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Open-label infliximab therapy in Crohn's disease: a long-term multicenter study of efficacy, safety and predictors of response

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ABSTRACT

BACKGROUND: Efficacy of infliximab in Crohn's disease (CD) showed by randomized controlled trials must be confirmed in clinical practice. We aimed to evaluate efficacy and safety of infliximab in CD patients of the Madrid area, looking for clinical predictors of response.

METHODS: Multicenter retrospective survey of all CD patients treated with infliximab in 8 University hospitals of the Madrid area (Spain) with a minimum follow up of 14wks.

RESULTS: 169 patients included (48% males, mean age 39 ± 12 yrs). 64% of them had perianal disease. 82% were under immunosuppressants. 1355 infliximab infusions administered (mean 8, range 1-30). 90% response rate and 48% remission rate were obtained with induction therapy. 73% followed maintenance treatment, and 78% of them maintained or improved the response after a mean follow up of 28 months (range 3.5-86). 24 patients lost response during the follow up, after a mean of 41wks (range 6-248). Only the prescription of maintenance therapy was predictive factor for favourable response ($p < 0.01$). 17 infusion reactions were reported (10% of the patients, 1.2% of the infusions; only one case was severe) and were the cause of treatment withdrawal in 7 patients. Co-treatment with immunosuppressive drugs and maintenance infliximab therapy were protective factors for infusion reactions ($p < 0.05$). Other adverse events occurred in 26% of the patients, and were cause of treatment withdrawal in 7 patients.

CONCLUSIONS: Infliximab is effective and safe for CD management but concomitant immunosuppressive drugs and maintenance treatment should be prescribed to obtain the best outcome. That confirms in a real life clinical setting the favourable results obtained in randomized clinical trials.

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ENFERMEDAD DE CROHN E INFLIXIMAB: ESTUDIO RETROSPECTIVO Y MULTICÉNTRICO SOBRE SU EFICACIA, SEGURIDAD Y FACTORES PREDICTIVOS DE RESPUESTA A LARGO PLAZO

OBJETIVO: La eficacia de infliximab en la enfermedad de Crohn (EC), demostrada por los diferentes ensayos clínicos, ha de ser confirmada en la práctica clínica. Nuestro objetivo fue evaluar la eficacia y la seguridad del infliximab en pacientes con EC del área de Madrid, buscando predictores de respuesta.

MÉTODOS: Estudio retrospectivo y multicéntrico que incluye los pacientes con EC tratados con infliximab en 8 hospitales de la Comunidad de Madrid, con un seguimiento mínimo de 14 semanas.

RESULTADOS: Se incluyó a un total de 169 pacientes (un 48% varones, con una edad de 39 ± 12 años), un 64% con enfermedad perianal y un 82% bajo tratamiento inmunosupresor. Se administraron un total de 1.355 perfusiones de infliximab (media, 8; rango, 1-30): un 90% de los pacientes respondió, un 48% alcanzó la remisión clínica, un 73% siguió tratamiento de mantenimiento, y un 78% mantuvo o mejoró su respuesta tras un seguimiento medio de 28 meses (rango, 3,5-86). Se perdió la respuesta durante el seguimiento de 24 pacientes, tras una media de 41

semanas (rango, 6-248). Sólo la prescripción de tratamiento de mantenimiento fue un predictor favorable de respuesta (p < 0,01); se contabilizaron 17 reacciones infusionales (en el 10% de los pacientes, el 1,2% de las perfusiones; sólo se constató un caso grave) y fueron causa de la suspensión del tratamiento en 7 pacientes. El cotratamiento con los inmunosupresores y el tratamiento de mantenimiento con infliximab fueron los factores protectores para sufrir reacciones infusionales (p < 0,05). Otros efectos adversos se produjeron en el 26% de los pacientes, y fueron causa de suspensión del tratamiento en 7 pacientes.

CONCLUSIONES: Infliximab es eficaz y seguro en el tratamiento de la EC, pero deberían prescribirse el tratamiento de mantenimiento y el concomitante con inmunosupresores para obtener los mejores resultados. Esto confirma en un escenario de práctica clínica real los resultados obtenidos en ensayos clínicos.

