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ORIGINAL ARTICLES

Immune-mediated skin lesions related to biological disease-modifying antirheumatic drugs

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ABSTRACT

Introduction: Immune-mediated skin lesions (IMSL) can be very disabling leading to treatment discontinuation. Although these lesions have rarely been previously described, the true incidence is unknown. Objective: To explore the cumulative incidence, management and outcomes of IMSL related to bDMARD in a large cohort of patients with chronic inflammatory rheumatic diseases. To explore possible associations and risk factors for IMSL development.
Methods: A retrospective single-center study of patients with rheumatoid arthritis (RA), spondylarthritis (SpA) and psoriatic arthritis (PsA) that had been treated with at least one bDMARD for at least 6 months was conducted. IMSL related to bDMARD characteristics and outcomes were collected.
Results: A total of 989 patients with RA, SpA and PsA were included. Twenty-seven patients (2.7%) presented IMSL potentially related to bDMARD, being psoriasis the most common IMSL (n=12, 44.4%), followed by drug-induced lupus erythematosus (n=6), alopecia areata (n=3) and leukocytoclastic vasculitis (n=2). IMSL led to withdrawal of bDMARD in 18 of the 27 patients (66.7%). Patients with IMSL had younger age at diagnosis (p=0.038), longer disease duration (p=0.018), longer duration of bDMARD treatment (p=0.008), and higher number of previous bDMARDs (p<0.001) than patients without IMSL. In the group of patients with IMSL there was a significantly higher percentage of patients treated with adalimumab (p<0.001). In multivariable regression model, the number of previous bDMARDs (OR 2.13, 95%CI 1.47-3.10, p<0.001) and treatment with adalimumab (OR 4.60, 95%CI 1.96-10.80, p<0.001) were statistically significant predictive factors for IMSL development.
Conclusion: In our study, IMSL related to bDMARDs had an estimated cumulative incidence of 2.7%. Younger age at diagnosis, longer disease duration, longer duration of bDMARD treatment, higher number of previous bDMARDs and treatment with adalimumab were independently associated with an increased risk of IMSL development.

Keywords: Biological therapies; DMARDs; Rheumatoid arthritis; Spondyloarthropathies; Psoriatic arthritis; Skin

KEY MESSAGES

- Immune-mediated skin lesions (IMSL) related to bDMARDs had an estimated cumulative incidence of 2.7%.
- Psoriasis (n=12, 44.4%) was the most common IMSL, followed by drug-induced lupus erythematosus (n=6, 22.2%).
- Number of previous bDMARDs and treatment with adalimumab were statistically significant predictive factors for IMSL development.

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INTRODUCTION

Biological disease-modifying antirheumatic drugs (bDMARDs) have revolutionized the treatment of chronic inflammatory rheumatic diseases, such as rheumatoid arthritis (RA), spondylarthritis (SpA) and psoriatic arthritis (PsA), over the past 2 decades[1].

Although it is evident that bDMARDs have improved the clinical outcomes of patients with rheumatic diseases, the physician and the patient should be aware of possible side effects. Some known side effects include injection site and infusion reactions, increased risk of infections (bacterial, fungal, and viral infections), reactivation of tuberculosis and hepatitis B and C, non-melanoma skin cancer, hepatotoxicity and paradoxical adverse events[2-4]. Immune-mediated skin lesions (IMSL) is an entity that includes psoriasiform lesions, leukocytoclastic vasculitis, lupus-like syndrome, among others[5]. In the most severe forms, IMSL can be very disabling leading to treatment discontinuation[6]. Although these lesions have rarely been

previously described, the true incidence is unknown[6]. Some concerns remain regarding the incidence of IMSL, the possible effect of the dosage of the bDMARD and the etiopathogenic link between these events and bDMARD.

Thus, this study aimed to explore the cumulative incidence, risk factors, management and outcomes of IMSL related to bDMARD in a large cohort of patients with chronic inflammatory rheumatic diseases. Furthermore, this study aimed to explore possible associations and risk factors for IMSL development.

