

CONSENSUS STATEMENT

Reactions to Infliximab Infusions in Dermatologic Patients: Consensus Statement and Treatment Protocol

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Abstract. Infliximab is a chimeric monoclonal antibody that binds to and blocks tumor necrosis factor α and is the most effective biologic agent approved for the treatment of moderate-to-severe psoriasis. It is administered by intravenous infusion, usually in day hospitals on an outpatient basis. The main problem with the administration of infliximab is the possibility of infusion reactions, which may be immediate or delayed; these reactions are related to the immunogenicity of this monoclonal antibody, leading to the production of anti-infliximab antibodies. Infusion reactions to infliximab are not usually anaphylactic (ie, they are not mediated by immunoglobulin E), and re-exposure of the patient using specific protocols to prevent and treat these reactions is therefore possible. The extensive experience in the use of infliximab for the treatment of rheumatic conditions and chronic inflammatory bowel disease has made it possible to develop infusion reaction management protocols; these can be applied to dermatologic patients, who constitute a growing proportion of patients treated with intravenous biologic agents. The aim of this review is to draw up a consensus protocol for the treatment of infusion reactions in dermatologic patients treated with infliximab.

Key words: infliximab, psoriasis, infusion reactions, monoclonal antibody, immunogenicity.

REACCIONES A LA INFUSIÓN DE INFLIXIMAB EN PACIENTES DERMATOLÓGICOS

Resumen. Infliximab, un anticuerpo monoclonal quimérico que se une y bloquea al factor de necrosis tumoral alfa, constituye el agente biológico más eficaz aprobado para el tratamiento de la psoriasis moderada a grave y se administra mediante infusión intravenosa, generalmente en Hospitales de Día de forma ambulatoria. Las reacciones infusionales, que pueden ser agudas y retardadas, constituyen el principal problema en la administración rutinaria de este fármaco, y están relacionadas con la inmunogenicidad del anticuerpo monoclonal que da lugar a la producción de anticuerpos dirigidos contra el mismo. Las reacciones infusionales a infliximab son en la mayoría de los casos no anafilácticas (mediadas por inmunoglobulina E [IgE]), lo que no excluye el retratamiento de los pacientes empleando protocolos específicos de prevención y tratamiento de las mismas. Existe una amplia experiencia sobre el uso de este fármaco en pacientes con enfermedades reumatológicas y enfermedad inflamatoria idiopática intestinal, lo que ha permitido desarrollar protocolos de tratamiento de las reacciones a la infusión aplicables a los pacientes dermatológicos, que constituyen un grupo cada vez más numeroso de los que son tratados con agentes biológicos por vía intravenosa. El objeto de la presente revisión es desarrollar un protocolo de tratamiento consensuado de las reacciones a la infusión en pacientes dermatológicos tratados con infliximab.

Palabras clave: infliximab, psoriasis, reacciones a la infusión, anticuerpo monoclonal, inmunogenicidad..

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Introduction

In recent years, the introduction of a number of biologic agents has revolutionized the treatment of various immune-mediated inflammatory disorders, such as rheumatoid arthritis, Crohn disease, and psoriasis. The most widely used of these agents is infliximab, a chimeric monoclonal antibody that binds tumor necrosis factor α (TNF- α) neutralizing the activity of this cytokine. The safety and efficacy of infliximab has been demonstrated in the treatment of Crohn disease, rheumatoid arthritis, autoimmune uveitis, ankylosing spondylitis, pyoderma gangrenosum, and moderate-to-severe psoriasis. Infliximab was approved by the European Medicines Agency (EMA) for the treatment of moderate-to-severe psoriasis on September 29, 2005. It is the biologic agent for which the largest body of accumulated evidence is available, with a total of 1 008 000 patients treated to date across all indications, 10263 for psoriasis (data supplied by Schering-Plough).