INTRODUCTION

The therapeutic approach to Crohn's disease (CD), a chronic and disabling inflammatory bowel disease, has evolved intensely in the last decade. Since steroids are not useful in maintaining long-term remission, as documented in classic population-based studies[1-4], immunosuppression with thiopurinic agents (i.e. azathioprine or mercaptopurine) or methotrexate have been widely used, even though they all have limited value for induction of response and can only benefit less than half of the patients that suffer from steroid dependency or resistance[5-9].

Despite the above, this conventional therapy is far from achieving a satisfactory control of the disease in a majority of the patients: Less than 50% of the CD patients seem to be asymptomatic 2 years after the initial diagnosis[3]. This frequently unfavourable course of the disease leads the patients to complications that may require surgery, even though resection of the affected portion of intestine does not affect the disease outcome[10]. Moreover, the widespread use of immunosuppressive therapies does not seem to modify the risk of surgery[11]. In this respect, modern biologic therapies may be the key to a disease modifying therapy.

Cytokines play a central role in modulating inflammation, and they may, therefore, be a logical target for inflammatory bowel disease therapy using specific cytokine inhibitors[12-15]. Tumor necrosis factor alpha (TNFα) is a key proinflammatory cytokine in Crohn's disease and in other chronic inflammatory conditions including rheumatoid arthritis and psoriasis[12-14]. Infliximab (Remicade®, Centocor; Malvern, Pennsylvania, USA) is an intravenously administered chimeric monoclonal immunoglobulin G1 antibody to TNF□. Several randomized controlled trials have shown infliximab to be an effective therapy for CD patients with moderate-severe and fistulizing disease, not responding to conventional drug treatment[12-14,16-19]. Thus, infliximab was approved by the United States Food and Drug Administration (FDA) in 1998 and by the European Medicines Agency (EMEA) in 1999 for the treatment of active, as well as fistulizing CD[20], and the efficacy to induce response and remission that is reported in placebo controlled trials has been confirmed in some open observational studies[21-28].

Even though it seems clear that maintenance therapy with infliximab every 8 weeks is the optimal regimen for patients treated for refractory luminal or fistulizing CD[19], there are only few and small studies that assess efficacy and safety of the long-term maintenance treatment with infliximab in the real clinical setting[29-33] and some controversial issues exist about the convenience and the duration of long-term maintenance therapy.

Although randomized clinical trials are mandatory, observational studies are needed to obtain data from the real life clinical setting. Therefore, we aimed to communicate the corporate experience with the clinical use of infliximab in CD patients in a group of major public hospitals in the area of Madrid, Spain; it is a large multicenter retrospective study that includes long-term followed up patients in maintenance treatment.

TABLE I. **Crohn's Disease Activity Index (CDAI)**

Item	Factor
Number of liquid stools*	X 2
Abdominal pain* (0 = no; 1 = mild; 2 = moderate; 3 = severe)	X 5
General web being* (good: 0; acceptable: 1; bad: 2; very bad: 3; terrible: 4)	X 7
Number of these clinical manifestations Arthritis/arthralgia Iritis/uveitis Eritema nodossum/pyoderma/aftae Anal fissure/fistulae/abcess Other fistulae	
Fever > 38.5 oC in the previous week	X 20
Intake of antidiarrhoeics (no: 0; yes: 1)	X 30
Hematocrite (47: males) (43: females)	X 6
% under the ideal weight	X 1

*In the 7 previous days.

METHODS

We retrospectively reviewed the records of all the CD patients that have received infliximab at some time in 8 hospitals of the Madrid area (Spain) with a minimum follow up of 14 weeks.

Demographical data were collected in all cases, as well as updated follow-up data concerning the evolution of the disease, including time of evolution of the disease, smoking habit, concomitant treatments, dose and number of infusions, the type of treatment (single, on demand or scheduled) and adverse events.

Regarding the activity of the disease and the response to infliximab therapy, Crohn's disease activity index (CDAI, table I) was calculated before the beginning of the infliximab therapy and by the 6th week after starting the treatment, as well as at the longest follow up on every case (the so called long-term response). In those cases where some CDAI score was missing, it was retrospectively calculated.

Response was defined as a significant reduction in the CDAI (at least 70 points), which should be below 150 points to be considered clinical remission. In those patients that were under steroid therapy, a significant decrease in the dose was also required for the definition of response, and a full discontinuation for considering clinical remission. For

fistulizing disease, direct evaluation was performed in all cases and fistula improvement (response) was defined as closure of 50% of particular fistulas that were actively draining at baseline, spontaneously or with gentle compression, and fistula remission was defined as closure of all particular fistulas what means absence of drainage, spontaneous or with gentle compression.

