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TOPIC HIGHLIGHT

Javier P Gisbert, Professor; Fernando Gomollón, Dr., MD, PhD, *Series Editors*

Are we giving biologics too late? The case for early *versus* late use

Elena Ricart, Orlando García-Bosch, Ingrid Ordás, Julián Panés

Elena Ricart, Orlando García-Bosch, Ingrid Ordás, Julián Panés, Gastroenterology Department, Hospital Clinic, CIBER-EHD, C/Villarroel 170, Barcelona 08036, Spain
Author contributions: All authors contributed equally to this work.
Correspondence to: Elena Ricart, MD, Gastroenterology Department, Hospital Clinic, CIBER-EHD, C/Villarroel 170, Barcelona 08036, Spain. ericart@clinic.ub.es
Telephone: +34-93-2275418 Fax: +34-93-2279387
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Abstract

Corticosteroids and immunomodulators have been the mainstay therapies for Crohn's disease. Corticosteroids are highly effective to control symptoms in the short-term, but they are not effective in maintaining remission, they heal the mucosa in a reduced proportion of cases, and long-time exposure is associated with an increased risk of infections and mortality. Immunomodulators, azathioprine and methotrexate, heal the mucosa in a higher proportion of patients that corticosteroids but their onset of action is slow and they benefit less than half of patients with Crohn's disease. In the last decade, medical therapy for Crohn's disease has experienced a remarkable change due to the introduction of biologic therapy, and particularly the use of anti-tumour necrosis factor-alpha agents. Infliximab, adalimumab, and certolizumab pegol have demonstrated efficacy for induction and maintenance of remission in active Crohn's disease. These agents have raised the bar for what is a suitable symptomatic response in Crohn's disease and modification of the natural history of the disease has become a major goal in the treatment of Crohn's disease. There are several data in the literature that suggest that early use of biologic therapy and achievement of mucosal healing contribute to disease course modification. However, many questions on early biological therapy for Crohn's disease remain still unanswered.

Key words: Biologic therapy; Crohn's disease; Corticosteroids; Immunomodulators

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INTRODUCTION

To date, medical therapy for Crohn's disease has been restricted to treat the signs and symptoms of the disease, to prevent steroid dependence by using immunomodulating agents (azathioprine, 6-mercaptopurine, methotrexate), to maintain clinical remission, and to minimize medication toxicity. The introduction of biologic therapy, particularly the use of anti-tumor necrosis factor alpha (TNFα) agents (infliximab, adalimumab, certolizumab pegol), has provided a poweful instrument in the treatment and management of Crohn's disease that has lead to an expansion of goals in Crohn's disease therapy. These include a rapidly achieved and sustained clinical remission, complete and sustained healing of the bowel mucosa, reduction in steroid use, reduction in hospitalizations and surgeries, avoidance of complications of the disease (stenoses, fistulas), and improvement of patients' overall quality of life. Infliximab, adalimumab, and certolizumab pegol have demonstrated efficacy for induction and maintenance of remission in Crohn's disease. However, biologic agents are still used with reluctance, being the high cost and the uncertainty about long-term safety of these agents the most frequently cited reasons. An important question facing physicians that take care of Crohn's disease patients is at what point of the disease should biological therapy be used.

STEP-UP APPROACH

The standard treatment in Crohn's disease is based on a step-up approach in which "traditional" therapies thought to be more secure are used early and then successive therapies are added in case of lack of response or toxicity. Under this scheme, agents with low efficacy such as aminosalicylates may be used for long periods of time without any benefit. Patients who fail to respond to aminosalicylates are then treated with prednisone or budesonide if the disease is limited

to the ileum or the right colon. Corticosteroids are efficacious to induce remission in Crohn's disease patients but do not induce long-lasting remission[1]. About 40% of patients will develop a steroid-dependent or steroid-refractory course of the disease. In these cases, treatment with immunomodulating agents such as azathioprine, 6-mercaptopurine or methotrexate is started. Immunomodulation has long-term efficacy in inflammatory bowel disease but has limited value for induction of remission and benefits to less than half of the patients dependent or resistant to corticosteroids[2-6]. Under this therapeutic approach, population-based studies show that only 42% of Crohn's disease patients are symptom-free at 2 years after the initial diagnosis and 12% after 10 years, and that 10% of patients have chronically active disease in 2 years and 1% in 10 years[7]. Relapsing or chronically active disease leads to complications that often require surgical treatment that, unfortunately, does not cure or interrupt the progression of the disease[8]. Rates of surgical intervention remain high, with as many as one third of patients requiring surgey within a year of beginning oral corticosteroids[1] and with no significant decrease in the need of surgery in the last decades despite the earlier and increasing use of immunomodulators[9]. In the last years it has become also apparent that immunomodulators carry a significant safety risk for patients treated long term, including the risk of infection[10], lymphoma[11], cervical carcinoma[12], and nodular regenerative hyperplasia[13].

