

# The skin tissue is adversely affected by TNF-alpha blockers in patients with chronic inflammatory arthritis: a 5-year prospective analysis

Natalia P. Machado,<sup>1</sup> Edgard Torres dos Reis Neto,<sup>1</sup> Maria Roberta M. P. Soares,<sup>1</sup> Daniele S. Freitas,<sup>1</sup> Adriana Porro,<sup>II</sup> Rozana M. Ciconelli,<sup>III</sup> Marcelo M. Pinheiro<sup>I</sup>

<sup>I</sup>Universidade Federal de São Paulo, Escola Paulista de Medicina (Unifesp/EPM), Rheumatology Division, São Paulo/SP, Brazil. <sup>II</sup>Universidade Federal de São Paulo, Escola Paulista de Medicina (Unifesp/EPM), Dermatology Department, Psoriasis Clinic, São Paulo/SP, Brazil. <sup>III</sup>Universidade Federal de São Paulo, Escola Paulista de Medicina (Unifesp/EPM), Center for Health Economics, São Paulo/SP, Brazil.

**OBJECTIVE:** We evaluated the incidence of and the main risk factors associated with cutaneous adverse events in patients with chronic inflammatory arthritis following anti-TNF- $\alpha$  therapy.

**METHODS:** A total of 257 patients with active arthritis who were taking TNF- $\alpha$  blockers, including 158 patients with rheumatoid arthritis, 87 with ankylosing spondylitis and 12 with psoriatic arthritis, were enrolled in a 5-year prospective analysis. Patients with overlapping or other rheumatic diseases were excluded. Anthropometric, socioeconomic, demographic and clinical data were evaluated, including the Disease Activity Score-28, Bath Ankylosing Spondylitis Disease Activity Index and Psoriasis Area Severity Index. Skin conditions were evaluated by two dermatology experts, and in doubtful cases, skin lesion biopsies were performed. Associations between adverse cutaneous events and clinical, demographic and epidemiological variables were determined using the chi-square test, and logistic regression analyses were performed to identify risk factors. The significance level was set at  $p < 0.05$ .

**RESULTS:** After 60 months of follow-up, 71 adverse events (73.85/1000 patient-years) were observed, of which allergic and immune-mediated phenomena were the most frequent events, followed by infectious conditions involving bacterial (47.1%), parasitic (23.5%), fungal (20.6%) and viral (8.8%) agents.

**CONCLUSION:** The skin is significantly affected by adverse reactions resulting from the use of TNF- $\alpha$  blockers, and the main risk factors for cutaneous events were advanced age, female sex, a diagnosis of rheumatoid arthritis, disease activity and the use of infliximab.

**KEYWORDS:** TNF-alpha Blockers; Skin; Adverse Events; Rheumatoid Arthritis; Ankylosing Spondylitis.

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E-mail: mpinheiro@uol.com.br

Tel.: 55 11 5576-4239

## INTRODUCTION

A number of studies have demonstrated that TNF- $\alpha$  blockers, including monoclonal antibodies (infliximab [IFX], adalimumab [ADA] and golimumab [GOL]) and soluble TNF receptors (etanercept [ETN]), are effective in the treatment of rheumatoid arthritis (RA) (1), ankylosing spondylitis (AS) (2), psoriatic arthritis (PA) (3), juvenile idiopathic arthritis (JIA) (4), psoriasis (5) and inflammatory bowel disease (6). However, these medications are

associated with the occurrence of skin manifestations (dermatosis and dermatitis), with a frequency ranging from 10% to 60% (7-9).

Undesirable events generally quickly resolved after the withdrawal of TNF- $\alpha$  blockers or with the use of glucocorticoid steroids (GCs) (10,11) or antimicrobial agents. In some cases, it is possible to maintain treatment or to switch to another TNF- $\alpha$  blocker or biologic agent, such as rituximab (RTX), abatacept (ABT) or tocilizumab (TCZ) (1).

Among the types of acute lesions, the main differential diagnoses include allergic, urticariform and infectious manifestations caused by viruses (especially herpes), bacteria (e.g., staphylococcus and streptococcus), fungi (candida) and parasites (especially scabies) (7,8,12,13).

The majority of chronic lesions consist of psoriasis-like eczema (13,14), although herpetiform dermatitis, small vessel vasculitis, alopecia areata, palmoplantar pustulosis, atopic dermatitis, lichenoid rash, purpura, skin neoplasms,

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polymorphic and multiform erythema have also been reported (7,8,15).

