The effect of induction therapy with infliximab or vedolizumab on hepcidin and iron status in patients with Inflammatory Bowel Disease

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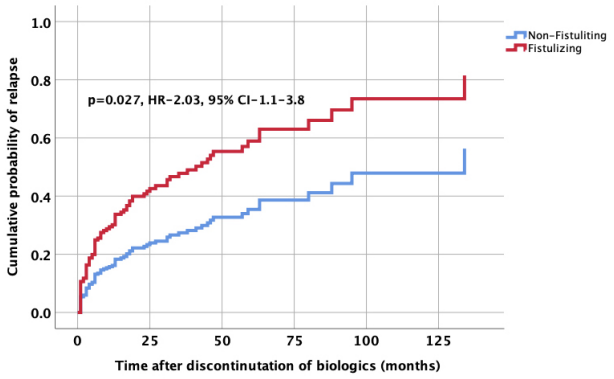
Published in:
Journal of Crohn's and Colitis

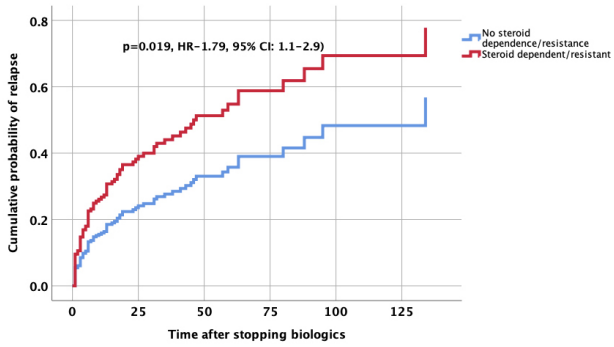
DOI:
10.1093/ecco-jcc/jjab232.304

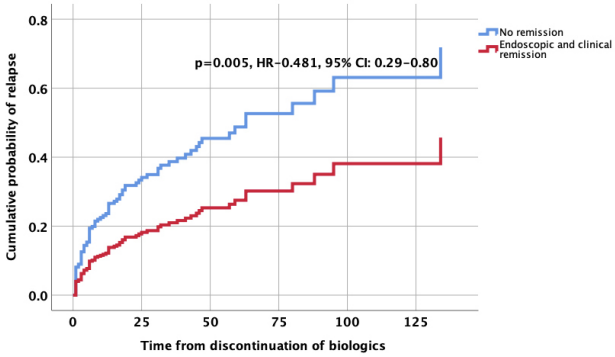
Publication date:
2022

87/274 (32%) relapsed after stopping biologics. 187/274 (68%) were in remission over a median follow up of 24 months (IQR: 10–51 months). 52/87(60%) relapsed in first year and 67/87(77%) in 2 years. Most relapses were mild and responded to steroids 43 (49.4%) or re-treatment with biologics 34 (39%). 10 patients (11%) needed surgery. On Cox proportional hazard analysis, perianal/fistulizing disease (HR-2.03, 95% CI-1.1–3.8, p=0.027) and steroid dependent/resistant disease (HR-1.79, 95% CI-1.1–2.9, p=0.019) were associated with a higher risk of relapse after withdrawal of therapy. Patients who stopped after clinical and endoscopic remission had lower likelihood of relapse after biologics discontinuation(HR-0.48, 95% CI-0.29–0.80, p=0.005).

	P	HR	95.0% CI for Exp(B)	
			Lower	Upper
Age	0.748	0.997	0.980	1.015
Sex	0.999	1.000	0.631	1.583
Smoking status	0.754	0.793	0.186	3.384
Duration of disease	0.460	0.999	0.995	1.002
Diagnostic delay	0.749	1.001	0.994	1.008
Clinical and endoscopic remission	0.005	0.481	0.289	0.803
Family History of IBD	0.948	0.974	0.436	2.175
Type of IBD (CD vs UC)	0.072	0.584	0.325	1.048
Extra0intestinal manifestation EIM	0.404	0.811	0.496	1.326
Duration of therapy	0.219	1.008	0.995	1.022
Fistulizing vs non-fistulizing	0.027	2.034	1.086	3.811
Steroid Dependent/ resistant	0.019	1.793	1.103	2.916
Concomitant immunosuppressant use	0.257	0.769	0.488	1.211
Infliximab (IFX) vs non IFX biologics	0.263	0.754	0.460	1.236







Conclusion: The relapse rates on discontinuation of biologic therapy was low in patients with clinical and endoscopic remission particularly in non-fistulizing, disease. Most relapses were mild. Majority of the patients with an initial severe disease had a milder course post withdrawal of biologic therapy suggesting that biologics could alter the natural course of the disease. Further multi-centre and long term studies are warranted.