Statistical analysis

For quantitative variables, mean and standard deviation were calculated. For categorical variables, percentages and corresponding 95% intervals (95%CI) were provided. A p value < 0.05 was considered statistically significant. Categorical variables were compared with the χ^2 test, and quantitative variables with the Student t test.

RESULTS

There were 169 CD patients who received infliximab therapy for refractory luminal or fistulizing disease in 8 major public hospitals in the Madrid area (Spain).

Demographics

Patients were almost equally distributed in gender: 48% of them were males and 52% were females. Regarding age, patients were between 18 and 92 years of age (mean age 39 ± 12 years). Active smoking habit was reported by 61% of the patients when infliximab therapy was started.

Characteristics of the disease before infliximab therapy

The distribution of the patients according to the Montreal Classification was as follows: Regarding the age of diagnosis, 11% were diagnosed at 16 years or under (A_1), 77% between 17 and 40 years (A_2), and 12% were diagnosed over the age of 40 (A_3); regarding the localization of the disease, 14% affected the terminal ileum (L_1), 26% the colon (L_2) and 60% had ileocolic disease (L_3); 40% of the patients included had inflammatory behaviour (B_1), 11% had stricturing behaviour (B_2), and 48% had fistulizing disease (B_3). Perianal disease was documented in 64% of the patients, including 6 cases of rectovaginal fistula.
Before starting infliximab therapy, 82% of the patients were receiving immunosuppressants: 78% were under thiopurinic agents, 4% were under methotrexate. Only 18% of the patients were receiving no immunosuppressive drugs before infliximab.
Previous surgery related to the CD was reported in 67% of the patients included: 22.5% of the patients had undergone surgery related to luminal or stricturing complications, 30% had needed surgery due to perianal disease, and 14% had needed surgery for both reasons.

Infliximab therapy

Most of the patients (156; 92%) started this treatment with the usual induction therapy (infusion administered at the 0, 2nd and 6th week), with a response rate of 90% (95%CI, 85-95) and 48% (95%CI, 39-56) remission rate by the end of this period. Most of the patients (114; 73%) who started induction therapy followed maintenance treatment, and 90 (78%; 95%CI, 67-84) of them maintained or improved the response obtained by the 6th week. In the remaining 24 patients (22%) who lost response, dose was increased in 10 of them, infusion interval was shortened in 5, and treatment was withdrawn in 9 patients. Among the 15 patients whose infliximab administration was modified, 10 achieved a good outcome that lasted for a mean of 19 weeks (range, 4-40 weeks). When response was lost, it occurred after a mean period of 41 weeks (range 6-248 weeks) after the initial dose of infliximab.
After a mean follow up of 28 months (range 3.5-86 months), the total number of infliximab infusions was 1355 (mean 8 infusions per patient; range 1-30) and 95 patients (56% of the total number of patients initially included) had achieved complete response since they were considered to be in clinical remission, 52 patients (31%) had reached partial response and 22 patients (13%) were considered treatment failures.
We found no relationship of statistical significance between the clinical outcome and sex, age, smoking habit, Montreal classification (including the presence of fistulizing disease), number of years of evolution of the disease, surgical records or the immunosuppressive concomitant therapy. The only predictive factor that we found for the long-term favourable response to infliximab was the prescription of scheduled maintenance treatment ($p < 0.01$).

Safety issues

Despite the fact that 78% of the patients received premedication with steroids or antihistaminics, 17 cases of infusion reactions were reported, which means 10% (95%CI, 5.5-15) of the patients, 1.2% (95%CI, 0.8-2) of the infusions. Eight of them were immediate, and 9 were delayed reactions; regarding its severity, 50% were mild, 43% moderate, and only 1 case of severe infusion reaction was reported.
The infusion reactions were managed as follows: No therapeutic intervention was required in most cases (53%), additional steroids were needed in 6%, the infusion had to be slowed in 7%, and had to be stopped in 33% of the cases. Infusion reactions were the cause of treatment withdrawal in only 7 patients (30% of the patients that had to stop the treatment). We found no relationship of statistical significance between the presence of infusion reactions and sex, age, smoking habit, Montreal classification, number of years of evolution of the disease or surgical records. Co-treatment with immunosuppressive drugs and administration of maintenance infliximab therapy were the only protective factors for infusion reactions ($p < 0.05$).
Other adverse events were documented in 26% of the

patients, including headache (5 cases), gastrointestinal symptoms (5 cases), asthenia (4 cases), arthralgia (4 cases), myalgia (7 cases), fever (2 cases) and pruritus (2 cases). Adverse events not clearly labelled as infusion reactions were responsible for treatment withdrawal in 7 cases. No case of opportunistic infection or active tuberculosis was reported during the follow-up. Taking all these safety issues into account, 14 out of the 169 patients included (8%; 95% CI, 4.1-12) had to abandon infliximab therapy due to adverse events.

