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Lack of Anti-drug Antibodies in Patients with Psoriasis Well-controlled on Long-term Treatment with Tumour Necrosis Factor Inhibitors

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Psoriasis treatment has undergone a revolution with the use of tumour necrosis factor-alpha (TNF-α) inhibitors. Three TNF-inhibitors are registered for treatment of psoriasis. Unfortunately, not all patients respond favourably to anti-TNF treatment. Some patients either do not respond at all or have insufficient response, while others respond initially, but have later relapses despite increased dosage and/or more frequent administration of the drugs. The mechanisms underlying these response failures are not entirely understood (1). Immunogenicity is indeed a potential hazard of all protein drugs, and there is evidence that repeated injections of biopharmaceuticals trigger anti-drug antibody (aDAb) responses in some patients. Few studies have examined aDAb in patients with psoriasis (2–5).

The aim of this study was to investigate the presence of aDAb/functional inhibitor levels in patients with psoriasis who have been well-controlled for > 18 months on 1 of the 3 TNF-inhibitors, along with functional blood levels of the drugs.

MATERIALS AND METHODS

A total of 45 patients with psoriasis vulgaris was randomly selected from among patients treated for > 18 months with adalimumab, etanercept or infliximab and seen at a standard visit at the clinic. Every patient answered the Dermatology Life Quality Index (DLQI) questionnaire. The severity of psoriasis was measured with the Psoriasis Area and Severity Index (PASI). Together with the standard safety blood test, a blood sample was drawn. The duration between last administration and blood sampling (days), other immunosuppressive treatment, previous biological treatment, drug dosage and duration of treatment (months) were recorded.

The blood samples were analysed at Biomonitor A/S (Copenhagen, Denmark) under blinded conditions. Two different radioimmunoassays (RIAs) were used: one quantified functional adalimumab, etanercept and infliximab levels as assessed by TNF binding, the other tested for aDAb towards adalimumab, etanercept and infliximab, respectively.

Adalimumab, etanercept and infliximab levels (TNF binding to serum IgG) were quantified by a slight modification of a previously described RIA (6, 7). The inter- and intra-assay variations were < 15% and < 10%, respectively. aDAb against adalimumab, etanercept and infliximab were determined by a slight modification of a previously described RIA (6, 7). As infliximab and adalimumab are IgG constructs consisting only of kappa light chains, and because etanercept does not contain any light chain, an anti-human lambda light chain antibody and, in the case of etanercept, an anti-human kappa and lambda light chain antibody were used to distinguish between free TNF inhibitor and TNF-inhibitor in complex with any class of lambda-containing human immunoglobulin or, in the case of etanercept, lambda/kappa-containing human immunoglobulin. The lower limit of detection of these assays was 10 laboratory units (U)/ml (laboratory standards of aDAbs were arbitrarily set at 100 U/ml), and the inter- and intra-assay variations were less than 20% and less than 10%, respectively.

Compared with frequently used bridging enzyme-linked immunoassays (ELISAs) for aDAb, which are extremely sensitive to the presence of drug (8), RIA is drug-insensitive and not affected by the levels of adalimumab, etanercept and infliximab found at the times of testing (6).

RESULTS

The characteristics of the patients and therapies are shown in Table I. The 15 patients treated with adalimumab and the 15 patients treated with etanercept all received a standard drug dosage. The 15 patients treated with infliximab received a median dose of 5.1 mg/kg (range 4.6–6.5 mg/kg) every 8 weeks (range 6–8 weeks). All patients included in the study responded well to treatment. PASI and DLQI values are shown in Table I.

The blood tests were planned to be drawn immediately before the next treatment with anti-TNF. For adalimumab, however, 3 patients had blood samples drawn 1, 2 and 4 days after the last administration. For etanercept, 4 patients had samples drawn one day and one patient 2 days after drug administration. For infliximab, one patient had a relatively short interval (7 days), between the last administration and blood sampling. None of the 45 patients had detectable aDAb. Functional trough drug levels were detected in all patients. Omitting the patients with short intervals between treatment and blood sampling did not change the result significantly. One of 15 patients (6.7%) treated with adalimumab, 2/15 (13%) treated with etanercept, and 10/15 patients (67%) treated with infliximab received concomitant immunosuppressive therapy. Nine of 15 patients (60%) treated with adalimumab, 5/15 (33%) treated with etanercept, and 2/15 (13%) treated with infliximab had previously received another biological treatment.