MATERIALS AND METHODS

Study design

A retrospective single-center study of patients with RA, SpA and PsA followed at the Department of Rheumatology of a University Hospital between April 2000 and December 2021 was conducted. All patients had been treated with at least one bDMARD for at least 6 months: their first administration of bDMARD occurred between April 2000 and June 2021 and the last until December 2021.

Participants

Patients with 18 years or older diagnosed with RA [according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria[7]], axial and/or peripheral SpA [according to Assessment of Spondylarthritis International Society (ASAS) classification criteria[8]] and PsA [according to CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria[9]] registered on the reuma.pt were included. Patients with psychiatric or cognitive disorders that could interfere with data collection, physically or psychologically unable to communicate, or unable to speak Portuguese were excluded. Patients with important missing data were also excluded.

Data collection

Data were collected mainly from the Portuguese Rheumatic Diseases Register (Reuma.pt) but also from local medical records.

Sociodemographic characteristics, including age and gender, were obtained. Clinical evaluation included body mass index (BMI), disease duration, age at diagnosis, comorbidities, smoking and drinking habits and rheumatic diseases characteristics. The concomitant immunosuppressive therapies (systemic corticosteroids, methotrexate, leflunomide, sulfasalazine, among others) were also fully detailed. Data regarding the type and the dosage of bDMARD administered, the dates of the first and the last administration of each bDMARD, and the number of bDMARD previously prescribed were collected.

IMSL

Only IMSL occurring after the start of a bDMARD were studied. IMSL were diagnosed by a dermatologist and/or by a skin biopsy. Skin manifestations linked to SpA, such as psoriasiform lesions, were included only if there was no previous personal or family history of psoriasis.

For all patients with IMSL, age at onset, disease duration at the time of the IMSL manifestation, culprit bDMARD and duration of the treatment, concomitant immunosuppressive treatment (conventional synthetic DMARDs - csDMARDs - and glucocorticoids), number of previous bDMARDs received during the follow-up were collected.

For patients who did not present an immune-mediated skin complication, we also recorded the current bDMARD and duration of the treatment, the concomitant immunosuppressive medications and the number of previous bDMARDs received during the follow-up.

Management and outcome of IMSL

For each patient with IMSL, we collected the specific management (topical, systemic treatment or both, need for hospitalization) and therapeutic response. Management of bDMARD (maintenance of the same bDMARD, switch to another bDMARD, or bDMARD withdrawal) and outcomes were collected.

STATISTICAL ANALYSIS

Descriptive statistics for continuous variables were presented with mean and standard deviation. Categorical variables were presented with absolute and relative (percentage) frequencies. Sociodemographic and clinical variables were described for each rheumatic disease. To examine the differences between groups with and without IMSL we performed independent samples t-test for normally distributed continuous data, Mann-Whitney U test for not normally distributed continuous data and chi-square tests for categorical variables. Also, a multivariable logistic regression analysis was performed to identify possible predictive factors for the occurrence of IMSL. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Data analysis was performed using IBM SPSS for Windows (version 26, IBM Corporation Software Group, New York, NY, USA). Statistical significance was set at a p-value <0.05.

The Guideline for Good Clinical Practice of the International Conference on Harmonization and the ethical principles of the Declaration of Helsinki were followed. All patients signed informed consent and data were anonymised in accordance with the Portuguese Data Protection Law and the General Data Protection Regulation.

RESULTS

Sample characterization

A total of 989 patients with RA, SpA or PsA were included. The majority were female (63.4%), with mean age of 54.3 ± 12.8 years. The most prescribed bDMARD was adalimumab (21.8%, n=216) and csDMARDs were frequently prescribed in association with bDMARD (47.6%, n=471). Twenty-seven patients (2.7%) presented IMSL potentially related to the treatment. More detailed information is described in Table I.