DISCUSSION

Even though infliximab was approved by the FDA for refractory CD almost 10 years ago, it is remarkable that post-marketing studies are still scarce. We believe that independent observational studies are necessary to confirm in the clinical setting the outcome from the large randomized clinical trials, in terms of both efficacy and safety. Moreover, long-term follow-up series of infliximab treated patients in real clinical practice are clearly lacking. We present the current experience with infliximab in CD in a group of several major hospitals of the Madrid area, which provides long-term follow-up data.

Induction therapy with infliximab obtained a very good outcome, which was almost twice than that reported in randomized controlled trials. The reason that may explain this outstanding difference between clinical trails and clinical practice should be found in the selected patient population, since the daily practice indication to receive infliximab seems to be stricter than the ACCENT inclusion criteria[17,34]. Regulations concerning clinical trials required to register a new drug do not always reproduce the clinical reality.

As previously stated in the ACCENT trials, systematic scheduled treatment every 8 weeks is the optimal strategy for infliximab to be administered[17,19,34]. This was confirmed in our experience since those patients who did not undergo scheduled maintenance treatment with infliximab were those who achieved a poorer outcome. On the other hand, most of our patients were under immunosuppressive drugs at the time of starting infliximab therapy. This has been previously pointed out as a predictive factor for response in some studies[35-37] but it has not been confirmed by our experience in terms of clinical efficacy although it seems to be important in terms of safety, as it has been highlighted by our results.

Therefore, maintenance infliximab therapy and combined therapy with immunosuppressive drugs are the only predictive factors of good outcome that we found in our experience, which is very consistent with previously reported data obtained from randomized clinical trials[12,17,19]. Some other clinical predictive factors have been proposed in previous studies (stricturing behaviour[38], smoking habit[36,37] or the presence of rectovaginal fistula[39]), but none of them was useful in our experience. The factors that we found to be predictive of outcome are believed to be related to the development of antibodies to infliximab (ATI): Episodic instead of scheduled maintenance treatment is more immunogenic and related with higher levels of ATI; these high ATI levels are related to a reduction in the serum concentration of infliximab, and consequently to a reduction in the strength and the duration of the response[40-43]. As a matter of fact, recently published pharmacokinetic studies show that the clinical outcome is strongly related with the serum concentration of infliximab and the presence of ATI might be a surrogate marker for the effects of absent serum infliximab[43,44]. On the other hand, concomitant immunosuppressive agents are thought to prevent the development of these ATI[40-43], even though differences in efficacy between patients with or without ATI, with or without concurrent immunomodulators, have not been clearly found[40,43]. Therefore, our experience confirms that those patients that receive concomitant immunosuppressive therapy and are enrolled in scheduled maintenance therapy are more likely to obtain good response in the long-term.

Long-term follow up data show that patients may loose the obtained response to infliximab. Almost one of every four patients treated in our study lost their response in a relatively short period of time, which is consistent with the data obtained from randomized controlled trials[17,34]. The management of these cases is not clearly stated in the literature, but it seems that increasing the infliximab dose or shortening the interval between doses may be rational alternatives[19]. By doing so, we obtained good outcome in most of the patients that had lost their response to infliximab but, once again, for a limited period of time. There is no doubt that the long follow up carried out in this study allowed this complication arise in a remarkable proportion of the patients. The management of this further situation is beyond scientific evidence, and it is not described in randomized trials. Once again, the presence of ATI is believed to be the cause of this phenomenon[40] and therefore availability of new anti-TNF molecules may be the key for these patients to keep the infliximab induced response[45].