TOP-DOWN APPROACH

The ability of anti-TNFα agents to rapidly control disease symptoms and to heal the mucosa has raised the question of whether the early use of biological therapy in patients with newly diagnosed Crohn's disease can alter the course and natural history of the disease. In patients with early rheumatoid arthritis, initial combination therapy with high doses of prednisone and methotrexate or initial combination therapy with infliximab and methotrexate has shown to be more effective than sequential monotherapy or step-up combination therapy to prevent disease progression[14-18].

This concept, applied to Crohn's disease, has been tested in a trial carried out in Belgium, Holland and Germany by D'Haens *et al*[19]. This study included 133 patients with early Crohn's disease (defined as a diagnosis within the past 4 years) not previously treated with corticosteroids, immunomodulators or biological agents. Patients were randomly assigned to receive combined immunosuppression induction with azathioprine and three infusions of infliximab at weeks 0, 2, and 6 (n = 65) (top-down group), or to conventional therapy with two tapering courses of corticosteroids, and if indicated with azathioprine and then with infliximab (n = 64) (step-up group). Patients who were intolerant to azathioprine in both groups received methotrexate. Patients in the top-down group were given additional infliximab infusions in an "on-demand" basis and corticosteroids, if necessary, to control disease activity. The primary outcome was the combination of remission without corticosteroids and without bowel resection at weeks 26 and 52. At week 26, 39/65 (60%) of patients in the top-down group were in clinical remission without corticosteroids and without surgery compared to 23/64 (36%) in the step-up group (P = 0.0062) with an absolute difference of 24% (95% CI 7.3-40.8). At week 52, 40/65 (61.5%) in the top-down group were in remission compared to 27/64 (42.2%) in the step-up group (P = 0.0278), with an absolute difference of 19.4% (95% CI 2.4-36.3). After week 52, the proportion of patients in remission did no differ between the two groups. The median time to relapse was longer for patients in the top-down group (329 d, IQR 91-not reached) compared to patients in the step-up group (174.5 d, IQR 78.5-274, P = 0.031). Results from the IBDQs paralleled those of disease activity. At week 10, mean IBDQ score increased by 59.2 ± 36.6 points from baseline in the top-down group and by 37.4 ± 32.8 points in the step-up group (95% CI 8.7-34.9, P = 0.0014). Patients in the top-down group received significantly less methylprednisolone than patients in the step-up group. The 95th percentile of the daily methylprednisolone dose was 35 mg for patients in the step-up group and 0 mg for those in the top-down group. On the contrary, by the end of the trial 76% of patients in the step-up group were receiving an immunomodulator agent. After the completion of the induction course of infliximab in the top-down group, the proportion of patients on infliximab was similar in both groups. There were not important differences in the occurrence of adverse avents between the two groups, although the study was not primarly designed to address safety differences between the two strategies. The strongest argument for the top-down approach changing the natural history of Crohn's disease lies in the findings of the endoscopic studies performed in 49 patients of the study. At week 104, no ulcers were seen in 19/26 (73.1%) of patients in the top-down group compared with 7/23 (30.4%) in the step-up group (P = 0.0028). Endoscopic scores were 0.7 ± 1.5 and 3.1 ± 2.9, respectively (P < 0.001). This difference was marked despite the fact that there was no difference in disease activity scores between the top-down and step-up approaches at this timepoint. This leads to the notion that early introduction of biological therapy has direct benefits at an specific organ level (bowel) that far outreach the benefits of steroid sparing and overall clinical efficacy. The benefit of the early use of biological therapy has been demonstrated in rheumatoid arthritis, where the early introduction of biological therapy results in less joint damage on X-ray compared to a standard therapeutic approach using disease-modifying agents, regardless of similar clinical activity scores[16]. Mucosal healing has been associated with a reduction in hospitalizations and surgery for complications of Crohn's disease[20,21]. In the ACCENT I (A Crohn's disease Clinical study Evaluating Infliximab in a New long term Treatment regimen) trial[20], patients with short-term (week 10) and long-term (week 54) mucosal healing did no require hospitalization and patients with mucosal

healing at only one visit required fewer hospitalizations compared with patients without mucosal healing (18.8% *vs* 28%, respectively). If mucosal healing predicts a true change of natural history of the disease, these findings are of major significance.

