REV ARGENT COLOPROCT | 2021 | VOL. 32, N° 1: 33-34
DOI: 10.46768/racp.v32i01.33

Role of Surgery for the Treatment of Ileocecal Crohn's Disease in the Age of Biological Drugs

Nicolás Avellaneda, Mariano Vaingurt, Juan Pablo Muñoz
New Proctology Center, CABA, Argentina.

The treatment of inflammatory bowel disease in general and Crohn's disease in particular, has been revolutionized since the discovery of the role that tumor necrosis factor alpha (TNF-α) plays in the onset and progression of the disease.[1] After this finding, the development of drugs designed to block its action has managed to radically modify the activity of the disease.[2] Such is the case of infliximab, a human-mouse chimeric monoclonal antibody of IgG1 subclass with anti TNF-α.[3]

The primary objective of these drugs is to induce remission of disease activity and sustain it over time in patients with moderate-severe involvement who do not respond to first-line drugs.[4] We know that up to 70% of patients with Crohn´s disease (CD) will require more than one surgical intervention to treat their complications (stenosis, fistula) throughout their lives,[5] so the secondary objective is to reduce this high rate of surgeries.

CD involves the ileocecal region in up to 2/3 of cases.[6] When the clinical pattern is inflammatory, anti-TNF drugs represent a second line of treatment in the following situations:

- Lack of response to conventional drugs (corticosteroids, thiopurines).
- Resistance to corticosteroids (patient with active disease after doses equivalent to prednisolone 1 mg/kg for 4 weeks).
- Dependence on corticosteroids (patient unable to reduce the dose of prednisolone below 10 mg/day or budesonide 3 mg/day after 3 months of treatment without relapse of their disease, or patients who suffers a relapse before 3 months of having discontinued corticosteroid therapy).[7]

Regardless of the drug used, more than 1/3 of patients with disease restricted to the ileocecal region require surgical treatment within 5 years of starting the medication, either due to resistance to treatment or complications of the disease (strictures or fistulas). These figures have changed little with the advent of anti-TNF drugs.[8,9]

Patients in whom first-line drugs have failed, or those resistant or dependent on corticosteroids without associated complications (stenosis, fistulas), are candidates for both biologic drugs and surgical resection of the affected segment. The arguments for and against each alternative will be developed.

Regarding infliximab, although it has a high degree of responses, carries a significant associated cost. A meta-analysis from 2011 analyzed studies that contemplated this variable in hospitals in England, concluding that during the induction phase the cost to the health system amounts to £17-92 million per year and £140-200 million per year during maintenance.[10]

On the other hand, its chronic use to sustain remission has an impact on the patient; there is an increase in the rate of serious infections, as well as in the incidence of skin tumors and lymphoproliferative disorders.[11] Other serious complications that have been recorded, although to a lesser extent, are stroke and pulmonary embolism.[12]

The sustained use of infliximab is related to long-term loss of effectiveness requiring an increase in dose and/or shortening of the intervals between infusions. According to a review published in the American Journal of Gastroenterology, this decrease in effectiveness occurs at a rate of 13% per patient per year.[13] It should be noted that treatment with biologics must be administered at regular intervals, which implies a transfer to hospital units, proper monitoring and long-term follow-up. Jones et al.,[14] have studied the direct impact on the quality of life and the mental state of patients, with an emphasis on those who reside far from their health centers.

In contrast, the results of elective surgery for patients with ileocecal CD have proved to be satisfactory. Performed by an experienced team and laparoscopically, low morbidity, high degree of well-being, significant improvement in the quality of life sustained over time and a early return to normal activities are registered.[15-17] Up to 50% of these patients remain asymptomatic and with no need for treatment for up to 7 years after surgery.[18]

The "LIRIC" trial, which involves 29 hospitals in the Netherlands and the United Kingdom, included patients with ileocecal CD with an inflammatory clinical pattern and no greater than 40 cm of ileal extension. Patients with failure to the first line treatment were randomized into two arms, one received Infliximab and the other laparoscopic ileocecal resection.[19] As variables of result, morbidity and quality of life (using 2 questionnaires:

Nicolas Avellaneda
n.avellaneda86@gmail.com
Received: July 2020. Accepted: September 2020.