Description and characterization of IMSL

Regarding the patients with IMSL, 55.6% were females, mean age at the onset of IMSL was 48.4 ± 12.0 years, mean duration of treatment with bDMARDs was 4.3 ± 4.5 years and mean duration of the treatment with the culprit bDMARD was 2.3 ± 2.1 years. The majority of patients had SpA (n= 14), followed by RA (n=10) and PsA (n=3). Adalimumab was the culprit agent in half of the patients (n=14), followed by etanercept (n=4), golimumab (n=3), infliximab (n=3), rituximab (n=2) and tocilizumab (n=1). Thirteen patients (48.1%) were examined by a dermatologist. Four patients (14.8%), 2 patients with leukocytoclastic vasculitis and 2 patients with drug-induced lupus erythematosus, required hospitalization in order to carry out clinical, laboratory and histological investigations to establish a definitive diagnosis. The lesions of the majority of patients resolved completely with the correct treatment. IMSL led to withdrawal of bDMARD in 18 of the 27 patients (66.7%). Supplementary data (Table I) described the characteristics of patients that needed to stop bDMARD.

Psoriasis was the most common IMSL (n=12, 44.4%) and the type of psoriasis is described in Table III. Topical treatment was prescribed in 8 of the 12 patients and phototherapy in 1 patient. Withdrawal of the current bDMARD occurred in 5 patients, 3 patients with plaque psoriasis,1 with inverse psoriasis and 1 with palmoplantar pustulosis. All patients improved with the treatment. The second most common IMSL was drug-induced lupus erythematosus (DILE, n=6). Besides the cutaneous manifestations described in table II, these patients also developed Raynaud phenomenon (n=2), constitutional symptoms (n=1), abrupt worsening of polyarthritis (n=1), lymphopenia and anemia (n=1), positive ANA (n=6), positive anti-dsDNA (n=6) and positive anti-histone antibodies (n=2). Withdrawal of the current bDMARD occurred in all patients. Three patients were treated with systemic steroids and one patient with hydroxychloroquine. All patients improved with the prescribed treatment. Alopecia areata (AA) was diagnosed in 3 patients, 2 with localized alopecia and 1 with alopecia universalis. Two patients were treated with topical agents and bDMARD was maintained. One of these 2 patients didn't recover from alopecia. The third patient stopped bDMARD and a complete recovery was observed. Leukocytoclastic vasculitis was observed in 2 patients. Systemic steroids were prescribed, bDMARD was discontinued and both patients had a complete recovery. Generalized urticaria was observed in 2 patients, bDMARD was discontinued in both patients and a complete resolution of the lesions was observed. One patient developed rosacea and was treated with topical agents and withdrawal of the bDMARD. Other patient developed erythema nodosum that completely resolved after bDMARD withdrawal. More information about the age at IMSL onset, disease duration, culprit bDMARD and duration of treatment with bDMARD in each type of IMSL is described in Table II.

Description and analysis of groups with and without IMSL

Comparing the groups with and without IMSL, no differences were found regarding age, gender, BMI, presence of concomitant csDMARD or type of rheumatic disease. Patients with IMSL have a significant younger age at diagnosis (p=0.038), a longer disease duration (p=0.018) and a longer duration of treatment with bDMARDs (p=0.008). Patients with IMSL also have a higher number of previous bDMARDs (p<0.001). Furthermore, in the group of patients with IMSL there was a significantly higher percentage of patients treated with adalimumab (p<0.001). Table III describes the demographic and clinical features of these two groups.

In a multivariable regression model adjusted for age, gender and disease duration, the number of previous bDMARDs (OR 2.13, 95% CI 1.47 to 3.10, p<0.001) and treatment with adalimumab (OR 4.60, 95% CI 1.96 to 10.80, p<0.001) were statistically significant predictive factors for IMSL development (Table IV).

DISCUSSION

Nowadays, bDMARDs are frequently used and their potential side effects must be clearly known, namely adverse skin lesions, since the skin is one of the most frequently affected organs in these adverse reactions[6,10,11].

In our study, IMSL related to bDMARDs had an estimated cumulative incidence of 2.7%. The most frequent IMSL were psoriasis and cutaneous manifestations of DILE and the most frequent culprit bDMARD was adalimumab. The majority of patients didn't need hospitalization and had a complete resolution of IMSL. IMSL led to withdrawal of bDMARD in two thirds of patients.