The aim of the present study was to evaluate the incidence and the main risk factors associated with cutaneous adverse events (CAEs) in patients with chronic inflammatory arthropathies (CIAs) who receive TNF- $\alpha$  blockers.

## ■ PATIENTS AND METHODS

A total of 257 patients with active CIA and who were receiving TNF- $\alpha$  blockers were evaluated, including 158 (61.5%) patients with RA (ACR, 1987) (16), 87 (33.8%) with AS (modified New York criteria, 1984) (17) and 12 (4.7%) with PA (CASPAR, 2006) (18), in a prospective analysis from January 2005 to December 2009. All of the patients were regularly followed at the Immunobiological Clinic of the Rheumatology Division of the Universidade Federal de São Paulo/Escola Paulista de Medicina (Brazil), and all of the patients demonstrated moderate to severe disease activity and had received anti-TNF- $\alpha$  therapy for the previous 6 months (19,20). The patients were evaluated in the same manner every 3 months, regardless of the type of TNF-blocker administration (i.e., intravenous or subcutaneous).

The following exclusion criteria were applied: inability to answer the questions on the questionnaires; active or chronic active infections, including hepatitis B, hepatitis C and human immunodeficiency virus; overlapping of other autoimmune rheumatic diseases; pulse with methylprednisolone; recurrent infections involving the skin and/or mucosal tissue, such as erysipelas, furunculosis, human papillomavirus and herpes simplex; and classic contraindications for TNF- $\alpha$  inhibitors (solid and hematological neoplasms, demyelinating disease and heart failure).

Anthropometric, socioeconomic, demographic and clinical data were evaluated, including the Disease Activity Score-28 (DAS28) (21), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (22), Psoriasis Area and Severity Index (PASI) (23) and Health Assessment Questionnaire (HAQ).

Comorbidities were grouped based on the International Classification of Diseases (10th revision) (<http://www.icd10data.com>), and concomitant medications were classified according to the Dictionary of Pharmaceutical Specialties (version 2009, Brazil) (<http://www.epuc.com.br/DEF/Home.htm>). Certain drugs have been associated with drug-induced skin conditions, and others have been shown to increase the odds of infection. For this reason, these drugs were analyzed separately, including analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), GCs, disease-modifying anti-rheumatic drugs (DMARDs; including methotrexate, leflunomide, cyclosporine, sulfasalazine, and azathioprine), hypertension medications (methyldopa, hydralazine, angiotensin-converting-enzyme inhibitors), anticonvulsants and treatment for latent tuberculosis infection (isoniazid).

Skin conditions were evaluated by two experienced dermatologists. In cases of doubt or a lack of agreement between the examiners, a biopsy of the skin lesion was performed following the standard routine procedures. Staining with hematoxylin-eosin was used in all cases. Special stains, direct immunofluorescence and cultures of fragments were performed when necessary. An adverse

event was defined as any unexpected medical occurrence that arose following the onset of anti-TNF- $\alpha$  therapy. A serious adverse event was defined as any unexpected medical occurrence that resulted in death, endangered the patient's life or required or prolonged hospitalization. These events did not necessarily have a causal relationship with the factors evaluated in the study.

Immunological reactions to the drugs were defined, according to the classification proposed by Gell and Coombs (1963), as type I (allergy or anaphylaxis, such as urticariform reaction), type II (antibody-mediated cytotoxic reaction, such as hemolytic anemia, thrombocytopenia and nephritis), type III (immune complex-mediated reactions, such as psoriasis-like lesions and drug-induced lupus) or type IV (cell-mediated reaction, such as contact dermatitis) hypersensitivity (24). Infectious events were classified as viral, parasitic, fungal or bacterial, depending on the clinical condition or on identification of the etiological agent through direct study, culture or specific staining.

The incidence was calculated based on the time interval between the first day of TNF- $\alpha$  blocker use and the first CAE. Recurring conditions were not included in this analysis. The decision to maintain or discontinue (temporarily or definitively) the medication was made by the medical team based on the risks, benefits, severity, duration, likelihood and temporality between the CAEs and the TNF- $\alpha$  inhibitors.

Descriptive data are expressed as the means  $\pm$  standard deviations, and categorical variables are expressed as percentage values. For the inferential analysis, Student's t-test and the chi-square test were used for numerical data, and the Mann-Whitney and Fisher's exact test were used for categorical variables. Analysis of variance and Tukey's post-hoc test were used for the comparison of non-numerical data. All of the data were initially evaluated for distribution normality. Associations between CAEs and the clinical, demographic and epidemiological variables were evaluated using the chi-square test and logistic regression models for the identification of associated risk factors. The dependent variables were the CAEs. The Statistical Package for Social Sciences (SPSS, version 15.0) was used for all of the analyses, with the level of significance set at 5% ( $p < 0.05$ ).