Our experience confirms in a clinical setting that infliximab is safe, as infusion reactions were rare and most of them were mild or needed no therapeutic intervention. The presence of ATI is related to a 12% increase of infusion reactions[40,43]; scheduled maintenance treatment and concomitant immunosuppressive agents were the only protective factors for infusion reactions in our experience, and this might be related to the reduction in the incidence of ATI that these two strategies provide in the long-term[43]. Moreover, only a small minority of our patients had to quit from infliximab due to intolerance. On the other hand, serious infectious complications have not been described in our experience, and this fact must be related to the generalized compliance of the recommendations made by the Spanish Working Group on CD and UC (GETECCU) for the use of Infliximab in CD that were published in 2002 and updated in 2005[46,47].

In conclusion, this real life clinical setting experience

confirms results from previous randomized controlled clinical trials: Infliximab is safe and effective for treating CD patients, but its immunogenicity represents a clinical problem in the long-term, so scheduled maintenance therapy and concomitant immunosuppressive drugs are needed to obtain the best outcome. Moreover, loss of response is a fact in the long-term clinical practice. Updated strategies to preserve the infliximab induced response must be defined.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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REFERENCES

1. Munkholm P, Langholz E, Davidsen M, Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. Gut. 1994;35:360-2.
2. Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology. 2001;121:255-60.
3. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol. 1995;30:699-706.
4. Lapidus A, Bernell O, Hellers G, Lofberg R. Clinical course of colorectal Crohn's disease: a 35-year follow-up study of 507 patients. Gastroenterology. 1998;114:1151-60.
5. Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med. 1980;302:981-7.
6. Candy S, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. Gut. 1995;37:674-8.
7. Bouhnik Y, Lemann M, Mary JY, Scemama G, Tai R, Matuchansky C, et al. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. Lancet. 1996;347:215-9.
8. Feagan BG, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. N Engl J Med. 1995;332:292-7.
9. Feagan BG, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. N Engl J Med. 2000;342:1627-32.
10. Caprilli R, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. Gut. 2006;55 Suppl 1:36-58.
11. Cosnes J, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre JP. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. Gut. 2005; 54:237-41.
12. Rutgeerts P, Van Assche G, Vermeire S. Optimizing anti-TNF treatment in inflammatory bowel disease. Gastroenterology. 2004; 126:1593-610.
13. Siddiqui MA, Scott LJ. Infliximab: a review of its use in Crohn's disease and rheumatoid arthritis. Drugs. 2005;65:2179-208.
14. Ardizzone S, Bianchi Porro G. Biologic therapy for inflammatory bowel disease. Drugs. 2005;65:2253-86.
15. Van Deventer SJ. Review article: targeting TNF alpha as a key cytokine in the inflammatory processes of Crohn's disease: the mechanisms of action of infliximab. Aliment Pharmacol Ther. 1999;13 Suppl 4:3-8; discussion 38.
16. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398-405.
17. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. 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. Rutgeerts P, Van Assche G, Vermeire S. Review article: infliximab therapy for inflammatory bowel disease: seven years on. Aliment Pharmacol Ther. 2006;23:451-63.
20. Kornbluth A. Infliximab approved for use in Crohn's disease: a report on the FDA GI Advisory Committee conference. Inflamm Bowel Dis. 1998;4:328-9.
21. Ricart E, Panaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. Am J Gastroenterol. 2001; 96:722-9.
22. Mortimore M, Gibson PR, Selby WS, Radford-Smith GL, Florin TH. Early Australian experience with infliximab, a chimeric antibody against tumour necrosis factor-alpha, in the treatment of Crohn's disease: is its efficacy augmented by steroid-sparing immunosuppressive therapy? The Infliximab User Group. Intern Med J. 2001;31:146-50.
23. Cohen RD. Efficacy and safety of repeated infliximab infusions for Crohn's disease: 1-year clinical experience. Inflamm Bowel Dis. 2001;7 Suppl 1:17-22.
24. Hommes DW, Van de Heisteeg BH, Van der Spek M, Bartelsman JF, Van Deventer SJ. Infliximab treatment for Crohn's disease: one-year experience in a Dutch academic hospital. Inflamm Bowel Dis. 2002;8:81-6.
25. Sample C, Bailey RJ, Todoruk D, Sadowski D, Gramlich L, Milan M, et al. Clinical experience with infliximab for Crohn's disease: the first 100 patients in Edmonton, Alberta. Can J Gastroenterol. 2002;16:165-70.
26. Ardizzone S, Colombo E, Maconi G, Bollani S, Manzionna G, Petrone MC, et al. Infliximab in treatment of Crohn's disease: the Milan experience. Dig Liver Dis. 2002;34:411-8.
27. Van Balkom BP, Schoon EJ, Stockbrugger RW, Wolters FL, Van Hogezand RA, Van Deventer SJ, et al. Effects of anti-tumour necrosis factor-alpha therapy on the quality of life in Crohn's disease. Aliment Pharmacol Ther. 2002;16:1101-7.
28. Gheorghe L, Gheorghe C, Badea M, Vadan R, Parvulescu I, Toader C, et al. Infliximab for Crohn's disease in clinical practice: the experience of a single center in romania. Rom J Gastroenterol. 2003;12:7-13.
29. Choi KD, Song HJ, Kim JS, Jung HC, Song IS. Efficacy and safety of treatment with infliximab in Crohn's disease-the experience of single center in Korea. Korean J Gastroenterol. 2005; 46:48-55.
30. Lamireau T, Cezard JP, Dabadie A, Goulet O, Lachaux A, Turck D, et al. Efficacy and tolerance of infliximab in children and adolescents with Crohn's disease. Inflamm Bowel Dis. 2004;10:745-50.
31. Wenzl HH, Reinisch W, Jahnel J, Stockenhuber F, Tilg H, Kirchgatterer A, et al. Austrian infliximab experience in Crohn's disease: a nationwide cooperative study with long-term follow-up. Eur J Gastroenterol Hepatol. 2004;16:767-73.
32. Stephens MC, Shepanski MA, Mamula P, Markowitz JE, Brown KA, Baldassano RN. Safety and steroid-sparing experience using infliximab for Crohn's disease at a pediatric inflammatory bowel disease center. Am J Gastroenterol. 2003;98: 104-11.
33. Mendoza JL, García-Paredes J, Cruz Santamaría DM, Lana R, Ramírez Fernández E, Rodríguez Asteaga E, et al. Infliximab treatment and prognostic factors for response in patients with Crohn's disease. Rev Esp Enferm Dig. 2002;94:269-79.
34. Sands BE, Blank MA, Patel K, Van Deventer SJ. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. Clin Gastroenterol Hepatol. 2004;2:912-20.

