REVIEW

INTESTINAL RESEARCH

ISSN 1598-9100(Print) • ISSN 2288-1956(Online)
http://dx.doi.org/10.5217/ir.2013.11.4.256
Intest Res 2013;11(4):256-260

Biological Therapy for the Prevention and Treatment of Postoperative Endoscopic Recurrence in Crohn's Disease: Time for Acceptance?

Paulo Gustavo Kotze, Rogério Saad-Hossne[1]

Department of Surgery, Catholic University of Paraná (PUCPR), Curitiba, Department of Digestive Surgery, São Paulo State University (UNESP), Botucatu[1], Brazil

In most patients, postoperative endoscopic recurrence (PER) occurs 1 year after abdominal resection for Crohn's disease (CD). Preventing PER is essential for disease control, as most patients develop further clinical and surgical recurrences. Conventional therapy with nitroimidazoles, aminosalicylates, and immunomodulators have limited efficacy for preventing PER. Initial trials with biological therapy (infliximab and adalimumab) showed promising results in preventing PER, and the efficacy of these drugs seems higher than that with conventional therapy. The aim of this review is to outline the results of studies that used infliximab or adalimumab for preventing and treating PER in CD patients. Data with both agents are available, and a few, small prospective trials have shown the efficacy of these drugs in patients with a high risk for recurrence. We believe that, in 2013, biological agents will be better accepted for the prevention PER in CD patients, in addition to the already existing data. Larger trials are still underway, and their results will certainly determine the role of these agents in PER, which develops after bowel resection for CD. **(Intest Res 2013;11:256-260)**

Key Words: Tumor necrosis factor alpha; Crohn's disease; Recurrence

INTRODUCTION

More than 80 years after the initial description of CD in 1932, a cure for this interesting and difficult entity has not been discovered, and it seems that science is still far from achieving this objective.[1] Even with the development of new therapies such as immunomodulators and biological agents, surgery still plays a significant role in the management of CD. In the biological area, we still do not know if surgical rates in CD are decreasing. Some population studies have not demonstrated this advantage,[2] but data from referral centers have indicated a reduction.[3] Therefore, patients are still undergoing surgery and small bowel and colonic resections worldwide, even with the currently available best medical therapy.

Postoperative endoscopic recurrence (PER) after abdominal resection for CD occurs in nearly 75% of patients 1 year after the surgical procedure.[4,5] It develops earlier than clinical recurrence and, most commonly, years before the need for a repeated resection. Several studies have demonstrated the effect of different medications aimed at reducing PER rates. Probiotics and aminosalicylates have not been effective in this scenario.[6] Metronidazole and ornidazole were more effective than placebo in 2 randomized controlled trials, but only in a 3-month period.[7] Azathioprine was also more effective than placebo and aminosalicylates in preventing PER.[6,8] However, even with these therapies, a significant number of patients developed recurrence and disease progression over time.

Biological agents seem proportionally more effective than conventional therapy in preventing PER in various studies. Since the initial trial published in 2009 by Regueiro et al.,[9] various authors have studied the effect of both infliximab (IFX) and adalimumab (ADA) in reducing PER rates or treating

Received October 3, 2013. **Revised** October 4, 2013.
Accepted October 5, 2013.
Correspondence to Paulo Gustavo Kotze, Rua Bruno Filgueira, 369/conj.1205, Curitiba, PR 80220-240, Brazil. Tel: +55-41-3243-0033, Fax: +55-41-3243-0033, E-mail: pgkotze@hotmail.com

Financial support: None. **Conflict of interest:** None.

http://dx.doi.org/10.5217/ir.2013.11.4.256 • Intest Res 2013;11(4):256-260

early recurrence in patients receiving conventional therapy. This paper aimed to critically review studies on biological therapy for the management of PER.

INFLIXIMAB

IFX was the first agent approved for CD management, and is used worldwide with concrete experience in various indications including induction and maintenance of clinical remission, fistulizing, and pediatric CD. Most studies on the efficacy of biologics in preventing PER were performed with IFX.

