Anti-TNFα therapy in the management of psoriasis: experience of a state referral center*

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Abstract: BACKGROUND: Psoriasis is a chronic immune-mediated disease, characterized by increased levels of TNFα. Anti-TNFα agents have revolutionized the treatment of severe psoriasis by targeting an important molecule involved in its pathogenesis.
OBJECTIVES: We report the experience of a state referral center that uses anti-TNFα agents for psoriasis.
METHODS: We conducted a retrospective case series. Seventy-four out of 120 patients met the inclusion criteria. Clinical and laboratory data was analyzed using the chi-squared, Wicoxon and McNemar's tests. Associations were considered statistically significant when p-value<0.05.
RESULTS: Forty-one subjects (55.40%) were male, with a mean age of 47.69±14.99 years. Median disease duration and pre-treatment PASI were 14.0 months (IQR 9.0-20.0), and 13.55 points (IQR 8.5-20.32). Sixty patients (81.10%) had arthropathic psoriasis. Forty-six subjects (62.20%) had comorbidities; the most frequent was dyslipidemia (25.70%). In 55.40% of patients, insufficient response to conventional therapies was the principal indication for using anti-TNFα drugs. Clinical improvement occurred in 93.20% of cases, and the post-treatment PASI median was 0.0 points (IQR 0.0-0.0). Adverse effects occurred in 6.80% of patients. Infections and elevation of transaminases occurred in 28.40% and 8.10% of cases, respectively.
CONCLUSION: Post-treatment reduction in PASI was satisfactory and the occurrence of adverse effects was minor, mostly mild infusion effects and local reactions at drug administration sites.
Keywords: Psoriatic arthritis; Psoriasis; Tumor necrosis factor-alpha

INTRODUCTION

Psoriasis is a chronic immune-mediated disease, characterized erythematous scaly lesions and is currently recognized as an inflammatory disorder with systemic impact, whose pathogenesis involves the deregulation of lymphocyte function, whereas the clinical repercussions of the disease are caused by signaling processes that culminate in abnormal proliferation of keratinocytes.[1-4] These factors mean that psoriasis can be considered a prototype of Th1/Th17 disease: increased pro-inflammatory cytokines, such as IL2, INFγ and TNFα, and decreased anti-inflammatory cytokines, such as IL10.[5] Parallel to these findings, psoriasis treatment has progressed considerably, targeting the specific immunological events of this condition. Biopharmaceuticals represent an alternative to conventional treatment for severe and resistant forms of the disease. The Dermatology Service of the Complexo Hospitalar Universitário Prof. Edgar Santos (C-HUPES/UFBa) introduced the use of these drugs in the Brazilian Northeast in 2005, for the treatment of psoriatic arthritis and plaque psoriasis. The present study describes the experience of seven years of immunobiological drugs for psoriasis in our outpatient clinic.

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METHODS

A case series was conducted with patients attending the outpatient clinic of the Psoriasis C-HUPES/UFBa in Salvador, Bahia, Brazil, including patients with regular follow-up at the service and using immunobiological agents for at least 90 days. Clinical and laboratory data were collected through patients' medical records, which included age, gender, time of disease, clinical form of psoriasis, previous treatment, familial history, PASI, history of infections, side effects during treatment with biologic, comorbid conditions, serum transaminases and others. The study protocol was duly approved by the Research Ethics Committee of the establishment.

The data were stored and analyzed with SPSS® 18.0 for Windows. Descriptive statistics were used to characterize the population studied (mean, standard deviation, absolute and relative frequency). Median and interquartile ranges (IQR) were used for variables with asymmetrical distribution (time of disease, treatment duration and PASI). To investigate the association between the variables, we used the chi-squared, Wicoxon and McNemar's tests, and associations were considered significant when the calculated *p*-value was lower than 0.05.

RESULTS

The medical records of 120 patients treated in our outpatient clinic were assessed and 74 met the previously established inclusion criteria. Forty-one patients (55.40%) were male and the mean age of the population studied was 47.69±14.99 years, ranging from 13.0-92.0. The median time of disease was 14.0 months (IQR 9.0-20.0). The most prevalent clinical form was arthropathic psoriasis, in 60 patients (81.10%). Only 8 subjects (10.85%) had a positive familial history for the condition. The summarized clinical data for these patients is displayed in table 1.

