

Clin Rheumatol (2013) 32:1819–1822
DOI 10.1007/s10067-013-2361-9

CASE BASED REVIEW

A case of infliximab-induced lupus in a patient with ankylosing spondylitis: is it safe switch to another anti-TNF- α agent?

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Received: 1 June 2013 / Revised: 8 July 2013 / Accepted: 31 July 2013 / Published online: 17 August 2013
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Abstract Anti-TNF- α therapies are the latest class of medications found to be associated with drug-induced lupus, a distinctive entity known as anti-TNF- α -induced lupus (ATIL) (Williams et al., *Rheumatology (Oxford)* 48:716–20, 2009; De Rycke et al., *Lupus* 14:931–7, 2005; De Bandt et al., *Clin Rheumatol* 22:56–61, 2003). With the widespread use of these agents, it is likely that the incidence of ATIL will increase. The onset of ATIL in patients with rheumatoid arthritis and Crohn's disease has been described, but the literature regarding the occurrence of this entity in patients with ankylosing spondylitis (AS) is scarce (De Bandt et al., *Clin Rheumatol* 22:56–61, 2003; Ramos-Casals et al., *Autoimmun Rev* 9:188–93, 2010; Perez-Garcia et al., *Rheumatology* 45:114–116, 2006). To our knowledge, few reports of switching anti-TNF- α therapy after ATIL in AS have been reported (Akgül et al., *Rheumatol Int*, 2012). Therefore, it is not clear whether the development of ATIL should prohibit switch to another therapy, since patients may respond to another anti-TNF- α agent (Akgül et al., *Rheumatol Int*, 2012; Bodur et al., *Rheumatol Int* 29:451–454, 2009; Mounach et al., *Clin Exp Rheumatol* 26:1116–8, 2008; Williams and Cohen, *Int J Dermatol* 50:619–625, 2011; Ye et al., *J Rheumatol* 38:1216, 2011; Wetter and Davis, *Mayo Clin Proc* 84:979–984, 2009; Cush, *Clin Exp Rheumatol* 22:S141–147, 2004; Kocharla and Mongey, *Lupus* 18:169–7, 2009). A lack of published experience of successful anti-TNF- α switching is a cause of concern for rheumatologists faced with this challenging clinical scenario. We report the case of a 69-year-old woman

with AS who developed infliximab-induced lupus, which did not recur despite the subsequent institution of etanercept. The authors review and discuss ATIL and the possible implications for subsequent treatment with alternative anti-TNF- α agents.

Keywords Ankylosing spondylitis · Anti-TNF- α · Anti-TNF- α -induced lupus · Drug-induced lupus · Infliximab

Case presentation

A 69-year-old female patient, with active ankylosing spondylitis (AS) (according to the modified New York criteria), was referred to our department. The patient was initially treated with sulfasalazine and nonsteroidal anti-inflammatory drugs with an inadequate clinical response. Sulfasalazine was discontinued, and she was started on infliximab 5 mg/kg every 6 weeks with subsequent remission of the disease. Eight months after the initiation of infliximab, she gradually developed general malaise, dyspnea, and acute thoracic pain.

On admission, she presented with dyspnea on exertion, decreased breath sounds in the lung bases, and low arterial oxygen saturation (94 %). The patient did not have fever or skin lesions.

Laboratory investigations revealed positive titers of antinuclear antibody (ANA; 1:1,280), anti-double-stranded antibody (anti-dsDNA, 23.8 U/ml; normal, <4.2 U/ml), and anti-histone antibodies (45 U/ml; normal, <40 U/ml). Other anti-extractable nuclear antigens as well as anti-cardiolipin antibodies were negative. Additionally, C-reactive protein (CRP) was 13.7 mg/dl (normal, <0.5 mg/dl), and erythrocyte sedimentation rate (ESR) was 100 mm (normal, <20 mm/h). Full blood count, renal function, and serum C3 and C4 complement component levels were all within the normal range. Chest radiography revealed cardiomegaly and diffuse bilateral infiltrates. High-resolution computed tomography demonstrated pericardial and small bilateral pleural effusions.