Table I. Sociodemographic, clinical and treatment characteristics and IMSL data of included patients.

	RA (n=441)	SpA (n=386)	PsA(n=162)	Total (n=989)
Age, mean ± SD, years	60.0 ± 11.1	48.4 ± 12.2	52.6 ± 11.5	54.3 ± 12.8
Female, n (%)	364 (82.5)	180 (46.6)	83 (51.2)	627 (63.4)
Disease duration, mean ± SD, years	19.3 ± 10.7	20.6 ± 12.0	16.1 ± 9.1	19.3 ± 11.1
Age at diagnosis, mean ± SD, years	42.6 ± 12.8	34.4 ± 11.4	39.90 ± 11.61	38.9 ± 12.6
Current/Former smoker, n (%)	122 (27.7)	160 (41.5)	55 (34.0)	337 (34.1)
Alcohol consumption, n (%)	61 (13.8)	63 (16.3)	34 (21.0)	158 (16.0)
Comorbidities, n (%)				
Hypertension	124 (28.1)	44 (11.4)	39 (20.1)	207 (20.9)
Diabetes mellitus	41 (9.3)	13 (3.4)	18 (1.1)	72 (7.3)
Cardiovascular disease	45 (10.2)	16 (4.1)	9 (0.6)	70 (7.1)
Thyroid disease	26 (5.9)	7 (1.8)	3 (1.9)	36 (3.6)
Current treatment, n (%)				
Glucocorticoids	312 (70.7)	48 (12.4)	59 (36.4)	419 (42.4)
Concomitant csDMARD				
MTX	143 (32.4)	33 (8.5)	67 (41.4)	243 (24.6)
LFN	59 (13.4)	1 (0.3)	14 (8.6)	74 (7.5)
SLZ	14 (3.2)	56 (14.5)	6 (3.7)	76 (7.7)
HCQ	18 (4.1)	0 (0.0)	0 (0.0)	18 (1.8)
>1 csDMARD	52 (11.8)	6 (1.6)	2 (1.2)	60 (6.1)
bDMARD				
Etanercept	82 (18.6)	48 (12.4)	33 (20.4)	163 (16.5)
Adalimumab	49 (11.1)	122 (31.6)	45 (27.8)	216 (21.8)
Infliximab	12 (2.7)	57 (14.8)	11 (6.8)	80 (8.1)
Golimumab	21 (4.8)	60 (15.5)	23 (14.2)	104 (10.5)
Certolizumab pegol	4 (0.9)	28 (7.3)	9 (5.6)	41 (4.1)
Tocilizumab	71 (16.1)	0 (0.0)	2 (1.2)	73 (7.4)
Rituximab	98 (22.2)	0 (0.0)	0 (0.0)	98 (9.9)
Abatacept	16 (3.6)	0 (0.0)	1 (0.6)	17 (1.7)
Secukinumab	0 (0.0)	29 (7.5)	22 (13.6)	51 (5.2)
Ustekinumab	0 (0.0)	2 (0.5)	3 (1.9)	5 (0.5)
Anakinra	4 (0.9)	0 (0.0)	0 (0.0)	4 (0.4)
None	84 (19.0)	40 (10.4)	13 (8.0)	137 (13.8)
IMSL, n (%)	10 (2.3)	14 (3.6)	3 (1.9)	27 (2.7)

SpA: spondyloarthritis, bDMARD: biological disease-modifying antirheumatic drug, csDMARD: conventional synthetic disease-modifying antirheumatic drug, HCQ: hydroxychloroquine, IMSL: immune-mediated skin lesions, LFN: leflunomide, MTX: methotrexate, PsA: psoriatic arthritis, RA: rheumatoid arthritis, SD: standard deviation, SLZ: sulfasalazine.

Table II. Description of the number of cases, age at IMSL onset, disease duration and duration of treatment with the culprit bDMARD for each type of IMSL.