## Ethics

All of the patients were informed about the study, and those who agreed to participate signed a statement of informed consent. This study received approval from the Human Research Ethics Committee of the Universidade Federal de São Paulo/Escola Paulista de Medicina (no. 1478/09).

## ■ RESULTS

After 60 months of follow-up, 71 (27.6%) patients experienced some type of adverse event involving the skin (Table 1). The incidence of CAE was 73.85/1000 patient-years. No patient presented evidence of a similar pre-existing clinical condition. The first CAE appeared between 2 weeks and 45 months after the onset of anti-TNF- $\alpha$  therapy (mean:  $11.2 \pm 4.7$  months). The diagnosis of skin lesions, including lepromatous leprosy (LL), systemic lupus erythematosus (SLE), psoriasis-like lesions and vulvar lichen planus, was confirmed through biopsy of the affected area.



**Table 1** - The frequency of 71 new CAEs in 257 patients with chronic inflammatory arthritis taking TNF- $\alpha$  blockers after 60 months of follow-up.

	Frequency, n (%)
Urticaria	18 (25.3%)
Local erythema	12 (16.9%)
Scabies	8 (11.3%)
Impetigo	6 (8.4%)
Onychomycosis	4 (5.6%)
Psoriasis-like lesions	3 (4.2%)
Chronic eczema	3 (4.2%)
Tinea corporis/cruris	3 (4.2%)
Boils	2 (2.8%)
Recurrent furunculosis	2 (2.8%)
Erysipelas	2 (2.8%)
Soft tissue abscess	2 (2.8%)
Herpes simplex	
Oral	1 (1.4%)
Genital	1 (1.4%)
Herpes zoster	1 (1.4%)
Lichen planus	1 (1.4%)
Lepromatous leprosy	1 (1.4%)
Systemic lupus erythematosus	1 (1.4%)

Onychomycosis was proved according to the positivity of the direct mycological test.

Table 2 displays the clinical characteristics of the 257 patients according to the presence of CAEs. Older individuals and those with a more elapsed time since their diagnoses, those with greater disease activity and severity, those of female sex, those with a history of diabetes mellitus, those with a diagnosis of RA and those with regular use of IFX demonstrated a greater likelihood of experiencing a CAE.

Allergic and immune-mediated phenomena were the most frequent types of CAEs (n=37; 52.1%), followed by infectious conditions (n=34; 47.9%) involving bacterial

(47.1%), parasitic (23.5%), fungal (20.6%) and viral (8.8%) agents (Figure 1; Table 3).

When the 71 patients with CAE were grouped according to the mechanism involved (immune-allergic *vs.* infectious), the only significant variable associated with the greater frequency of the latter group was a diagnosis of diabetes mellitus. In addition, there was a tendency toward infectious CAEs occurring more frequently in patients under prolonged treatment with GCs, regardless of the dose (Table 4).

Although the severity of the events was considered moderate to severe in most patients, the resolution of the CAEs was satisfactory in the vast majority of cases following withdrawal of the anti-TNF- $\alpha$  agent and with the use of specific medications, such as anti-histamines, GCs, antibiotics and antiviral, antiparasitic and antimycotic agents, depending on the event and needs of each case. Table 5 displays the strategies regarding the discontinuation (temporary or definitive) of TNF- $\alpha$  blockers. Among those patients for whom therapy was temporarily discontinued, the same medication was reintroduced without recurrence of the CAE. The replacement of anti-TNF- $\alpha$  agents was the most frequent action undertaken following the definitive discontinuation of the first blocker, with no recurrence of the CAE during the first 6 months following replacement.

Among those who needed to switch medications to another TNF- $\alpha$  inhibitor, the majority switched from monoclonal antibody therapy to soluble receptor therapy (53.8%), followed by from treatment with one monoclonal antibody to another monoclonal antibody (33.1%) and from treatment with a soluble receptor to a monoclonal antibody (13.1%). Only four patients switched to a non-TNF- $\alpha$  blocker, including three who used RTX and one who used ABT.

Three CAE (4.22%) cases required hospitalization and were therefore classified as serious. In all of the cases, the

**Table 2** - Clinical characteristics of the 257 patients with chronic inflammatory arthritis taking TNF- $\alpha$  blockers according to the presence of CAEs.