Comorbidities were observed in 46 patients (62.20%), and dyslipidemia was the most common (19 subjects, 25.70%). The frequencies of the comorbid conditions found in our patients are shown in table 2.

Seventy-one patients (95.90%) had been treated with traditional therapies before the indication of immunobiologics. Forty-nine individuals (66.20%) were treated simultaneously with methotrexate, in doses ranging from 10 to 15mg/week. Other therapeutic modalities used with anti-TNFα agents included acitretin, cyclosporine and phototherapy. Table 3 illustrates the frequencies of their utilization with and before biologic therapy.

The main indication for therapy with immunobiologics was an insufficient response to standard therapies, in 55.40% (41) of patients. The combination of insufficient response or toxicity to conventional therapies and disease severity accounted for 37.80% (28) of the reasons for indication. Individually, the toxicity of other treatments and severity of psoriasis accounted for 4.10% (3) and 2.40% (2) of indications, respectively.

TABLE 1: Summarized clinical data of the 74 patients. Age is described as mean ± standard deviation, and time of disease is displayed as median and interquartile range. All other variables are displayed as relative and absolute frequency (outside and inside the parentheses, respectively)

Gender		
	Male	55.4% (41)
	Female	44.6% (33)
Age (years)		
	Mean	47.69±14.99
	Range	13.0-92.0
Time of disease (years)		
	Median	14
	Interquartile range	9,0-20,0
Comorbid conditions		
	Yes	62.2% (46)
	No	37.8% (28)
Clinical forms of disease		
	Arthropathic	81.1% (60)
	Vulgar	16.2% (12)
	Palmoplantar	1.4% (1)
	Pustular	1.4% (1)
Familial history for psoriasis		
	Positive	10.85% (8)
	Negative	89.12% (66)

TABLE 2: Frequency of comorbid conditions in the 74 patients. Relative and absolute frequency are displayed outside and inside the parentheses, respectively

Comorbid condition	**Frequency**	
Dyslipidemia	25.7%	(19)
Arterial hypertension	24.3%	(18)
Depression	13.5%	(10)
Diabetes mellitus	12.2%	(9)
Obesity/overweight	6.8%	(5)
Atopy	1.4%	(1)
Others*	24.3%	(18)
No comorbid condition	37.8%	(28)

*Other comorbidities include hepatitis C, HTLV infection, nephrolithiasis, bipolar disorder, coronary artery disease, heart failure, portal fibrosis, renal failure, osteopenia and hydronephrosis.

Table 3: Frequency of use of other therapeutic modalities before and during treatment with anti-TNFα agents

	During anti-TNFα treatment		Before anti-TNFα treatment		p-value*
Methotrexate	42	(56.75%)	65	(87.83%)	0.00116
Acitretin	0	(0%)	33	(44.59%)	0.00011
Cyclosporine	0	(0%)	33	(44.59%)	0.00011
PUVA	1	(1.35%)	19	(25.67%)	0.00000

*McNemar's Test

The immunobiologicals available in our service are infliximab, etanercept and adalimumab, with the following, respective, frequency rates of use: 48.60% (36 patients), 32.4% (24 patients) and 18.90% (14 patients). The median treatment period with anti-TNFα agents was 18.0 months (IQR 9.0-36.0). These data are shown in table 4. The median pre-treatment PASI was 13.55 points (IQR 8.5-20.32), and the post-treatment PASI was 0.0 points (IQR 0.0-0.0), measured after completing treatment or at the last consultation (Table 5). Clinical improvement occurred in 93.20% (69) patients, taking into account the PASI (Wicoxon test *p*-value=0,062).

