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CONCISE COMMUNICATION

Viewpoint on handling anti-TNF failure in psoriasis

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Abstract An association among the occurrence of anti-drug antibodies (ADAs), diminished trough serum drug levels (TSDLs) and non-response or loss of response has been described for several tumor necrosis factor alpha (TNF) blocking agents in a variety of diseases, including psoriasis. In a series of ten psoriasis patients with primary or secondary failure, or adverse reactions during anti-TNF therapy, we measured ADAs and TSDLs in patient serum using radioimmunoassay and ELISA, respectively. By proposing a treatment algorithm derived from research in this field, we show that measuring ADAs and TSDLs in psoriasis patients provides a more structured approach to clinical decision making for psoriasis patients who fail anti-TNF therapy.

Keywords Psoriasis · Biologics · Anti-TNF · Immunogenicity · Anti-drug antibodies (ADA) · Drug trough levels

Introduction

Biologic agents such as the tumor necrosis factor alpha (TNF) antagonists etanercept, adalimumab and infliximab, as well as the interleukin (IL)-12/IL-23 antagonist ustekinumab, are available for the treatment of moderate to severe plaque psoriasis [9]. Although these biologics have proven to be highly efficacious, a significant number of patients will discontinue their first biologic because of primary failure (lack of initial efficacy), secondary failure (loss of efficacy with time) or because of adverse reactions [16]. For clinicians considering the treatment options for a patient who has failed one TNF antagonist, it remains a challenge to determine the optimal next therapeutic step. In current clinical practice, drug switching is carried out without the knowledge of factors that may explain the failure.

An association between the occurrence of antidrug antibodies (ADAs), diminished trough serum drug levels (TSDLs) and non-response or loss of response has been described for several biologics in a variety of diseases, including psoriasis [3, 14, 25]. Nevertheless, studies investigating immunogenicity in psoriasis are scarce, and most of our current knowledge comes from studies in patients with rheumatoid arthritis (RA) or Crohn's disease [14]. By presenting ten cases of psoriasis patients with primary or secondary failure, or adverse reactions to a TNF antagonist and reviewing relevant articles, we want to show the clinical relevance of measuring TSDLs and/or ADAs in psoriasis patients and how this can direct a clinician's decision making.

Materials and methods

Ten patients with primary or secondary failure, or adverse reactions to a TNF antagonist (infliximab, etanercept, adalimumab) were seen at the Department of Dermatology at the Ghent University Hospital. Treatment success was defined as achieving PASI 75 and treatment failure when PASI 50 was not achieved, according to the European consensus guidelines [22]. Serum was collected at drug trough level (just before next administration of the drug), and the samples were analyzed at The Laboratory for Monoclonal Therapeutics, Sanquin Diagnostics, Amsterdam (the

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Netherlands). ADAs were detected by radioimmunoassay (RIA) and TSDLs were measured by enzyme linked immunosorbent assay (ELISA). The antibody test was considered positive when antibody concentrations exceeded 12 AE/ml. Therapeutic TSDLs are: adalimumab ≥5 μg/ml, infliximab ≥1 μg/ml and etanercept ≥2 μg/ml (values provided by Sanquin Diagnostics, Amsterdam, the Netherlands).

Results

Primary failure

Patient 1 did not respond to treatment with adalimumab and had a pronounced psoriasis exacerbation after 20 weeks. Anti-adalimumab antibodies were negative, and TSDLs were adequate (13 μg/ml). We continued treatment and after 24 weeks PASI 50 was achieved, and PASI 100 after 35 weeks.

Patient 2 had not achieved PASI 75 after 16 weeks of treatment with adalimumab. Testing showed no ADAs and adequate TSDLs (7 μg/ml). Finally, after 21 weeks of treatment, PASI 75 was achieved. Unfortunately, 8 weeks later, psoriasis relapsed. With addition of methotrexate (MTX) 7.5 mg/week, PASI 75 was achieved after 2 months. The patient is currently still in remission (1 year and 9 months later).

Secondary failure

Patient 3 received adalimumab treatment for 1 year, stopped treatment for 6 weeks, and was subsequently non-responsive to treatment for the following 7 months. Anti-adalimumab antibodies (800 AE/ml) were present in the patient's serum at this point in time, yet TSDLs were undetectable as treatment had already been interrupted. Therapy was subsequently switched to ustekinumab, and PASI 100 was achieved after 12 weeks.

Patient 4 rapidly responded to adalimumab, but became non-responsive after 9 months. Temporary addition of MTX 5 mg/week (3 months) had no effect. Anti-adalimumab antibodies were detected (18 AE/ml), but TSDLs were within therapeutic range (14 μg/ml). Therapy was switched to infliximab, but treatment was prematurely discontinued (see adverse reactions). Good clinical response was achieved by switching to ustekinumab.