Inflammatory Bowel Disease Questionnaire and Short Form-36) were studied. The conclusion was that both alternatives were valid, with no significant differences. In a second stage, the costs associated with the treatment were studied and the result yielded an average difference of € 8,931 in health system expenses in favor of patients undergoing surgery during the first year.[20]

Our group evaluated the quality of life of patients with the same questionnaires before and 4 months after undergoing laparoscopic ileocecal resection. In a period of 30 months, 20 patients had bowel resection due to complications of their disease (stenosis or fistula) and failure of second-line medical treatment. It should be noted that a significant number of patients underwent surgery under suboptimal physical status due to prolonged conservative treatments. As a result, both questionnaires reflected a statistically significant improvement in quality of life, with low morbidity and a high satisfaction index (paper sent for publication, in review stage).

In our opinion, uncomplicated ileocecal CD generates a favorable context for elective surgical treatment, regardless of the advent of anti-TNF drugs, or as an alternative.

We consider that an early surgical resection can offer excellent results and reduce costs for the health system, and avoids deterioration of the patient who fails to respond to different medical alternatives. On the other hand, we believe that the role of anti-TNF drugs in the postoperative period is important in order to reduce the number of recurrences.

REFERENCES

1. Van Deventer SJH. Tumor necrosis factor and Crohn's disease. Gut 1997;40:443-48.
2. Brynskov J, Nielsen OH, Ahnfelt-Ronne I, Bendtzen K. Cytokines (immunoinflammatory hormones) and their natural regulation in inflammatory bowel disease (Crohn's disease and ulcerative colitis): a review. Dig Dis 1994;12:290-304.
3. Knight DM, Trinh H, Le J, Siegel S, Shealy D, McDonough M, et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol 1993;30:1443-53.
4. Van Assche G, Vermeire S, Rutgeerts P. The potential for disease modification in Crohn's disease. Nat Rev Gastroenterol Hepatol 2010;7:79-85.
5. Michelassi, F, Balestracci, T, Chappell, R, Block, GE. Primary and recurrent Crohn's disease. Experience with 1379 patients. Ann Surg 1991;214:230-38.
6. Thoreson R, Cullen J. Pathophysiology of inflammatory bowel disease: An overview. Surg Clin North Am 2007;87:575-85.
7. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management. J Crohns Colitis;2017:3-25.
8. Bouguen G, Peyrin-Biroulet L. Surgery for adult Crohn's disease: what is the actual risk? Gut 2011;60:1178-81.
9. Burke J, Velupillai Y, O'Connell PR, Coffey JC. National trends in intestinal resection for Crohn's disease in the post-biologic era. Int J Colorectal Dis 2013; 28:1401-06.
10. Dretzke J, Edlin R, Round J, Connock M, Hulme C, Czeczot J, et al. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-α) inhibitors, adalimumab and infliximab, for Crohn's disease. Health Technol Assess 2011;15:1-252.
11. Papamichael K, Mantzaris GJ, Peyrin-Biroulet L. A safety assessment of anti-tumor necrosis factor alpha therapy for treatment of Crohn's disease. Expert Opin Drug Saf 2016;15:493-501.
12. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Safdi M, Popp JW Jr, et al. Infliximab for Crohn's disease: more than 13 years of real-world experience. Inflamm Bowel Dis. 2018;24:490-501.
13. Gisbert J, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: 2009; 104(3):760-7.
14. Jones J, Nguyen GC, Benchimol EI, Bernstein CN, Bitton A, Kaplan GG, et al. The Impact of Inflammatory Bowel Disease in Canada 2018: Quality of Life. J Can Assoc Gastroenterol 2019;2 (Suppl 1):S42–S8.
15. Thirlby RC, Sobrino MA, Randall JB. The long-term benefit of surgery on health-related quality of life in patients with inflammatory bowel disease. Arch Surg 2001;136:521-27.
16. Wright EK, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Krejany EO, et al. Effect of intestinal resection on quality of life in Crohn's disease. J Crohns Colitis. 2015;9:452-62.
17. Nordgren SR, Fasth SB. Öresland TO, Hultén LA. Long-term follow-up in Crohn's disease. Mortality, morbidity, and functional status. Scand J Gastroenterol 1994;29:1122-28.
18. Cullen G, O'Toole A, Keegan D, Sheahan K, Hyland J, O'Donoghue DP. Long-term clinical results of ileocecal resection for Crohn's disease. Inflamm Bowel Dis 2007;13:1369-73.
19. Ponsioen CY, de Groof EJ, Eshuis EJ, Gardenbroek TJ , Bossuyt PMM, Hart A , et al. Laparoscopic ileocecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomized controlled, open-label, multicenter trial. Lancet 2017; 2:785-92.
20. de Groof EJ, Stevens TW, Eshuis EJ, Gardenbroek TJ, Bosmans JE, van Dongen H, et al. Cost-effectiveness of laparoscopic ileocecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR!C Trial. Gut 2019; 68:1774-80.