Of the 74 patients included, 14 (18.90%) needed to change their immunobiologic agent, the main reason being insufficient responses to the drugs used, in 13.50% (10 patients). Three patients (4.10%) had indication to change the immunobiologic due to side effects. One patient (1.40%) had his medication substituted due to a combination of these two factors. A second change of immunobiologic drug was necessary in 3 patients (4.10%), and a third in 1 patient (1.40%), all motivated by an unsatisfactory response to therapy. Adverse events occurred in 5 patients (6.80%), the most common being infusion reactions in 4 patients (80% of them)

During the assessment to indicate treatment with immunobiologics, 19 patients (25.70%) tested positive for tuberculin, who then underwent 6 months of chemoprophylaxis with isoniazid. There were no cases of active infection with the tuberculosis bacillus.

Table 4: Distribution of anti-TNFα treatment according to frequency and duration of treatment (as mean ± standard deviation) in months

	Frequency
Anti-TNFα agent used	
Infliximab	48.6% (36)
Etanercept	32.4% (24)
Adalimumab	18.9% (14)
Duration of treatment (months)	
Mean	22.06±15.7
Range	3-72

Table 5: PASI values before and after treatment with anti-TNFα agents, described as median and interquartile range

	PASI (points)	p-value*
Pre-treatment		0.062
Median	13.55	
Interquartile range	8.5-20.32	
Post-treatment		
Median	0.0	
Interquartile range	0.0-0.0	

*Wicoxon test.

During treatment, infections occurred in 28.40% (21) of patients. The most common was respiratory tract infection (12.20%; 9 patients), followed by urinary tract infection (2.70%; 2 patients), pneumonia (2.70%; 2 patients) and other infections (10.80%; 10 patients).

Elevated hepatic enzymes in amounts at least twice greater than the reference value were observed in 6 (8.10%) patients. The presence of comorbid conditions was positively correlated with the occurrence of transaminase elevations (chi-squared test *p*-value<0.05), and 3 were taking concomitant methotrexate.

DISCUSSION

The advent of immunobiological agents revolutionized the treatment of psoriasis. Our outpatient clinic is the state referral center in dermatology, performing the treatment of the vast majority of patients with moderate to severe psoriasis in Bahia, Brazil. Data from our series show that most patients using immunobiologics are middle-aged males, previously treated with more than one conventional therapy and having at least one comorbidity, particularly hypertension and dyslipidemia. Compared with the general population, patients with psoriasis are more likely to have associated comorbities, including heart disease, depression, arthritis, hypertension and dyslipidemia.[6] A study carried out at our institution has demonstrated that psoriasis is associated with overweightness and obesity, the etiopathogenic link being chronic and mild systemic inflammation.[7]

Psoriatic arthritis is considered a common manifestation, observed in 40% of patients with moderate to severe psoriasis. In our study, the prevalence was much greater, affecting 81% of the subjects. The prevalence of depression in our patients was 13.5%, considerably lower than the rate mentioned in publications from this field (about 32 to 60%).[8] We believe that this condition has been underestimated, requiring greater attention in order to intervene effetcively in improving the quality of life of patients.

Many indications for treatment were due to the safety profile of immunobiological agents regarding liver and kidney toxicity (31 patients; 41.90%), contraindicating other therapies. The safety profile of anti-TNFα agents for patients with comorbidities was analyzed recently by Kimball *et al*. No significant difference has been demonstrated regarding changes in blood pressure, blood glucose or bodyweight, when compared with placebo. Also, the same study found no difference in the occurrence of serious adverse events among the same population.[6]

Biologics seem to be a safe choice for patients with chronic infections. Our series includes a 72-year-old man with psoriatic arthritis, and infected with the hepatitis C virus (HCV), who was successfully treated using etanercept for 3 years and infliximab for 2 years, without any complications registered thus far. The management of patients with hepatitis C and psoriasis is seen as a major challenge, since most traditional therapies are hepatotoxic and/or immunosuppressive drugs, while the main treatment for HCV worsens psoriasis.[9] Another patient of ours with positive serological tests for HTLV, has been on etanercept for 18 months without intercurrences.

One of our patients developed Hodgkin lymphoma during treatment with adalimumab, after 18 months using the medication. Once treatment was interrupted, the patient was taken to the hematology-oncology service, which initiated chemotherapy, with good responses. The risk of patients on adalimumab-developing this malignancy has been researched previously. Although the risk for patients with psoriasis vulgaris is equal to zero relative to the overall population, the respective values for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and juvenile idiopathic arthritis, are 0.12, 0.2, 0.08, 0.08 and 0.08.[10] Though further studies are required to clarify this association, we recommend caution with regard to this complication.

