Biomarkers of neutrophil activity and extracellular matrix turnover predict long-term response to vedolizumab in patients with Crohn's disease

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The impact of disease duration and early biologic treatment on transmural healing in Crohn's disease

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Background: Although transmural healing (TH) has not yet been considered a formal target in CD, it is considered a desired goal, as it seems to be associated with better outcomes. Early biologic treatment has been shown to lead to higher clinical remission and increased endoscopic healing. However, to date, there is no information on the impact of disease duration on TH. We aimed to assess the efficacy of early biologic treatment on the achievement of TH.
Methods: Unicentre retrospective cohort study comparing patients who started early and late biologic therapy (defined as ≤ 12 months vs > 12 months from diagnosis). We included patients with CD who were receiving biologic therapy, and had a baseline computed tomography enterography (CTE) or magnetic resonance enterography (MRE) before the initiation of a biologic (median 2.5, IQR 0–50 months), and a follow-up CTE/MRE performed 12 ± 6 months after therapy initiation. Endoscopic healing was defined as a SES-CD score <3. Three experienced radiologists blinded to the therapeutic group reviewed every CTE and MRE and assessed several pre-defined parameters of cross-sectional inflammation. TH was defined as the absence of active inflammation, extra-enteric signs, and CD-related complications (strictures, fistulas or abscesses). The effect of early biologic treatment on transmural healing was analysed using logistic regression.
Results: 60 patients were included (51.7% males), with a median age at diagnosis of 24.5 years old (IQR 17.5–32.5). Most patients had ileocolonic disease (58.3%) and non-stricturing non-penetrating phenotype (60%). Twenty-eight patients (46.7%) started biologic therapy within the first 12 months of diagnosis. There were no significant differences in baseline clinical features or baseline radiologic assessment between the groups, except for the extension of the most affected segment, which was higher in the group of late biologic therapy (197 vs 129.5mm, p=0.05) (Table 1). Patients on early biologic treatment achieved endoscopic healing more frequently than those on late biologic treatment (65.4% vs 23.3%, p=0.002). Early biologic treatment was also associated with increased transmural healing (OR 4.1, 95% CI 1.2–13.6, p=0.02). In a multivariate model including baseline characteristics of the disease, only the use of biologics within the first 12 months and the absence of ileocolonic disease were significant predictors of the achievement of transmural healing (Figure 1).
Conclusion: Early biologic treatment seems to be independently associated with higher transmural healing rates, further adding to the relevance of early intervention in CD. Our findings are limited by the small sample size and short follow-up.

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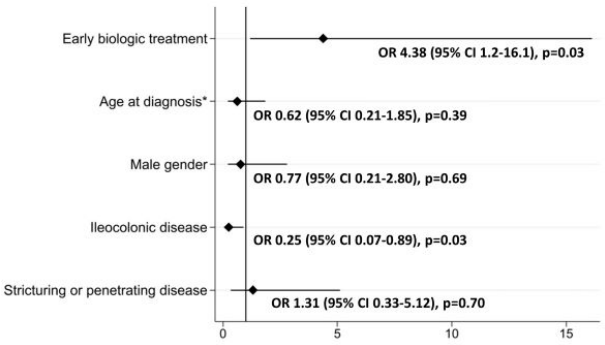
Table 1 – Comparison of baseline characteristics between patients who started early and late biologic treatment

Variable	Early biologic treatment (≤12 months) (n=28)	Late biologic treatment (>12 months) (n=32)	*p-value*
Age at diagnosis	27.2 (±13.1) years-old	27.4 (±14.8) years-old	0.95
Male gender	57.1% (16)	46.9% (15)	0.43
Disease duration (from diagnosis to biologic treatment)	4.5 (IQR 2-6.5) months	78 (IQR 35-173) months	<0.001
Disease location			
Ileon (L1)	39.3% (11)	21.9% (7)	0.14
Colon (L2)	7.14% (2)	15.6% (5)	0.31
Ileo-colic (L3)	53.6% (15)	62.5% (20)	0.48
Disease behaviour			
Inflammatory (B1)	64.3% (18)	56.3% (18)	0.53
Stricturing (B2)	14.3% (4)	21.9% (7)	0.45
Fistulizing (B3)	21.4% (6)	21.9% (7)	0.97
Perianal disease	57.1% (16)	43.8% (14)	0.30
Endoscopic evaluation 3 months before biologic			
Presence of deep ulcers	28.6% (8)	25% (8)	0.76
Presence of large ulcers	46.4% (13)	59.4% (19)	0.32
Presence of strictures	21.4% (6)	40.6% (13)	0.11
Cross-sectional imaging at baseline			
Extension of the most affected segment	129.5 (±97.7) mm	197 (±154.1) mm	0.05
Bowel wall thickness	6.6 (±2.6) mm	7.3 (±2.9) mm	0.33
Number of segments affected	1.6 (±1.1)	1.8 (±1.2)	0.49
Sinus tract	14.3% (4)	6.3% (2)	0.32
"Comb sign"	71.4% (20)	81.3% (26)	0.25
Fibrofatty proliferation	7.1% (2)	15.6% (5)	0.29
Stricture	14.3% (4)	12.5% (4)	0.88
Fistula	25% (7)	25% (8)	0.94
Abscess	7.1% (2)	9.4% (3)	0.73
Biologic started			
Infliximab	89.3% (25)	78.1% (25)	0.25
Adalimumab	10.7% (3)	18.8% (6)	0.38
Vedolizumab	0% (0)	3.1% (1)	0.35
Concomitant steroids at the initiation of biologic	3.6% (1)	9.4% (3)	0.37
Concomitant thiopurines at the initiation of biologic	71.4% (20)	50% (16)	0.09