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The effect of induction therapy with infliximab or vedolizumab on hepcidin and iron status in patients with Inflammatory Bowel Disease

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Background: Differentiating absolute iron deficiency from functional iron restriction is challenging in active Inflammatory Bowel Disease (IBD). Hepcidin, the systemic iron regulator, could be the key in the diagnosis and management of absolute iron deficiency. In this study, we assessed hepcidin as a diagnostic iron deficiency marker and we explored the relationship between hepcidin, inflammation, hypoxia, and iron deficiency in patients receiving induction therapy with infliximab (IFX) or vedolizumab (VEDO).

Methods: 130 patients with IBD, who received induction therapy with IFX or VEDO for active disease, were included in this study. Clinical and biochemical data were extracted from medical records. Serum samples at baseline and week 6 of induction therapy were retrieved from the University Medical Center Groningen (UMCG) biobank and analysed for: hepcidin, inflammation (e.g., interleukins [IL] 6, 10, and Tumour Necrosis Factor-α [TNFα]), oxidative stress (free thiols), and hypoxia (e.g., erythropoietin [EPO], Macrophage Inflammatory Protein-3α [MIP3α]). For comparison, serum samples from 50 age- and gender-matched healthy controls were obtained from pre-donation biobank at the UMCG. Response to therapy was defined by either General Physician's Assessment at week 14 of induction therapy, normalisation or at least a three-point decrease in clinical scores: Harvey-Bradshaw Index (HBI) for Crohn's Disease, Simple Clinical Colitis Activity Index (SCCAI) for ulcerative colitis.

Results: Hepcidin correlated with ferritin and sTfR/log ferritin index [ρ = 0.74 and ρ = -0.79, respectively; $P < 0.001$ for both markers], while inflammation- and hypoxia-associated markers showed only marginal correlations. Hepcidin accurately identified absolute iron deficiency: $AUC_{(hepcidin)}$ = 0.89 [95% CI: 0.82–0.95; $P < 0.001$]. Induction with either IFX or VEDO decreased hepcidin [13.5 ng/mL vs. 9.5 ng/mL; $P < 0.001$], ferritin [45.5 ug/L vs. 37.0 ug/L, $P < 0.05$], and inflammatory markers at week 6, while transferrin increased [2.4 g/L vs. 2.5 g/L, $P < 0.001$]. In total, 75.4% of patients responded to the induction therapy. Hepcidin and ferritin decreased, while transferrin increased ($P < 0.001$ for all changes) in patients who responded to the therapy. In addition, hypoxia (EPO and MIP3α) and inflammatory markers such as faecal calprotectin, IL-6, IL-22, and TNFα improved significantly. In contrast, none of these improvements were observed in patients who did not respond to the therapy.

Conclusion: Hepcidin reflects iron deficiency in active IBD, but inflammation masks the severity of the deficiency. Induction therapy with either IFX or VEDO modulates hepcidin and iron indices, especially in patients who respond to the therapy.

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Validation of UC Intestinal Ultrasound (UC-IUS) Index for children with Ulcerative Colitis

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Background: Transabdominal bowel ultrasound (TABUS) is an ideal tool to assess transmural inflammation in children with Ulcerative Colitis (UC). The UC intestinal US (UC-IUS) Index was developed and validated using endoscopy with strong correlation between UC-IUS Index and Mayo subscore (ρ 0.830; p<0.001). Our aim was to determine how bowel wall thickness (BWT) and UC-IUS Index performed in children at diagnosis in comparison to endoscopy using the Mayo score.