Infliximab, like any exogenous protein, can give rise to acute and delayed infusion reactions. While the proportion of patients affected is relatively small, the percentage varies considerably across different studies and depending on the underlying disease. The clinical manifestations of these reactions are discussed in greater detail below. In patients with Crohn disease, for example, it is estimated that infusion reactions occur in 5% to 10% of cases.¹ In one large series (165 consecutive patients who received 479 infliximab infusions), the overall incidence of infusion reactions was 6.1%, with the severity being mild to moderate in 42% of the acute reactions.¹ It is estimated that 20% of patients with rheumatoid arthritis who have been included in clinical trials have experienced some kind of infusion reaction, and that such reactions lead to discontinuation of treatment in 3% of patients every year.² Acute infusion reactions have been observed in approximately 10% of the patients treated with infliximab for plaque psoriasis.^{3,4} In the European Infliximab for

Psoriasis (Remicade) Efficacy and Safety Study (EXPRESS), Reich et al⁵ reported infusion reactions in 3% of the patients treated with infliximab as compared to 2% in the placebo group. However, Gottlieb et al⁶ reported a higher incidence of infusion reactions in patients treated with infliximab at doses of 3 and 5 mg/kg (18% and 22% of the patients, respectively) than in the placebo group (2%) during induction therapy. In the Evaluation of Infliximab for Psoriasis in an Efficacy and Safety Study (EXPRESS II), in which Menter et al⁷ compared continuous maintenance regimens (every 8 weeks) with intermittent treatment (as needed), infusion reactions occurred more often in the patients treated with 3 mg/kg (11.5% of the patients) than in those treated with 5 mg/kg (9.6%), and the incidence was higher in the group receiving intermittent treatment than among the patients on a continuous maintenance regimen.⁴ In general, it is estimated that infusion reactions develop in between 3% and 22% of patients with psoriasis treated with infliximab,⁸ making it a common adverse event.

The Experience of the Present Authors

The Table summarizes the clinical experience of the authors of this article.

In the largest case series (contributed by L. Puig), which comprised 43 patients, 5 of whom received 2 courses of treatment, 9 patients (20.9%) had infusion reactions. Only 1 of these 9 patients was receiving concomitant treatment (with methotrexate). The presence of antinuclear antibody titers greater than 1:320 correlated significantly with the development of infusion reactions (4 of the 9 patients; 44.4%). In 2 of these patients, the development of a severe acute infusion reaction was preceded by a loss of response (rebound effect, with a Psoriasis Area Severity Index [PASI] >125% of baseline).

The infusion reactions observed in this case series were acute (occurring during the infusion or within hours of its

Table. Clinical Experience Contributed by the Authors

Author	Year of First Treatment	No. of Patients/Courses of Treatment	No of Infusions	No of Patients with Acute Reactions	No of Patients with Repeat Acute Reactions	No of Patients with Delayed Reactions	No of Withdrawals due to a Reaction
L. Puig	2004	43/48	352	6	2	1	5
X. Bordas	2005	17/17	ND	1	0	0	1
M. Sánchez-Regaña	2007	15/15	95	3	0	0	0
F. Gallardo	2006	28/28	ND	7	0	0	3
J. Luelmo	2005	16/16	156	1	0	0	1

Abbreviation: ND, no data available.

completion) in 8 cases. In the ninth case, the reaction was delayed (occurring some 36 hours after the second infusion) and in that patient no subsequent reaction occurred with the administration of prophylactic therapy. Infusion reactions occurred in response to the second infusion in 2 cases, to the third infusion in 2 cases, to the fifth in 2 cases, and to the seventh in 1 case. Repeat mild-to-moderate reactions occurred in the third, fourth, and fifth infusions in one patient, and in the first to the fourth infusion of the second course of treatment in another.

In 5 patients, acute infusion reactions were severe and required withdrawal of treatment. In 1 of these patients, the infusion reaction (severe) was associated with self-limiting arthritis in the ankle. The onset of the arthritis was associated with a rebound in the severity of psoriasis (PASI >125% of baseline) and occurred before the infusion reaction. The reaction resolved a week after infliximab was discontinued, and the patient subsequently responded to treatment with etanercept without incident. Another patient developed respiratory failure and required hospitalization. In a sixth case, it was possible to complete the infusion despite a severe reaction, and the patient experienced no further reactions and continued to receive infusions in conjunction with prophylactic therapy. In 2 patients, repeat mild-to-moderate reactions occurred in response to several different infusions, but these were adequately controlled with premedication (intravenous [IV] diphenhydramine 50 mg) before each infusion. In 1 of these patients, treatment with infliximab was subsequently discontinued due to loss of efficacy, while the other continued to receive treatment in conjunction with the prophylactic therapy. In the patient who developed a delayed reaction after the second infusion, no reaction occurred during subsequent infusions administered with prophylactic treatment (premedication with oral antihistamines and corticosteroids).

