

# *Immediate complications of 3,555 injections of anti-TNF $\alpha$*

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## ABSTRACT

**Objective:** To evaluate the immediate complications of anti-TNF $\alpha$  drugs at the “Center for Dispensation of High Cost Medications” of HC-FMUSP. **Patients and Methods:** All patients who received anti-TNF $\alpha$  agents between August 2007 and March 2009 were included in this study. Immediate complications (up to 1 hour after the injection) were classified as mild (headache, rash, dizziness, itching, nausea), moderate (fever, urticaria, palpitation, chest pain, dyspnea, blood pressure variations between 20 and 40 mmHg), or severe (fever with chills, dyspnea with wheezing, variations in blood pressure > 40 mmHg). **Results:** Two hundred and forty-two patients were evaluated: 94 (39%) with rheumatoid arthritis, 64 (26%) with ankylosing spondylitis, 32 (13%) with psoriatic arthritis, 26 (11%) with juvenile idiopathic arthritis; and 27 (11%) with other diagnoses. A total of 3,555 injections were administered: 992 (28%) adalimumab, 1,546 (43%) etanercept, and 1,017 (29%) infliximab. Immediate adverse events were observed in 39/242 (16%) patients. Injection-related complications were observed in 46/3,555 (1.2%) injections. They were more common with infliximab than adalimumab (3.7% vs. 0.5%,  $P < 0.0001$ ) and etanercept (3.7% vs. 0.25%,  $P < 0.0001$ ). Complications were classified as mild 14/45 (31%), moderate 21/45 (47%), and severe 10/45 (22%), and occurred mainly in the first six months of treatment (56%) and after intravenous injections, especially (76%) in the first hour. **Conclusion:** Although rare, acute reactions can be severe, being observed more commonly after the initial injections, both intravenous and subcutaneous. More studies are necessary to define whether those immunobiological agents should be administered only in facilities capable of managing medical emergencies.

**Keywords:** anti-TNF $\alpha$ , infliximab, etanercept, adalimumab, acute adverse reactions.

## INTRODUCTION

The introduction of tumor necrosis factor-alpha (TNF $\alpha$ ) antagonists have resulted in considerable progress in the treatment of rheumatologic diseases, especially rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and spondyloarthropathies refractory to conventional treatment disease-modifying anti-rheumatic drugs (DMARDs).<sup>1-6</sup> With increasing experience in the use of those biological agents,

besides concerns regarding their efficacy, it is necessary to guarantee the safety during administration. Acute reactions represent an important problem associated with the use of those agents.<sup>1,4,7-18</sup>

Anti-TNF $\alpha$  agents currently approved for use in Brazil to treat patients with rheumatic disorders include infliximab, etanercept, and adalimumab. Infliximab is an anti-TNF $\alpha$  chimeric monoclonal antibody composed by a sequence of

Received on 07/01/2009. Approved on 03/03/2010. We declare no conflict of interest.

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peptides, 75% human and 25% murine, and it is the agent most commonly associated with acute infusion reactions.<sup>1,7,12</sup> Etanercept is a soluble recombinant TNF $\alpha$  receptor composed by a dimeric fusion protein containing a human IgG1 constant region and variable regions of the murine antibody.<sup>2</sup> Similar to infliximab, adalimumab is a monoclonal antibody that causes direct blockade of TNF $\alpha$ , but differ from that agent since it is fully humanized.<sup>4</sup>

Local reactions are among the most common side effects in patients treated with subcutaneous anti-TNF $\alpha$  antagonists (etanercept and adalimumab),<sup>4,5,14</sup> but, usually, they do not represent a contraindication to continue the treatment. On the other hand, acute reactions can be severe and, although subcutaneous agents are prescribed for in-home administration, side effects are not restricted to intravenous drugs. Anaphylaxis and angioedema have been reported with both administration routes, reinforcing the need of patient supervision.<sup>11,15-17</sup>

Acute reactions could be explained both by immunologic mechanisms (IgE-mediated), such as urticaria, bronchospasm, hypotension, and tachycardia, and non-allergic mechanisms, resulting in non-specific reactions, such as rubor, diaphoresis, chills, nausea, headache, and chest pain.<sup>7-13</sup>

Usually, signs and symptoms associated with immediate reactions improve by reducing the rate of administration, in the case of infliximab, and treatment with acetaminophen and antihistamines. Severe cases require the use of corticosteroids, NS, and even adrenaline.