Methods: Subjects (0–18 years old) with suspected inflammatory bowel disease (IBD) were prospectively enrolled. Baseline TABUS (excluding rectum due to poorly seen) done prior to endoscopy. Pediatric Ulcerative Colitis disease Activity Index (PUCAI) and Mayo were calculated, albumin, C-reactive protein (CRP) and fecal calprotectin (FCP) collected. The UC-IUS Index was calculated for each segment – sigmoid (SC), descending (DC), transverse (TC) and ascending (AC) [bowel wall thickness (BWT) (mm): > 2 =1, >3 =2 and >4 =3; doppler: spots=1 and stretches =2, abnormal haustrations = 1 and fat wrapping =1]. Spearman's rank (rho) and Pearson's correlation (r) assess for a correlation. Receiver operating characteristic [ROC] analysis performed for BWT to determine sensitivity and specificity of BWT cut-offs in the UC-IUS.

Results: Of the 75 subjects recruited for suspected IBD, 26 had UC with mean age 15 years (SD 3.33) and 5 had normal US. Twenty three have extensive pancolitis. Mean PUCAI score: 60 (SD 23.28), CRP 22.62 (SD 39.5) mg/l, albumin 35.6 (SD 6.96) g/l and fecal calprotectin of 2223 (SD 1757) mg/kg. ROC curves generated using a total of 122 colonic segments. BWT of 2 mm discriminates between active and inactive:Mayo 0 and Mayo1-3 [sensitivity 84.9%; specificity 86.2%; an area under the curve [AUC] 0.900]; a cut-off of 3mm discriminates between Mayo 1 from Mayo 2–3 [sensitivity of 61.3%; specificity 90.5%; AUC 0.858]; a cut of 4mm discriminates Mayo 3 (sensitivity 64.7%; specificity 85.7 %; AUC 0.876). BWT and UC-IUS scores of all colonic segments correlated highly positively with the Mayo score of corresponding segments (rho=0.684, r=0.660, p<0.001) and (rho=0.750, r=0.722, P<0.001) respectively. The UC-IUS Index correlates poorly with CRP, ESR, and Fecal Calprotectin - r = 0.262, 0.346 and 0.100 respectively; p>0.05.

Conclusion: BWT and UC-IUS Index correlated highly positively with the Mayo subscore in children with UC. UC-IUS has a better correlation than BWT. BWT cut-off of 2mm discriminate between normal and mild Mayo is optimal. Cut-offs of 3 mm and 4 mm for moderate and severe Mayo may be too high in children with lower sensitivity. A larger cohort of children with UC will need to be studied to determine optimal BWT cut-off for moderate and severe disease.

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Fecal incontinence and rectal anal function in Crohn's Diseases patients

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Background: Anoperineal damage in Crohn's Disease (CD) is caused by inflammation, its sequelae, and the surgery's sequelae. Fecal incontinence (FI) is an important complaint reported by patients with CD. Literature data regarding to FI, anatomical and functional abnormalities and its associated clinical factors are controversial, with few surveys with a limited number of participants.[1] The aim of this study is to analyze FI and the associated manometric and clinical findings in patients with CD.

Methods: Observational, cross-sectional study in patients older than 18 years old with CD under outpatient follow-up at a tertiary center, who, after sign informed consent, were submitted to specific questionnaire, anorectal manometry and medical record review.

The Jorge and Wexner Fecal Incontinence Scale was applied to grade incontinence.[2]

SPSS 21.0 (SPSS, Chicago, IL, USA) was used for statistical analysis, with description of categorical variables with absolute and relative frequency, and continuous variables with median and interquartile range (IIQ). To study the association, we used Pearson's Chi-Square and Mann Whitney test. The null hypothesis was rejected with p<0.05.

Results: Of 104 patients with CD, 51% were male, median age of 41 years old (IIQ 29.2–50.0) and median disease duration of 6.1 years (IIQ 2.5 to 11 .5). Most of the sample was diagnosed between 17 and 40 years old, (68.3%), with non-penetrating, non-stricturing disease (63.4%), with colonic location (77.9%), isolated (30.8%) or with ileal involvement (47.1%); 78.8% had disease in remission and 11.5% had mild disease, representing 90,4% of our casuistic, according to the Harvey Bradshaw Index. Among patients; 41.3% had perianal disease, and 49%