The Mechanisms that Produce Infusion Reactions

Although the mechanisms responsible for infusion reactions are not completely understood, it is thought that they are not generally allergic (type 1 hypersensitivity immunoglobulin [Ig] E-mediated reactions).¹ A more probable hypothesis is that they are related to the presence of soluble immune complexes, a premise that would explain both acute and delayed reactions.⁹ Under this hypothesis, the formation of the complexes would depend on the relative quantities of the antigen (infliximab) and the antibody. The presence of an antigen overload might reduce the formation of such complexes and consequently decrease the number of reactions.

The human immune system reacts to monoclonal antibodies by producing antibodies to different sites on the molecule; these can be anti-idiotypic, antiallotypic, or antimurine. As would be expected, chimeric monoclonal antibodies are more immunogenic than human antibodies, but all foreign proteins give rise to antibodies. Techniques have been developed to detect anti-murine and anti-allotypic (against the constant region of IgG1) antibodies directed against infliximab. Typically, the only antibodies detected in treated patients are antimurine antibodies, which are currently known as antibodies to infliximab (ATI). Several authors have measured ATI; most of these studies have been carried out with a test supplied by Centocor (Malvern, Pennsylvania, USA) that determines the presence of anti-murine and anti-idiotypic antibodies directed against the constant region of human IgG1.

Given that infliximab itself interferes with this technique, the presence of these antibodies can only be measured when infliximab is not detected in the patient's serum, although "indeterminate" samples can be considered negative, and, in any case, the ATI levels would be very low compared to the infliximab overload.¹⁰ Prometheus (San Diego, California, USA) sells a polyclonal test that has not yet been compared with Centocor, and Sanquin Diagnostic Services (Amsterdam, Holland) has recently brought out a test that measures ATI (IgG4) levels with an enzyme-linked immunosorbent assay.

The formation of ATI is associated with an increased risk of infusion reactions and a loss of treatment efficacy.^{11,12} The effect is not at all uncommon, with the reported frequency ranging from 6% to 61% of patients although typically it varies between 6% and 15%.¹⁰ This variability may in part be due to the different methods used in different studies, to the infliximab dose regimens used (single dose, induction therapy, continuous or intermittent treatment), and to the concomitant administration in some cases of immunosuppressive therapy or premedication with hydrocortisone.¹⁰ The dosage regimen used, which involves induction therapy followed by scheduled maintenance therapy, is designed to maximize immunological tolerance and minimize the production of antibodies.¹⁰

This need to reduce the immunogenicity of infliximab was already observed in early clinical trials in the treatment of rheumatoid arthritis. When the drug was given in a single dose (1, 3, or 10 mg/kg), the frequency of ATI was 53%, 21%, and 7% respectively. However, when it was administered in combination with methotrexate, these percentages dropped to 15%, 7%, and 0%, respectively.¹³ The concept of an induction regimen was introduced in the phase III trial carried out by the ATTRACT Study Group.¹⁴ In that study, infusions at weeks 0, 2, and 6 were followed by maintenance infusions given every 8 weeks,

and ATI were only detected in 8% of the patients without detectable serum levels of infliximab.