	Total (n = 257)	No CAE (n = 186)	With CAE (n = 71)	p-value
Age (years)	47.5 $\pm$ 12.3	46.8 $\pm$ 11.6	50.3 $\pm$ 10.7	0.03
Years since diagnosis	13.6 $\pm$ 7.2	12.5 $\pm$ 7.8	15.8 $\pm$ 8	0.02
Female sex, n (%)	165(64.2%)	107(57.5%)	58(81.7%)	<0.001
DAS28 (n = 170)	5.92 $\pm$ 1.34	5.47 $\pm$ 1.13	5.88 $\pm$ 1.41	0.02
BASDAI (n = 91)	5.2 $\pm$ 1.9	4.9 $\pm$ 1.8	5.3 $\pm$ 2.0	0.03
PASI (n = 12)	8.7 $\pm$ 4.2	7.3 $\pm$ 3.9	9.5 $\pm$ 4.6	0.04
HAQ	1.72 $\pm$ 0.61	1.63 $\pm$ 0.5	1.79 $\pm$ 0.6	0.04
Associated disease				
DM, n (%)	64 (24.9%)	39 (21%)	25 (35.2%)	0.02
Concomitant medication				
GCs, n (%)	151 (58.8%)	98 (52.7%)	53 (74.6%)	0.04
DMARDs, n (%)	238 (92.6%)	173 (93%)	65 (91.5%)	0.29
Antihypertensive, n (%)	96 (37.4%)	71 (38.2%)	25 (35.2%)	0.42
Anticonvulsant, n (%)	6 (2.3%)	4 (2.1%)	2 (2.8%)	0.78
Chronic inflammatory arthritis				
RA, n (%)	158 (61.5%)	107 (57.5%)	51 (71.9%)	
AS, n (%)	87 (33.8%)	72 (38.7%)	15 (21.1%)	
PA, n (%)	12 (4.7%)	7 (3.8%)	5 (7%)	<0.001
TNF- $\alpha$ blockers				
IFX, n (%)	132 (51.4%)	94 (50.5%)	38 (53.5%)	
ADA, n (%)	75 (29.2%)	56 (30.1%)	19 (28.2%)	
ETN, n (%)	50 (19.4%)	36 (19.3%)	14 (16.9%)	<0.001

CAEs: cutaneous adverse events; DAS28: Disease Activity Score-28; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; PASI: Psoriasis Activity and Severity Index; HAQ: Health Assessment Questionnaire; DM: diabetes mellitus; GCs: glucocorticoid steroids; DMARDs: disease-modifying anti-rheumatic drugs; RA: rheumatoid arthritis; AS: ankylosing spondylitis; PA: psoriatic arthritis; IFX: infliximab; ETN: etanercept; ADA: adalimumab.