1. Infliximab in the Prevention of Postoperative Endoscopic Recurrence

A randomized, 2-armed, double-blind, placebo-controlled trial that evaluated the efficacy of IFX in preventing PER was first performed in the United States.[9] Twenty-four patients with ileal or ileocolic CD undergoing resection received either IFX infusions (5 mg/kg) or placebo at 0, 2, and 6 weeks, and then every 8 weeks for 1 year (11 patients in the IFX group and 13 in the placebo group). IFX treatment was started 2 weeks after the procedures. The primary endpoint was the proportion of patients with endoscopic recurrence 1 year after surgery (defined at colonoscopy by a Rutgeerts score ≥i2). PER occurred in 1 of the 11 patients (9.1%) receiving IFX therapy and in 11 of the 13 patients (84.6%) in the placebo group (P<0.0006). The main limitation of this study was the small sample size, although statistical significance was achieved. This trial provided strong evidence that IFX is effective in preventing endoscopic recurrence after ileocolic resection for CD (Fig. 1).

In a review article, Yamamoto[10] identified smoking, penetrating phenotype of CD, and granulomas in the specimen as the most important risk factors for PER. Anastomosis type, patient age, familial history of CD, anatomic site of the operation, specimen length, and postoperative complications did not significantly associate with PER. These findings play a significant role in this setting, primarily because most patients with penetrating CD are good candidates for biological therapy. Therefore, the maintenance of biologics after surgery may be the best option in these cases to reduce PER rates.

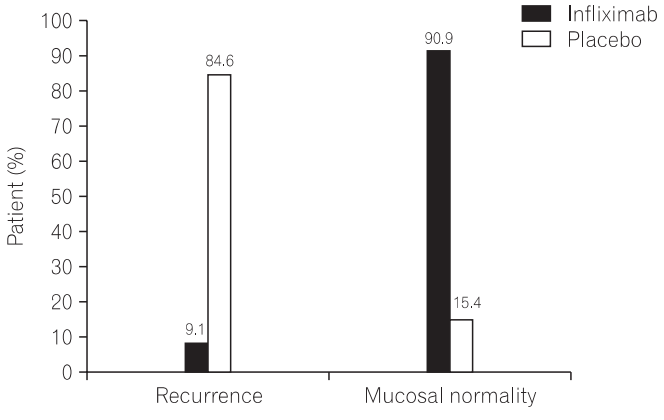

Fig. 1. Efficacy of infliximab in the prevention of postoperative endoscopic recurrence after one year in a prospective study with 24 patients. Recurrence, Rutgeerts ≥i2; mucosal normality, Rutgeerts ≤i1. Adapted from the article of Regueiro et al.[9] (Gastroenterology 2009;136:441-450).

In a prospective pilot study, Sorrentino et al.[11] compared endoscopic outcomes after CD surgery in terms of postoperative management in 2 groups of patients. In the group of patients receiving IFX therapy, none of the 7 patients had PER or clinical recurrence. In the group of patients receiving mesalamine, only 4 of 16 patients (25%) were disease-free 2 years after surgery with no PER. In 2010, the same authors subsequently performed a prospective cohort study including 5 more patients (n=12) who were followed up for 3 years after the procedures.[12] The authors found that no patient experienced PER or clinical recurrence. IFX was discontinued in all patients, and after 4 months, another colonoscopy was performed. Of the 12 patients, 10 presented with PER and received IFX again after a drug holiday. The authors found that mucosal normality was achieved in all patients with a lower IFX dose (3 mg/kg) and suggested that this dose can be effective in treating PER. This prospective study demonstrated that IFX therapy immediately after surgery effectively prevents clinical and endoscopic recurrence at 3 years, and medication discontinuation can cause endoscopic recurrence in a short period. They also showed that IFX reintroduction in lower doses could lead to mucosal healing.

In an open-label, prospective study, Sakuraba et al.[13] evaluated the safety and efficacy of IFX in preventing PER in CD patients who underwent multiple surgical resections (≥2). IFX was started 2-4 weeks after surgery and administered every 8 weeks. In total, 10 patients were included. The mean number of resections was 4, and IFX treatment prevented clinical and endoscopic/radiological recurrence in 60% and 40% of patients at risk for recurrence, respectively. The difference between this study and the others is that only patients with penetrating CD and previous resections were included - a bias that could explain the higher PER rates.