A considerable amount of evidence is available in the clinical trials carried out in patients with Crohn disease. For example, in the ACCENT I trial, Hanauer et al¹⁵ observed ATI in 30% of the patients treated with a single induction dose compared to 10% and 7% respectively of the patients who received 3 induction doses followed by a maintenance regimen of either 5 or 10 mg/kg. In the same study, scheduled maintenance therapy was found to induce less formation of ATI than episodic treatment,¹⁶ and the addition of immunosuppressants was shown to be of only limited benefit.¹⁷

Gottlieb et al,⁶ who studied the use of infliximab in the treatment of psoriasis, reported an incidence of ATI before week 26 of 27% in patients treated with 3 mg/kg and 20% in patients treated with 5 mg/kg. Nine of the 38 patients (24%) with ATI developed infusion reactions, compared to 25 of the 116 patients (22%) in whom no antibodies were detected. These percentages can be compared with those relating to patients treated for Crohn disease, which were 36% and 24%, respectively.¹⁵ Five of the 22 (23%) ATI-positive patients who were retreated at week 26 after a 20-week drug-free interval developed an infusion reaction as compared to 6 of the 73 patients (8%) without antibodies.¹⁰ In the EXPRESS trial, 27% of the specimens obtained before week 66 were ATI positive, and the incidence of ATI at weeks 46 and 66 was 22% and 19%, respectively.⁵ In that trial, the presence of ATI was associated with a reduction in the percentage of patients who maintained a PASI 75 response at week 10: 39% of the ATI-positive patients compared to 81% of those who were antibody negative. However, the chief marker of loss of response was the presence of preinfusion infliximab serum concentrations under 1 µg/mL at week 30 and thereafter (100% compared to 0%).⁵ The EXPRESS study investigators reported 38 infusion reactions, 4 of which were serious, in the group of 298 patients treated with infliximab, but did not give details of the number of patients affected, either overall or by ATI status. In the EXPRESS II study, ATI were detected through week 66 in 49 (35.8%) and 59 (41.5%) of the patients treated with 5 mg/kg in the groups receiving continuous and intermittent treatment respectively; the figures for the patients treated with 3 mg/kg were 69 (51.5%) and 60 (46.2%) respectively.⁷ In that study, the presence of ATI was associated with a lower probability of a sustained response at week 50. Moreover, ATI-positive patients had a higher risk of developing infusion reactions than the patients without antibodies; 2 of the 5 infusion reactions (severe in both cases) occurred in patients with ATI, 1 during the first infliximab infusion. In the 3 other cases, no information was available on the patients' antibody status.

Although the use of immunosuppressants was not

considered in the clinical trials carried out in patients with psoriasis and the summary of product characteristics does not address this possibility, there is evidence that combined treatment with 6-mercaptopurine, azathioprine, methotrexate, or corticosteroids reduces ATI formation.¹⁰ In the ACCENT I trial, for example, the incidence of ATI in patients treated with immunomodulators was 10% compared to 18% in the group not receiving such treatment.¹⁵ In the ACCENT II trial, 13% of the patients treated with corticosteroids, 11% of those treated with immunomodulators, and 4% of those receiving combined treatment with both drugs developed ATI compared to 24% of the patients receiving infliximab alone.¹⁸ In this respect, it is interesting to note that acute infusion reactions appear to be less frequent in rheumatic patients when the patient is receiving concomitant treatment with low doses of oral corticosteroids.¹⁹ In one trial, routine IV administration of hydrocortisone (200 mg) prior to infusion, as compared to placebo, gave rise to lower median ATI levels and a reduction, albeit not statistically significant, in ATI formation: 21% versus 29% of patients at week 8, and 26% versus 42% of patients at week 16.¹² It has therefore been proposed that premedication with hydrocortisone should be considered in patients with Crohn disease receiving single-drug therapy with infliximab because of intolerance to immunomodulators or at the start of immunomodulatory treatment.¹⁰

Clinical Presentation

Infusion reactions to infliximab (or any monoclonal antibody) can be classified as acute when they occur within 24 hours of the start of an infusion (but usually between 10 minutes and 4 hours). A reaction is characterized as delayed when it appears between the second and fourteenth day after the infusion (but usually between the fifth and seventh day). Both types of reaction can be further classified as mild, moderate, or severe depending on the severity of the symptoms. The clinical signs and symptoms of acute reactions include an evanescent macular rash that disappears within minutes or hours, chest tightness, dizziness or shortness of breath, headache, hypotension, hypertension, nausea, sweating, and hyperthermia among others (see Appendix 1). Urticaria, bronchospasm, and laryngeal edema are manifestations of anaphylactic reactions, and the last 2 are indications of a serious reaction. Acute reactions may (very rarely) be anaphylactic (type 1 IgE-mediated hypersensitivity reactions) or (in most cases) anaphylactoid (nonallergic but with an immune etiology). True anaphylactic reactions are characterized by dyspnea and chest tightness, suffocation, hypotension, bronchospasm, and urticaria; in the absence of either of the last 2 symptoms listed, it is unlikely that an acute