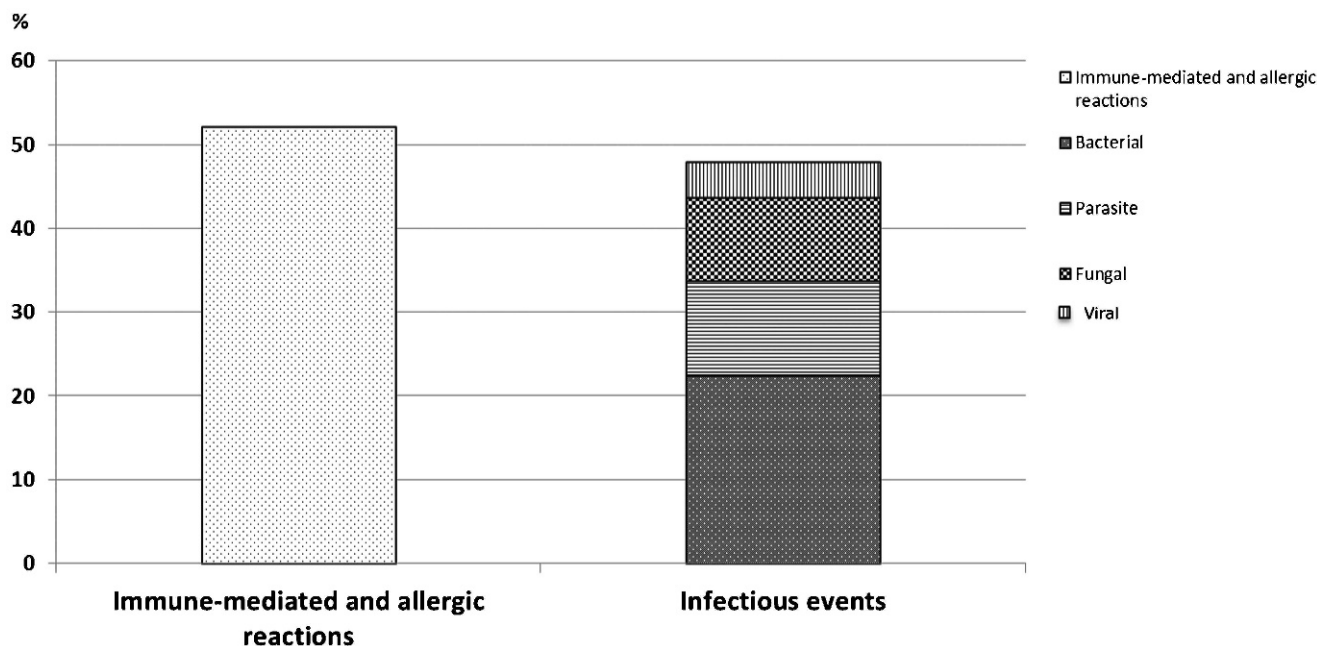


Figure 1 - Grouping of CAEs according to mechanism involved (immune-allergic vs. infectious)

reason for hospitalization was an acute bacterial condition (erysipelas, recurring furunculosis and soft tissue abscess), with toxemia and/or evidence of septicemia and/or an inadequate response to outpatient treatment. In addition, there was a close temporal and causal relationship between the study procedures or therapeutic agent employed and the patient's classification as moderately severe, based on the investigator's opinion. No cases resulted in death. These serious adverse events exhibited satisfactory evolution following antibiotic therapy, with complete resolution of the disease process. In all three cases, the anti-TNF- $\alpha$  agent

was switched (to ETN in two of the cases and to RTX in the other case). No statistically significant association was found between serious adverse events and age, years since diagnosis, functional capacity, concomitant medications or associated diseases.

In the logistic regression model, the main risk factors significantly associated with CAE were advanced age, female sex, greater disease activity, diagnosis of RA and the use of GCs and IFX. HAQ, DMARDs and other concomitant medications, as well as the presence of diabetes mellitus, did not achieve statistical significance as risk

Table 3 - Clinical characteristics of the 71 CAEs according to the mechanism involved (immune-allergic vs. infectious).

	Total (n = 71)	Immune-allergic (n = 37)	Infectious (n = 34)	
Age (years)	50.3 ± 10.7	49.2 ± 10.9	50.6 ± 12.1	0.31
Years since diagnosis	15.8 ± 8	14.4 ± 7.4	15.8 ± 8.2	0.46
Female sex, n (%)	58(81.7%)	30(81.1%)	28(82.3%)	0.26
DAS28 (n=170)	5.88 ± 1.41	5.81 ± 1.27	5.97 ± 1.35	0.51
BASDAI (n=91)	5.3 ± 2	5.0 ± 1.7	5.4 ± 1.9	0.44
HAQ	1.79 ± 0.6	1.71 ± 0.6	1.82 ± 0.6	0.17
Associated disease, n (%)				
DM, n (%)	25 (35.2%)	8 (21.6%)	17 (50%)	0.03
Concomitant medication				
GCs, n (%)	53 (74.6%)	24 (64.9%)	29 (85.3%)	0.06
DMARDs, n (%)	65 (91.5%)	34 (91.9%)	31 (91.2%)	0.58
Antihypertensive, n (%)	25 (35.2%)	15 (40.5%)	10 (29.4%)	0.29
Anticonvulsant, n (%)	2 (2.8%)	2 (5.4%)	0 (0%)	0.32
Chronic inflammatory arthritis				
RA, n (%)	51 (71.9%)	24 (64.9%)	27 (79.4%)	0.14
AS, n (%)	15 (21.1%)	9 (24.3%)	6 (17.6%)	0.25
PA, n (%)	5 (7%)	2 (5.4%)	3 (8.8%)	0.37
TNF $\alpha$ blockers				
IFX, n (%)	38 (53.5%)	22 (59.5%)	16 (47.1%)	0.07
ADA, n (%)	19 (28.2%)	13 (35.1%)	8 (23.5%)	0.25
ETN, n (%)	14 (16.9%)	10 (27%)	4 (11.8%)	0.09

DAS28: Disease Activity Score-28; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; HAQ: Health Assessment Questionnaire; RA: rheumatoid arthritis; AS: ankylosing spondylitis; PA: psoriatic arthritis; DM: diabetes mellitus; GCs: glucocorticoid steroids; DMARDs: disease-modifying anti-rheumatic drugs; IFX: infliximab; ETN: etanercept; ADA: adalimumab.