In a prospective trial performed in Italy, Armuzzi et al.[14] compared the PER rates between IFX and azathioprine postoperative treatments. In a small sample of 22 patients at high risk for recurrence, the authors found no significant difference between the groups in terms of PER (40% in the azathioprine group *vs*. 9% in the IFX group, P=0.14). However, severe histological activity was significantly higher in the azathioprine group (80%) than in the IFX group (18%, P=0.008) after 1 year of follow-up. Although statistical significance was not achieved because of the small sample size, this study clearly demonstrated that biological therapy seems more effective than conventional treatment with immunomodula-

tors in preventing PER.

2. Infliximab in the Treatment of Postoperative Endoscopic Recurrence

In Japan, Yamamoto et al.[15] investigated the effect of IFX on early endoscopic lesions after resection for CD in a single-center prospective study. In this trial, PER in 26 consecutive patients was managed prospectively with 3 treatment arms. In the first period, all patients received mesalamine (3 g/day) after resection for 6 months. Over the following 6 months, 10 patients were treated with continuous mesalamine (3 g/day), 8 patients were treated with azathioprine (50 mg/day), and the other 8 patients were treated with IFX (5 mg/kg, every 8 weeks). Endoscopic inflammation improved in 75% of patients in the IFX group, 38% in the azathioprine group, and 0% in the mesalamine group (P<0.006). There was a good correlation between cytokine levels and endoscopic inflammation. The cytokine levels significantly decreased in the IFX group, increased in the mesalamine group, and did not change in the azathioprine group. The authors concluded that IFX therapy showed clear suppressive effects on endoscopic disease activity and mucosal cytokine production in patients with early endoscopic lesions after resection for CD, demonstrating the effectiveness of biological therapy in treating PER.

In a prospective, open-label, nonrandomized multicenter study, Sorrentino et al.[16] compared the efficacies of IFX and mesalamine for the treatment of PER after resection for CD in 6 different Italian centers. In total, 24 patients were included: 13 were treated with IFX and 11 were treated with mesalamine. After 54 weeks, 50% of the patients receiving IFX had endoscopic remission and 69% had an improved endoscopic score in comparison with 0% of endoscopic remission in the mesalamine group. The authors concluded that IFX was superior to mesalamine in reinducing mucosal integrity after PER in CD.

ADALIMUMAB

ADA was the second agent approved for CD management, and experience with this medication has increased over the years. Data demonstrated the important role of ADA in the induction and maintenance of clinical remission[17,18] as well as mucosal healing.[19] More recently, studies have demonstrated the importance of ADA in the management of PER.

1. Adalimumab in the Prevention of Postoperative Endoscopic Recurrence

The first case series that evaluated the efficacy of ADA in preventing PER was completed in Spain[20] and published in 2010. In an open-label prospective study, the authors started ADA therapy in 20 patients following ileocolic resection for CD. After 1 year, the patients underwent colonoscopies, and the PER rates were described according to the Rutgeerts score. The results demonstrated that only 2 of 20 enrolled patients (10%) had PER, defined by a Rutgeerts score of >i2.

In 2012, Aguas et al.[21] also studied the role of ADA in preventing PER in 29 patients at high risk for recurrence. In this observational prospective study, there was a good correlation between PER and morphological recurrence in imaging tests in a significant number of patients. Only 20.7% of the patients receiving ADA therapy developed PER, and 36.8% of the patients who underwent magnetic resonance imaging enterography after resection presented with morphological recurrence.

A prospective multicenter trial performed in Australia and New Zealand compared the effect of ADA and azathioprine in preventing PER in high-risk patients.[22] The results of this trial, named POCER were presented at Digestive Disease Week 2013 and have not been published to date. In 101 high-risk patients who underwent colonoscopy 18 months after the ileocolic resection, 28 were receiving ADA therapy and 73 were receiving azathioprine after following the tailored treatment algorithm. The PER rates (Rutgeerts score ≥i2) were significantly lower in the ADA group than in the azathioprine group (21% *vs*. 45%, P=0.02).