reaction is anaphylactic, and it should therefore be considered nonallergic. In most cases, these anaphylactoid reactions can be prevented by the administration of premedication and by slowing down the rate of infusion.¹ In the case of true anaphylactic reactions, desensitization protocols have been proposed.²⁰ These protocols will rarely be necessary in the treatment of patients with psoriasis because of the characteristics of the disease and the availability of alternative biologic agents.

Delayed infusion reactions are characterized by skin rash, diffuse joint pain, general malaise, and myalgias. They are similar to mild forms of serum sickness, and probably represent type III hypersensitivity reactions mediated by immune complexes. Delayed reactions must be differentiated from other states that may produce similar symptoms, such as a concomitant viral syndrome or a lupus-like reaction that very occasionally occurs in patients receiving TNF- α blockers.

Treatment Protocol

Clinical experience relating to the management of infusion reactions in patients with rheumatoid arthritis or Crohn disease can generally be extrapolated to patients with psoriasis.

The protocol for the treatment of infusion reactions proposed by this Working Group is given in Appendices 1 and 2. This protocol is based on the evidence currently available in the literature^{1,10,21,22} and on the clinical experience accumulated in the general day hospital of the Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, both in the treatment of psoriasis with infliximab—a case series including the 43 patients who have received 352 infusions since 2004—and in the treatment of patients with any disease treated with infliximab (2800 infusions). This protocol was evaluated and agreed upon by all the departments involved in the day hospital (pharmacy, rheumatology, gastroenterology, and dermatology) as well as by the coauthors, the clinicians responsible for prescribing and administering infliximab to patients with moderate-to-severe psoriasis in various dermatology departments in Catalonia, and the members of the Working Group that has met on various occasions specifically for this purpose.

The process of identifying acute infusion reactions and assessing their severity is based on the signs and symptoms listed in Appendix 1. Infusion is always stopped immediately, and the IV line is kept open with physiological saline solution in case IV drug administration should become necessary. The patient's vital signs are monitored (temperature, heart rate, blood pressure, and PaO₂ in case oxygen therapy is required). When bronchospasm occurs it must be detected promptly because it is a marker of

severity. The day hospital nursing staff is trained to assess the severity of these adverse reactions and to take immediate action while promptly notifying the physician responsible for the patient's care. The protocol is shown in Appendix 2 in the form of an algorithm.

The fact that a patient develops an acute infusion reaction does not necessarily preclude continuation of treatment with infliximab in the future—except in the case of severe or anaphylactic reactions—depending on the clinical criteria.

If an acute reaction is considered mild by the treating physician, treatment can be restarted the same day using the dosing regimen given in Appendix 2, which is characterized by a gradually increasing infusion rate.

In patients with mild or moderate infusion reactions, the following prophylactic treatment should be administered in subsequent infusions: oral diphenhydramine (25-50 mg) and paracetamol (500 mg) 90 minutes before starting the infusion; a nonsedating antihistamine (for example, levocetirizine 5 mg) can be administered orally 4 to 5 days before the infusion as an alternative to the diphenhydramine pretreatment.

In patients who have experienced severe infusion reactions, premedication with IV hydrocortisone acetate 100 mg 20 minutes before the infusion or with oral prednisone 50 mg the day before the infusion is optional, at the discretion of the treating physician.

In these patients, the next infusion should be started at a flow rate of 10 mL/h for the first 15 minutes after which the rate should be increased gradually according to the regimen shown in Appendix 2. If the patient develops another mild-to-moderate reaction and the physician decides to continue treatment, the same procedure should be used for subsequent infusions. If the reaction does not recur, all subsequent infusions can be started at the standard flow rate and the premedication regimen should be maintained.