The corresponding author certifies that all authors approved the entirety of the submitted material and contributed actively to the study.

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Cultures of bronchoalveolar lavage were negative for bacteria and fungi.

The diagnosis of infliximab-induced lupus-like syndrome was established, and this medication was discontinued. Under methylprednisolone (16 mg/day), diuretics, and oxygen therapy, the pericardial and pleural effusion regressed dramatically. Her general health status improved, and on the 30th day of treatment, CRP was 1.6 mg/dl, and ESR was 12 mm/h.

Twelve weeks later, she presented a severe flare of AS, with widespread peripheral arthritis. Methotrexate was initiated at increasing doses up to 25 mg/week, associated with methylprednisolone (6 mg/day). A repeat antibody profile showed that anti-dsDNA antibody titers had decreased (7.44 U/ml). At 6 months, her disease remained off control, and the patient was started on etanercept (50 mg/week). Her symptoms responded promptly to this medication. At the most recent evaluation (8 months after starting etanercept), the patient remained asymptomatic with no recurrence of lupus symptoms, with anti-dsDNA being undetectable.

Discussion

Most of the previously reported cases of switch therapy after anti-TNF- α -induced lupus (ATIL) occurred in patients with rheumatoid arthritis (RA), psoriatic arthritis, and Crohn's disease [3]. Only a few cases were reported in AS [6]. Our patient has tolerated the switch to etanercept without recurrence of ATIL, suggesting that its occurrence should not prohibit switching patients from one anti-TNF- α to another. The

presence of ATIL is less frequently observed in AS than in RA. The latest update of the Spanish Study Group of Biological Agents in Autoimmune Diseases (BIOGEAS) registry reported only ten (7 %) patients with AS, compared to 101 patients (72 %) with RA, in a total of 140 patients who developed ATIL [4]. Unfortunately, the total number of patients exposed to the risk per disease group is not provided in the publication.

ANA positivity after anti-TNF- α therapy is well documented in AS (over 50 % of infliximab-treated patients and 10 % of etanercept-treated patients); however, this phenomenon has not been associated with a greater risk of developing ATIL [4].

Hereafter, the authors highlight relevant questions for rheumatologists faced with this challenging scenario in clinical practice. To this purpose, we made a careful search and review of case series and single case reports published in the literature on patients who have received an alternative anti-TNF- α after ATIL (Table 1) [6–11]. A total of 15 cases were identified (including our patient).

Are the diverse anti-TNF- α agents associated with different risks of ATIL?

ATIL has been reported to occur with all anti-TNF- α agents, thus seemingly representing a class effect [1, 2]. A retrospective French national study of patients with rheumatic diseases on anti-TNF- α therapies estimated the incidence ATIL at around 0.19 % for infliximab-treated patients, 0.18 % for etanercept-treated patients, and 0.10 % for adalimumab-

Table 1 Summary of the reports describing patients treated with an alternative anti-TNF- α agent after ATIL

Article	Patient number	Diagnosis	Anti-TNF- α -inducing ATIL	Anti-TNF- α after ATIL	Time between the two therapies (months)	Follow-up (months)	Lupus symptoms recurrence
Cush [12]	1	RA	IFX	ADA	Nr	Nr	No
	2	RA	ETA	ETA	Nr	Nr	No
	3	Crohn's disease	ETA	ETA	Nr	Nr	No
	4	RA	ETA	ETA	Nr	Nr	No
Wetter and Davis [11]	1	Crohn's disease	IFX	ADA	38	6	No
	2	Crohn's disease	IFX	ADA	2	42	No
	3	RA	IFX	ETA	19	41	No
	4	RA	IFX	ADA	8	2.5	No
	5	Crohn's disease	IFX	ETA, IFX, ADA	0	2	Yes (arthritis)
Kocharla and Mongey [13]	1	Crohn's disease	IFX	ADA	13	9	No
Ye et al. [10]	1	RA	ADA	ETA	1	48	No
	2	RA	IFX	ETA	36	30	No
Williams and Cohen [9]	1	RA	ADA, ETA	Gol	0	6	No
Akgül et al. [6]	1	AS	IFX	ETA	1	3	No
This study	1	AS	IFX	ETA	6	6	No

IFX infliximab, ADA adalimumab, ETA etanercept, Gol golimumab, Nr not reported

treated patients [5]. Only one patient was reported to have developed ATIL while receiving certolizumab [2]. No cases were reported with golimumab.