Adverse events were rare, occurring only in 5 (6.75%) patients. In 60% (3) of these cases, gravity was enough to indicate achange of anti-TNFα. Though these events occurred predominantly during treatment with infliximab, there was no statistical significance in this association. Current literature suggests that most common adverse events are infusion reactions for infliximab, and injection site reactions for etanercept and adalimumab.[11,12]

A prospective study involving 174 patients carried out in Holland found that 28% of patients experienced serious adverse events related to biological therapy, including an increased risk of nonmelanoma skin cancer.[13] In our experience with immunobiologics, no patient has developed skin cancer or presented serious adverse reactions.

Most patients remain on the same drug throughout treatment. At the time of analysis, 36 subjects were using infliximab, 24 were on etanercept, and 14 were using adalimumab. This distribution stems from several factors, including the first release and provision of infliximab and etanercept by the State Health Secretary (high-cost medications program). Meanwhile, loss of drug response was the main reason for patients being indicated for changes inimmunobiologics.

Despite belonging to the same pharmacological group, anti-TNFα agents have individual characteristics which differentiate them from one another, thus providing different results. The risk involved in patients receiving monoclonal anti-TNFα agents to produce neutralizing antibodies is well-known, and it could be a reason for loss of drug response, although we cannot confirm this in the subjects examined. The presence of these antibodies was detected in 49% of patients receiving adalimumab after 24 weeks of therapy. The degree of therapeutic response was also inversely proportional to the serum levels of these antibodies.[14] The EXPRESS 2 study also correlated the presence of neutralizing antibodies to a decrease in clinical response to infliximab, though its mere presence is not regarded as constituting treatment failure.[11,15,16] Regarding etanercept, it is known that up to 5% of patients develop antibodies against the medication. However, their involvement in drug efficacy is unclear. Thus, primary and secondary failures occur in response to all inhibitors of TNFα agents, but the presence of antibodies cannot be considered the only explanation for loss of effectiveness.[17]

Serum levels of the drug must also be considered in the context of a therapeutic failure. The infliximab dose is calculated per kilogram of bodyweight, while etanercept and adalimumab are administered infixed doses, which could explain an inadequacy of serum levels of the substance in certain patients. In a study by Van Lumig*et al*., of the 5 patients that used etanercept and adalimumab and experienced therapeutic failure, 3 were obese. They responded well to adalimumab with increased doses and frequency of injections.[18] We believe that patients with significant obesity experience loss of response due to the inadequacy of the dose/body weight ratio.

In our assessment, 93.2% of patients showed clinical improvement with the introduction of immunobiologic agents. This improvement was assessed by dermatological consultation, physical examination and improved quality of life. Although we did not observe a statistically significant difference between the pre- and post-treatment PASI (Wicoxon test *p*-value=0.062) in this study, this is probably due to the relatively small number of patients included and the inherent methodological limitations of a retrospective study.

Regarding the risk of infections, 21 patients presented infectious processes during treatment, and infection of the upper airways was the most prevalent. Although most infectious processes were mild, 1 patient treated with infliximab died due to urinary tract infection sepsis. It was an elderly individual with multiple comorbid conditions, whose medication was discontinued immediately after initiation of the clinical picture. Although there is a theoretical risk of an increase in infectious processes when treating with biological therapy, no studies comparing placebo with TNFα inhibitors have shown a statistically significant increase in infection rates.[11]

In 6 patients, there was an increase in liver enzyme levels, all of which were under twice the reference value. In 3, methotrexate was associated with biological treatment, and they all had comorbid conditions (chi-squared *p*-value<0.05), 2 with schistosomotic portal fibrosis and 1 with a history of alcoholism.

CONCLUSION

Although immunobiologics are available for a considerable period of time, investigation into their long-term safety and side effects is still needed. The high costs associated with treatment and the fear of long-term effects remain important factors in selecting these drugs.

Finally, though the present study has several limitations inherent to a retrospective design, we emphasize the importance of disseminating local experiences of use of these drugs. ❑

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