The objective of the present study was to evaluate the prevalence and severity of immediate adverse reactions in a large number of intravenous and subcutaneous administrations of those drugs in a university reference center.

## PATIENTS AND METHODS

### Patients undergoing anti-TNF $\alpha$ therapy

From August 2007 to March 2009, 242 patients who received anti-TNF $\alpha$  at the Center for Dispensation of High Cost Medications (CEDMAC, from Portuguese) of Hospital das Clínicas of the Medical School of Universidade de São Paulo (HC-FMUSP) were evaluated. All patients signed an informed consent approved by the Ethics Commission for Analysis of Research Projects of HC-FMUSP # 1298/06.

Diseases with indication of anti-TNF $\alpha$  therapy included: RA, ankylosing spondylitis (AS), psoriatic arthritis (PA), and JIA. All patients fulfilled the American College of Rheumatology (ACR)<sup>19</sup> classification criteria for RA, New York<sup>20</sup> criteria for AS, European Spondyloarthropathy Study

Group-ESSD criteria,<sup>21</sup> Moll and Wright classification<sup>22</sup> for PA, and International League of Associations for Rheumatology (ILAR) classification criteria<sup>23</sup> for JIA.

### Routine administration of anti-TNF $\alpha$ drugs

All drugs evaluated were administered at the CEDMAC with supervision for both intravenous (infliximab) and subcutaneous (adalimumab and etanercept) drugs. All patients were evaluated, by a nurse or physician, before every administration, to screen for infections and adverse events.

The following intervals, recommended by the manufactures for the administration of the drugs, were followed: infliximab (at 0, 2, 6 weeks and after every 8<sup>th</sup> week), adalimumab (every 2 weeks), and etanercept (weekly). For infliximab, patients were pre-treated with intravenous anti-histamines (50 mg of diphenhydramine), followed by the intravenous infusion of the drug over 2 hours, for doses of up to 350 mg, or 3 hours, for higher doses, always diluting the medication in 250 mL of NS; this was followed by a 1-hour observation period.

Adalimumab and etanercept were administered subcutaneously, followed by a 1-hour observation period, after the first dose, or 30 minutes, after posterior doses, monitored continuously to detect adverse reactions.

### Immediate complications secondary to the administrations

All signs and symptoms observed by the nursing staff and/or physician, or reported by patients, were considered immediate complications. They were classified as mild (headache, rash, dizziness, pruritus, nausea), moderate (fever, urticaria, palpitation, chest pain, dyspnea, hypotension or hypertension with variation in systolic blood pressure between 20 and 40 mmHg), or severe (high fever with chills, dyspnea with wheezing, hypotension or hypertension with variation in systolic blood pressure > 40 mmHg), according to the literature.<sup>24</sup>

### Statistical analysis

Results are presented in numbers (%). Fisher exact test was used to compare the percentage of immediate adverse reactions for all three anti-TNF $\alpha$  drugs.  $P < 0.05$  was considered statistically significant.

## RESULTS

Among 242 patients evaluated, 94 (39%) had a diagnosis of RA, 64 (26%) AS, 31 (13%) PA, 26 (11%) JIA, and 27

(11%) with other diagnoses (8 enteropathies, 6 adult Still’s disease, 5 Behçet’s disease, 3 reactive arthritis, 1 Schnitzler syndrome, 1 Sjögren’s disease, 1 inflammatory orbital pseudo-tumor, 1 chronic recurring focal osteomyelitis, and 1 fibroblastic rheumatism). During the study period, those patients received 3,555 injections of anti-TNF $\alpha$  agents, 1,017 (29%) for infliximab, 992 (28%) adalimumab, and 1,546 (43%) etanercept.

Immediate complications had an incidence of 45/3,555 (1.3%), affecting 39/242 (16%) patients. The administration of the anti-TNF $\alpha$  agent was discontinued and/or changed in 7/39 (18%) patients with acute reactions. Among those, 5/10 (50%) were patients with severe reactions, and 2/21 (9.5%) were patients with moderate reactions. Patients with adverse reactions were treated immediately at the dispensation center and, whenever necessary, they were transferred to HC-FMUSP emergency room.

