Moderate to severe psoriasis treated with infliximab - 53 patients: patients profile, efficacy and adverse effects *

Psoríase moderada a grave tratada com infliximabe em 53 pacientes: perfil dos pacientes, eficácia e efeitos adversos

Artur Antonio Duarte [1] Flavia Barbour Chehin [2]

Abstract: BACKGROUND: Psoriasis exerts a significant negative effect on quality of life and is associated with comorbidities. The inflammatory activity of the psoriasis plaques is partially triggered by activation of the Th1 lymphocytes, which release proinflammatory cytokines such as TNF-alpha. Infliximab neutralizes the biological activity of TNF-alpha. Adverse reactions that occur during infusion or up to 24 hours afterwards are referred to as acute reactions. Delayed reactions are those occurring between 24 hours and 14 days after an infusion.
OBJECTIVE: To evaluate the profile of patients with moderate to severe psoriasis that is resistant to conventional treatment, and to assess adverse reactions to infliximab. Methods: Fifty-three patients, 40 men and 13 women, were treated with infliximab. The dose used was 5 mg/kg in weeks 0, 2 and 6 (induction phase), followed by maintenance therapy every 8 weeks.
RESULTS: Of the 53 patients, 6 participated only in the induction phase. These patients reached Psoriasis Area Severity Index (PASI) of 90-100 and opted to discontinue treatment. Forty-seven patients continued therapy with the drug for at least 2-3 years. Of these, 55.3% (n=26) experienced some type of adverse event. Acute adverse events were recorded in 34% of the patients and delayed adverse events in 36.1%. The prevalence of comorbidities was 57.4%.
CONCLUSION: In the present study, infliximab was found to constitute a safe and effective form of therapy. Of the comorbidities recorded in the patients in this study, obesity was associated with a delayed and less effective response to treatment. When adequately monitored, neither acute nor delayed adverse events require discontinuation of therapy, since they do not represent an uncontrolled risk to the patient.
Keywords: Biological treatment; Immunity; Psoriasis; Therapeutics

Resumo: FUNDAMENTOS: A psoríase leva a um impacto negativo significativo na qualidade de vida e está associada a comorbidades. A atividade inflamatória das placas psoríacas se inicia, em parte, pela ativação de linfócitos Th1, que liberam citocinas pró-inflamatórias, como TNF alfa. Infliximabe neutraliza a atividade biológica do TNF alfa. Reações adversas que ocorrem durante a infusão e até 24 horas após são chamadas de agudas. Reações tardias ocorrem entre 24 horas e 14 dias após infusão.
OBJETIVO: Avaliar o perfil dos pacientes com psoríase moderada a grave e resistente ao tratamento convencional, bem como as reações adversas ao infliximabe.
MÉTODO: Foram tratados com infliximabe 53 pacientes: 40 homens e 13 mulheres. A dose utilizada foi 5 mg/kg nas semanas 0, 2 e 6 (fase de indução), seguida da fase de manutenção a cada oito semanas.
RESULTADO: Dentre os 53 pacientes, seis se submeteram apenas à fase de indução, obtiveram Pasi 90-100 e não receberam mais a droga. Quarenta e sete pacientes continuaram recebendo a medicação por pelo menos dois, três anos. Deles, 55,3% (26) apresentaram algum efeito adverso. Os efeitos adversos precoces foram observados em 34% dos pacientes, e os tardios, em 36,1% dos pacientes. Foi encontrada uma prevalência de 57,4% de comorbidades nesses pacientes.
CONCLUSÃO: O infliximabe mostrou-se seguro e eficaz no presente estudo. Dentre as comorbidades associadas aos pacientes neste estudo, a obesidade se relacionou com uma resposta mais tardia e menos eficiente. Efeitos adversos precoces e tardios, quando bem monitorados, não impedem a manutenção da terapêutica e não expõem os pacientes a riscos não controlados.
Palavras-chave: Imunidade; Psoríase; Terapêutica; Tratamento biológico

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[1] Doctorate degree in Dermatology. Head Professor, Santo Amaro School of Medicine, Santo Amaro University (UNISA), São Paulo, Brazil.
[2] Dermatologist, Department of Dermatology, Santo Amaro School of Medicine, Santo Amaro University (UNISA), São Paulo, Brazil.