Type of IMSL	Number of patients, n (%)	Age at IMSL onset, mean ± SD, years	Female, n (%)	Disease duration, mean ± SD, years	Culprit bDMARD, n	Duration of treatment with culprit bDMARD, mean ± SD, years
Psoriasis	**12**	49.3 ± 14.5	6 (50.0)	19.5 ± 15.3	Adalimumab, 4 Golimumab, 3 Etanercept, 2 Infliximab, 2 Rituximab, 1	1.9 ± 1.7
Plaque psoriasis	5 (41.7)					
Palmoplantar pustulosis	4 (33.3)					
Guttate psoriasis	1 (8.3)					
Inverse psoriasis	1 (8.3)					
Undefined	1 (8.3)					
DILE	**6**	40.8 ± 2.9	4 (66.7)	15.2 ± 7.8	Adalimumab, 4 Golimumab, 1 Etanercept, 1	2.4 ± 1.4
Malar Rash	1 (16.7)					
Alopecia	2 (33.3)					
Chilblains	2 (33.3)					
Subacute cutaneous LE	1 (16.7)					
LE tumidus	1 (16.7)					
Alopecia areata	3	42.4 ± 6.7	1 (33.3)	12.2 ± 6.7	Adalimumab, 2 Etanercept, 1	1.2 ± 0.6
Leukocytoclastic vasculitis	2	60.9 ± 2.8	0 (0)	14.7 ± 13.0	Adalimumab, 1 Infliximab, 1	2.9 ± 3.6
Generalized urticaria	2	57.3 ± 15.9	2 (100)	27.8 ± 22.1	Adalimumab, 1 Tocilizumab, 1	0.9 ± 1.2
Rosacea	1	48	1 (100)	18.5	Rituximab, 1	9.7
Erythema nodosum	1	60	1 (100)	40.7	Etanercept, 1	2.9

AA: Alopecia areata, DILE: drug-induced lupus erythematosus, IMSL: Immune-mediated skin lesions, LE: lupus erythematosus, SD: standard deviation.

Few data are available on the incidence of IMSL in large series of patients treated with bDMARDs. Furthermore, the majority of these studies only included patients under anti-TNF-α agents[6, 10-17]. Based on previous studies including patients with Inflammatory bowel disease (IBD) under anti-TNF-α, cutaneous lesions were reported in up to 22%. However, these authors included not only IMSL, but also cutaneous infections, skin cancers, toxic manifestations, acute or delayed infusion reactions and injection site reactions[10, 12].

In the majority of the previous studies with patients with IBD or with rheumatic diseases under anti-TNF-α, the most frequent IMSL was psoriasis with a frequency ranging from 5.3-10.1%[10-13], which supports our findings. A systematic review found 216 published cases of new-onset psoriasis (102 biopsy-proven) attributed to anti-TNF-α therapy[18]. The most common lesions were plaque psoriasis (44.8%) and palmoplantar pustulosis (36.3%), and appeared on average 14 months after the start of anti-TNF-α therapy (range 1–120 months). Topical steroids were the most common treatment (76.5%)[18]. Resolution of psoriatic lesions occurred more frequently after stopping anti-TNF-α therapy or after switching to a different anti-TNF-α agent but, in some cases, the resolution occurred despite maintaining the same anti-TNF-α agent (32.9%)[18]. Concerning our data, among rheumatic patients, we found that a high percentage of patients with induced psoriasis persist with the same bDMARD (n=7), with a complete resolution or with low-severity skin lesions, supporting that it is safe to maintain the same bDMARD in patients with mild psoriasis[15].

Concerning DILE, the previously reported prevalence

Table III. Demographic and clinical features in patients with and without IMSL.

