

## Rapid Application of Infliximab. Efficacy and Complications

David Bañuelos-Ramírez,<sup>a</sup> María Magdalena Ramírez-Palma,<sup>b</sup> María Elena Balcázar-Sánchez,<sup>c</sup> and Silvia Sánchez-Alonso<sup>a</sup>

<sup>a</sup>Hospital de Especialidades UMAE, Centro Médico Nacional Gral. de Div. Manuel Ávila Camacho, IMSS, Puebla, México

<sup>b</sup>Unidad de Medicina Familiar núm. 1, IMSS, Puebla, México

<sup>c</sup>Consulta Especializada de Reumatología, Hospital de Especialidades UMAE, Centro Médico Nacional Gral. de Div. Manuel Ávila Camacho, IMSS, Puebla, México

**Objective:** To compare the clinical safety of the rapid infusion of infliximab (30–45 min) with the traditional one (2 h).

**Patients and method:** Open, prospective study with the consecutive inclusion of 150 patients with rheumatoid arthritis (RA) and/or spondyloarthritis (AS), resistant to conventional treatment. Patients were randomly distributed to receive 1.5 or 3 mg/kg (according to medical criteria) into 2 groups of 75 patients. Group A: patients received a rapid infusion of infliximab (30–45 min) and group B: traditional intravenous infusion (2 h). The rhythm of infusion was regulated through drip counts and the rule of 3, and time was counted on a digital chronometer. Data was obtained from all patients included on possible side effects, as well as efficacy parameters (visual analog scale for pain, tender, and swollen joint counts), and comparisons were made between the rapid infusion group and the traditional infusion group.

**Results:** All patients concluded the study without serious complications. In the rapid infusion group 3 patients had hypersensitivity in the infusion arm and erythema was present in 7 more. The presence of side effects was not significantly different in relation with the infusion speed.

Differences were not found in relation to the dosage or the type of illness (RA and/or AS) either. The efficacy of infliximab for symptom control showed no differences using both types of infusion.

**Conclusions:** The absence of noticeable secondary effects associated with the reduction in the time of infusion of infliximab permits us to point out that a reduction in the time of infusion of infliximab can be a method to optimize hospital resources concerning the outpatient clinic for biologic therapy.

**Key words:** Infliximab. Rapid infusion. Safety. Efficacy.

---

### Infliximab en infusión intravenosa rápida. Eficacia y complicaciones

**Objetivo:** Comparar la seguridad clínica de la infusión de infliximab rápida (30–45 min) con la tradicional (2 h).

**Pacientes y método:** Estudio abierto, prospectivo, con inclusión consecutiva de 150 pacientes con artritis reumatoide (AR) y/o espondiloartritis (EA) rebeldes al tratamiento convencional. Se distribuyó aleatoriamente a los pacientes incluidos para que recibieran 1,5 o 3 mg/kg de peso (según criterio médico) en dos grupos de 75 pacientes: grupo A: pacientes con infusión intravenosa de infliximab rápida (30–45 min) y grupo B: infusión intravenosa tradicional (2 h). El ritmo de infusión se reguló con goteo y regla de 3 y el tiempo se cronometró con reloj digital. De todos los pacientes incluidos se recogieron datos sobre posibles efectos secundarios, así como parámetros de eficacia (escala analógica visual del dolor, número de articulaciones dolorosas y tumefactas), y se comparó las del grupo de infusión rápida de infliximab con las del de infusión tradicional.

**Resultados:** Todos los pacientes concluyeron el estudio sin complicaciones serias. En el grupo de infusión rápida 3 pacientes manifestaron sensibilidad en el brazo canalizado y se presentó enrojecimiento facial en 7 más. La presencia de efectos secundarios no fue significativamente diferente en relación con la velocidad de infusión. Tampoco se observaron diferencias con respecto a la velocidad de infusión en relación con la dosis y la enfermedad de base de los pacientes (AR y/o EA). Con ambas formas de infusión, infliximab se mostró eficaz en el control de los síntomas de los pacientes, sin diferencias significativas entre ellas.