This study has a number of aspects that should be pointed out. First, patients in the top-down group did not receive maintenance therapy with both azathioprine and infliximab. Rutgeerts *et al*[21] reported a significantly higher proportion of patients with mucosal healing in a maintenance infliximab group compared with those patients who received episodic treatment (50% *vs* 7%; $P = 0.007$). Thus, the study may have underestimated the benefit of combination therapy with an immunomodulator and infliximab administered on a regular basis. Second, the data suggest that infliximab might be used as a bridge to maintenance of remission with azathioprine. In a study by Lémann *et al*[22], 113 patients with steroid-dependent active Crohn's disease were randomized to azathioprine plus placebo or infliximab 5 mg/kg at weeks 0, 2, and 6. At weeks 24 and 54, the percentage of patients in remission and off steroids was higher in the infliximab group compared to the placebo group (57% *vs* 29%; $P = 0.003$ at week 24, and 40% *vs* 22%; $P = 0.04$ at week 54). However, episodic treatment is associated with immunogenicity that leads to hypersensibility reactions and loss of response to infliximab[23]. Third, in this study, azathioprine was started after two courses of corticosteroids, that may have underestimated the benefit of early introduction of conventional therapy with azathioprine. In a pediatric study by Markowitz *et al*[24], 55 children with newly diagnosed Crohn's disease were randomized to receive prednisone 40 mg/d with either 6-MP or placebo. Only 9% of the 6-MP treated group relapsed during a 18-mo follow-up period compared with 47% of the controls ($P = 0.007$). Candy *et al*[3] reported similar results in 63 adult patients with active Crohn's disease that were treated with a 12 wk diminishing dose of prednisolone and at the same time entered into a randomized, double blind 15 mo trial of either azathioprine (2.5 mg/kg) or placebo. Remission rates between the two groups were compared at 12 wk and at 15 mo. There was no significant difference in the proportion of patients who achieved and maintained remission by week 12, but at 15 mo there was a highly significant difference in the proportion of patients in remission (42% receiving azathioprine *vs* 7% receiving placebo, $P = 0.001$). Recent practice guidelines suggest that azathioprine should be introduced with the first course of corticosteroids[25]. Fourth, this study also underscores the fact that a proportion of patients will have a good clinical outcome at 12 mo irrespective of which treatment they receive. In other words, there is a proportion of patients with newly diagnosed Crohn's disease who do not require early intense treatment with biologic therapy.

BIOLOGICS IN EARLY CROHN'S DISEASE

Beyond achieving mucosal healing, the time of initiation of therapy might be crucial considering that a longer duration of the disease leads to more irreversible damage. There are several data in the literature that suggest higher response and remission rates to biologics in patients with a recent diagnosis of Crohn's disease compared to those patients with long-lasting disease. In a pediatric study that included 22 children, Lionetti *et al*[26] observed that the best response to infliximab was seen in children with a disease duration < 1 year. In addition, 5/6 children with early Crohn's disease had a complete closure of all fistulas compared with 2/7 children with a disease duration of more than 1 year. Kagathasan *et al*[27] showed a remarkably prolonged duration of response after a single infusion of infliximab in children with early compared to late Crohn's disease. In this study, among the 14/15 patients who responded, three of six children (50%) with early disease maintained clinical response through the 12-mo trial period, compared with none of eight children with late disease.

The CHARM (Crohn's trial of the fully Human antibody Adalimumab for remission Maintenance) study[28] was a double-blind, placebo-controlled phase 3 trial designed to determine the efficacy and safety of adalimumab 40 mg weekly *versus* every other week for maintenance of clinical remission in patients with moderate-to-severe Crohn's disease. A subanalysis of the CHARM study showed that disease duration was a significant contributor to the likehood of achieving remission. Remission rates at weeks 26 and 54 were highest when adalimumab was started in patients within the first 2 years after Crohn's disease diagnosis compared with patients diagnosed within > 5 years (59% *vs* 41%, respectively at week 26; 51% *vs* 35%, respectively at week 54). The PRECISE 2 (The Pegylated Antibody Fragment Evaluation in Crohn's disease: Safety and Efficacy 2) study was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy of certolizumab pegol maintenance therapy in adults with moderate-to-severe Crohn's disease[29]. In a subanalysis of the study, a high rate of response and remission was observed at week 26 in patients with Crohn's disease diagnosed within the last 2 years and treated with certolizumab pegol compared with all patients included in the study (83.5% *vs* 62.8%, respectively; 61.5% *vs* 47.9%, respectively; $P < 0.02$)[30,31].