In another prospective trial from Italy, Saverino et al.[23] compared the role of ADA with that of azathioprine and mesalamine after resection. The authors concluded that the PER rates after ileocolic resection in the 18 patients treated with ADA (6.3%) were significantly lower than those in the 17 patients treated with azathioprine (64.7%) and in the 16 patients treated with mesalamine (83.3%) after 2 years of follow-up (P=0.0017) (Fig. 2).

The number of patients in these studies was not high, and

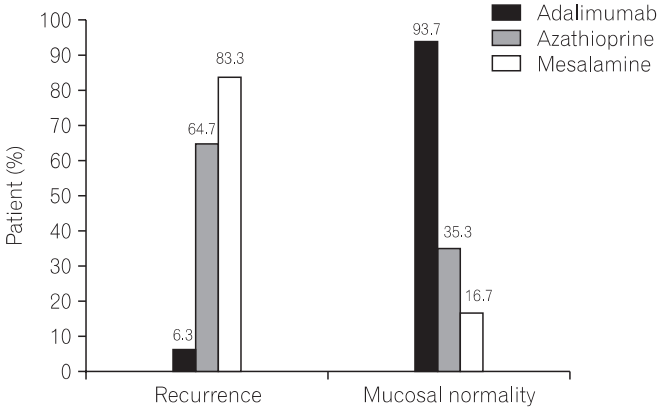

Fig. 2. Adalimumab in the prevention of postoperative endoscopic recurrence. Prospective study 2 years after ileocecal resections in CD patients, in comparison with azathioprine and mesalamine. Recurrence, Rutgeerts ≥i2; mucosal normality, Rutgeerts ≤i1. Adapted from the article of Saverino et al.[23] (Am J Gastroenterol, October 2013 [Epub ahead of print]).

http://dx.doi.org/10.5217/ir.2013.11.4.256 • Intest Res 2013;11(4):256-260

several limitations were noticed in each publication. However, ADA may be proven more effective than conventional therapy in preventing PER, primarily in patients at high risk for recurrence.

2. Adalimumab in the Treatment of Postoperative Endoscopic Recurrence

A pilot study from Greece prospectively investigated the occurrence of PER after ileocolic resection in high-risk patients.[24] The 23 patients in this small open-label study were allocated to 2 groups: 8 patients received ADA 2 weeks after resection (for recurrence prevention) and the other 15 patients received ADA after colonoscopy with documented PER 6 months after surgery (recurrence treatment). In both groups, ADA demonstrated efficacy. After 2 years, all except 2 patients in the prevention group had endoscopic normality (6/8), and 9 of 15 patients (60%) in the treatment group had mucosal healing after the documented PER. This study, although performed in a small sample of patients, demonstrated the efficacy of ADA not only in preventing but also in treating PER. Prospective randomized trials are needed to better access strategies for comparison as described in the IFX studies.

FUTURE TRIALS AND OTHER BIOLOGICS

As previously stated, most studies on the efficacy of IFX and ADA in preventing PER had clear limitations. Mostly, they were performed in small samples of patients. No studies published to date have considered the role of certolizumab pegol or new biological agents in the postoperative prevention setting. The POCER trial with ADA had a larger patient sample; however, only part of the sample was treated with biological therapy.[22] A large multicenter study with IFX, the PREVENT trial, is being performed, and certainly, more solid data with a significant sample of individuals in long-term follow-up will soon be published, and will lead specialists to a better knowledge of the real role of biologics in this scenario.

CONCLUSIONS

Even with the limitations of the few studies that address the effect of biologics in preventing PER after resection for CD, a significant efficacy of this class of medication is observed in comparison with conventional therapy. The endoscopic recurrence rates in patients undergoing biological therapy are lower than those in patients receiving azathioprine, the most important medication used in non-biological management. More studies should be conducted in this field. Thus far, combination therapy with biologics in addition to immunomodulators has not been compared with monotherapy with biologics in this scenario. Some controversies exist regarding the patients who were using biologics before surgery in comparison with those who started these medications shortly after surgery. Clearly, safety and cost are significant issues that should be considered in the complex algorithm of patient management, mainly to avoid overtreatment. However, current data demonstrate that a better acceptance of biological agents in preventing PER in high-risk CD patients can be considered in 2013, and can be essential for disease control for a life-long disease.