As these biologic agents have similar mechanisms of action, it is difficult to understand the differences in the development of ATIL, but one of the hypothesis is that it may be due to differences in bioavailability, the stability of the drug/TNF complex, and possibly, the development of autoantibodies and antidrug antibodies [5].

Should the occurrence of ATIL impose the withdrawal of the causative anti-TNF- α agent?

BIOGEAS recently issued guidelines for the management of autoimmune diseases associated with anti-TNF- α [4, 5]. They recommend that the treatment should be tailored to the severity of individual clinical and immunological presentation. For mild involvement (general features, articular, or cutaneous), the group recommends withdrawal of anti-TNF- α therapy but allows the option of continuing therapy under close supervision if the physician feels this to be indicated. For severe involvement (pulmonary, renal, or neurological), the cessation of anti-TNF- α therapy together with the initiation of corticosteroids and other immunosuppressive agents is required.

Our patient developed severe pulmonary involvement with pericardial and pleural effusion, and we decided to stop the anti-TNF- α agent and to start oral glucocorticoids.

In general, ATIL presents with mild findings that improve within several months (mean, 2.9 months; range, 1–6 months) after stopping the anti-TNF- α therapy [5]. In our case, the ATIL developed 8 months after therapy, and its manifestations ceased within 3 months after discontinuation of infliximab, which is consistent with previous reports.

Can patients with ATIL be safely switched to an alternative anti-TNF- α agent?

There is limited evidence to support or refute the safety of switching to another anti-TNF- α agent (Table 1). However, 14 of the 15 patients who were switched to another anti-TNF- α after ATIL tolerated the new treatment without recurrence of lupus symptoms [6–13].

One report describes four patients who successfully received an alternative anti-TNF- α agent after ATIL, without recurrence of symptoms; three patients continued treatment with the causative anti-TNF- α agent (etanercept); and the fourth patient received adalimumab [12]. Wetter and Davis' describe 14 patients with ATIL, of which five were rechallenged with alternative anti-TNF agents. In four cases initially treated with infliximab, the switch was successful to adalimumab (three patients) and etanercept (one patient) [11]. The fifth of these patients, who represents the only published case of recurrence of ATIL after anti-TNF switch, was initially

treated with etanercept and failed the switch to both adalimumab and infliximab in separate attempts. Williams and Cohen reported recently a successful case of initiation of golimumab for 6 months after etanercept-induced lupus in a patient with RA [9].

Recently, another investigator reported a patient with AS who developed infliximab-induced lupus but did not recur after switching to etanercept [6].

Based in our review, the mean follow-up after the switch was 17.7 months (range, 2–48 months), with four (36 %) patients having at least 24 months of follow-up (Table 1) [6–13].

Are all anti-TNF- α agents equally safe as alternative agents?

Adalimumab (six patients) and etanercept (nine patients) were the two alternative agents chosen for the 14 patients who attempted to continue anti-TNF- α therapy. Successful switch to infliximab or rituximab has not been documented. On the basis of this scarce evidence available, etanercept and adalimumab would seem to be the agents of choice as alternatives to infliximab and, to each other, in the case of ATIL. However, these findings have to be interpreted cautiously.

Based on our review of the literature and experience, many patients with ATIL will tolerate another anti-TNF- α agent without recurrence. Thus, the condition seems to be drug specific rather than class related. Hence, this condition should not be taken as an absolute contraindication to an alternative anti-TNF- α agent, even if these patients should be carefully monitored for signs and symptoms of relapse.

Disclosures None.

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