INTRODUCTION

Psoriasis is a dermatological condition commonly seen in routine clinical practice in Brazil and around the world. It is estimated to affect up to 3% of the population worldwide. [1-4] It is a chronic inflammatory disease with a predilection for the skin and articulations. Its etiology is multifactorial, a consequence of genetic and environmental effects. It is characterized by the hyperproliferation and abnormal differentiation of keratinocytes. The condition is immunologically mediated (Th1) and is associated with comorbidities, principally with the clinical manifestations of the metabolic syndrome, as well as spondyloarthropathies, uveitis and inflammatory bowel syndromes. Psoriasis exerts a significant negative effect on the patient's quality of life and is associated with decreased productivity, depression, alcoholism, smoking and a higher prevalence of malignant diseases. [1,5,6]

The inflammatory activity of plaque psoriasis is partially triggered by activation of T-lymphocytes in the epidermis and dermis. Th1 lymphocytes predominate in the lesions and release proinflammatory cytokines such as TNF-alpha and interleukins (IL) 6 and 8, among others. [7,5] TNF-alpha appears to be the proinflammatory mediator that exerts the greatest effect in the classic inflammation involved in psoriasis, and also participates in various other physiological reactions; consequently, inhibition of TNF-alpha improves psoriasis. The introduction of new therapies aimed at neutralizing these cytokines is therefore fundamental in treating this disease. [8]

Infliximab neutralizes the biological activity of TNF-alpha through its high affinity to the soluble and transmembrane TNF receptors, forming an antigen-antibody complex that prevents the TNF-alpha molecule from binding to receptors in the target cell. Consequently, the cell is no longer exposed to proinflammatory stimulation, inhibiting the cell proliferation that is characteristic of psoriasis and other TNF-alpha-mediated diseases such as rheumatoid arthritis, Crohn's disease, ulcerative rectocolitis and ankylosing spondylitis. [7,9,10]

Despite its efficacy, various side effects and adverse events have been described in the literature and observed in clinical practice with the use of this drug, including the induction and exacerbation of psoriasis [11,5], reactivation of a primary focus of tuberculosis [12,13], induction of pityriasis lichenoides chronica [14], anti-DNA antibody formation [1], lupus-like syndrome [15] and malignancies [16], among others. These adverse events may occur during or after infusions, [17] affecting 3-22% of psoriasis patients treated with anti-TNF-alpha monoclonal antibody [17] compared to 0-2% when the infusion contains only placebo. [18,9] The majority of these reactions are mild to moderate. [17]

Adverse reactions that occur during the infusion or up to 24 hours after it are referred to as acute; however, the majority of reactions occur during the infusion or in the first two hours afterwards. [17,19,20] Symptoms include flushing, a tightness across the chest, nausea, dyspnea, headache, hypo or hypertension, sweating, an increase in body temperature and other symptoms of anaphylaxis such as urticaria and bronchospasm. [17,19,10] Delayed reactions occur between 24 hours and 14 days following infusion, mostly after 5-7 days. The most common symptoms include arthralgia, myalgia, influenza-like symptoms, headache, tiredness, rash and urticaria. [17,9,19,21] The present paper reports the experience with infliximab infusions in 53 patients receiving treatment at the dermatology clinic of the University of Santo Amaro.

MATERIAL AND METHODS

Infliximab, the drug evaluated in this study, is a chimeric monoclonal antibody with a molecular weight of approximately 149,100 daltons. It is composed of human constant and murine variable regions. [1,17] The drug is commercialized in a sterile vial in the form of a white powder that has to be diluted in 10 ml of distilled water, resulting in a pH of approximately 7.2 After dilution, each vial contains 100 mg of infliximab for intravenous administration.

Psoriasis plaques are treated with 5 mg/kg of infliximab at baseline (week 0), at 2 weeks (week 2) and at 6 weeks (week 6) when the induction phase is complete. Infusions are then given every 8 weeks (maintenance phase). At this dose, the half-life of infliximab is between 7.7 and 9.5 days.

Between March 2003 and August 2009, 53 patients (40 men and 13 women) were treated with infliximab at the dermatology clinic of the University of Santo Amaro. The infusions were given in accordance with the guidelines for the use of this drug and the mean time of infusion was approximately two and a half hours.