**Table 4 - Final logistic regression model of the significant risk factors associated with CAEs in 257 patients with chronic inflammatory arthritis taking TNF- $\alpha$  blockers.**

	OR (95% CI)	p-value
Age †	1.09 (1.05-3.72)	0.03
Female sex	2.84 (1.90-5.63)	<0.001
RA	1.89 (1.11-4.62)	0.02
Disease activity index ††		
DAS28 (n = 170)	1.52 (1.2-4.68)	0.03
BASDAI (n = 91)	1.13 (1.02-6.37)	0.045
GCs	1.21 (1.09-8.15)	0.037
IFX	1.60 (1.06-4.01)	0.01

Final logistic regression model: RA: rheumatoid arthritis; DAS28: Disease Activity Score-28; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; GCs: glucocorticoid steroids; IFX: infliximab; CI: confidence interval; †: for each additional year; ††: for each additional unit.

**Table 5 - Strategies used regarding immunobiological agents following adverse skin events.**

Strategy – Discontinuation	n
Temporary	34 (47.9%)
Definitive	37 (52.1%)
Replace with other anti-TNF $\alpha$	33 (46.5%)
Replace with other non-TNF $\alpha$ blocker	4 (5.6%)

factors following multiple statistical adjustments. The time since diagnosis exhibited multi-collinearity with age and was therefore removed from the final model. No protection factors were identified. The PASI did not remain in the model following the statistical adjustments, whereas IFX remained in the model even after controlling for frequency, duration of use and exposure.

## DISCUSSION

TNF- $\alpha$  blockers are associated with a variety of potentially serious adverse events, especially allergic/immune-mediated phenomena and opportunistic infections or infections caused by common germs involving the skin and internal squamous mucosae.

Our findings demonstrate that CAEs are frequent in the clinical practice of rheumatology, affecting approximately 25% of patients with CIA who use TNF- $\alpha$  blockers, with a high incidence (73.85 in every 1,000 patient-years). Moreover, advanced age, female sex, RA, disease activity and current use of GCs and IFX were the main risk factors significantly associated with CAEs. Thus, patient-related aspects, the diagnosis and the TNF- $\alpha$  blocker itself play relevant roles in the clinical condition and management of affected individuals.

The pharmacological and biochemical properties of three TNF- $\alpha$  blockers could explain the variations in the risk of infection and other adverse reactions. Chimeric (IFX) and human (ADA/GOL) monoclonal antibodies neutralize soluble, membrane-bound TNF- $\alpha$  to a greater extent and for a longer time, whereas ETN only binds to the soluble fraction in an irreversible manner over a shorter time span. In addition, IFX and ADA/GOL more strongly promote apoptosis, along with significant dose-dependent reductions in the level of interferon-gamma (IFN- $\gamma$ ), whereas ETN does not demonstrate these characteristics. Furthermore, this

reduced level of IFN- $\gamma$  could be associated with the failed inhibition of pathogen growth, especially intracellular pathogens (25).

Notably, the spectrum of infectious conditions is quite variable, depending on the country of registry and the type of TNF- $\alpha$  blocker used. The French registry (RATIO) found that 33% of non-tuberculosis opportunistic infections among users of TNF- $\alpha$  blockers were bacterial (listeriosis, nocardiosis, atypical mycobacteria, non-typhoid salmonellosis), whereas 40% were viral (severe herpes zoster [shingles], chicken pox, disseminated herpes simplex, disseminated cytomegalovirus), 22% were fungal (pneumocystosis, invasive aspergillosis, cryptococcosis), and 4% were parasitic (leishmaniasis). Furthermore, nearly 25% of patients required hospitalization in intensive care, and the mortality rate was 10%. The main risk factors associated with these infections were treatment with IFX (OR = 17.6; 95% CI: 4.3 to 72.9;  $p < 0.0001$ ) or ADA (OR = 10; 95% CI: 2.3 to 44.4;  $p = 0.002$ ) vs. ETN and previous use of GCs (OR = 6.3; 95% CI: 2 to 20;  $p = 0.002$ ) (26). Lower hospitalization and mortality rates were observed in the present study, which was undertaken at a tertiary university hospital and which involved patients with long-standing diagnoses and other factors associated with a poorer prognosis; however, no cases of non-tuberculosis opportunistic infection were observed over the 5 years of follow-up.