	With IMSL (n=27)	Without IMSL (n=962)	p-value
Age, mean ± SD, years	55.5 ± 14.0	52.2 ± 12.7	0.598
Female, n (%)	15 (55.6)	612 (63.6)	0.390
BMI, mean ± SD	25.4 ± 4.8	27.2 ± 7.5	0.231
Current/Former smoker, n (%)	10 (37.0)	327 (34.0)	0.478
Alcohol consumption, n (%)	4 (14.8)	140 (14.6)	0.602
Rheumatic disease, n (%)			
Spondyloarthritis	14 (51.9)	372 (38.7)	0.373
Rheumatoid arthritis	10 (37.0)	431 (44.8)	
Psoriatic arthritis	3 (11.1)	159 (16.5)	
Disease duration, mean ± SD, years	24.4 ± 12.7	19.2 ± 11.1	**0.018**
Duration of treatment with all bDMARDs, mean ± SD, years	9.3 ± 4.4	6.6 ± 5.3	**0.008**
Duration of treatment with culprit or current bDMARD, mean ± SD, years	2.3 ± 2.1	3.9 ± 3.5	**0.021**
Age at diagnosis, mean ± SD, years	29.4 ± 12.8	35.0 ± 13.2	**0.038**
Number of previous bDMARDs,mean ± SD	1.6 ± 1.1	0.74 ± 0.84	**<0.001**
Presence of concomitant csDMARD, n (%)	10 (37.0)	467 (48.5)	0.237
Type of bDMARD prescribed, n (%)			
Adalimumab	14 (51.9)	211 (21.9)	**<0.001**
Etanercept	4 (14.8)	162 (16.8)	1.000
Golimumab	3 (11.1)	102 (10.6)	0.763
Certolizumab pegol	0 (0)	37 (3.8)	0.619
Infliximab	3 (11.1)	77 (8.0)	0.481
Tocilizumab	1 (3.7)	73 (7.6)	0.718
Rituximab	2 (7.4)	95 (9.9)	1.000
Abatacept	0 (0)	16 (1.7)	1.000
Secukinumab	0 (0)	49 (5.1)	0.643
Ustekinumab	0 (0)	5 (0.5)	1.000
Anakinra	0 (0)	4 (0.4)	1.000

bDMARD: biological disease-modifying antirheumatic drug, BMI: body mass index, csDMARD: conventional synthetic disease-modifying antirheumatic drug, SD: standard deviation.

was 0.1-0.8%[19-22]. Cutaneous manifestations in DILE due to anti-TNF-α agents are frequent[19]. In a French retrospective study, 11 of the 12 patients with lupus-like syndrome developed skin lesions that included papules, alopecia, rash, butterfly rash and photosensitivity. These authors also found 10 cases of limited cutaneous lupus and skin manifestations included pruritic rash (two cases), butterfly rash (three cases), photosensitivity (two cases), purpura (two cases) and chilblains (one case)[19]. Lesions generally appear in 9-11 months after anti-TNF-α therapy and are more common with infliximab, followed by etanercept[6,19]. However, cases have been reported with other bDMARDs and targeted synthetic (ts) DMARDs, namely golimumab, abatacept and tofacitinib in patients with RA[23-25]. In the majority of patients, the symptoms resolve spontaneously after treatment suspension or with a low dose of steroids[6, 19]. In contrast to the previous findings, in our study the adalimumab was the bDMARD most frequently related to DILE.

In respect to vasculitis, the prevalence of vasculitis reported in the literature in patients treated with anti-TNF-α agents is 3.9%[14]. The most frequent type of anti-TNF-α related vasculitis is leukocytoclastic vasculitis, being purpura the most frequent cutaneous feature, although other lesions, such as ulcers, nodules, or rash were also reported[6,16]. Vasculitis appears after a mean

Table IV. Multivariable analysis to identify predictive factors for the occurrence of immune-mediated skin lesions (IMSL).

	Multivariable analysis		
Factor	OR	95% CI	p-value
Age at diagnosis	0.99	0.95-1.03	0.682
Disease duration	1.03	0.99-1.08	0.131
Duration of treatment with all bDMARDs	0.98	0.90-1.08	0.727
Treatment with adalimumab	4.60	1.96-10.80	**<0.001**
Number of previous bDMARDs	2.13	1.47-3.10	**<0.001**

bDMARD biological disease-modifying antirheumatic drugs, CI confidence interval, OR odds ratio.

time of 38 weeks of anti-TNF-α therapy and improves with discontinuation of anti-TNF-α; however, in some cases, prednisone and other immunosuppressive agents were necessary to control the manifestations of vasculitis[6,16]. Our data reported 2 cases of leukocytoclastic vasculitis that appeared after a longer period of time under bDMARD (2.9 ± 3.6 years) than the previously reported.