All patients with moderate to severe psoriasis who failed to respond satisfactorily [Psoriasis Area Severity Index (PASI) ≥ 50] to conventional systemic treatment (methotrexate, cyclosporine, acitretin and phototherapy) or who experienced side effects with it and whose screening laboratory tests were normal or negative (full blood count, liver function tests, serology for HIV and hepatitis B and C, chest x-ray, PPD and test for antinuclear factor) were included in the study. Only patients with purified protein derivative (PPD) ≤ 5 and chest x-rays with no indication of tuberculosis were included.

The protocol for patients in the maintenance phase was as follows:

Clinical examination and laboratory tests (full blood count, urea, creatinine, transaminases) two weeks prior to infusion;

Clinical examination at the time of infusion;

Clinical examination and laboratory tests two weeks after infusion;

Test for antinuclear factor after the infusion phase and 4 weeks after the first, fourth and eighth maintenance doses.

The study evaluated the efficacy of the drug and the acute and delayed adverse events as reported in the literature. [1]

The patient with the longest time of clinical observation had received 40 applications (340 weeks; maintenance) at the time of preparing this report, while the patient with the shortest time of observation had received 7 applications (54 weeks; maintenance). The mean duration of observation of the patients in this study was 171 weeks (3.1 years).

RESULTS

Of the 53 patients, 6 were treated in the induction phase alone and achieved Psoriasis Area Severity Index (PASI) of 90-100, after which they opted not to continue with any further treatment. These patients remain under clinical observation. Three patients were followed up regularly for 24 months, achieving PASI 75/90 with topical medication, while one patient is stable at PASI 75 and undergoes further treatment with phototherapy (UVB) whenever new lesions appear. Three patients were followed up for 3-6 months after the induction phase and remained at PASI 75-100. They were lost to follow-up after this time. Therefore, a total of 47 patients remained under observation while receiving the drug for at least 15 months. Of these, 55.3% (n=26) experienced some type of adverse event. Acute adverse events were found in 34% of the patients and delayed reactions in 36.1%.

The mean age of the patients in this study was 49.2 years (range 19-73 years). The prevalence of comorbidities in these patients was 57.4%, the most common comorbidities being hypertension and obesity.

The acute adverse events consisted of: urticaria (4 patients), an increase in arterial pressure (5), tachycardia (7), cooling of the limb into which the infusion was given (2), sweating (5), dizziness (1) and renal colic (1). In the patient with renal colic, this adverse event led to discontinuation of the drug.

The delayed adverse events found were: positivity for antinuclear factor (ANF) (7 patients), a transitory increase in the levels of liver enzymes (5), unspecified weight increase (4), urinary tract infection (2), bronchopneumonia (1), tonsillitis (1), insomnia (1) and urticaria (1). All the delayed adverse effects were followed up and treated without the drug having to be interrupted.

Therapeutic response was evaluated in accordance with the Psoriasis Area Severity Index (PASI) achieved after the induction phase. Only one patient continued with the same PASI as prior to treatment and in this case the drug was stopped due to treatment failure. Overall, 21.2% of patients reached PASI 100 and 25.5% achieved PASI 90.

With respect to the efficacy in maintaining clinical response, the action of the drug was fast and effective, as shown by the fact that only one patient failed to respond satisfactorily within the first 8 weeks. Figure 1 shows the psoriasis plaque of a patient prior to and following the induction phase of infliximab treatment. Figure 2 shows a patient with nail psoriasis in whom excellent results were achieved after 10 weeks of treatment.

Despite the initial efficacy of the drug, a reduction was observed in response in 44% of the patients (n=21) between the fourth dose of the maintenance phase (the earliest relapse) and the eighth dose of the maintenance phase (the most delayed relapse), with a reduction in the PASI achieved during the induction phase, although response continued to be satisfactory. The minimum PASI was 50, i.e. reappearance of lesions in milder plaques and to a lesser extent than in the pretreatment phase, principally between the 7th and 8th weeks following the infusion. In these patients, a new infusion led to an improvement in their condition; however, efficacy was decreased compared to the response achieved in the induction phase. Three patients (6%) experienced a relapse between the 5th and 6th weeks following infusion and the maintenance drug was administered every 6 weeks thereafter, resulting in an effective response (PASI 75). Eight patients (17%), including the patients who only achieved PASI 50 in the induction phase, stopped responding to the drug between the 5th and 8th maintenance doses and were screened for the use of other immunobiological medications. Fifteen patients (31.9%) continued to have a satisfactory response similar to that achieved in the induction phase until the end of the follow-up period, with more than 10 maintenance doses, i.e. efficacy maintained for at least 80 weeks.