**Conclusiones:** La ausencia de efectos secundarios destacables asociados a la reducción del tiempo de infusión de infliximab permite señalar que la infusión rápida puede ser un método a tener en cuenta para optimizar las prestaciones de los hospitales de estancia corta para terapias biológicas.

**Palabras clave:** Infliximab. Infusión rápida. Seguridad. Eficacia.

---

Correspondence: Dr. D. Bañuelos-Ramírez.

Retorno del Bronce# 5, Fracc. San Bernardo. 72040 Puebla. México.

E-mail: davra@43yahoo.com; davra43@hotmail.com

Manuscript received December 18, 2005; accepted for publication March 22, 2007.

**TABLE . Signs, Symptoms, and Variation in the Vital Signs of 2 Groups Receiving Infliximab\***

	Infliximab in Reduced Time (n=75)			Infliximab in 2 h (n=75)			P
	Initial	Halfway Through Infusion	Final Infusion	Initial	Halfway Through Infusion	Final Infusion	
BP, mm Hg	100/74	130/80	115/70	110/60	120/70	110/70	NS
HR, beats/min	70	76	78	74	78	72	NS
RR, breaths/min	16	20	18	18	20	19	NS
Facial blushing, n	7						NS
Burning sensation on arm, n	4			1			NS

\*HR indicates heart rate; RR, respiratory rate; BP, blood pressure; NS, no statistical significant differences. No differences in *t* test with a weighed or paired variance and  $\chi^2$  test.

## Introduction

Tumor necrosis factor alpha (TNF $\alpha$ ) is a proinflammatory cytokine with multiple deleterious effects in diverse organs, mainly gastrointestinal and joints.<sup>1-4</sup>

TNF $\alpha$  circulates in plasma as a trimer that binds to transmembrane receptors for TNF, leading to the generation of a series of intracellular signals that participate both in acute as in chronic inflammation.<sup>5-7</sup> Its presence and increased levels have been widely studied, especially in spondyloarthropathies (SA) and in rheumatoid arthritis (RA) where they are more relevant.<sup>7-10</sup>

Infliximab (Remicade<sup>®</sup>) is a chimeric monoclonal antibody with the primary function of binding to transmembrane and soluble forms of TNF $\alpha$ , blocking it and leading to a loss in its actions and the signals it generates.<sup>11-14</sup> Infliximab has a prolonged half-life (9.5 days). A single dose of 3 to 10 mg rapidly reaches therapeutic concentrations that persist for 8 weeks.<sup>15</sup>

Manufacturer recommendations for the application of Remicade indicate that it must be based in a saline solution, in the form of an intravenous infusion for a period of 2 hours, under medical supervision. After the infusion, patients must be under observation for at least 1-2 h with the objective of identifying any potential adverse event. The frequency of secondary reactions varies from 8% to 19%.<sup>16,17</sup>

Apart from this information, which is widely documented in the literature, there is a scarcity of data on other forms of administration<sup>18</sup> and no widely distributed publications were found that analyze the security and efficacy of infliximab in rapid infusion. Only 1 letter to the editor<sup>19</sup> in 2005 mentions the possibility of reducing the administration time of infliximab<sup>20</sup>; with the object of amplifying the question and providing some answers such as the tolerance to variations in infusion time, we designed the present study, now published in an extended form, after a preliminary presentation<sup>21</sup> (Table).

## Patients and Method

A prospective and open study lasting 3 months (with a monthly infusion of infliximab) was carried out, with the consecutive inclusion of 150 patients with RA (according to the ACR criteria) and SA (according to the ASAS group criteria) and followed in the department of Rheumatology of our hospital. All of the patients included were refractory to conventional treatment according to the criteria of the Mexican College of Rheumatology and were randomly distributed to receive 1.5 or 3 mg/kg (depending on the clinicians criteria) into 2 groups of patients: group A: patients with an intravenous rapid infusion of (30-45 min) and group B: traditional intravenous infusion (2 h). All of the patients signed informed consent and the protocol was registered at the hospitals' local ethics committee (UMAE).