Patient 5 achieved a PASI 75 during treatment with infliximab and MTX (5 mg/week), but became non-responsive after 7 months. TSDLs were subtherapeutic, but no ADAs were detected. A good clinical response was achieved using ustekinumab. After 2 years treatment with infliximab, Patient 6 also became non-responsive but no ADAs were detected and TSDLs were therapeutic (17 μg/ml). Addition of MTX (5 mg/week) was sufficient to achieve disease control.

Patient 7 was successfully treated with etancercept for 2 years, after which psoriasis relapsed. Switching to adalimumab restored clinical response, but after 4 months psoriasis exacerbated again. Anti-adalimumab antibodies were positive (24 AE/ml). Readministration of etanercept for 18 months was unsuccessful. No anti-etanercept antibodies were detected, but TSDLs were subtherapeutic (0.3 μg/ml). Dose escalation (2 × 50 mg/w) did not improve efficacy. By switching to ustekinumab, PASI 75 was finally achieved.

Patient 8 became non-response to infliximab therapy after 1 year. Anti-infliximab antibodies were positive (2,900 AE/ml). Psoriasis improved by switching to etanercept, but the patient became non-responsive after 1.5 years of treatment. No anti-etanercept antibodies were detected. Subsequent treatment with ustekinumab was successful.

Adverse reactions

Patient 4 developed nausea, flushing, itching during infliximab infusion and treatment was subsequently terminated. No anti-infliximab antibodies were detected (1 year later).

Patient 9 developed a skin rash after 4 weeks etanercept treatment. This skin rash was pathologically scored as a vacuolopathic parakeratotic interphase dermatitis, indicating a toxic reaction to medication. No anti-etanercept antibodies were detected. Good clinical response was achieved with ustekinumab.

Patient 10 developed erythroderma during etanercept treatment. No anti-etanercept antibodies were detected. Therapy was switched to infliximab, but after two successful treatment years, psoriasis relapsed with the development of anti-infliximab antibodies (230 AE/ml). Switching to ustekinumab gave good disease control.

Discussion

In the 2 patients we describe with *primary failure* (patient 1 and 2), testing showed adequate TSDLs and no ADAs. Findings in RA patients suggest that the absence of ADAs in non-responders might reflect a lack of responsiveness to the mechanism of action shared by all anti-TNF agents and indicates the need to switch to a drug with a different mechanism of action [3, 11]. Accordingly, in patient 1 and 2, a switch to ustekinumab would be recommended (see Fig. 1a). Although some authors have showed the effectiveness and tolerability of switching between biologics in