### Nature of the complications

Table 1 shows all 45 adverse reactions observed, classified according to severity. Moderate reactions were more frequent, affecting approximately half of the patients (47.8%). Blood pressure variations between 20 and 40 mmHg contributed with 1/3 of the cases. Moderate to severe events represented 69.5% of the reactions, and one patient developed anaphylactic shock.

Ten reactions (22%), usually related to infliximab (8 patients), but also with adalimumab (1 patient), and etanercept (1 patient), were considered severe (Table 2). Fifty percent of those reactions resulted in discontinuation of the drug.

Severe adverse reactions related to adalimumab, etanercept, and infliximab were seen in 1/5 (20%), 1/4 (25%), and 8/36 (22%), respectively, of the total number of complications for each drug.

### Complications according to the drug and disease

Immediate complications were seen in 30 (3.7%) patients, with infliximab, 5 (0.5%) with adalimumab, and 4 (0.25%) with etanercept. Immediate complications were more common during infusions of infliximab than during the administration of adalimumab ( $P < 0.0001$ ) and etanercept ( $P < 0.0001$ ).

Regarding infliximab, complications were more common during the first hour of infusion (76% of the events) and in the initial phase of the treatment (50% up to the 5<sup>th</sup> administration, and 6% in the first infusion). However, reactions were observed up to the 29<sup>th</sup> infusion during the follow-up period. Among subcutaneous administrations, 3/9 (33.3%) were observed in the first administration, one after the administration of

**Table 1**  
Immediate adverse reactions after the administration of anti-TNF $\alpha$  agents

Adverse reactions	n = 45
<b>Mild</b>	<b>14 (31.1%)</b>
Rash	2 (4.4%)
Headache	4 (8.9%)
Dizziness/vertigo	1 (2.2%)
Nausea/vomiting	4 (8.9%)
Chills	1 (2.2%)
Lumbar pain	1 (2.2%)
Abdominal pain	1 (2.2%)
<b>Moderate</b>	<b>21(46.7%)</b>
Fever	1 (2.2%)
Chest pain	2 (4.4%)
Dyspnea	1 (2.2%)
Hypertension	14 (31.1%)
Hypotension	2 (4.4%)
Angioedema	1 (2.2%)
<b>Severe</b>	<b>10(22.2%)</b>
Hypertension	4 (8.9%)
Hypotension	3 (6.7%)
Anaphylactic shock	1 (2.2%)
Fever and chills	2 (4.4%)

adalimumab and two after etanercept. The remaining six reactions developed from three months up to one year of treatment.

The distribution of complications according to the diagnosis demonstrated that the rate is similar among the different diseases investigated ( $P > 0.05$ ): RA [18/94 (19%)], AS [7/64 (11%)], PA [4/31 (13%)], JIA [3/26 (12%)], and other diagnoses [7/27 (26%)].

### DISCUSSION

The present study showed that, although immediate reactions are rare, they are potentially severe, indicating that their administration should be monitored in centers capable of managing medical emergencies.

The advantage of the present study was the use of a standardized protocol for the systematic evaluation of immediate adverse events, which also includes subcutaneous anti-TNF $\alpha$  drugs. Therefore, due to the development, although rare, of severe immediate reactions, the current

**Table 2**Severe immediate complications after the administration of anti-TNF $\alpha$  agents in patients with rheumatic diseases

Gender	Age	Anti-TNF $\alpha$ agent	#	Complication	Treatment and evolution	Suspension	
1	F	56	Adalimumab	13	Hypotension associated with presyncope	Volume expansion	no
2	F	38	Etanercept	1	Hypotension	Volume expansion	yes
3	F	55	Infliximab	5	Fever 39.5 °C + chills	Antipyretics	yes
4	M	67	Infliximab	11	Hypertension	Captopril 50 mg	no
5	M	62	Infliximab	5	Fever 38.4 °C + chills + hypotension	Volume expansion + antipyretics	yes
6	F	37	Infliximab	5	Hypertension	Captopril 50 mg	no
7	F	53	Infliximab	4	Hypotension	Hydrocortisone + volume expansion	no
8	F	52	Infliximab	11	Hypertension	Propranolol	no
9	F	27	Infliximab	3	Anaphylactic shock	Adrenaline, hydrocortisone, volume expansion	yes
10	F	47	Infliximab	3	Hypertension followed by hypotension and suspected stroke	Nitrates + Captopril 50 mg + aspirin + volume expansion + ER Neurology	yes