DISCUSSION

The prevalence of comorbidities in the patients with psoriasis selected for treatment with infliximab in the present study was 57.4%. There may be a direct relationship between the increase in proinflammatory cytokine synthesis due to activation of the Th1-type cytokines such as TNF-alpha, for example, found in the physiopathogenesis of psoriasis and of comorbidi-

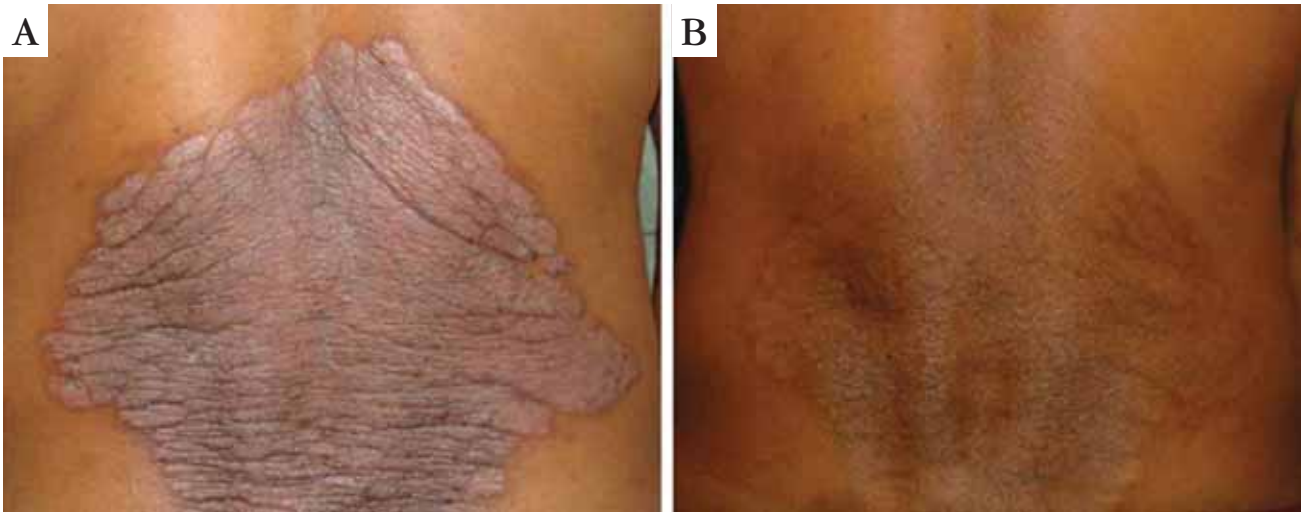

Figure 1: A. Prior to treatment ; **B.** Result after the induction phase

ties such as obesity, [22,23] arterial hypertension, insulin resistance, dyslipidemia and spondyloarthropathies. [20,10] Since these associations are common, it is therefore also possible to understand the increased risk of cardiovascular disease in these patients, a risk that is particularly associated with younger patients and those with more severe psoriasis. [1]

Obesity is one of the most prevalent comorbidities and may be directly related to the severity of the skin condition, since visceral fat is known to be a potential source of TNF-alpha synthesis. [22-24] The negative effect of psoriasis on patients' quality of life should also be taken into consideration, since it leads to social reclusion and changes in eating habits, consequently resulting in weight gain. [25,26] Patients with psoriasis who are overweight are at an increased risk of diabetes and hypertension, and have a significantly elevated atherogenic lipoprotein profile.

In 10% of the patients who received a diagnosis of moderate to severe psoriasis in the present study, spondyloarthropathy was diagnosed concomitantly. This prevalence rate is in agreement with data reported in the literature. Since symptoms in the joints may commence at a later stage, this prevalence may reach as high as 15-20%. [1,7,11,27-29]

Urticaria was the most common of the acute infusional reactions. Some authors do not consider this reaction to be anaphylactic [17,19,20] and the few studies conducted on this subject revealed only one case in which there was an increase in IgE antibodies. [22] The