TOP-DOWN TREATMENT: LIMITATIONS

There is a growing evidence that suggests that the benefits of anti-TNF therapy extend beyond just the measure of clinical efficacy and that they may have the potential to alter the natural history of the disease. However, to date, several factors limit the use of biologic agents as primary therapy for Crohn's disease patients and early intense therapy needs to be balanced against the potential risks of increased infections and malignancy. Approximately 50% of all patients with inflammatory bowel disease will never require corticosteroids. Thus, first-line therapy with biologic therapies in this group would expose patients to toxicity or immunogenicity

without the benefit of potentially changing the natural history of their disease. The TREAT registry in North America has not shown, to date, an increased risk for malignancies or serious infections related to the use of infliximab in Crohn's disease[32] but clinicians should be aware that opportunistic infections such as tuberculosis, hystoplasmosis or *Pneumocytes carinii* do develop in anti-TNFα-treated patients. Nevertheless, the TREAT registry also shows that in the overall population of the registry, steroid used but not infliximab treatment was an independent predictive factor for infectious complications, and this point has been confirmed in the prospective European ENCORE registry[33]. The recently reported cases of hepatosplenic T-cell lymphoma[34], a rare and aggressive tumour, which most frequently develops in young male adults treated with infliximab and concomitant immunosuppresive therapy, has raised the question of whether it is the best strategy to discontinue the immunomodulators after certain period of combined therapy, or to stop the biologic therapy and try to maintain remission with immunomodulators alone[35]. Clinicians should also balance the side effects of the new biological therapies against the well-known and frequent toxicity of both corticosteroids and immunomodulators.

CONCLUSION

At present, Crohn's disease therapy is based in a sequential step-up strategy and biologic therapies are placed on a late position in this treatment strategy, mirroring the design of pivotal randomized controlled trials. However, the failure of many patients to respond to conventional therapy and the assessment that step-up strategy does not significantly alter the natural course of the disease has encouraged clinicians and investigators to question whether this late position is the most appropriate for biologics. Challenge is to identify those Crohn's disease patients who will develop a complicated course of the disease in whom the introduction of early and more intensive treatment from the beginning of the disease can be justified. In a recent report by Beaugerie *et al*[36], young age at time of disease onset, presence of perianal disease, early need for corticosteroids, and isolated small bowel involvement were identified as clinical factors associated with poor clinical outcomes and disability. Combination of genetic and serologic profiles may have an additive value in stratifying the disease outcome[37,38] and this may help clinicians categorize patients into subgroups to better guide therapeutic decision-making.

REFERENCES

1 **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**: 255-260

2 **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**: 981-987

3 **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**: 674-678

4 **Bouhnik Y**, Lemann M, Mary JY, Scemama G, Tai R, Matuchansky C, Modigliani R, Rambaud JC. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Lancet* 1996; **347**: 215-219

5 **Feagan BG**, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995; **332**: 292-297

6 **Feagan BG**, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Koval J, Wong CJ, Hopkins M, Hanauer SB, McDonald JW. 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**: 1627-1632

7 **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

8 **Cosnes J**, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, Gendre JP. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002; **8**: 244-250

9 **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**: 237-241

10 **Toruner M**, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, Colombel JF, Egan LJ. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008; **134**: 929-936

11 **Kandiel A**, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005; **54**: 1121-1125

12 **Kane S**, Khatibi B, Reddy D. Higher incidence of abnormal Pap smears in women with inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 631-636

13 **Vernier-Massouille G**, Cosnes J, Lemann M, Marteau P, Reinisch W, Laharie D, Cadiot G, Bouhnik Y, De Vos M, Boureille A, Duclos B, Seksik P, Mary JY, Colombel JF. Nodular regenerative hyperplasia in patients with inflammatory bowel disease treated with azathioprine. *Gut* 2007; **56**: 1404-1409

14 **Bathon JM**, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Genovese MC, Wasko MC, Moreland LW, Weaver AL, Markenson J, Finck BK. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000; **343**: 1586-1593

15 **Breedveld FC**, Emery P, Keystone E, Patel K, Furst DE, Kalden JR, St Clair EW, Weisman M, Smolen J, Lipsky PE, Maini RN. Infliximab in active early rheumatoid arthritis. *Ann Rheum Dis* 2004; **63**: 149-155

16 **St Clair EW**, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, Dewoody K, Weiss R, Baker D. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004; **50**: 3432-3443

17 **Goekoop-Ruiterman YP**, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, Zwinderman AH, Ronday HK, Han KH, Westedt ML, Gerards AH, van Groenendael JH, Lems WF, van Krugten MV, Breedveld FC, Dijkmans BA. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005; **52**: 3381-3390