Regarding AA, a prospective study with patients treated with anti-TNF-α showed that AA were predominantly patchy affecting the scalp or beard and the mean duration of exposure to anti-TNF-α was 22.5 months (range 1-89 months)[17]. Anti-TNF-α agents were stopped in half of the cases and maintained in the remaining[17]. A complete or partial recovery occurred in 76% of the patients, with a mean time to improvement of 5 months[17]. AA was also reported with other bDMARDs, namely ustekinumab and secukinumab[26, 27]. In a case series of patients with psoriasis, SpA, PsA, RA and Crohn's disease that developed AA due to anti-TNF-α agents, adalimumab was the culprit agent in 88.9% of cases (8 of 9 cases)[28]. In our sample, adalimumab was the responsible bDMARD in 2 of our 3 cases of AA. So, adalimumab seems to be the anti-TNF-α agent with a higher probability of inducing AA.

Concerning others IMSL like urticaria, rosacea and erythema nodosum, Flendrie *et al.* also describe 1 case of rosacea, 1 case of erythema nodosum and 4 cases of urticaria in a cohort of patients with RA treated with anti-TNF-α agents[14].

The reason why some patients develop IMSL after bDMARD therapy is unclear, especially for conditions where these agents are considered effective and a treatment option, such as psoriasis[18]. In the literature, there are various possible explanations. First, genetic predisposition and environmental triggers might play a role. Second, bDMARDs might help to unmask asymptomatic or subclinical autoimmune diseases in patients with rheumatic diseases (such as lupus or vasculitis). Third, anti-TNF-α agents can cause a cytokine imbalance with an overproduction of interferon-α[29]. Also, bDMARDs can down-regulate the Th1 immune response, which might induce a shift of the Th1/Th2 balance towards Th2-dominated immune responses30. Regarding IL-17a inhibitors, a possible explanation of their paradoxical adverse effects is the selective blockade of IL-17a, leading to overexpression of other IL-17 isoforms[29].

Risk factors for the occurrence of IMSL in rheumatic patients are poorly known. In our cohort, we found that a younger age at diagnosis, longer disease duration, longer duration of bDMARD treatment, higher number of previous bDMARDs and treatment with adalimumab were independently associated with an increased risk of IMSL development. In a multivariable regression model, number of previous bDMARDs and adalimumab were statistically significant predictive factors for IMSL development. Flendrie *et al.* also reported that disease duration was a predictive factor for dermatological events in patients with RA treated with anti-TNF-α agents, corroborating our findings[14]. In a cohort of patients with IBD, a longer duration of the involved anti-TNF-α agent was significantly associated with psoriasiform lesions development[10].

In our study, adalimumab was the bDMARD with a higher risk for IMSL development. Andrade *et al.* reported that adalimumab was independently associated with a higher risk of psoriasiform lesions in patients with IBD[11]. Exarchou *et al.* found a higher prevalence of IMSL in patients with RA and SpA treated with infliximab, adalimumab and etanercept, however no statistically significant difference was found

between these anti-TNF-α agents[13]. Data regarding the association between the type of bDMARD and IMSL development are controversy and need to be clarified.

Some limitations of our study should be acknowledged. Major limitations are related to the single-center retrospective nature of the study, the filling in the database (Reuma.pt) being operator dependent and there may be a lack of register data regarding the development of IMSL, which may underestimate the incidence of these adverse events. Other limitations are a lack of a uniform dermatologic evaluation over 22 years, a lack of histopathological examination in some cases, the heterogeneous number of patients in the IMSL group and non-IMSL group and a small sample of patients under non-TNF-α bDMARD. Since the IMSL group was very small, generalization must be cautious. Further studies are needed to confirm these results, especially longitudinal studies with larger samples and more patients treated with non-TNF-α bDMARD. On the other hand, since psoriasis can be a manifestation of SpA and RA can be associated with systemic lupus erythematosus (as RHUPUS) and secondary vasculitis (due to the RA itself), the assumption of some lesions as IMSL induced by bDMARD may not always be accurate.

