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Does the location of an IBD centre impact the rates of early postoperative endoscopic recurrence after ileocecal resection in Crohn's disease? Results from the MULTIPER database

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Background: Early postoperative endoscopic recurrence (EPER) occurs in a significant percentage of Crohn's disease (CD) patients one year after ileocecal resection. Several aspects influence the EPER rates, mainly medical therapy after surgery and patient characteristics. There is lack of comparative data between different regions of the world in terms of EPER in CD patients. The aim of this study was to compare the rates of EPER between patients treated in 3 different countries.

Methods: The MULTIPER (Multicenter International Postoperative Endoscopic Recurrence) database was a retrospective analysis of EPER rates in CD patients after ileocecal resection, from 7 referral centres from 3 different countries. All consecutive patients submitted to ileocecal resections that had colonoscopies performed up to 12 months after surgery were included. Recurrence was defined as Rutgeerts' score equal or greater than i2. The patients were allocated in 3 groups, regarding the country of the referral centre: Brazil, Japan or Italy. The EPER rates were compared between the 3 groups. Statistical analysis was performed by Fischer and chi-square tests (qualitative variables), and by Student's t test and Mann-Whitney test (quantitative variables). ANOVA and Kruskal-Wallis methods were used in the comparison between the 3 groups. Multivariate analysis with adjusted logistic regression for recurrence was performed, with relevant clinical variables, with $p < 0.05$ considered significant.

Results: 231 consecutive patients were initially analyzed (63 excluded for missing data and for having the first colonoscopy after surgery longer than 12 months) and 168 were included in the database (72 treated in Brazil, 53 in Japan and 43 in Italy). The groups were homogeneous except for CD duration ($p = 0.002$), previous resections ($p < 0.001$) and perianal CD ($p = 0.004$). EPER occurred in 31.94% in Brazil (B), 37.74% in Japan (J) and 13.95% in Italy (I). In direct comparison: B vs. I: $p = 0.036$ (OR: 2.89; 95%CI: 1.06–7.89); J vs. I: $p = 0.012$ (OR: 3.74; 95%CI: 1.33–10.51) and J vs. B: $p = 0.501$ (OR: 1.29; 95%CI: 0.61–2.73). On multivariate analysis, using patients treated in Italy as reference, both patients treated in Brazil and Japan had higher risk for recurrence (OR = 2.37 and OR = 2.31, respectively).

Conclusions: In the MULTIPER database, patients treated in Italy had significantly lower rates of EPER when compared to the ones treated in Brazil and Japan. This can be explained by lower CD duration in the Italian group, among other baseline characteristics. Multicentric international prospective data collection on EPER rates could highlight eventual roles of other

features as genetic influence, diet and other environmental factors, in postoperative prevention of recurrence.

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Disseminated granuloma annulare associated with Crohn's disease: a rare extraintestinal manifestation

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Background: Approximately one-third of patients with Inflammatory Bowel Diseases (IBD) have extraintestinal manifestations. The most common disorders include dermatology, ophthalmology, arthropathies and hepatobiliary diseases. Cutaneous manifestations have been observed in 15% of the patients with Crohn's disease. Erythema nodosum and pyoderma gangrenosum are the most frequent manifestations.

Methods: We report the case of a 42-year-old woman with disseminated granuloma annulare (GA) diagnosed in 2001 involving her hands, legs and interscapular region who had failed dapsone, PUVA therapy, cyclosporine and systemic glucocorticoids.



In 2007 she was diagnosed with ileocolonic Crohn's disease (A2L3B2) and she started treatment with oral corticosteroids without response so two months later she was treated with azathioprine.

Despite treatment, the patient continued with abdominal pain, diarrhea and deterioration of GA, so we decided to start with anti-TNF therapy: adalimumab. An initial dose of 160 mg was administered subcutaneously followed by 80 mg two weeks later and a maintenance dose of 40 mg every two weeks.

Results: After a month of treatment, the patient was improved in her GA and in her Crohn's disease, so we decided to continue with maintenance treatment with adalimumab.

Conclusions: GA is a common cutaneous disorder presenting as annular groups of skin-colored to erythematous papules and associated with diabetes mellitus, malignancy, thyroid disease and dyslipidemia. GA is not an extraintestinal manifestation of IBD. There is just one case of Crohn's disease associated with GA and with response to biological therapy. GA seems to be parallel to the activity of the bowel disease, and it's important to the gastroenterologist the correct management of these lesions.

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Disparity between infliximab trough level and infliximab associated adverse events

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Background: Infliximab is an anti-TNF agent effective in the management of inflammatory bowel disease (IBD). However, patients frequently report infliximab-associated adverse events (AE) including skin rashes, arthralgias, neuropathy and infusion reactions. While these infliximab-associated AEs are well-documented their relationship to serum levels of infliximab has not been evaluated. The aim of this study was to measure the prevalence of infliximab-associated AEs in IBD patients and determine their relationship to infliximab trough levels.