Monitoring of patients included: blood pressure, heart rate, respiratory rate, temperature, questioning, and vigilance for the appearance of secondary effects and efficacy parameters (visual analog scale for pain, number of tender, and swollen joints). All of the applications were carried out in the infusion area and vital signs; the authors carried out vigilance and applications. The rate of infusion was regulated by drop count and a rule of 3 and the time was followed with a digital chronometer. Saline solution, venipuncture equipment and the rest of the instruments for infusion were similar in both groups. Infliximab (Remicade<sup>®</sup>) for intravenous infusion was prepared according to the indications of the manufacturer, diluting it in its vial of 100 mg with 250 mL of saline solution, once the patient had a venous line and its permeability was established. The first 50 mL underwent a slow infusion, after which the drop rate of group A was increased (rapid infusion group), allowing for the 250 mL infusion to be administered in the time allotted for this group (30-45 min). Patients receiving the traditional

infusion scheme (2 h) were treated in the same infusion area and during the same work shift. A nurse from the rheumatology department stood by during the whole infusion time and for the period of study duration, with one of the departments rheumatologists at hand, next to the infusion area, which was equipped with the necessary material to treat and revert any secondary event. Data considered as a study variable was registered in a separate sheet, designed on purpose, apart from the biologic and immunosuppressant drug registry used by our service. Final results were processed using descriptive statistics for continuous variables, employing Student *t* with a weighed variance, Student *t* for paired data and  $\chi^2$  for qualitative variables.

## Results

None of the patients in any group had severe adverse events that caused the suspension of treatment. Both treatment groups with infliximab (rapid infusion and traditional) were balanced with respect to the percentage of rheumatism included (RA and SA), and the regular treatment (methotrexate 15 mg weekly + NSAID and prednisone 5 mg every 24 h for RA, and NSAID for SA), which was continued in a stable manner throughout the study. In group A, 32 patients received a dose of 1.5 mg/kg and 43 received 3 mg/kg; in group B, 21 patients received a dose of 1.5 mg/kg, and 54 received a dose of 3 mg/kg, without any significant differences regarding the number of patients and the doses administered to them; in 6 of the eldest patients there were some problems finding an adequate vein to puncture, which was solved using a smaller bore (23) needle and without the use of ligature.

Vital signs were not noticeably modified during the infusion and only a moderate elevation in blood pressure was observed, without any significant differences between the groups, at the halfway point of the infusion and with a tendency to present itself again at the end of the infusion, with normalization 1 hour after concluding the procedure. In the rapid infusion group, 3 (5.33%) patients presented increased sensibility in the arm with the venous access during infusion, without any erythema, edema, or other sign of phlebitis, in contrast with only one in the traditional infusion group ( $P=NS$ ). In 7 (5.25%) patient of group A there was facial erythema that was initially periorbital and did not progress lower than the neck, while none presented this in group B. It disappeared in the first hour after the infusion and was not accompanied by any other associated complication. No patient was premedicated or received antihistamines in any infusion. During the time the study lasted we did not observe any case of bronchospasm, hypotension, headache, or other secondary effects that have been described in the

literature, related to the application of biologic drugs. Finally, there were significant differences with respect to the secondary effects between the 2 groups with relation to the administered dose of 1.5 and/or 3 mg/kg of infliximab. Regarding efficacy, both forms of infusion were effective, without any significant differences between them in the control of symptoms both in patients with SA (Visual Analog Scale for vertebral pain was reduced in 46%, from a mean 7.5 to 3.5 cm in both groups) as in patients with RA (the tender joint count was reduced on average 65% and swollen joints in 80%).