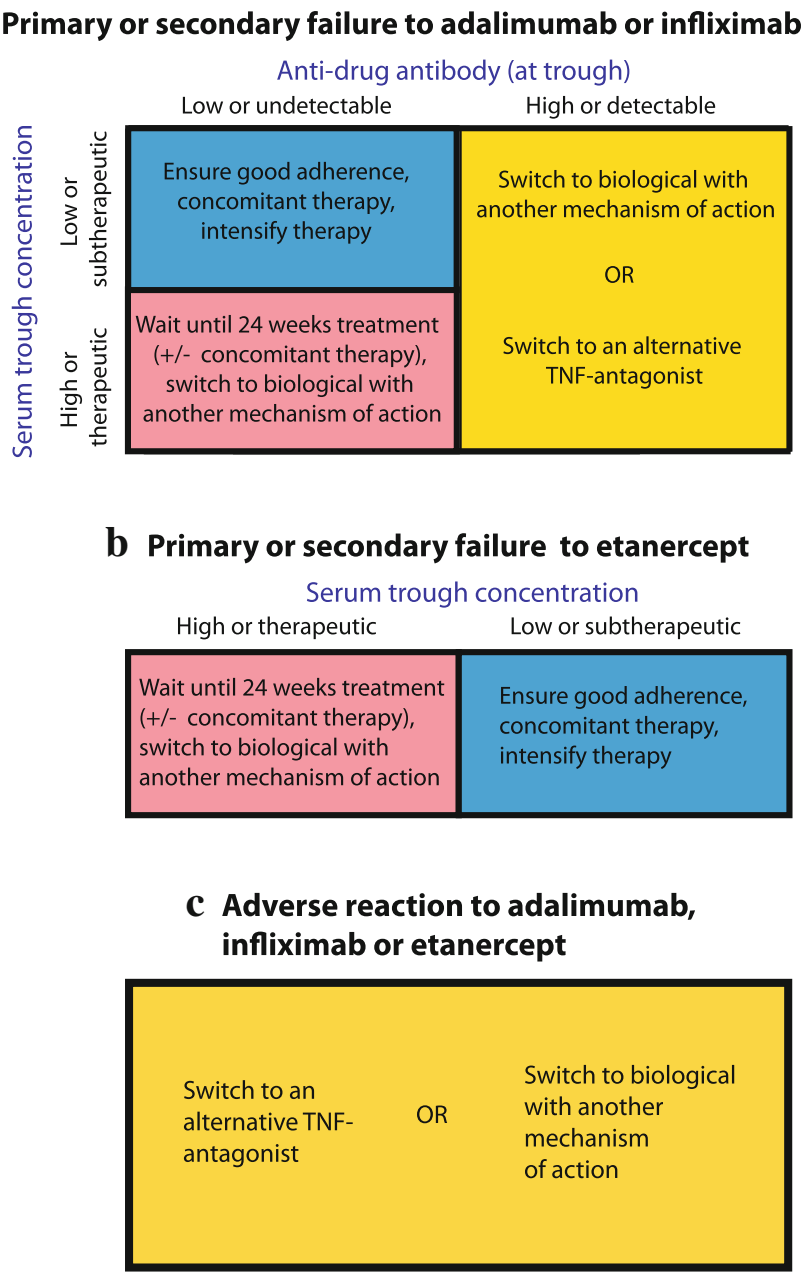

Fig. 1 Proposed treatment algorithm for psoriasis patients with primary or secondary failure, or adverse reactions to TNF antagonists **a** Primary or secondary failure to adalimumab or infliximab. Combining the results of trough serum drug levels (TSDLs) and anti-drug antibodies (ADAs) results in the following options: if the TSDLs are low, and no ADAs are detected, it is firstly important to ensure a good adherence. Concomitant treatment or intensification of treatment (increasing dosage or decreasing treatment interval) can be considered. In the case of therapeutic TSDLs without ADA formation, we recommend to wait until 24 weeks of treatment has passed before switching to a biologic with another mechanism of action. Concomitant therapy may be considered. When ADAs are present, both switching to an alternative TNF antagonist or a biologic with another mechanism of action are good options. **b** Primary or secondary failure to etanercept. In patients treated with etanercept, ADAs are reported to be non-neutralizing, and therefore only TSDLs are considered. If TSDLs are within the therapeutic range, we recommend switching to a biologic with another mechanism of action after a treatment period of 24 weeks. Concomitant therapy may be considered. In the case of low or subtherapeutic TSDLs, intensification of treatment, ensuring a good adherence, and/or concomitant therapy may enhance efficacy. **c** Adverse reaction to adalimumab, infliximab or etanercept. In the case of adverse reactions, the value of ADA or TSDL testing is questionable. Both a switch to an alternative TNF antagonist and a biologic with another mechanism of action are good options

psoriasis patients [13], it is not recommended to switch too often as intermittent treatment or re-exposure after a treatment free interval may be associated with an increase in immunogenicity [1, 15]. The National Institute for Health and Clinical Excellence (NICE) recommends evaluating the treatment success of biologics at 10 weeks for infliximab, 12 weeks for etanercept and 16 weeks for both adalimumab and ustekinumab [24]. However, in several studies, even more patients achieved PASI 75 after 24 weeks [17, 18, 21, 23]. Therefore, we recommend waiting at least 24 weeks before concluding the treatment is not working, particularly when ADAs are not detected, to avoid potentially unnecessary switching. Concomitant treatment may be considered as this may enhance efficacy [24] (Fig. 1a, b). Accordingly, as in patient 1 and 2 no ADAs were detected and TSDLs were adequate, we extended treatment and no switch was required as both patients achieved PASI 75 at 24 weeks.

In patients 3 and 4, *secondary failure* was associated with anti-adalimumab antibodies. Based on the literature, a switch to another TNF antagonist can be efficacious in such cases, as ADAs do not crossreact [3, 11, 16] (Fig. 1a). Unfortunately, patient 4 developed an infusion reaction during the first administration of infliximab, and therapy was switched to ustekinumab with good response.

Patient 5 became unresponsive to infliximab treatment. No ADAs were detected, but infliximab serum levels were subtherapeutic. In patients with subtherapeutic concentrations, infliximab dose escalation (i.e. increasing the dose or shortening of the administration interval between infusions) has been associated with a significantly increased clinical response compared to changing to another anti-TNF [2]. Another study also reported dose escalation to be a good choice in patients negative for ADAs with low serum infliximab levels [26]. Unfortunately, due to governmental reimbursement restrictions, dose escalation could not be performed in our patient. Patient 6 also became unresponsive to infliximab. No ADAs were detected, and TSDLs were therapeutic. Detectable infliximab trough concentrations have been associated with better clinical remission rates [19], but as discussed earlier; addition of concomitant treatments may enhance efficacy [8, 24]. Therefore, we decided to maintain the treatment dosing schedule in our patient, but additionally prescribed MTX (Fig. 1a) which resulted in an improved treatment efficacy.

