Table 2
Identification and characterization of the autoimmune thyroid disorder.

Symptoms revealing the thyroid disorder onset	
Symptoms	Number of cases ($n = 11$)
Fever	2
Weight loss	3
Asthenia	9
Tachycardia	4
Cardiac arrhythmia	1
Arterial hypertension	1
Goiter	1
Neck pain	1
Exophtalmos	1
Tremor	1

Paraclinical data identifying the autoimmune nature of the thyroid disorder	
Data	Number of cases ($n = 11$)
Hyper/hypo/euthyroidism	8/1/2
Anti-Thyroid peroxidase antibodies positivity	9
Thyroid stimulating antibodies positivity	5
Anti-thyroglobulin antibodies positivity	4
Positive ultrasonography	7
Positive scintigraphy	2

genicity of these patients towards their TNF-alpha blocking drug. The idea of a crossed-immunogenicity between the thyroid and the known immunogenicity of TNF-alpha blocking agents had already been suggested before [8].

It has already been shown that concomitant immunomodulating treatments can reduce immunogenicity of biologics [9]. It is interesting to note that our patients were either exclusively treated by anti-TNF-alpha drugs or with an associated low-dose of methotrexate for three of them, further emphasizing the possible link between AITD onset and TNF-alpha blockers' immunogenicity. Although drug causality is a difficult issue to address, this case series raises a legitimate suspicion that TNF-alpha blockers could be involved in the onset of AITDs as it has already been described for other immune-modulating drugs [10].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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TNFRII polymorphism is associated with response to TNF blockers in rheumatoid arthritis patients seronegative for ACPA

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1. Introduction

The advent of TNF inhibitors drugs has presented a huge therapeutic step forward in the treatment of rheumatoid arthritis (RA). However, after 10 years of use, the effect of these biologics remains very heterogeneous and unpredictable. Thus, identification of biomarkers to determine response to treatment is crucial for an optimized therapeutic strategy [1]. We aimed to evaluate 14 genomic biomarkers as predictors of the response to anti-TNF drugs in patients with RA.

2. Methods

Ten candidate genes (13 SNPs and one VNTR) were analyzed: IL1RA, IL10, LTA, TGFB1, TNF, TNF receptor II, TRAF1-C5, STAT4, TNFAIP3 and PTPN22. The principles of genotyping have been previously described [2]. We retrospectively included 59 RA patients, fulfilling the 2010 ACR/EULAR criteria (American College of Rheumatology/EUropean League Against Rheumatism) [3]. These patients were all followed in the university centre of Montpellier. The study was approved by the local ethics committee (Comité de Protection des Personnes Sud Méditerranée IV). Response to anti-TNF drugs was performed 6 months after the last anti-TNF use. A patient was considered to be a responder if the physician investigator decided to extend their treatment according to EULAR international guidelines [4].

3. Results

Baseline characteristics of RA patients are summarized in Table 1. After 6 months, 73% of the patients were responders. None of the 14 polymorphisms showed a significant association with response to anti-TNF therapy (Fisher's exact test, p value > 0.05). Only T/T genotype for TNFRII-codon 196 appeared to be more frequent in responders ($p = 0.129$).

Among the subset of RA patients without ACPA (15 patients), a significant association was found between the T/T genotype for TNFRII-codon 196 and response to treatment ($p = 0.0170$) (Table 2). A bootstrap test was performed to assess the robustness of this result. After random sampling of the table one thousand times, p value remained significant in 68% of cases. The same genotype was combined with other SNPs to get a better discrimination. This analysis was performed by pair of SNPs: SNP TNFRII x SNPX (with X ≠ TNFRII). Only SNP pair TNFRII x IL10-1087 ($p = 0.017$) and SNP pair TNFRII x LTA + 720 ($p = 0.022$) yielded significant results. For both combinations, RA patients without ACPA and holders of homozygous genotypes T/T for TNFRII-codon 196 with A/A for IL10-1087 or C/C for LTA + 720 responded significantly better to treatment with anti-TNF drugs.

Table 1
Baseline characteristics of RA patients in the global population of the study and with or without the presence of ACPA.

Variables	Global Population	ACPA +	ACPA –
Patients, N	59	41	15
Age (years), median [min-max]	58 [24–80]	58 [24–80]	56 [39–70]
Female, %	81	82.9	80
Ethnic			
Caucasian, %	93.2	92.7	93.3
North Africa, %	6.8	7.3	6.7
Disease duration (years), median [min-max]	17 [4–59]	16 [4–59]	16 [7–34]
RF positive, %	64.4	84.6*	6.7*
ACPA positive, %	66.1		
Erosive status, %	79.7	82.9	73.3
Naive biologics, %	40.7	39	40
Prior use of anti-TNF drugs			
1, %	44.1	46.4	40
2, %	15.3	14.6	20
Concomitant therapy			
Steroids, %	50.8	53.7	33.3
DMARDs, %	71.2	63.5	73.3
MTX, %	45.8	41.5	33.3
Anti-TNF drugs during the study			
Adalimumab, %	37.5	43.9	26.7
Etanercept, %	37.5	34.1	40
Infliximab, %	25	22	33.3
Responders at 6 months, %	72.3	75.6	66.7

N: number; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; DMARDs: disease modifying anti-rheumatic drugs; MTX: methotrexate.
* $P < 0.05$.

Table 2
Distribution of different genotypes depending on the response to anti-TNF drugs in patients without ACPA (15 patients, Fisher's exact test).