Patients who have experienced infusion reactions are not candidates for rapid administration of infliximab at fast flow rates (250 mL/h) to reduce the duration of the infusion to one hour. We propose this approach as normal clinical practice from the fifth infusion onwards in patients who do not present any kind of reaction.

In many of the patients who have developed infusion reactions (and in many patients in whom treatment has been suspended for any reason and is to be restarted) the possibility should be considered of reducing ATI formation by administering methotrexate at doses of between 7.5 and 10 mg/week.

The development of an infusion reaction correlates with a reduction in the duration of the clinical response to subsequent infusions.⁹ Conversely, in the clinical experience of the present authors, a loss of response (an increase in the PASI score) precedes the development of an acute infusion

reaction in some patients and could therefore be used as a criterion for starting concomitant treatment with methotrexate (unpublished data).

Only scant information exists concerning the factors predicting the development of infusion reactions. The presence of certain factors may, however, justify concomitant treatment to prevent the development of immunogenicity and the reactions themselves. The authors of a study in which 21% of the patients treated developed infusion reactions identified the following risk factors: positive baseline antinuclear antibody status (odds ratio [OR] 2.1), treatment with infliximab without methotrexate (OR 3.1), and single-drug therapy with infliximab (OR 3.6).²³ When the first 2 parameters were combined, the OR was 4.6. They also found an association between longer duration of disease or lower age at onset and the development of infusion reactions. In the same study, some 13% of the patients with spondyloarthropathies (including psoriatic arthritis) developed infusion reactions, but no significant risk factors were identified in this subgroup.

Delayed infusion reactions are very rare, and the lack of available data makes it difficult to establish treatment or prophylactic regimens for such reactions. Paracetamol or a nonsteroidal anti-inflammatory drug administered orally and a nonsedating antihistamine can be given, or else an oral corticosteroid. The treatment and regimen prescribed will depend, with respect to both dosage and duration, on the judgment of the treating physician. In the case of delayed infusion reactions that are mild and resolve quickly, retreatment with infliximab can be considered using a prophylactic regimen similar to that used for the treatment of acute reactions. Other authors have proposed increasing the dose of infliximab or shortening the interval between infusions in order to raise infliximab levels thereby creating an antigen overload that will reduce the formation of immune complexes.¹³

Conclusion

Infliximab is a biologic agent that has revolutionized the treatment of moderate-to-severe psoriasis, with rapid and spectacular improvements that were already reported in the first article published in Spain on this topic.²⁴ However, the immunogenicity of this chimeric antibody, which results in the production of specific antibodies against infliximab, appears to give rise to an increased risk of infusion reactions and a reduction in the response to treatment in the long term. The formation of such antibodies can be minimized by the use of induction therapy followed by a maintenance regimen with administration at fixed intervals and concomitant administration of immunosuppressants, such as methotrexate, or by reducing the interval between

infusions. The present consensus document facilitates appropriate management of infusion reactions based on immediate attention by the nursing staff in the day hospital, with a structured protocol for the diagnosis and treatment of such reactions and specific instructions concerning prophylaxis for use in patients continuing treatment. This protocol represents the currently available treatment regimen that obtains the highest PASI 75 and PASI 90 response rates in both the short and the medium term.

Final Note

During the period that has elapsed since this manuscript was submitted for publication, an article by the Amsterdam group on the same subject with similar conclusions has been published.²⁵

Conflict of Interest

The authors declare no conflicts of interest.

References

- 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.
- Lipsky PE, van der Heijde DM, 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.
- Mössner R, Reich K. Infliximab in the treatment of psoriasis. *Expert Rev Dermatol.* 2006;1:515-26.
- Saraceno R, Gottlieb AB. Infliximab in the treatment of plaque psoriasis. *Therapy.* 2007;4:399-406.
- Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet.* 2005;366:1367-74.
- Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol.* 2004;51:534-42.
- Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol.* 2007;56:31.e1-15.
- Kleyn CE, Griffiths CE. Infliximab for the treatment of psoriasis. *Expert Opin Biol Ther.* 2006;6:797-805.
- Sandborn W. Preventing antibodies to infliximab in patients with Crohn's disease: optimize not immunize. *Gastroenterology.* 2003;124:1140-5.