DISCUSSION

Our results show that aDAb against the 3 commonly used biological TNF-inhibitors could not be detected in the serum of our small group of psoriasis patients who were well-controlled > 18 months on these therapies. All patients included had detectable drug levels, which is in agreement with the fact that low levels of circulating drug before the next treatment is associated with failure of treatment and induction of aDAb (6, 9). Immunogenicity of

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Table I. *Characteristics of patients with psoriasis in anti-tumour necrosis factor (anti-TNF) treatment*

	Adalimumab ($n=15$)	Etanercept ($n=15$)	Infliximab ($n=15$)	Total ($n=45$)
Males/females, *n* (% males)	8/7 (53)	12/3 (80)	13/2 (87)	33/12 (73)
Age, years, median (range)	50 (26–74)	51 (22–79)	48 (29–80)	50 (22–80)
Body mass index, median (range)	30 (19–37)	27 (23–36)	27 (19–33)	27 (19–37)
Disease duration, years, median (range)	25 (10–49)	28 (7–66)	23 (11–65)	25 (7–66)
Patients with psoriasis arthritis, *n* (%)	7 (47)	8 (53)	3 (20)	18 (40)
Concomitant methotrexate, *n* (%)	1 (6.7)	2 (13)	9 (60)	12 (27)
Previously biological treatment, *n* (%)	9 (60)	5 (33)	2 (13)	16 (36)
Duration of treatment, months, median (range)	32 (17–58)	33 (17–72)	58 (18–120)	
Interval between last administration and blood sample, days, median (range)	9 (1–21)	6 (1–25)	53 (7–63)	
Psoriasis Area and Severity Index, median (range)	2.8 (0–7.2)	3.5 (0.8–10)	1.7 (0–5.1)	
Dermatology Life Quality Index, median (range)	1 (0–4)	1 (0–10)	0 (0–5)	
Drug concentration, µg/ml, median (range)	10 (2.3–24)	2.7 (0.2–6.6)	3.9 (1.1–15)	
Anti-drug antibodies concentration, U/ml	<10[a]	<10[a]	<10[a]	

[a]Lower limit of detection 10 U/ml.

TNF-inhibitors given to patients with rheumatoid arthritis or inflammatory bowel disease is well documented and associated with side-effects and therapeutic failure (1, 10–12). Concomitant treatment with immunosuppressive drugs seems to reduce, or at least postpone, the induction of anti-adalimumab or anti-infliximab aDAb. This has been suggested, at least partly, to be due to methotrexate-induced increased availability of infliximab (10).

In a large study of infliximab-treated psoriasis patients, efficacy of maintenance therapy was dependent on the achievement of stable serum infliximab concentrations, as indicated by a treatment regime with fixed intervals instead of a regime with treatment when needed. aDAb was also more common in the group who were treated as needed (4). In another study, aDAb to adalimumab was investigated in patients with psoriasis during 24 weeks of treatment. Antibodies were detected in 13 of 29 patients (45%) and were associated with lower serum adalimumab trough concentrations and loss of response to adalimumab (5). In a study of patients on long-term treatment with etanercept, aDAb was detected in 18% of the patients. The antibodies, however, did not have any apparent effect on safety or efficacy (3).

We have used a sensitive and specific RIA for semi-quantification of aDAb in serum and plasma (6, 7, 9). This assay has an important advantage compared with most enzyme immunoassays (EIAs), in that it is a fluid-phase assay, which is less susceptible to matrix effects and less likely to yield false-positive or false-negative results due to neo-epitope formation or epitope masking (13, 14).

Compared with most other patient groups receiving anti-TNF, treatment response is readily determined in patients with psoriasis and it is therefore easier for the clinician to discontinue treatment when the efficacy of a drug declines. Our results suggest that aDAb is not a problem and does not need to be measured in the selected group of continuously-treated psoriasis patients with well-controlled disease activity. However, in patients with loss of drug efficacy aDAb might be present and of importance. Further studies of this topic are required.

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