18 **Goekoop-Ruiterman YP**, de Vries-Bouwstra JK, Allaart

CF, van Zeben D, Kerstens PJ, Hazes JM, Zwinderman AH, Peeters AJ, de Jonge-Bok JM, Mallee C, de Beus WM, de Sonnaville PB, Ewals JA, Breedveld FC, Dijkmans BA. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007; **146**: 406-415

19 **D'Haens G**, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, De Vos M, van Deventer S, Stitt L, Donner A, Vermeire S, Van de Mierop FJ, Coche JC, van der Woude J, Ochsenkuhn T, van Bodegraven AA, Van Hootegem PP, Lambrecht GL, Mana F, Rutgeerts P, Feagan BG, Hommes D. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008; **371**: 660-667

20 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549

21 **Rutgeerts P**, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, Patel K, Wolf DC, Safdi M, Colombel JF, Lashner B, Hanauer SB. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006; **63**: 433-442; quiz 464

22 **Lemann M**, Mary JY, Duclos B, Veyrac M, Dupas JL, Delchier JC, Laharie D, Moreau J, Cadiot G, Picon L, Bourreille A, Sobahni I, Colombel JF. Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology* 2006; **130**: 1054-1061

23 **Baert F**, Noman M, Vermeire S, Van Assche G, D' Haens G, Carbonez A, Rutgeerts P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; **348**: 601-608

24 **Markowitz J**, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000; **119**: 895-902

25 **Lichtenstein GR**, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006; **130**: 940-987

26 **Lionetti P**, Bronzini F, Salvestrini C, Bascietto C, Canani RB, De Angelis GL, Guariso G, Martelossi S, Papadatou B, Barabino A. Response to infliximab is related to disease duration in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2003; **18**: 425-431

27 **Kugathasan S**, Werlin SL, Martinez A, Rivera MT, Heikenen JB, Binion DG. Prolonged duration of response to infliximab in early but not late pediatric Crohn's disease. *Am J Gastroenterol* 2000; **95**: 3189-3194

28 **Colombel JF**, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132**: 52-65

29 **Schreiber S**, Khaliq-Kareemi M, Lawrance IC, Thomsen OO, Hanauer SB, McColm J, Bloomfield R, Sandborn WJ. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007; **357**: 239-250

30 **Schreiber S**, Renisch W, Colombel JF, Sandborn WJ, Hommes DW, Li J, Kent JD, Pollack PF. Early Crohn's disease shows high levels of remission to therapy with adalimumab: Sub-Analysis of CHARM. *Gastroenterology* 2007; **132**: A147

31 **Schreiber S**, Hanauer SB, Lichtenstein GR, Sandborn WJ. Superior efficacy of certolizumab pegol in early Crohn's disease is independent of CRP status. *Gastroenterology* 2007; **132**: A510

32 **Lichtenstein GR**, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, Pritchard ML, Sandborn WJ. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006; **4**: 621-630

33 **Panes J**, Colombel JF, D'Haens G, Rutgeerts P, Ekbom A, Hommes DW, Barai U, van Hoogstraten, Wiekowski M, Antoni C. Corticosteroids pose an increased risk for serious infections: An interim safety analysis of the ENCORE registry. *JCC* 2008; **1**: A23

34 **Mackey AC**, Green L, Liang LC, Dinndorf P, Avigan M. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **44**: 265-267

35 **Van Assche G**, Magdelaine-Beuzelin C, D'Haens G, Baert F, Noman M, Vermeire S, Ternant D, Watier H, Paintaud G, Rutgeerts P. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. *Gastroenterology* 2008; **134**: 1861-1868

36 **Beaugerie L**, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. *Gastroenterology* 2006; **130**: 650-656

37 **Dubinsky MC**, Lin YC, Dutridge D, Picornell Y, Landers CJ, Farrior S, Wrobel I, Quiros A, Vasiliauskas EA, Grill B, Israel D, Bahar R, Christie D, Wahbeh G, Silber G, Dallazadeh S, Shah P, Thomas D, Kelts D, Hershberg RM, Elson CO, Targan SR, Taylor KD, Rotter JI, Yang H. Serum immune responses predict rapid disease progression among children with Crohn's disease: immune responses predict disease progression. *Am J Gastroenterol* 2006; **101**: 360-367

38 **Mow WS**, Vasiliauskas EA, Lin YC, Fleshner PR, Papadakis KA, Taylor KD, Landers CJ, Abreu-Martin MT, Rotter JI, Yang H, Targan SR. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. *Gastroenterology* 2004; **126**: 414-424

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