According to a recent retrospective analysis (1998 to 2005) involving more than 20,000 RA patients, including nearly 4,000 users of TNF- $\alpha$  blockers, the risk of hospitalization due to infection, especially of the skin or airways, was greater following the chronic use of GCs (hazard ratio [HR] = 2.14; 95% CI: 1.88 to 2.43), even after controlling for demographic variables, comorbidities and traditional DMARDs. With some TNF- $\alpha$  blockers, the risk was 24% greater (HR = 1.24; 95% CI: 1.02 to 1.5), particularly when IFX was used (HR = 1.51; 95% CI: 1.14 to 2.0). In addition, the hospitalization rate was 7%, mainly in the first 6 to 12 months of treatment (27).

In the present study, the use of GCs was associated with a greater chance of experiencing a CAE. Interestingly, the greater risk of infection among RA patients has not achieved statistical significance in randomized clinical trials, which might reflect the heterogeneity of the samples and the exclusion of patients with multiple comorbidities. However, the association has been significant in real-world reports, as observed in the present investigation and in previous observational studies (risk ratio [RR] = 1.67; 95% CI 1.49 to 1.87) (28). It should also be emphasized that current use of GCs was not a protective factor against allergic or immune-mediated CAEs in the present study.

Benucci et al. found no significant differences among TNF- $\alpha$  blockers in terms of the incidence of acute and late-onset hypersensitivity (infused or local) during the first year of treatment (29). In the present study, immune-mediated reactions, especially types I and III hypersensitivity, were more common than infectious CAEs, and interestingly, type II reactions were infrequent (7).

Four CAEs were unexpected in the present cohort, including two cases of immune-mediated reactions (psoriasis-like lesions and SLE) and two representative cases of latent infection (lepromatous leprosy and herpes zoster). Although TNF- $\alpha$  blockers have been widely used for the treatment of psoriasis and PA in patients with inadequate responses to conventional DMARDs (3,5), this treatment



might paradoxically also induce psoriasis-like lesions, even among individuals with no personal or family history of psoriasis, as observed in three patients in our sample. These lesions are generally new, but some studies have reported a worsening of preexisting lesions (psoriasis “de novo” or psoriasis-like rash) (30), and such lesions are more common in women, with a predilection for palm or plantar involvement or in uncommon regions of the body, such as the groin and pubic region, and they more commonly emerge between 12 weeks and 12 months after the onset of therapy (30-33). In the present study, serology was negative for human immunodeficiency virus, and no sex differences were found. Moreover, there was no evidence of palm or plantar involvement, and all of the cases were associated with IFX. Curiously, patients with inflammatory bowel disease who received IFX did not appear to be at a greater risk for CAEs, unlike those with CIA (15). Patients with JIA were reported to experience greater difficulty in controlling these lesions, even after the withdrawal of anti-TNF- $\alpha$  therapy (34).

According to the British Society for Rheumatology Biologics Registry (2001 to 2007), the incidence of psoriatic lesions in a group of 9,826 RA patients taking TNF- $\alpha$  inhibitors, especially those using ADA, was 1.04 per 1,000 patient-years (95% CI: 0.67 to 1.54), which is equivalent to 25 new cases of psoriasis. In contrast, no cases were found in the group of 2,880 patients with RA treated with DMARDs only (33).

The first hypothesis to explain this association would be initial diagnostic error, as these lesions could actually be part of the spondyloarthritis spectrum, and the association with psoriasis could be nothing more than the natural history of the disease (33). Subsequently, a modified Th1 response caused by TNF- $\alpha$  blockers and the direct role of TNF- $\alpha$  itself were indicated as the most likely mechanisms, as the inflammatory response in plaque psoriasis is traditionally initiated by the activation of T cells (30,35). Furthermore, the inhibition of TNF- $\alpha$  reduces the migration of lymphocytes from the skin to the lymph nodes, and this imbalance can promote a relative increase in IFN- $\gamma$  and intensive activation of T cells, with a resulting increase in psoriatic lesions (32). Other cytokine receptors have also been cited in this process, such as CXCR3 (36). In addition, IFN- $\alpha$ , IL-17 and IL-23 have recently been reported to constitute another pathophysiological mechanism involved in psoriasis-like processes (30,37). A number of authors also believe that greater exposure to infectious agents, stemming from heightened susceptibility following anti-TNF- $\alpha$  therapy, represents another probable hypothesis (31,38); the most commonly cited triggering microorganisms include Gram-positive cocci (39) and, more recently, chlamydia (31).