Methods: In this cross-sectional study of IBD patients on infliximab, consecutive patients were recruited from the University of Alberta IBD infliximab infusion clinic between 2012 and 2013. Charts were reviewed for infliximab-associated AEs (defined as skin rashes, arthralgias, neuropathy and infusion reactions documented by 2 patient self-reports and/or one physician report) at: (1) any time during the infliximab treatment history or (2) immediately before or during the infliximab infusion. Infliximab trough serum levels (ITL) were obtained immediately before the infliximab infusion and measured using an in-house ELISA assay. Results are presented as median ITL (range). Differences in median ITL were analyzed using non-parametric Mann-Whitney or Kruskal-Wallis tests.

Results: Of 87 consented patients, 12 were excluded due to insufficient infusion records. Of the remaining 75 patients, 36 (48.0%) had AEs at any time during their infliximab history, while 17 (22.7%) had AEs at the time of trough measurement. More females than males reported having had AEs at any time in their infliximab treatment history (66.7% vs. 33.3%, $p=0.015$). Otherwise there were no demographic variables associated with having AEs at any time in infliximab treatment history, or at the time of trough measurement. The median ITL was not significantly different between patients with and without AEs at the time of trough measurement [4.1 (0–19.5) $\mu\text{g/mL}$ vs 7.3 (0–30.0) $\mu\text{g/mL}$, $p=0.091$]. However, it was significantly higher in patients who reported dermatological AEs at the time of trough measurement [9.9 (0.2–19.5) $\mu\text{g/mL}$ vs. 0.1 (0–6.3) $\mu\text{g/mL}$, $p=0.020$], and significantly lower in patients who reported infusion AEs at the time of trough measurement [0.4 (0–6.3) $\mu\text{g/mL}$ vs. 9.9 (0–19.5) $\mu\text{g/L}$, $p=0.048$].

Conclusions: Nearly half of IBD patients on infliximab report some type of infliximab associated AEs over their infliximab treatment history. A low infliximab trough level was associated with infusion reactions, while a high infliximab trough level was associated with dermatological AEs. This disparity suggests that these infliximab associated reactions may have different pathological mechanisms that warrant further investigation.

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Disease-specific health-related quality of life in adult patients with mild to moderate ulcerative colitis receiving short-term and long-term daily treatment with MMX mesalazine

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Background: Symptoms (eg, rectal bleeding, stool frequency) experienced by mild-to-moderate ulcerative colitis (UC) patients, negatively affect health-related quality of life (HRQL). These analyses examine the magnitude of improvements in UC patients' HRQL following short-term and long-term treatment with MMX mesalazine.

Methods: Data were from a completed, open-label, prospective, multi-country trial of mild-to-moderate UC patients (NCT01124149). In the acute phase, adults with active UC received 8 wks MMX mesalazine 4.8g/d once daily (QD). Patients achieving complete remission (CR; modified UC Disease Activity Index [UCDAI] ≤ 1 ; rectal bleeding and stool frequency scores of 0; ≥ 1 -point reduction in endoscopy score) or partial remission (PR; modified UCDAI ≤ 3 ; combined stool frequency and rectal bleeding score ≤ 1 ; not in CR) by Wk 8 subsequently received 12 mos of maintenance with MMX mesalazine 2.4g/d QD.

Patients' HRQL (a tertiary endpoint), as impacted by UC symptoms, was assessed with the Shortened Inflammatory Bowel Disease Questionnaire (SIBDQ), a 10-item survey measuring inflammatory bowel disease (IBD)-specific HRQL over a 2-wk recall period. The SIBDQ has 4 domains: Bowel Symptoms (BS), Systemic Symptoms (SS), Emotional Function (EF), and Social Function (SF). Total score is used to assess overall IBD-related HRQL. Higher SIBDQ scores indicate better HRQL.

Changes over time were tested using paired-samples t-tests or repeated-measures analysis of variance models. Multiplicity was controlled using Bonferroni-adjusted P values. Cohen's d_z effect sizes for standardised differences in means for paired-samples were calculated to interpret magnitude of change.

Results: Patients who completed the 8 wk acute phase showed significant improvement in all SIBDQ scores, with mean increases of 4.5 points for BS ($n=425$), 2.1 for SS ($n=442$), 3.6 for EF ($n=439$), 3.0 for SF ($n=446$), and 13.2 for total score ($n=413$; all $P_s < 0.0001$). Effect sizes for change were all ≥ 0.77 , with BS showing the largest improvement ($d_z = 1.16$). Patients completing maintenance showed significant increases in all SIBDQ scores from baseline to Mo 12, with mean increases of 5.0 points for BS ($n=209$), 2.6 for SS ($n=221$), 4.6 for EF ($n=215$), 3.6 for SF ($n=221$), and 15.7 for total score ($n=198$; all $P_s < 0.0001$). There were no significant changes in any scores from the end of the acute phase to the Mo 12 visit (all changes ≤ 0.5 points; all $P_s > 0.24$).

Conclusions: Patients with active mild-to-moderate UC showed significant, medium to large improvements in disease-specific HRQL following 8 wks of MMX mesalazine 4.8g/d QD. These improvements were maintained among patients in CR or PR who subsequently received 12 mos of MMX mesalazine 2.4g/d QD.

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Disease-related knowledge in inflammatory bowel disease

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Background: Education of patients with inflammatory bowel disease (IBD) allows a greater understanding and acceptance of their disease assuming a critical role in adherence and therapeutic success. The aim of this study was to assess the disease-related knowledge in IBD patients and to identify factors that can influence its acquisition.