1130-0108/2015/107/10/583-585
Revista Española de Enfermedades Digestivas

Rev Esp Enferm Dig (Madrid
Vol. 107, N.º 10, pp. 583-585, 2015

EDITORIAL

Prevention of post-operative recurrence in Crohn's disease. Are we ready for a treat-to-target strategy?

Crohn's disease (CD) is chronic inflammatory bowel disease leading to progressive loss of intestinal function and disability mainly due to the need of surgical treatment in a high proportion of patients (1).

Surgery in CD is not curative, and post-operative recurrence (POR) is a frequent event. In the abscense of treatment, 65-90% of patients present with endoscopic recurrence within the first year of surgery, and by the third year it is found in 80-100% of cases; the clinical recurrence is about 20-25% per year, and the need of a new surgical procedure is estimated in 20% at 5 years (2,3).

Clinical and analytical assessment are of limited value for the diagnosis of the recurrence, and therefore, the ileocolonoscopy is considered the gold standard, by definig the presence and severity of morphologic recurrence by the Rutgeerts score (2) and predicting the long-term clinical course (3). The 5-year clinical recurrence in patients without or with mild endoscopic lesions (Rutgeerts score i0-i1) is < 10%, 20-25% in patients with a Rutgeerts score i2 and those patients with severe endoscopic lesions (score i3-i4) clinical recurrence is 50-100% and re-resection is often needed (2).

Strategies aimed at delaying or preventing POR have been proposed. These strategies account for a risk stratification, the plannification of a treatment to prevent the recurrence according to the stimated risk, and the monitoring of the response to optimise the treatment in case of lack of efficacy (4-6). These strategies perfectly fit into the concept of a "treat-to-target" approach (7).

The clinical factors associated to an increased risk of POR are smoking, prior intestinal surgery, penetrating disease behaviour, perianal location and extensive small bowel resection (3).

Several drugs have shown efficacy in preventing POR: 5-aminosalycilates (3), imidazole antibiotics (8), thiopurines (9) and the anti-TNF drugs infliximimab and adalimumab (10), each one with some drawbacks. The effect of mesalazine is low; the imidazole antibiotis are associated to adverse events that preclude its use in the long-term; thiopurines are often withdrawn because of side effects, and their efficacy is moderate; and anti-TNF drugs are expensive and concern exists about long-term safety.

With respect to monitoring, the gold standard is the endoscopy, but it is an invasive procedure. Alternative procedures (abdominal utrasound, magnetic resonance enterography and small bowel capsule endoscopy) have been assessed in this setting with promising results (3), but the their pronostic value have not been validated.

Finally, the Rutgeerts score have some limitations in a treatment monitoring setting. The score was described in patients without prophilactic treatment, and therefore its pronostic value in patients who are receiving treatment have not been studied. Second, it has been proposed that anastomotic lesions could be secondary to ischemic changes and its pronostic could be better than aftoids or skipped lesions (11). Finally, the presence of endoscopic lesions in the study by Rutgeerts did not lead to a treatment modification, and the impact of such a modification on the disease course is not well known.

One of the challenges of a "treat-to-target" strategy to control the disease beyond the symptoms is that the theoretical benefits of such control on the disease course have not been yet proven (7). However, in the case of the POR prevention two clinical trials (12,13) and a retrospective study (14) support these strategies.

The POCER study (12) was designed to assess the endoscopic recurrence (Rutgeerts score i2-i4) at 18 months after surgery. One hundred and seventy-four patients were included, which were stratified into low or high risk of recurrence, and a basal treatment was initiated according to the risk. Patients were randomized in two arms: Active care (a colonoscopy was performed at 6 months after surgery and treatment was intensified in case of endoscopic recurrence) and a standard care (no colonoscopy was performed until the end of the study). Patients who suffered from clinical recurrence were dropped out from the study. The patients on active care showed a lower endoscopic recurrence rate than those on standard care (49% *vs.* 67%, p = 0.03). However, the patients dropped out because of symptomatic clinical recurrence were similar in both groups (11% *vs.* 17%, p = 0.23, active *vs.* standard care, respectively) and the percentage of patients with clinical recurrence defined as CDAI > 200 did not reach significant differences (27% *vs.* 40%, p = 0.008, active *vs.* standard care, respectively).

Ferrante et al. (13) compared, in patients with risk factors of recurrence, the efficacy at week 102 of systematic treatment with azathioprine (administered to all the patients) to that of a endoscopy-driven treatment depending on the results of a colonoscopy at 26 and 52 weeks. The primary objective was the endoscopic remission defined by a Rutgeerts score i0-i1. The study was interrupted because a low recruitment (63 patients of an estimated sample size of 100 patients per group). In the endoscopy-driven group, 14 out of 31 (45.1%) started azathioprine. The endoscopic remission rate was similar in both groups (50% in the systematic treatment *vs.* 42% in the endoscopy-driven group, p = 0.52). No differences were found in the clinical remission rate defined as CDAI < 150 (62% in systematic treatment *vs.* 55% in endoscopy-driven treatment, p = 0.54). Among the 46 patients who received azathioprine, 6 (13%) suffered relevant side effects.

Baudry et al. (14) retrospectively studied 132 patients, stratified by the risk of recurrence, and assessed the clinical recurrence in two groups: Those who received a colonoscopy at 6-12 months from surgery and whose treatment was adjusted according to a prestablished protocol, with those patients who did not received a control colonoscopy. The 25% of patients with an endoscopy-driven treatment showed clinical recurrence, compared with 54% of patients who did not received control colonoscopy. The time to clinical recurrence was longer in patients controlled by endoscopy (31 *vs.* 25 months) and the probability of recurrence at 3 and 5 years was significatively lower in patient with endoscopy control (21% *vs.* 31 and 26 *vs.* 52%, respectively, p = 0.001).