REFERENCES

1. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. JAMA 1932;99:1323-1329.
2. Jones DW, Finlayson SR. Trends in surgery for Crohn's disease in the era of infliximab. Ann Surg 2010;252:307-312.
3. Peyrin-Biroulet L, Oussalah A, Williet N, Pillot C, Bresler L, Bigard MA. Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn's disease. Gut 2011;60:930-936.
4. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99:956-963.
5. De Cruz P, Kamm MA, Prideaux L, Allen PB, Desmond PV. Postoperative recurrent luminal Crohn's disease: a systematic review. Inflamm Bowel Dis 2012;18:758-777.
6. Doherty G, Bennett G, Patil S, Cheifetz A, Moss AC. Interventions for prevention of post-operative recurrence of Crohn's disease. Cochrane Database Syst Rev 2009;(4):CD006873.
7. Rutgeerts P, Hiele M, Geboes K, et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. Gastroenterology 1995;108:1617-1621.
8. Reinisch W, Angelberger S, Petritsch W, et al; International AZT-2 Study Group. Azathioprine versus mesalazine for prevention of postoperative clinical recurrence in patients with Crohn's disease with endoscopic recurrence: efficacy and safety results of a randomised, double-blind, double-dummy, multicentre trial. Gut 2010;59:752-759.
9. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009;136:441-450.
10. Yamamoto T. Prevention of recurrence after surgery for Crohn's disease: efficacy of infliximab. World J Gastroenterol 2010;16:5405-5410.
11. Sorrentino D, Terrosu G, Avellini C, Beltrami CA, Bresadola V, Toso F. Prevention of postoperative recurrence of Crohn's disease by infliximab. Eur J Gastroenterol Hepatol 2006;18:457-459.
12. Sorrentino D, Paviotti A, Terrosu G, Avellini C, Geraci M, Zarifi D. Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease. Clin Gastroenterol Hepatol 2010;8:591-599.
13. Sakuraba A, Sato T, Matsukawa H, et al. The use of infliximab in the prevention of postsurgical recurrence in polysurgery Crohn's disease patients: a pilot open-labeled prospective study. Int J Colorectal Dis 2012;27:947-952.

14. Armuzzi A, Felice C, Papa A, et al. Prevention of postoperative recurrence with azathioprine or infliximab in patients with Crohn's disease: an open-label pilot study. J Crohns Colitis 2013. [Epub ahead of print]
15. Yamamoto T, Umegae S, Matsumoto K. Impact of infliximab therapy after early endoscopic recurrence following ileocolonic resection of Crohn's disease: a prospective pilot study. Inflamm Bowel Dis 2009;15:1460-1466.
16. Sorrentino D, Terrosu G, Paviotti A, et al. Early diagnosis and treatment of postoperative endoscopic recurrence of Crohn's disease: partial benefit by infliximab--a pilot study. Dig Dis Sci 2012;57:1341-1348.
17. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130:323-333; quiz 591.
18. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52-65.
19. Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology 2012;142:1102-1111.
20. Fernández-Blanco I, Monturiol J, Martinez B, et al. Adalimumab in the prevention of postoperative recurrence of Crohn's disease. Gastroenterology 2010;138(Suppl 1):S692.
21. Aguas M, Bastida G, Cerrillo E, et al. Adalimumab in prevention of postoperative recurrence of Crohn's disease in high-risk patients. World J Gastroenterol 2012;18:4391-4398.
22. De Cruz P, Kamm MA, Hamilton AL, et al. Optimising postoperative Crohn's disease management: best drug therapy alone versus colonoscopic monitoring with treatment step-up. The POCER study. Gastroenterology 2013;144;S164.
23. Savarino E, Bodini G, Dulbecco P, et al. Adalimumab Is more effective than azathioprine and mesalamine at preventing postoperative recurrence of Crohn's disease: a randomized controlled trial. Am J Gastroenterol 2013. [Epub ahead of print]
24. Papamichael K, Archavlis E, Lariou C, Mantzaris GJ. Adalimumab for the prevention and/or treatment of post-operative recurrence of Crohn's disease: a prospective, two-year, single center, pilot study. J Crohns Colitis 2012;6:924-931.