In patient 7, readministration of etanercept therapy after adalimumab failure was not successful. No ADAs were detected, but TSDLs were subtherapeutic. Potential explanations for low TSDLs without ADA formation include patient non-compliance, or an inadequate drug dosage for the degree of inflammation as has been described for infliximab [7, 26]. Thus, patient 7 was treated with an increased dose of etanercept. Unfortunately, the patient remained non-responsive. Similarly, in patient 8, switching to etanercept after previous TNF-antagonist failure was not successful. Although etanercept may represent an effective and well-tolerated alternative treatment for psoriasis patients who have failed to respond to other therapies (traditional or biologic), it has been reported that etanercept was more effective in biologic naive patients [20]. However, the rate of response to a second TNF antagonist is usually inferior to that of the first [16]. On the other hand, patients who discontinued their first anti-TNF agent due to *adverse effects* are more likely to respond to another TNF antagonist than those who experienced inefficacy [10]. Adverse reactions were observed in patients 9 and 10 during treatment with etanercept. Patient 10 indeed responded well to a switch to infliximab. However, after 2 years, ADAs against infliximab developed and therapy was switched to ustekinumab. In patient 9, therapy was immediately switched to ustekinumab. Patient 4 developed an acute infusion reaction to infliximab. No anti-infliximab antibodies were detected (1 year later). Although anti-infliximab antibodies may favor the occurrence of infusion reactions, their presence is not specific [4].

From a clinical and economic perspective, testing of ADAs and TSDLs may not be worthwhile in the case of

Table 1 Trough serum drug levels and anti-drug antibody levels of 10 psoriasis patients

Patient	Biologic agent	TSDLs[a] (μg/ml)	ADAs[b] IgG totaal (AE/ml)	Primary (P) or secondary (S) failure, or adverse (A) reaction
1	Adalimumab	13	<12	P
2	Adalimumab	7	<12	P
3	Adalimumab	*<0.002*	800	S
4	Adalimumab	14	18	S
	Infliximab	*N/A*	*<12 (after 1 year)*	A
5	Infliximab	0.7	<12	S
6	Infliximab	17	<12	S
7	Adalimumab	*<0.002*	24	S
	Etanercept	0.3	<12	S
8	Infliximab	*<0.002*	2900	S
	Etanercept	3	<12	S
9	Etanercept	*<0.007*	<12	A
10	Etanercept	*<0.002*	<12	A
	Infliximab	*<0.002*	230	S

Italic blood drawn after discontinuation of treatment

[a] Therapeutic TSDLs adalimumab ≥5 μg/ml, infliximab ≥1 μg/ml, etanercept ≥2 μg/ml (values provided by Sanquin Diagnostics, Amsterdam, the Netherlands)

[b] ADAs positive >12 AE/ml

adverse reactions as switching is the only option in the case of severe adverse reactions [15]. In such a setting, different TNF-antagonists or biologics with different mechanisms of action are viable treatment alternatives (Fig. 1c).

In none of the patients treated with etanercept (patients 7, 8, 9 and 10), ADAs against the drug were detected. In general, anti-etanercept antibodies have only been reported scarcely [6]. However, two studies in RA patients showed that non-responders to etanercept obtain lower serum drug levels compared to responding patients [5, 12]. Therefore, in etancercept-treated patients, we suggest to only consider testing of TSDLs. In the case of subtherapeutic etanercept trough levels, we propose the etanercept dosage to be increased. In the case of therapeutic trough levels, a switch to another class is recommended (Fig. 1b).

Despite some methodological shortcomings with respect to blood samples drawn from patients post-treatment (see Table 1), we show that measuring ADAs and/or TSDLs can guide a dermatologist's decision-making process in a more pragmatic way. Looking at TNF antagonists from a pharmacological point of view (measuring therapeutic trough levels and titrate dose accordingly) is rather new, and could in the future help us to dose these drugs in a more cost effective manner (e.g., in case of good response and high trough levels one could lower the dose of drug).

In conclusion, we show on a case-by-case basis that measuring ADAs and TSDLs can optimise biologic treatment in psoriasis patients. Our report provides a first step towards a more structured approach when dealing with non-response or loss of response to biologics. Our preliminary treatment algorithm provides a new viewpoint, which encompasses the currently available literature. Further research is needed to clarify its applicability to improve the outcomes of patients treated with TNF antagonists.

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Conflict of interest None.

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