SNP	Genotypes	Responders	Non responders	*P* value
LTA + 720	A/A	1 (10%)	0 (0%)	0.720
	A/C	5 (50%)	4 (80%)	
	C/C	4 (40%)	1 (20%)	
IL10-1087	A/A	3 (30%)	1 (20%)	0.776
	A/G	5 (50%)	4 (80%)	
	G/G	2 (20%)	0 (0%)	
TNFRII-codon 196	G/G	0 (0%)	1 (20%)	0.017[a]
	G/T	1 (10%)	3 (60%)	
	T/T	9 (90%)	1 (20%)	

SNP: single nucleotide polymorphism; IL10: interleukin 10; LTA: Lymphotoxin alpha; TNFRII: TNF receptor type 2.
[a] Significant by false discovery rate correction.

4. Discussion

Despite the methodological limitations related to retrospective collection and small sample size, our study emphasizes the importance of combining a biomarker of RA severity (ACPA) with one or more genetic polymorphisms such as SNPs (TNFRII, LTA + 720 and IL10-1087) to predict the response to anti-TNF drugs as suggested by several recent studies [5–7]. There seems to be a common genetic determinant for the response to the class of anti-TNF drugs [8–10]. These encouraging results need to be explored in a larger cohort of patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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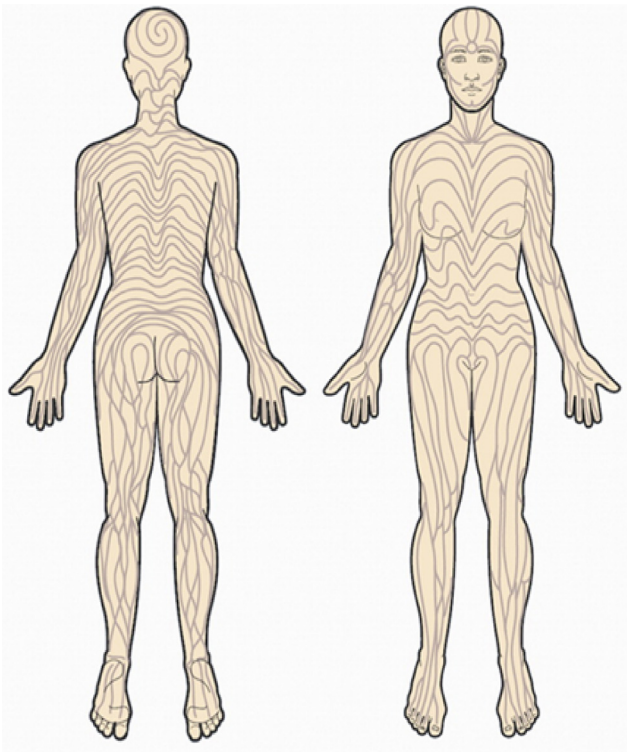

Fig. 1. Lines of Blaschko (from New England Journal of Medicine, Ivan V et al., 2012;367:24–7).

Blaschkitis under certolizumab for rheumatoid arthritis

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Blaschkitis is a rare inflammatory skin condition presenting as pruritic papules and vesicles along multiple Blaschko's lines over the whole body and affecting adults. Lines of Blaschko represent pathways of epidermal cell migration and proliferation during foetal development and reflect the existence of cutaneous mosaicism [1]. They do not follow any known nervous, vascular or lymphatic structures in the skin (Fig. 1). They represent a pattern followed by many skin disorders including epidermal naevi, linear psoriasis, linear cutaneous lupus erythematosus or linear morphea [1]. The aetiology and physiopathology of Blaschkitis remain unknown. Histological examination shows spongiotic dermatitis. The lesions often disappear spontaneously in a few weeks, sometimes leaving transient hypopigmentation, but may reoccur several times [1]. TNF blockers are a milestone in the treatment of rheumatoid arthritis (RA). Some paradoxical events have been described during treatment with TNF-α blockers, notably skin diseases such as psoriasis [2].

A 40-year-old woman was diagnosed at the age of 26 with nonerosive, ACPA positive, rheumatoid-factor-negative RA. In her personal and family history no skin diseases, including psoriasis and atopy, were reported. Initially she received hydroxychloroquine, followed by methotrexate with poor results. Finally certolizumab pegol, a TNF-α blocker, was started in combination with methotrexate in accordance with the standard protocol. After two months of TNF-blocker therapy, the articular symptoms rapidly improved but she developed an acute linear inflammatory non-pruritic rash on her left lower limb following Blaschko's lines (Fig. 2). She did not receive any rash-causing medication. The inflammatory markers were normal (CRP 3 mg/L, VS 11 mm after the first hour). The antinuclear antibodies and anti-native-DNA antibodies were negative. No biopsy was performed because of the typical clinical presentation of blaschkitis. Because of the self-limited course of the eruption and the high efficacy of certolizumab, treatment was pursued. Three months later, the rash disappeared spontaneously without any sequelae.

To our knowledge, this is the first case of blaschkitis occurring with certolizumab. Several cases of dermatoses following Blaschko's lines occurring during anti-TNF therapy have previously been described: adalimumab (one case) [3], infliximab (one case) [4] both prescribed for extended psoriasis, and etanercept, (a patient treated for RA) [5]. Certolizumab is a recombinant humanized pegylated monoclonal antibody. Like other TNF-α blockers, it could paradoxically cause inflammatory skin disorders such as psoriasis. One possible explanation is that artificial TNF-α blockade may disturb the cytokine balance between TNF-α and interferon alpha, which plays a central role in lichenoid reactions [6]. Many skin eruptions, including certain epidermal nevi, linear psoriasis, and linear cutaneous lupus erythematosus, may follow Blaschko's lines. In our patient, Blaschko-linear psoriasis or lichen planus could also be the differential diagnosis. Such a case raises the issue of the causative role of certolizumab in the occurrence of the blaschkitis. The spontaneous resolution of the blaschkitis without stopping the TNF-α blockade could also indicate that certolizumab is not solely responsible. A viral infection or environmental