LETTERS

**Adalimumab-induced lupus erythematosus in Crohn’s disease patients previously treated with infliximab**

The efficacy and safety profile of anti-tumour necrosis factor (TNF) α agents has led to their increasing use in inflammatory bowel diseases (IBD). Infectious complications and immunogenicity are the main drawbacks of these drugs. Among the latter, drug-induced lupus erythematosus (DILE) has been reported among infliximab but not adalimumab-treated IBD patients. We read with interest the article by Sandborn and coworkers (Gut 2007;56:1252–9), in which no cases of DILE among patients in the CLASSIC-I trial were reported, suggesting that this was less likely with adalimumab than infliximab. We would, however, like to report two cases that suggest that this optimistic viewpoint may not be justified.

**CASE 1**

A 29-year-old woman, with a history of autoimmune aortitis and steroid-dependent ileocolonic Crohn’s disease, started adalimumab because of persistent disease activity despite subcutaneous methotrexate, which was also maintained. She had a left hemicolectomy two years earlier and developed severe side effects to several drugs (acute pancreatitis to tiotiapirines, granulomatous hepatitis to mesalazine, inverted psoriasis to infliximab). After two years of maintained remission on adalimumab, she presented with diffuse myalgia and signs of arthritis in the hands and wrists. Serological studies revealed positive (1/2560) antinuclear antibodies (ANA), negative anti-double-stranded DNA, and positive antihistone. Adalimumab was discontinued and oral steroids and hydroxychloroquine were started, with a slow but progressive clinical recovery after four weeks.

**CASE 2**

A 45-year-old woman was diagnosed with colonic Crohn’s disease 17 years earlier. Seven years after diagnosis, she was successfully treated with methotrexate as a result of steroid dependency and thiopurine intolerance but she lost response five years later. Infliximab was then prescribed but a severe acute infusion reaction prompted its discontinuation after the third infusion, leading to the initiation of adalimumab. One year later, while remaining in remission on adalimumab and subcutaneous methotrexate, she developed disabling arthritis and erythema in both hands. ANA were positive (1/2560), with negative anti-dsDNA. Adalimumab was then discontinued and oral steroids were started together with hydroxychloroquine, with a slow improvement after four months.

The development of ANA after infliximab therapy is a well-known side effect, with an incidence ranging from 22% to 57%. 1 DILE is a rare event, however, even in patients with developing or pre-existing ANA, with a reported incidence of 1.6%. 2 DILE seems to occur less often in patients treated with adalimumab. In the CLASSIC-II trial, the incidence of ANA formation was estimated at 19% after one year and no cases of DILE were noted. It has been suggested that an increase of apoptotic particles and antigens from apoptotic cells, or the downregulation of the mechanisms that control B-cell hyperactivity and promote humoral autoimmunity, may be the potential pathogenic pathways of the induction of autoantibodies and DILE upon anti-TNF therapy.

In rheumatological diseases, in which there is a wider expension in the use of anti-TNF agents, a lower incidence of DILE has been reported. A French retrospective study on 7700 patients treated with anti-TNF agents for rheumatic diseases found an incidence of 0.19% of DILE among infliximab and etanercept users. 3 The BIOGEAS project, a registry of systemic autoimmune diseases, reported a total of 92 cases of lupus secondary to biological agents from January 1990 to December 2006, 15 of them associated with adalimumab. 4 In our own experience, DILE seems to be more prevalent among adalimumab-treated IBD patients than in those who receive only infliximab (2/12 vs 2/150, respectively). Previous exposure to infliximab may, however, be a potential risk factor for developing DILE when another anti-TNF agent is prescribed. DILE has been reported in another patient with rheumatoid arthritis who was switched to adalimumab after infliximab therapy and induced the development of anti-dsDNA. The authors suggested that adalimumab could have boosted the infliximab-induced mechanisms for anti-dsDNA development. 5 Baseline ANA (before infliximab treatment) were negative in both of our patients but they became positive at the time adalimumab was started, with concomitant anti-dsDNA in one of them.

In summary, gastroenterologists should be aware about the development of DILE in patients with infliximab-induced ANA who are switched to another anti-TNF agent.

**Author’s reply**

We read with interest the letter by Mañoasa and colleagues and thank the editors of Gut for the opportunity to provide a brief response.

Drug-induced lupus erythematosus (DILE) is a rare disorder infrequently observed during the treatment of patients with current anti-tumour necrosis factor (TNF) therapies for a variety of autoimmune diseases, including Crohn’s disease. In a published overview of the safety of adalimumab in the treatment of rheumatoid arthritis, for example, 13 cases of ‘lupus-like syndrome’ were reported during 12 406 patient-years of drug exposure. 6 In the comprehensive adalimumab clinical development programme for Crohn’s disease, investigators ascertained three cases of lupus or lupus-like syndrome with 1506 patient-years of exposure. 7 Of note is the fact that not all these patients met accepted diagnostic criteria for DILE. One patient was asymptomatic and diagnosis was based strictly on the development of a positive antinuclear antibodies (ANA) and anti-double-stranded DNA titre. Furthermore, symptoms in another patient were well controlled during continuing adalimumab treatment.

Mañoasa et al describe two patients who received adalimumab and developed symptoms consistent with DILE. Both patients had been treated earlier with infliximab and were negative for ANA before beginning infliximab therapy. These patients became symptomatic of DILE and were ANA positive one and two years, respectively, after initiating adalimumab therapy. It is not known, however, when these patients became ANA positive, as it appears these measurements were not conducted during or after infliximab therapy nor before adalimumab use. In both cases, anti-dsDNA measurements were negative, as described in the case reports.

The authors conclude that gastroenterologists should be aware of DILE development in patients with infliximab-induced ANA who are switched to another anti-TNF agent. We

**REFERENCES**


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