (10 weeks)	17 (of ANA-positive patients at 10 weeks)	1.5 (of ANA-positive patients) ENA + anti-histone positive	1 (arthralgia, malar rash, dsDNA, no organ involvement)
Crohn's	Nancey et al., 2005 [13]	Infliximab	53 (1 year)	35 (1 year)	0	1 (symptoms not given)
Crohn's	Atzeni et al., 2005 [18]	Infliximab	49.1	21.5	NS	NS

NR: not reported; NS: not stated.

TABLE 2. Features of patients with ATIL based on case reports and case series to date

ACR diagnostic criteria for lupus	BSRBR data [47], (Britain) (n=41)	Costa et al., 2008 [31], (USA) (n=33)	Ramos-Casal et al., 2007 [45], (Spain) (n=72)	De Bandt et al., 2005 [44], (France) (n=12)
Malar rash, n (%)	_[a]	_[a]	_[a]	5 (42)
Discoid rash, n (%)	25 (61)[a]	24 (73)[a]	48 (67)[a]	0
Photosensitivity, n (%)	4 (10)	_[a]	_[a]	5 (42)
Oral ulcers, 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
Haematological disorder, n (%)	1 (2)	20 (61)	Cytopenia—16 (22)	6 (50)
Immunological disorder, n (%)	4 (10)	29 (88)	dsDNA—52 (72)[b] anti-Sm—7 (10)	11 (92)
Anti-nuclear antibodies, n (%)	13 (32)	32 (97)	57 (79)	12 (100)

[a]Data on cutaneous features not given; subdivided into individual categories. Also includes 'unspecified rash' as a category. [b]Individual patient data not listed, so unable to ascertain if some patients had more than one of these features.

ANA and ssDNA IgG antibody titres [29]. Interestingly, patients with high levels of ssDNA IgG more frequently had to discontinue infliximab treatment because of skin rashes or systemic anaphylactoid reactions. Three of these patients went on to develop dsDNA IgG antibodies and one developed a lupus-like syndrome.

Clinical characteristics of patients with suspected ATIL

In the first years after the introduction of anti-TNF, most cases of ATIL were reported in infliximab-treated patients with RA [10, 30–31], PsA or Crohn's disease [30–33]. The fact that etanercept [31, 34–41] and adalimumab [31, 41–43] became available after infliximab may explain the smaller numbers of ATIL cases reported with these agents. A few retrospective case series have been published (Tables 2 and 3) [31, 44–45]. A national survey of all French centres prescribing anti-TNF therapies for rheumatic disease described 22 patients with ATIL [44]. Ten patients developed isolated dsDNA autoantibody-positive cutaneous lupus and 12 had 'full-blown' DIL with at least 4 of the 11 ACR diagnostic criteria for SLE [5, 6]. The overall incidence of ATIL in this study was estimated to be 0.19% for infliximab-treated and 0.18% for etanercept-treated patients in France. Most patients with 'full-blown' ATIL had fever or other systemic features (75%). Other SLE symptoms were rash, arthritis, haematological abnormalities and autoantibodies (ANA and dsDNA) (Table 2). Serositis (25%) and myositis (33%) were slightly less common, and one patient had a cranial nerve deficit. None of the French patients had lupus nephritis. The frequency and distribution of ATIL features in the French survey were similar to those observed in case series in the USA and Spain [31, 45].

The frequency and type of ATIL symptoms in the 33 patients in the US case series [31] were compared with a previously described cohort of patients with classical DIL [46]. Systemic features such as malaise and fever, arthralgia, myalgia and pleurisy were common to both diseases, while cutaneous involvement seemed to be more common in ATIL than classical DIL (72% compared to 9–27%) [31, 45].

The US case series also found significant differences between classical DIL and ATIL with regard to autoantibody profiles (Table 3) [31, 45]. As previously known, classical DIL was strongly associated with ANA (>99%) and anti-histone antibodies (>95%), while anti-dsDNA antibodies were essentially absent (<1%) [31, 45]. In contrast, of the 33 ATIL cases only 57% were anti-histone positive, while 90% were anti-dsDNA positive [31]. Positive ENAs and hypocomplementaemia were also more common in ATIL compared with classical DIL in the US study.