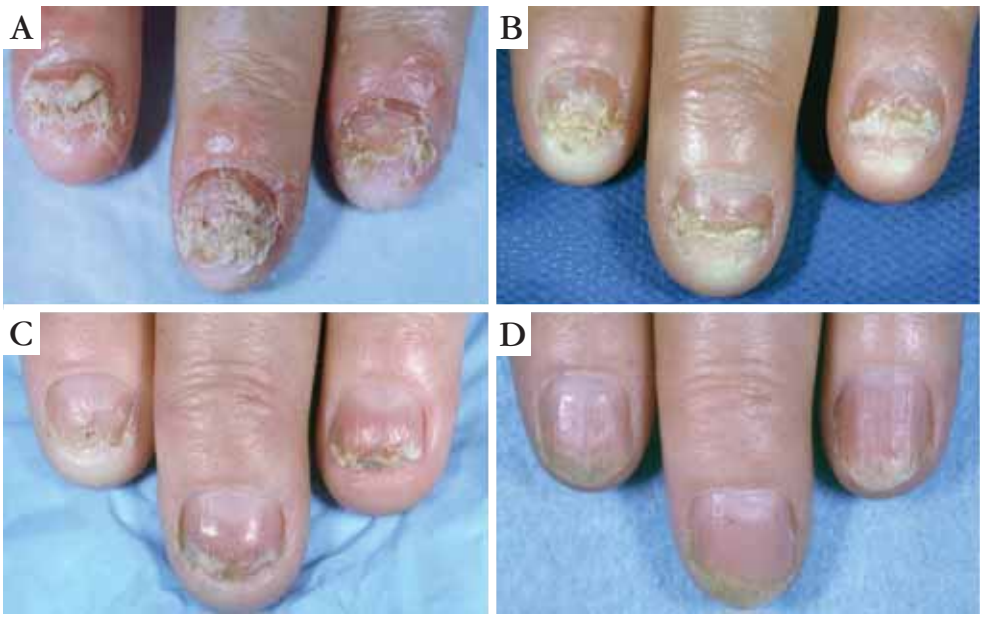

Figure 2: A. Prior to treatment; **B.** Two weeks after the first dose; **C.** After eight weeks of treatment; **D.** After 10 weeks of treatment

symptoms of urticaria normally disappeared when the velocity of the infusion was reduced, which is not characteristic of IgE-mediated reactions. Another relevant point is that for an anaphylactic reaction to occur, there has to have been prior exposure to the antigen; however, cases of urticaria have been reported at the first infusion. [20] In this case, urticaria is explained as an anaphylactoid reaction resulting from the degranulation and direct activation of mastocytes caused by the drug. [17] In the present study, the four patients who developed urticaria at the first infusion obtained complete remission of the symptoms after the velocity of the infusions was reduced and an ampoule of promethazine hydrochloride was administered intramuscularly. The patients who also had urticaria at the following infusion were given 25 mg of hydroxyzine preventively 24 hours prior to the next infusion, on the day of the infusion and 24 hours later. There was no further occurrence of this adverse reaction.

Symptoms such as tachycardia, sweating, increased arterial pressure and cooling of the limb into which the infusion was given, which were observed during our clinical experience, have also been reported as acute adverse events in the literature; however, the mechanism through which this occurs is unknown. Some investigators consider them anaphylactoid reactions, i.e. not immune reactions. [23] The increases in blood pressure were treated with 25 mg of captopril, while the other symptoms were resolved by reducing the velocity of the infusion. [17]

One effect observed during infusion that has not been reported in the literature was very intense renal colic in one patient, which did not improve when the velocity of the infusion was reduced. The infusion had to be stopped and the patient was treated with strong analgesics. Renal colic occurred during the maintenance phase (4th application) and recurred when a second attempt was made to administer the infusion. Investigation by imaging and biochemical exams showed no kidney abnormalities in this patient.

Delayed infusional reactions are considered immune-mediated, generally resulting from a type III hypersensitive reaction. [23,22]

Positivity for antinuclear auto-antibodies (ANF) was the most common delayed adverse event/laboratory abnormality in this study. Only patients #19 and #21 failed to undergo ANF testing prior to initiating the infusions. Antinuclear antibodies have been reported in various studies on infliximab for the treatment of both psoriasis and other pathologies such as rheumatoid arthritis and Crohn's disease, with an approximate prevalence that may reach as high as 29% of patients. The production of antinuclear antibodies depends on the characteristics of the biological agent used, and at first can be explained by high exposure to various auto-antigens released during the cell apoptosis that results from infliximab treatment. [24,25] Some authors have also referred to lymphocyte B activation induced by the frequent bacterial infections. [24]

Despite the high frequency of infliximab-induced antinuclear antibodies, few cases of lupus or lupus-like symptoms were reported. The most recent retrospective study showed an incidence of infliximab-induced systemic lupus of 0.19%. [23] In this study group, there was no clinical manifestation of lupus-like lesions or laboratory findings indicative of the presence of anti-double-stranded DNA antibodies that would justify this diagnosis. All the patients were able to continue treatment without any specific complication.