35. Vermeire S, Louis E, Carbonez A, Van Assche G, Noman M, Belaiche J, et al. Demographic and clinical parameters influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment in Crohn's disease. Am J Gastroenterol. 2002; 97:2357-63.
36. Parsi MA, Achkar JP, Richardson S, Katz J, Hammel JP, Lashner BA, et al. Predictors of response to infliximab in patients with Crohn's disease. Gastroenterology. 2002;123:707-13.
37. Arnott ID, McNeill G, Satsangi J. An analysis of factors influencing short-term and sustained response to infliximab treatment for Crohn's disease. Aliment Pharmacol Ther. 2003;17: 1451-7.
38. Lichtenstein GR, Stein RB, Lewis JD, Deren J. Response to infliximab is decreased in the presence of intestinal strictures in patients with Crohn's disease. Am J Gastroenterol. 1999;94: 2691A.
39. Topstad DR, Panaccione R, Heine JA, Johnson DR, MacLean AR, Buie WD. Combined seton placement, infliximab infusion, and maintenance immunosuppressives improve healing rate in fistulizing anorectal Crohn's disease: a single center experience. Dis Colon Rectum. 2003;46:577-83.
40. 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.
41. Baert F, Noman M, Vermeire S, Van Assche G, Carbonez A, Rutgeets P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med. 2003;348:601-8.
42. 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.
43. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol. 2006;4:1248-54.
44. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet. 2005;366:1367-74.
45. Hinojosa J, Gomollon F, García S, Bastida G, Cabriada JL, Saro C, et al. Efficacy and safety of short-term adalimumab treatment in patients with active Crohn's disease who lost response or showed intolerance to infliximab: a prospective, open-label, multicentre trial. Aliment Pharmacol Ther. 2007;25:409-18.
46. Domenech E, Esteve-Comas M, Gomollon F, Hinojosa J, Obrador A, Panes J, et al. Recommendations for the use of infliximab (Remicade) in Crohn's disease. GETECCU 2001. Gastroenterol Hepatol. 2002;25:162-9.
47. Domenech E, Esteve M, Gomollon F, Hinojosa J, Panes J, Obrador A, et al. GETECCU-2005 recommendations for the use of infliximab (Remicade) in inflammatory bowel disease. Gastroenterol Hepatol. 2005;28:126-34.