#: number of doses; F: female; M: male; ER: emergency room.

recommendation of non-supervised administration of subcutaneous agents at home could be rediscussed. The uniformity of the administration protocol for each of the drugs, therefore validating the development of those events, is another important aspect of this study. The use of prophylactic premedication like corticosteroids or anti-histamines has been related with a reduction in the incidence of acute reactions.<sup>25</sup> The findings of the present study are similar to those reported in recent studies that show 8.6% to 23%<sup>8-10,24,26</sup> prevalence of immediate reactions in RA patients, and 13.2%,<sup>8</sup> in AS patients, during the infusion of infliximab. In the majority of the cases, complications occur between the 4<sup>th</sup> and 6<sup>th</sup> administration of the drug,<sup>10,24</sup> which was also observed in the present study. On the other hand, the incidence of those events in JIA observed in the present study, *i.e.*, 12%, is much lower than the 43% reported by a multicenter Brazilian study with children and adolescents with rheumatic diseases (especially JIA) who were treated with infliximab.<sup>26</sup> The route of administration seems to be the most important factor to explain this discrepancy, since all JIA patients in our study were treated with etanercept.

Most immediate reactions were moderate, requiring medical intervention; as for mild reactions, similarly to other reports in the literature, we observed that headache and rash are the most common symptoms.<sup>10,26</sup> Interruption of the drug administration in moderate events was much lower than that of severe events. Comparison with the literature was hindered due to the non-standardized classification of those events in

previous studies.<sup>8,25</sup> Most of the reactions observed could be classified as immune-mediated, since they developed after the first administration, after previous antigen exposure.

Adverse events were much more common with intravenous infusions, with a similar frequency to that of prior studies, especially in groups premedicated with anti-histamines.<sup>27</sup> They do not seem to be related to the disease because the distribution was similar in the different diseases and it is similar to prior studies.<sup>27,28,29</sup>

Systemic reactions to anti-TNF $\alpha$  drugs administered subcutaneously are rarely described, being restricted to case reports, such as angioedema of the face,<sup>17</sup> and retrospective analysis of medical records.<sup>29</sup> The prospective, standardized design of supervised administration of the present study is associated with more reliable identification of those reactions that, although rare, they do occur and are potentially severe. Those findings suggest the need of medical supervision during the administration.

To conclude, immediate reactions to anti-TNF $\alpha$  drugs are rare and potentially severe. They develop, predominantly, in the initial injections, both with subcutaneous and intravenous drugs. Thus, immediate reactions to the administration of those biological agents should be the focus of future studies to assess, more precisely, the need to recommend that subcutaneous agents should also be administered in reference centers capable of handling emergencies.

## ACKNOWLEDGEMENTS

This study received grants from the Research Support Foundation of São Paulo (FAPESP, from Portuguese – 06/61303-7, for CEDEMAC), the National Scientific and Technological Development Council (CNPQ, from Portuguese; 300248/2008-3, for CASS, and 305468/2006-5, for EB), and the Federico Foundation, for JFC and EB. We are grateful to nurse Ana Cristina Yano Endo, nurse's aides Janaina Aragão Silvério, Marta Aparecida Santos, and Sandra da Silva, and the secretaries, Maria Josélia da Silva Pinto, Elaine Cristina Melo de Camargo, and Ivonete Assis Corrêa.