## Discussion

In multiple occasions the necessity to optimize resources arises in health systems, and must be done without jeopardizing the general state of the subjects of these services. In our hospital the population growth and the possibility of offering the benefits of new treatments to a greater number of rheumatic patients have impelled to us to prove different therapeutic schemes. One of them is the one that we have presented here, reducing the time of infusion of infliximab and, in light of the excellent results regarding security and effectiveness shown this study, we have continued carrying out this therapeutic scheme more frequently. Reported data does not show differences with respect to the effectiveness of the drug between the 2 infusion schedule, independent from the baseline disease presented by the patient (RA or SA), which would support the fact that the effectiveness of infliximab would be more directly related to the average life of the drug and the administered dose that with the time of infusion.<sup>15,16</sup> In our study no patient displayed any serious complication that forced us to suspend treatment. The percentage of adverse events found, 9.33% of subjects with facial erythema and 5.33% with burning sensation in the infusion arm, is not beyond what is reported in the literature, which shows 8% to 19% of cases presenting similar events.<sup>17,18</sup> We did not find differences in the appearance of adverse events with relation to gender, age, or baseline illness. In both groups, a moderate elevation of blood pressure in a percentage of patients was observed, without any significant differences among them. This elevation of blood pressure was observed during the infusion, and disappears soon after, making it possible that it was related to the saline solution administered as part of the infusion. Finally and in general, it is important to emphasize that in this study no significant differences with respect to the appearance of adverse events between both infusion groups have been observed, and when the data is compared separately depending

on the administered dose, of 1.5 mg/ and/or 3 mg/kg, indicating that both doses and both infusion rates are safe. Although van Vollenhoven et al<sup>19</sup> has published similar results infusing infliximab in 1 h, our study is the first study that supports the security of an increased rate of infusion for infliximab.<sup>20</sup> The present study was carried out using 3 doses of infliximab, which are not the most common current clinical treatment schedules for these diseases. The doses were applied according to the clinician's criteria for each patient and were chosen taking into account the economic limitations of our institution, trying to benefit the greatest number of patients with this therapy. On the other hand, the 3 dose of mg/kg of weight is the one most commonly employed in patients with RA. In addition, recent studies indicate that up to 60% of patients with SA could be effectively treated with doses of 3 mg/kg of weight. Our study, nevertheless, has several weaknesses that make it difficult to extrapolate this data to daily clinical practice: *a)* we compare the security of infliximab in both RA and SA, when those diseases can present different security profiles regarding infliximab. Nevertheless, the data from the literature indicate that the profiles are similar and in addition, in the subanalysis separating patients according to disease, we have not found differences; and *b)* the administered doses of 1.5 and 3 mg/kg do not constitute recommended treatment, specially for patients with SA (5 mg/kg). This can obviously lead to the supposition that the rate of infusion (dose administered per minute) is equal for 1.5 mg/kg in rapid infusion and for 5 mg/kg in 2 h. Nevertheless, when one analyzes the results only with the patients who received 3mg/kg of weight of infliximab (dose recommended for RA and used occasionally in SA), no differences have been observed as far as indirect effect with relation to the 2 rates of infusion. Some of the patients who received infliximab in rapid infusion already had received it with the traditional infusion rate.<sup>21</sup> Other studies have recognized that the appearance of serious adverse events, mediated by antibodies and other mechanisms of hypersensitivity, is increased with the number of infusions or with readministration after an infliximab-free interval of 2-4 years, but none of these circumstances occurred in either study groups. In a recent communication<sup>22</sup> data on the experience, security and satisfaction of patients treated in a day-clinic was obtained, suggesting that there are some possibilities worth exploring concerning biological therapy. In conclusion, the data allows the suggestion that an infusion of infliximab, at a 3 mg/kg dose, is safe in a form lasting 30-45 min. Confirmation of this data with larger studies and using doses that are currently applied in the daily practice might be very interesting to plan and reduce the costs of biological therapy.