In the current issue of the *Spanish Journal of Gastroenterology,* Gonzalez-Lama et al. bring new data that reinforce the relevance of the endoscopy-driven management of POR in CD (15). The group from the Hospital Puerta de Hierro (Madrid, Spain) retrospectively assessed the clinical evolution of 122 patients who received medical prophilaxis of POR, and who received a control endoscopy, and studied the impact of the endoscopic-driven management on the course of the disease. Fifty-seven percent of patients presented endoscopic recurrence (Rutgeerts score i2-i4), and in 75% of them the treatment was intensified. The patients with endoscopic recurrence whose treatment was intensified showed a lower probability of clinical recurrence at 5 years compared to those whose treatment was not modified (42% *vs.* 74%, repectively, p = 0.001).

These data confirm the usefulness of the Rutgeerts score in patients with or without prophylactic treatment of POR in CD. On the other hand, the eficcacy of an endoscopy-driven management in this setting is reinforced, as it reduces the endoscopic (12) or clinical recurrence (14,15), or it allows to avoid a immunosuppresant treatment in a relevant percentage of patients without a negative impact on the disease course (13).

Nevertheless, some interesting points remain to be answered. First, an endoscopy-driven approach implies a treatment scalation in assymptomatic patients, with exposition to adverse events and an increasing farmacoeconomic impact. Second, the beneficial long-term impact of this approach described in retrospective studies needs to be confirmed by the long-term follow-up of the POCER and Ferrante's cohorts. Finally, it would be very interesting to learn if the subclassification of Rutgeerts score i2 into two subgroups with different recurrence risk could be applied to the endoscopy-driven management.

At this moment, we are perhaps we are at the doors of the confirmation of the applicability of a "treat-to-target" strategy in the prevention of POR, which could be included in the future management of CD guidelines.

VH has received an intensification grant through the European Commission supported "BIOCAPS" project (FP-7-REGPOT 2012-2013-1, Grant agreement no. FPT-316265).

Vicent Hernández-Ramírez
Department of Digestive Diseases. Instituto de Investigación Biomédica. Xerencia de Xestión Integrada. Vigo, Spain

REFERENCES

1. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lémann score. Inflamm Bowel Dis 2011;17:1415-22. DOI: 10.1002/ibd.21506
2. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99:956-63. DOI: S0016508590003596 [pii]
3. Van Assche G, Dignass A, Reinisch W, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. Journal of Crohn's and Colitis 2010; 4:63-101. DOI: 10.1016/j.crohns.2009.09.009
4. De Cruz P, Kamm MA, Prideaux L, et al. Postoperative recurrent luminal Crohn's disease: A systematic review. Inflamm Bowel Dis 2012;18:758-77. DOI: 10.1002/ibd.21825
5. Schwartz M, Regueiro M. Prevention and treatment of postoperative Crohn's disease recurrence: An update for a new decade. Curr Gastroenterol Rep 2011;13:95-100. DOI: 10.1007/s11894-010-0152-x
6. Sorrentino D. State-of-the-art medical prevention of postoperative recurrence of Crohn's disease. Nat Rev Gastroenterol Hepatol 2013;10:413-22. DOI: 10.1038/nrgastro.2013.69
7. Sandborn WJ, Hanauer S, Van Assche G, et al. Treating beyond symptoms with a view to improving patient outcomes in inflammatory bowel diseases. J Crohn's Colitis. European Crohn's and Colitis Organisation 2014;8:927-35. DOI: 10.1016/j.crohns.2014.02.021
8. Rutgeerts P, Hiele M, Geboes K, et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. Gastroenterology 1995;108:1617-21. DOI: 10.1016/0016-5085(95)90121-3
9. Peyrin-Biroulet L, Deltenre P, Ardizzone S, et al. Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: A meta-analysis. Am J Gastroenterol 2009;104:2089-96. DOI: 10.1038/ajg.2009.301
10. Carla-Moreau A, Paul S, Roblin X, et al. Prevention and treatment of postoperative Crohn's disease recurrence with anti-TNF therapy: A meta-analysis of controlled trials. Dig Liver Dis 2015;47:191-6. DOI: 10.1016/j.dld.2014.11.005
11. Domènech E, Mañosa M, Bernal I, et al. Impact of azathioprine on the prevention of postoperative Crohn's disease recurrence: Results of a prospective, observational, long-term follow-up study. Inflamm Bowel Dis 2008;14:508-13. DOI: 10.1002/ibd.20359
12. De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: A randomised trial. Lancet 2015;385:1406-17. DOI: 10.1016/S0140-6736(14)61908-5

13. Ferrante M, Papamichael K, Duricova D, et al. Systematic versus endoscopy-driven treatment with azathioprine to prevent postoperative ileal Crohn's disease recurrence. J Crohn's Colitis 2015;9:617-24. DOI: 10.1093/ecco-jcc/jjv076.
14. Baudry C, Pariente B, Lourenço N, et al. Tailored treatment according to early post-surgery colonoscopy reduces clinical recurrence in Crohn's disease: A retrospective study. Dig Liver Dis 2014;887-92. DOI: 10.1016/j.dld.2014.07.005
15. González-Lama Y, Blázquez I, Suárez CJ, Oliva B, Matallana V, Calvo M, et al. Impact of endoscopic monitoring in postoperative Crohn's disease patients already receiving pharmacological prevention of recurrence. Rev Esp Enferm Dig 2015;107:586-90. DOI: 10.17235/reed.2015.3836/2015