CONCLUSION

Treatment of inflammatory rheumatic diseases has dramatically changed with the introduction of bDMARDs. However, these drugs aren't exempt from risks and infection and skin lesions are the most frequent adverse reactions. Physicians should be aware of the possibility of IMSL development and should have a basic understanding of how to manage these patients.

There is a lack of studies exploring IMSL in patients with rheumatic diseases under bDMARDs, especially regarding non-anti-TNF-α bDMARDs. To the best of our knowledge, this is the first retrospective study that has studied the cumulative incidence, risk factors, management and outcomes of IMSL related to bDMARDs in a large cohort of of patients with chronic inflammatory rheumatic diseases over a 22-year follow-up period.

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SUPPLEMENTARY DATA

Supplementary Table I. Characteristics of patients that needed to withdraw the biological disease-modifying antirheumatic drugs (bDMARD) due to development of immune-mediated skin lesions (IMSL).

Patient number	Gender and age at IMSL onset	Rheumatic disease	Type of IMSL	Culprit bDMARD	Treatment and management
1	F, 66	RA	Psoriasis	ADA	Topical steroids, withdrawal of culprit bDMARD and switch to RTX
2	M, 38	SpA	Psoriasis	ADA	Topical steroids, withdrawal of culprit bDMARD and switch to ETN
3	M, 38	SpA	Psoriasis	ADA	Topical steroids, withdrawal of culprit bDMARD and switch to GOL
4	F, 66	RA	Psoriasis	ADA	Topical agents, phototherapy, withdrawal of culprit bDMARD and switch to GOL
5	F,53	SpA	Psoriasis	ADA	Topical agents, phototherapy, withdrawal of culprit bDMARD and switch to ETN
6	F, 43	RA	DILE	ADA	Withdrawal of culprit bDMARD and switch to GOL
7	M, 36	SpA	DILE	ADA	Systemic steroids, withdrawal of culprit bDMARD and switch to certolizumab
8	F, 42	SpA	DILE	ADA	Systemic steroids, withdrawal of culprit bDMARD and switch to secucinumab
9	F, 39	SpA	DILE	GOL	Systemic steroids, withdrawal of culprit bDMARD and switch to secucinumab
10	M, 43	PsA	DILE	ETN	Systemic steroids, withdrawal of culprit bDMARD and switch to tofacitinib
11	F, 39	RA	DILE	ADA	Systemic steroids, withdrawal of culprit bDMARD and switch to upadacitinib
12	M, 62	SpA	Leukocytoclastic vasculitis	IFX	Systemic and topical steroids, withdrawal of culprit bDMARD and switch to ADA
13	M, 58	SpA	Leukocytoclastic vasculitis	ADA	Systemic steroids, withdrawal of culprit bDMARD and switch to secucinumab
14	F, 68	RA	Generalized urticaria	TCZ	Antihistamines, withdrawal of culprit bDMARD and switch to abatacept
15	F, 46	SpA	Generalized urticaria	ADA	Antihistamines, withdrawal of culprit bDMARD and switch to certolizumab
16	F, 46	SpA	Alopecia areata	ADA	Topical agents, withdrawal of culprit bDMARD and switch to ETN
17	F, 48	RA	Rosacea	RTX	Topical agents, withdrawal of culprit bDMARD and switch to tofacitinib
18	F,60	RA	Erythema nodosum	ETN	Systemic steroids, withdrawal of culprit bDMARD and switch to RTX

ADA adalimumab, bDMARD biological disease-modifying antirheumatic drugs, DILE drug-induced lupus erythematosus, ETN etanercept, F female, GOL golimumab, IMSL immune-mediated skin lesions, IFX infliximab, M male, PsA psoriatic arthritis, RA rheumatoid arthritis, RTX rituximab, SpA spondylarthritis, TCZ tocilizumab.