The BSR Biologics Register (BSRBR) includes 11 394 anti-TNF-α patients followed for a total of 26 927 person-years, as well as a control group receiving only DMARD therapy [47]. Of these, 40 anti-TNF-α-treated patients developed a new lupus

TABLE 3. Autoantibody profiles of reported cases of ATIL/lupus-like syndrome

Autoantibody	Costa et al., 2008 [31], (Britain) (n=33)	Ramos-Casals et al., 2007 [45], (Spain) (n=72)	De Bandt et al., 2005 [44], (France) (n=12)
ANA, n (%)	32/32[a] (100)	57 (79)	12 (100)
dsDNA, n (%)	29/32 (91)	52 (72)	11 (92)
Histone, n (%)	16/28 (57)	NR	2 (17)
aPL, n (%)	NR	8 (11)	6 (50)
ENAs (any), n (%)	10/19 (53)	Anti-Sm 7 (10)[b] Anti-Ro/La 9 (12) Anti-RNP 5 (7)	5 (42)

NR: not reported. [a]ANA/dsDNA reported in only 32 subjects. [b]Unclear from data given whether some patients had more than one positive ENA or if these all occurred in separate patients.

event, compared to only one of the DMARD-treated patients [adjusted incidence rate ratio (aIRR) 3.17 (95% CI 0.38, 26.26)]. Although the number of events was small, there was a trend towards an increased incidence of lupus events in those receiving anti-TNF therapies. The most common lupus symptom was skin rash, whereas lupus nephritis or neuropsychiatric symptoms were not reported. This British study made no distinction between isolated cutaneous lupus or 'full-blown' ATIL.

Overall, the paucity of published case reports and small case series indicates that ATIL is a rare complication of anti-TNF-α treatment. CNS and renal involvement are rare in classical DIL, but were reported in 3% and 7%, respectively, of those patients included in the Spanish case series of patients with ATIL [45]. Renal involvement (nephritis) was even more common in the US case series, affecting 9% of patients with ATIL [31].

Proposed mechanisms for development of ATIL

Reduced TNF-α levels in New Zealand Black mice predispose the animals to severe lupus-like autoimmunity [48, 49]. Replacement therapy with recombinant TNF-α delays the development of lupus in these mice [50]. Following on from these findings in animal models, several different mechanisms have been proposed to explain the occurrence of lupus or lupus-like syndromes in patients treated with anti-TNF-α therapy. The 'cytokine shift' hypothesis proposes that pharmacological systemic blockade of TNF-α suppresses production of Th1 cytokines, thereby driving the immune response towards Th2 cytokine production, IL-10 and IFN-α. This change in cytokine balance would then induce a cascade of downstream events ultimately resulting in production of the autoantibodies and a lupus-like syndrome [16, 51–53]. Another hypothesis is based on the assumption that systemic inhibition of TNF-α could interfere with apoptosis, affect the

clearance of nuclear debris [19, 54–55] and thus promote autoantibody production against DNA and other nuclear antigens [19]. Similarly, TNF-α-induced apoptosis of mature cytotoxic T cells is an important mechanism for termination of T lymphocyte-driven responses. Anti-TNF-α therapy may interfere with this process and thereby promote autoantibody formation against nuclear antigens [56]. Alternatively, inhibition of cytotoxic T cells by anti-TNF-α therapy could reduce the elimination of autoantibody-producing B cells [57].

Some nuclear antigens, namely nucleosomes, become detectable in the plasma of RA patients after the start of anti-TNF-α therapy [58]. Interestingly, such a rise in plasma nucleosome levels might contribute to a break of tolerance and thereby induce autoantibodies in susceptible individuals [58]. This notion is supported by a recent study, which found that the occurrence of anti-nucleosome antibodies correlated strongly with the presence of ANA in anti-TNF-α-treated RA patients [25].

Treatment of ATIL

There are currently no recommendations for the prevention of ATIL in anti-TNF-treated patients. However, ATIL is preceded by the appearance of autoantibodies. It has been suggested that concurrent use of DMARDs might reduce the incidence of autoantibody formation and thereby reduce the incidence of ATIL. MTX can exert a suppressive effect on the production of autoantibodies in patients with isolated cutaneous lupus [59]. 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 [10, 19].