TNF- $\alpha$  blockers are associated with the generation of autoantibodies, including human anti-chimeric and anti-human antibodies, as well as potentially clinically important autoimmune involvement (39-41). The most prevalent autoantibodies are generally directed against the nucleus (AAN, anti-histone and anti-DNA), but antibodies are also formed against membrane phospholipids (anticardiolipin) (40,41). Clinically, these autoantibodies can induce SLE, preferentially affecting the skin, joints and, less frequently, the blood and kidneys (42-46).

No risk factors (previous positivity for autoantibodies, age, prolonged GC use or administration of other medications traditionally related to drug-induced lupus) have yet

been identified as being associated with a greater chance of stimulating lipopolysaccharide-induced TNF production. Although a recent literature review indicated that IFX and ETN represented the drugs most associated with lipopolysaccharide-induced TNF production (42), no recommendations have been reported for the study of autoantibodies in patients with an indication for anti-TNF- $\alpha$  therapy. In one patient in the present study, lipopolysaccharide-induced TNF disappeared following the discontinuation of ETN and initiation of GCs, and adequate clinical and laboratory control of the disease was achieved with RTX.

Because TNF is important for the formation and maintenance of granulomas, TNF- $\alpha$  blockers can disorganize this process, resulting in the reactivation of latent granulomatous infections, such as tuberculosis and LL. According to the Food and Drug Administration database, the incidence of infection with *Mycobacterium leprae* is low (0.1%) and more closely related to IFX therapy (47). In the present sample, the Virchowian form of Hansen’s disease emerged soon after the use of ADA, requiring prolonged specific treatment and difficult management of the joint condition (10).

Anti-TNF- $\alpha$  therapy could also be associated with the reactivation of latent viral infections, such as herpes zoster, which has traditionally been reported in patients with some degree of immunosuppression. The incidence of viral reactivation per 1,000 patient-years was shown to be approximately two-fold greater (11.1; 95% CI: 7.9 to 15.1) for patients treated with monoclonal antibodies, compared to those treated with traditional DMARDs (5.6; 95% CI: 3.6 to 8.3), especially among older patients and among those using concomitant GCs (12). After assessing the German biologics registry database (RABBIT) and more than 5,000 RA patients administered biologic agents between 2001 and 2006, Strangfeld et al. identified 86 cases (16.3%) of reactivation of shingles in 82 individuals; of these, 39 cases were temporarily related to treatment with ADA or IFX, 23 were related to ETN, and 24 were related to traditional DMARDs (11). Similarly, in a retrospective study, McDonald et al. assessed more than 20,000 RA patients from the Veterans Affairs Healthcare System (1998 to 2005), and they found an incidence of 9.96 episodes/1,000 patient-years. The main risk factors in this previous study were age, prolonged GCs, cancer, chronic liver and lung disease, immunosuppressants and kidney failure; ETN and ADA exhibited a smaller risk than IFX (12).

Non-melanoma skin tumors constitute another commonly reported skin manifestation among patients taking TNF- $\alpha$  blockers, with a relative risk of 2.02, according to a recent meta-analysis involving three TNF- $\alpha$  blockers (15). These findings suggest that factors related to the immunopathology of the skin, especially cells of the innate immune system, such as dendritic cells, could play a crucial role in the interrelationship of these events. However, further prospective studies are needed to better establish this association.

The present study demonstrated certain strengths that should be highlighted, such as the long-term follow-up of patients with CIA who were taking TNF- $\alpha$  inhibitors. Moreover, the diagnostic accuracy of CAEs using gold-standard methods, including dermatologic evaluation, biopsies and cultures, should be noted. However, the lack of a control group using DMARDs only was the main limitation of this longitudinal cohort study.



Rheumatologists and dermatologists should be aware of the potential risks with TNF- $\alpha$  blockers, especially infectious and immune-mediated adverse skin events, to establish an early diagnosis and to make proper treatment decisions. Furthermore, the adequate determination of epidemiological and personal historical data (previous or recurrent infectious conditions, subclinical fungal infections, oral microbiota and oral health status) is fundamental to the recognition and minimization of CAEs related to immunobiological therapy.

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## AUTHOR CONTRIBUTIONS

Machado NP performed the clinical and rheumatologic examinations, sample collection and processing, data analysis and drafting of the manuscript. Soares MR and Freitas DS recruited patients and helped with the data analysis. Soares MR participated in the design of the study and helped with the data analysis. Neto ET and Ciconelli RM participated in the design of the study and helped with the data analysis and drafting of the manuscript. Machado NP and Porro A performed the skin biopsies. Pinheiro MM participated in the design of the study, performed the rheumatologic examinations and helped with the data analysis and drafting of the manuscript.

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