10. Mayer L, Young Y. Infusion reactions and their management. *Gastroenterol Clin N Am*. 2006;35:857-66.
11. Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med*. 2003;348:601-8.
12. Farrell RJ, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology*. 2003;124:917-24.
13. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum*. 1998;41:1552-63.
14. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet*. 1999;354:1932-9.
15. Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol*. 2004;2:542-53.
16. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology*. 2004;126:402-13.
17. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359:1541-9.
18. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350:876-85.
19. 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.
20. Puchner TC, Kugathasan S, Kelly KJ, Binion DG. Successful desensitization and therapeutic use of infliximab in adult and pediatric Crohn's disease patients with prior anaphylactic reaction. *Inflamm Bowel Dis*. 2001;7:34-7.
21. Cheifetz A, Mayer L. Monoclonal antibodies, immunogenicity, and associated infusion reactions. *Mt Sinai J Med*. 2005;72:250-6.
22. Hommes DW, Oldenburg B, van Bodegraven AA, van Hogezaand RA, de Jong DJ, Romberg-Camps MJ, et al. Dutch Initiative on Crohn and Colitis (ICC). Guidelines for treatment with infliximab for Crohn's disease. *Neth J Med*. 2006;64:219-29.
23. 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.
24. Revenga F, Juan A, Ros I, Nadal C, Taberner R. Tratamiento de la psoriasis con infliximab. *Actas Dermosifiliogr*. 2004;95:44-50.
25. Lecluse LLA, Piskin G, Mekkes JR, Bos JD, de Rie MA. Review and expert opinion on prevention and treatment of infliximab-related infusion reactions. *Br J Dermatol*. 2008;159:527-36.

Appendix 1. Administration of Infliximab. Guidelines for the Management of Adverse Effects: Infusion Reactions

Description

Intravenous (IV) administration of infliximab (Remicade), a tumor necrosis factor- α antagonist biologic therapy. Infliximab, a chimeric antibody, is administered in the form of periodic infusions (0, 2, and 6 weeks and, depending on the subsequent course of the disease, every 6 to 8 weeks thereafter). It is approved for therapeutic use in the following diseases: rheumatoid arthritis, active Crohn disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and psoriasis..

Contraindications to Treatment

- Known hypersensitivity to the drug or to murine proteins
- Active systemic or localized infections
- History of infection related to a prosthesis that remains in place.
- Infection with human immunodeficiency virus
- Active infection with hepatitis B virus
- Congestive heart failure classified on the New York Heart Association scale as functional class III/IV
- History of demyelinating disease
- History of cancer (except when there has been no recurrence in the preceding 5 years and in the case of patients with basal cell carcinoma)
- Patients with a history of systemic lupus erythematosus
- Live vaccines should not be administered during treatment: yellow fever, German measles, measles, polio, or bacillus Calmette-Guérin (BCG).

Patient Care during IV Administration of Infliximab

Objectives

- To prepare patients physically and psychologically so that they undergo treatment in the best possible conditions
- To ensure the patient's safety throughout the infusion process
- To prevent treatment-related problems and ensure prompt detection of any such problems.

Preparation of the Patient before the Procedure

- Ascertain what the patient knows about the treatment they are about to receive.
 - Patients may eat breakfast or lunch and take their usual medication unless they have a history of moderate-to-severe infusion reactions (risk of vomiting).
 - Make the patient comfortable in a seat or bed, depending on the preference and physical state of each individual.
 - Check whether the patient's chart includes an order for laboratory testing before the procedure, and whether premedication has been prescribed.
- Personnel: nursing staff.

Procedure

Personnel: nursing staff

Materials:

- Esmarch bandage
- Cotton
- Antiseptic
- 20 G catheter
- Catheter securement dressings
- Pump
- Filter (pore size $\leq 1.2 \mu$)
- Infusion pump
- 10-mL syringe
- 21 G needle
- 10 mL of double-distilled water for each vial of infliximab
- Infliximab (store in refrigerator at between 2°C and 8°C)
- 250 mL of 0.9% saline solution.