Infections also manifested as delayed adverse effects: urinary infection, bronchopneumonia and tonsillitis; however, they were treated with specific antibiotics and no complications occurred. The infections normally occurred 2-3 weeks after an infusion.

The increase in liver enzymes found in some patients was transitory and did not lead to suspension of infliximab. With respect to the weight increase reported by four patients, no causal relationship was established with infliximab.

Patient #6 developed alopecia areata two weeks after an infusion of infliximab, following the 34th maintenance dose. There are no references in the literature reporting alopecia areata with infliximab and it may represent a random adverse event. The patient was treated with clobetasol propionate topical solution and regrowth was rapid.

With respect to efficacy, only one patient (#4) was considered unresponsive to the use of the drug, since minimum satisfactory response failed to occur in the induction phase. No clinical or laboratory characteristics were found that would allow a correlation to be made between lack of response and the patient's characteristics except for a severe urticaria-like reaction at the first infusion that resulted in a substantial reduction in the velocity of infusion (3.5 hours). At the following infusions, the patient took hydroxyzine prior to the procedure and no further reactions occurred. No reports were found in the literature of any association between the formation of anti-infliximab antibodies and a lack of response; however, anti-infliximab antibody testing was not performed in this patient.

Infliximab was found to be highly effective in the induction phase and of great value in the treatment of severely affected patients who needed a rapid clinical response. In the maintenance phase, if PASI 75 alone is considered indicative of excellent response, efficacy was achieved in 30% of patients;

however, when patient satisfaction in general is analyzed (PASI 50), treatment could be considered effective in approximately 70% of the patients. It should also be taken into consideration that six patients only underwent treatment in the induction phase but nevertheless continued for at least six months without developing any lesions. In fact, three of these patients remained at PASI 75 or above for 24 months without the use of infliximab. It is not yet possible to define what leads to this variability in response; however, aspects such as psoriasis genes may be involved. [27] Environmental effects and the association with obesity may also have an effect in stimulating the phenotype. All the patients who failed to respond to infliximab were obese, highlighting the importance of treating the patient as a whole. Two of the patients who were submitted to doses of infliximab in the induction phase alone and who achieved PASI 75 lost a significant amount of weight over the study period through diet and the practice of physical exercise.

CONCLUSION

In the present study, infliximab was found to be safe and effective for the treatment of patients with recalcitrant plaque psoriasis and patients for whom the use of conventional drugs was contraindicated. The appropriate, meticulous selection of patients and rigorous clinical and laboratory follow-up during treatment is fundamental in assuring both the success and safety of the treatment.

Of the comorbidities found in the patients in this study, obesity was associated with delayed therapeutic response and poorer efficacy, highlighting the need to treat the patient as a whole in order to guarantee optimal therapeutic response. There was no correlation between any of the other comorbidities and therapeutic response.

Both acute and delayed adverse events are common; however, when well monitored they do not preclude the continuation of treatment and do not expose patients to uncontrolled risks. Only one severe acute adverse effect was found (renal colic) in which administration of the drug had to be suspended. In the literature, reactions severe enough to warrant interruption of therapy have been reported in less than 1% of cases. [22]

Efficacy with infliximab treatment was high and response in the induction phase was rapid, with more than 70% of patients achieving PASI 75-100. Only one patient failed to respond in the induction phase.

The satisfactory response found with infliximab was maintained over the long term; however, efficacy may diminish from the fourth dose of the maintenance phase onwards and a few patients, including the obese, may fail to achieve any response at all. ❑

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Mailing Address / Endereço para correspondência:
Flavia Barbour Chehin
Rua Carlos Steinen, 335, ap. 12
04004-012 São Paulo, SP, Brazil
E-mail: fchehin@uol.com.br

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