## References

1. Generini S, Giacomelli R, Fedi R, Fulminis A, Pignone A, Frieri G, et al. Infliximab in spondyloarthropathy associated with Crohn's disease: an open study on the efficacy of inducing and maintaining remission of musculoskeletal and gut manifestations. *Ann Rheum Dis.* 2004;63:1664-9.
2. Demetter P, de Vos M, van Huysse JA, Baeten D, Ferdinand L, Peeters H, et al. Colon mucosa of patients both with spondyloarthritis and Crohn's disease is enriched with macrophages expressing the scavenger receptor CD163. *Ann Rheum Dis.* 2005;64:321-4.
3. Bell S, Kamm MA. Antibodies to tumour necrosis factor alpha as treatment for Crohn's disease. *Lancet.* 2000;355:858-60.
4. van den Bosch F, Kruihof E, Baeten D, Herrens A, de Keyser F, Mielants H, et al. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (infliximab) versus placebo in active spondyloarthropathy. *Arthritis Rheum.* 2002;46:755-65.
5. Yazdani-Biuki B, Stadmaier E, Mulabecirovic A, Brezinschek R, Tilz G, Demel U, et al. Blockade of tumour necrosis factor . significantly alters the serum level of IgG and IgA rheumatoid factor in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2005;64:1224-6.
6. Barrera P, Joosten LA, den Broeder AA, van de Putte LB, van Riel PL, van den Berg WB. Effects of treatment with a fully human anti-tumour necrosis factor . monoclonal antibody on the local and systemic homeostasis of interleukin 1 and TNF. in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2001;60:660-9.
7. Kruihof E, Baeten D, van den Bosch F, Mielants H, Veys EM, de Keyser F. Histological evidence that infliximab treatments leads to downregulation of inflammation and tissue remodelling of the synovial membrana in spondyloarthropathy. *Ann Rheum Dis.* 2005;64:529-36.
8. van Oosterhout M, Levarht EWN, Sant JK, Huizinga TWJ, Toes REM, van Laar JM. Clinical efficacy of infliximab plus methotrexate in DMARD naïve and DMARD refractory rheumatoid arthritis is associated with decreased synovial expression of TNF. and IL18 but not CXCL12. *Ann Rheum Dis.* 2005;64:537-43.
9. Keller C, Webb A, Davis J. Cytokines in the seronegative spondylarthropathies and their modification by TNF blockade: a brief report and literature review. *Ann Rheum Dis.* 2003;62:1128-32.
10. Temekonidis TI, Alamanos Y, Nikas SN, Bougias DV, Georgiadis AN, Volugari PV, et al. Infliximab therapy in patients with ankylosing spondylitis: an open label 12 month study. *Ann Rheum Dis.* 2003;62:1218-20.
11. Familian A, Voskuyl AE, van Mierlo GJ, Heijst HA, Twisk JW, Dijkamns BA, et al. Infliximab treatment reduces complement activation in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2005;64:1003-8.
12. Akinson JP. C-reactive protein: a rheumatologist's friends revisited. *Arthritis Rheum.* 2001;44:995-6.
13. Kruihof E, Baeten D, van den Bosch F, Mielants H, Veys EM, de Keyser F. Histological evidence that infliximab treatment leads to downregulation of inflammation and tissue remodeling of the synovial membrane in spondyloarthropathy. *Ann Rheum Dis.* 2005;64:529-36.
14. Elliot MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Katsikis P, et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. *Arthritis Rheum.* 1993;36:1681-90.
15. Maini R, St Clair EW, Breedved F, Furst D, Kolden J, Weissman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized phase III trial. ATTRACT Study Group. *Lancet.* 1999;354:1932-9.
16. Fitzcharles MA, Clayton CS, Menard HA. The use of infliximab in academic rheumatology practice: an audit of early clinical experience. *J Rheumatol.* 2002;29:2525-30.
17. Neven N, Vis M, Voskuyl AE, Wolbink GJ, Nurmohamed MT, Dijkmans BAC, et al. Adverse events in patients with rheumatoid arthritis treated with infliximab in daily clinical practice. *Ann Rheum Dis.* 2005;64:645-6.
18. Nikas SN, Temekonidis TI, Zikou AK, Argyropoulou MI, Efremidis S, Drosos AA. Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: a pilot study. *Ann Rheum Dis.* 2004;63:102-3.
19. van Vollenhoven, Gullström, Klareskog L. Feasibility of 1 hour infliximab infusions [carta]. *Ann Rheum Dis.* 2005;64:654.
20. Bañuelos-Ramírez D, Rojas-Rodríguez J, Holguín-Dorador IG. Anticuerpos monoclonales anti-TNF $\alpha$ , más metotrexato en artritis reumatoide resistente. *Rev Mex Reumat.* 2003;18:281-6.