Implement laboratory testing order, if any, prior to infusion. Administer prescribed premedication, if any. This can only be diphenhydramine or hydrocortisone.

- Check arterial blood pressure, heart rate, respiratory rate, and temperature at the start and after completion of infusion and whenever required by the patient's physical condition.
- Preparation of the drug
 - Aseptic technique
 - Reconstitute each 100 mg vial of infliximab with 10 mm of double-distilled water.
 - Aim the double-distilled water against the side of the vial to prevent foaming.
 - Ensure that the contents of the vial have dissolved completely, but avoid prolonged and energetic movements.
 - Allow the solution to stand for 5 minutes
 - The solution should be colorless to slightly yellowish and may contain translucent particles (protein).
 - The solution should not be administered if it is inappropriately colored or contains visible opaque particles.
 - From the bottle of saline solution, withdraw a volume of saline equal to the volume of infliximab solution to be used in order to obtain a final volume of 250 mL and a concentration of between 0.4 and 4 mg/ml.
 - The solution must be infused within 3 hours of reconstitution.
 - Never dissolve infliximab in dextrose solution.

(Continúa)

Appendix 1. Administration of Infliximab. Guidelines for the Management of Adverse Effects: Infusion Reactions (continued)

- Cannulate the venous line.
- Administer the drug using a volumetric infusion pump.
 - The first, second, third, and fourth infusions should be administered over 2 hours (125 mL/hour).
 - Starting with the fifth infusion, the dose can be infused in 1 hour (250 mL/hour).
- Assess response to treatment; if the patient does not present any anomalous symptoms, he or she can be discharged and return to normal daily activity.
- Patients must be instructed to telephone their physician or the nursing staff if they experience any reaction symptoms after the infusion.

Observations

Infusion time can be modified by the physician responsible for the patient.

Description of Problems Related to the Procedure and Remedial Action

Acute infusion reactions

<i>Mild In the presence of</i>	<i>Moderate In the presence of</i>	<i>Severe In the presence of</i>
Headache	The same symptoms as mild reactions	The same symptoms as moderate reactions
Diaphoresis	+	+
Throat irritation	Dysphagia	+
Lumbar pain	Hypotension or hypertension	Severe hypotension or hypertension
Hyperemia	(±20 mmHg with respect to baseline)	(± 40 mmHg with respect to baseline)
Nausea	Chest pain or tightness	Hyperthermia and chills (≥39°C)
Palpitations	Edema of the face, hands, or lips	Swelling of the larynx or pharynx with stridor
Itching	Suffocating sensation	Dyspnea
Cutaneous eruption	Hyperemia (accompanied by a sensation of heat or fever)	Severe bronchospasm
Flushing	Hyperthermia (<39°C)	Convulsive seizure
Vertigo	Palpitations, tachycardia	Clinically significant chest pain
Vomiting	Urticaria	

Action to be taken:

- Stop the infusion
- Monitor blood pressure, heart rate, respiratory rate, and temperature
- Notify the treating physician.
- If the reaction does not resolve, while waiting for the doctor to arrive see Appendix 2 (procedure to be followed in the case of an acute reaction to infusion of infliximab).
- If extravasation occurs, stop the infusion immediately, notify the treating physician, attempt to aspirate the extravasated fluid with a 10 to 20 mL syringe, withdraw the IV line, mark the affected area, and follow the hospital's treatment protocol covering such events.

Important Points

- To ensure early detection of infusion reactions, monitor the patient's response to treatment.
- Ensure that the intravenous line is open.

Assessment Indicators

- The nursing record should include details of the results of vital signs monitoring before and after treatment.
- The nursing record should provide details of the assessment of tolerance to treatment, that is, the occurrence or absence of incidents.

Records

The following information must be recorded on the Day Hospital Patient Record Sheet:

- Vital signs
- The assessment and preparation of the patient prior to treatment
- Incidents (presence or absence) related to the procedure
- Assessment of the patient's condition after treatment

References

Infliximab Summary of Product Characteristics February 28, 2006.

Appendix 2. Procedure to be Followed in the Case of an Acute Reaction to Infliximab Infusion