ATIL appears to respond to withdrawal of the anti-TNF therapy in most cases. The Spanish Study Group of Biological Agents in Autoimmune Diseases (BIOGEAS) reported that lupus-like symptoms in patients receiving anti-TNF-α therapy disappeared in 94% of cases after withdrawal of the anti-TNF-α therapy [45]. Forty per cent of the patients also received corticosteroids, while 12% required additional immunosuppression with MTX, LEF, AZA, mycophenolate or cyclophosphamide [45].

The BIOGEAS group stratified all Spanish 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 [45]. For mild disease, the group suggested the withdrawal of anti-TNF, but left open the option of continuing therapy under close supervision if the physician felt this was indicated. However, for severe disease the group suggested immediate cessation of the offending drug and the addition of corticosteroids and other immunosuppressive agents where appropriate. 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 [60].

Evidence for ATIL as a distinct clinical syndrome

Case series and single case reports support the notion that anti-TNF-α therapy can induce a lupus-like syndrome, which shares some features with classical DIL (Tables 2 and 3). Is it possible that anti-TNF-α therapy induced a change in the patients' disease from RA to SLE? It is recognized that patients may evolve from RA into SLE and vice versa [61]. In a large cohort of 1507 patients with RA and 893 with SLE, 7 were reported to initially have SLE and subsequently evolve into RA [62]. In a minority of patients, the two conditions have been reported to coexist as 'rhupus' [61]. The estimates for the occurrence of the rhupus in RA cohorts have varied from 1 out of 464 [61] to 6 out of 7000 [63] to 13 out of 1507 RA patients [62]. Panush *et al.* [63] found a prevalence of rhupus of 0.09% in their cohort of RA and SLE patients, which was estimated to be similar to the concurrence of RA and SLE by

chance (1.2%). Cohen and Webb [64] who described 11 cases of rhupus disagreed with that but did not carry out a statistical analysis. The estimated prevalences of rhupus and ATIL are similar, which might lead to speculation as to whether some RA patients diagnosed with ATIL had rhupus instead. However, this would still not explain the occurrence of ATIL in patients receiving anti-TNF-α drugs for AS, PsA or Crohn's disease.

Could it be that patients classified as ATIL in these studies actually had SLE presenting with prominent articular manifestations, which, following treatment with anti-TNF-α therapy evolved into 'full-blown' lupus? The fact that only one DMARD-treated patient but 40 anti-TNF-α-treated patients [aIRR 3.17 (95% CI 0.38, 26.26)] on the BSRBR developed a so-called 'lupus event' argues against this [47].

The future

The use of anti-TNF therapy has increased dramatically over the last decade. The occurrence of ATIL, however, has raised a number of issues regarding these therapies that require further research. First, are soluble TNF receptor fusion proteins and anti-TNF antibodies all equally likely to cause ATIL? Secondly, can patients with ATIL be safely switched to another anti-TNF? Furthermore, is the occurrence of ATIL sufficient justification for switching to another anti-TNF therapy? If not, should ATIL patients automatically be switched to an alternative treatment such as rituximab? In terms of preventing ATIL, will the concurrent use of MTX or HCQ with anti-TNF therapy reduce the likelihood of developing ATIL? Finally, two areas of research which may improve our understanding of the pathogenesis of SLE are: investigating whether inhibiting other cytokines also leads to ATIL; examining if the new biological therapies blocking other specific immune targets involved in the pathogenesis of RA using antibodies or soluble receptors produce ATIL?

Conclusions

Anti-TNF-induced autoantibodies are common following therapy with all of the currently available anti-TNF-α therapies. However, the incidence of 'full-blown' ATIL is rare. Nevertheless, cerebral and renal involvement has been reported more frequently in ATIL compared with classical DIL. The incidence/prevalence of dsDNA antibodies and hypocomplementaemia is also greater in ATIL, whilst anti-histone antibodies, the serological hallmark of classical DIL, are less commonly found. Due to the potentially serious complications of ATIL, screening for this prior to and during anti-TNF therapy might assume greater importance. If the diagnosis is suspected then anti-TNF therapy should be withdrawn unless symptoms are very mild.

Rheumatology key messages

- Autoantibody induction is common with anti-TNF but ATIL is rare.
- ATIL appears distinct from classical DIL with a phenotype more similar to idiopathic SLE.
- ATIL is generally self-limiting after stopping anti-TNF therapy but may require corticosteroids and immunosuppressives.

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