## REFERÊNCIAS

### REFERENCES

- Lipsky PE, van der Heijde DMFM, St. Clair EW, Furst DE, Breedveld FC, Kalden JR *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000, 343:1594-602.
- Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC *et al.* A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000, 343:1586-93.
- Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS *et al.* Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004, 50:1400-11.
- Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA *et al.* Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003, 48:35-45.
- van de Putte LB, Atkins C, Malaise M, Sany J, Russel AS, van Riel PLCM *et al.* Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004, 63:508-16.
- Van der Laken CJ, Voskuyl AE, Roos JC, van Walsum M, de Groot ER, Wolbink G *et al.* Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis. *Ann Rheum Dis* 2006, 66:253-6.
- Cassinotti A, Travis S. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: A critical systematic review. *Inflamm Bowel Dis* 2009.
- Kapetanovic MC, Larsson L, Truedsson L, Sturfelt G, Saxne T, Geborek P. Predictors of infusion reactions during infliximab treatment in patients with arthritis. *Arthritis Res Ther* 2006, 8:R131.
- Augustsson J, Eksborg S, Ernestam S, Gullström E, van Vollenhoven R. Low-dose glucocorticoid therapy decreases risk for treatment-limiting infusion reaction to infliximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007, 66:1462-6.
- Botsios C, Ostuni P, Todesco S. Incidence and management of infusion reactions to infliximab in 186 Italian patients with rheumatoid arthritis: the Padua experience. *Reumatismo* 2005, 57:44-51.
- Chávez-López MA, Delgado-Villafañá J, Gallaga A, Huerta-Yáñez G. Severe anaphylactic reaction during the second infusion of infliximab in a patient with psoriatic arthritis. *Allergol Immunopathol (Madr)* 2005, 33:291-2.
- Baeten D, Kruithof E, Van den Bosch F, Heressens A, Mielants H, Keyser F *et al.* Systematic safety follow up in a cohort of 107 patients with spondyloarthritis treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? *Ann Rheum Dis* 2003, 62:829-34.
- Paltiel M, Gober LM, Deng A, Mikdashi J, Aleseeva I, Saini SS *et al.* Immediate type I hypersensitivity response implicated in worsening injection site reactions to adalimumab. *Arch Dermatol* 2008, 144:1190-4.
- Zeltser R, Valle L, Tanck C, Holyst MM, Ritchlin C, Gaspari AA. Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept: a recombinant tumor necrosis factor alpha receptor: Fc fusion protein. *Arch Dermatol* 2001, 137:893-9.
- Houtman PM, Jansen TL, Blanken R. Anaphylactic reaction in a patient with rheumatoid arthritis: a rare side effect of methotrexate with etanercept as a provoking factor? *J Clin Rheumatol* 2006, 12:321-2.
- Sánchez-Cano D, Callejas-Rubio JL, Ortego-Centeno N, Ruiz-Villaverde R. Urticaria and angioedema in a patient with Behçet's disease treated with adalimumab. *Clin Exp Rheumatol* 2006, 24:S128.
- Nikas SN, Voulgari PV, Drosos AA. Urticaria and angioedema-like skin reactions in a patient treated with adalimumab. *Clin Rheumatol* 2007, 26:787-8.
- Beuthien W, Mellinghoff HU, von Kempis J. Skin reaction to adalimumab. *Arthritis Rheum* 2004, 50:1690-2.
- Arnett FC, Edworthy SM, Bloch DA, Mchane DJ, Fries JF, Coope NS *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988, 31:315-24.
- Bennett PH, Wood PHN. *Population Studies of the Rheumatic Diseases*. New York: Excerpta Medica; 1968, pp. 456.
- Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A *et al.* The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991, 34:1218-27.
- Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973, 3:55-78.
- Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J *et al.* International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004, 31:390-2.
- Protocolo de actuação em caso de reacção à infusão de infliximab. Grupo de Estudos de Artrite Reumatoide da Sociedade Portuguesa de Reumatologia. *Acta Reum Port*. 2005, 30:355-9.
- Bermejo F, López San Román A, Algaba A, van Domselaar M, Carneros JA, Rivero M *et al.* Efficacy of premedication with intravenous corticosteroids and antihistaminics in preventing infusion reactions to infliximab. *Gastroenterol Hepatol*. 2008, 31(10):629-32.

26. Barbosa CMPL, Terreri MTRA, Oliveira SKF, Rodrigues MCF, Bica BERG, Sacchetti S *et al*. Efeitos adversos durante a infusão de infliximabe em crianças e adolescentes: estudo multicêntrico. *Rev Bras Reumatol* 2008, 48(5):278-82.
27. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L *et al*. The incidence and management of infusion reactions to Infliximab: a large center experience. *Am J Gastroenterol* 2003, 98:1315-24.
28. Lequerré T, Vittecoq O, Klemmer N, Goëb V, Pouplin S, Menard JF *et al*. Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. *J Rheumatol* 2006, 33:1307-14.
29. Levälampi T, Korpela M, Vuolteenaho K and Moilanen E. Etanercept and adalimumab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: adverse events and other reasons leading to discontinuation of the treatment. *Rheumatol Int* 2008, 28:261-9.