Figure 1: Multivariate logistic regression model for the prediction of the achievement of transmural healing



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Background: Crohn's disease (CD) is a form of inflammatory bowel disease characterized by high infiltration of immune cells into the intestinal tissue, resulting in increased proteolytic mediated extracellular matrix (ECM) remodeling. Disease management has improved with the use of biologics such as vedolizumab (VEDO). However, considering the high rate of primary non-response to VEDO, there is an unmet need for predictive serum biomarkers capable of determining response to treatment prior to its initiation. This study investigated whether biomarkers of neutrophil activity, mucosal damage, and ECM remodeling could serve as non-invasive tools for predicting long-term response to VEDO in patients with CD.
Methods: Serum biomarkers of human neutrophil elastase (HNE)-derived fragment of calprotectin (CPa9-HNE [serum calprotectin]) and

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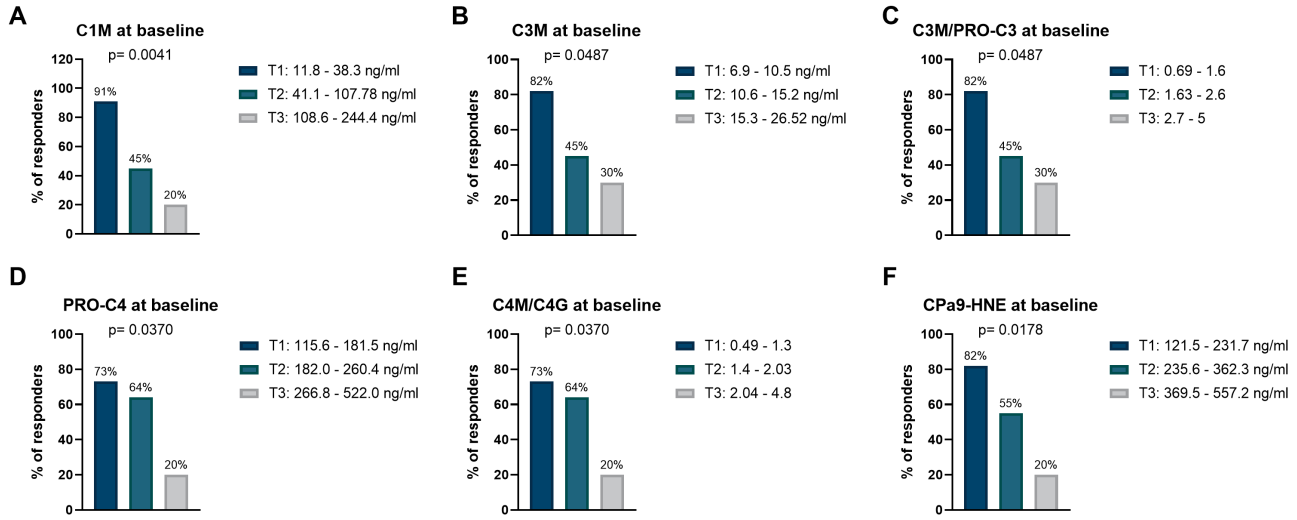

matrix metalloproteinase (MMP)-derived fragments of type I (C1M), III (C3M), IV (C4M), type III collagen formation (PRO-C3), basement membrane turnover (PRO-C4) and T-cell activity (C4G), were measured using protein fingerprint assays in patients with CD (n=32) before VEDO therapy initiation. The ratio C4M/C4G (myeloid/lymphoid mediated degradation) was computed. Long-term response was defined as the continuation of treatment beyond one year after the start of therapy. Baseline biomarker levels were compared between responders and non-responders using Mann-Whitney U-tests, and area under the curve (AUC) values were generated using receiver operating characteristics (ROC) statistics. Biomarker levels were divided into tertiles and chi-square tests were used to investigate the relationship between tertiles and response proportions.

Results: Biomarkers CPa9-HNE, C1M, C3M, C4M, PRO-C3, C3M/PRO-C3, and C4M/C4G were significantly increased at baseline in non-responders compared with responders (all P<0.05). All markers were able to predict response to VEDO at baseline (AUC [95% CI]: CPa9-HNE 0.81 [0.66–0.96]; C1M 0.85 [0.75–0.98]; C3M 0.79 [0.62–0.95]; C4M 0.77 [0.6–0.93]; C3M/PRO-C3 0.78 [0.6–0.95]; C4M/C4G 0.74 [0.56–0.92] all P<0.05). Proportions of long-term VEDO users were highest in the first tertiles for all the markers (73–91%) and decreased in a concentration-dependent manner across the second and third tertiles, indicating that patients with the lowest concentrations of these markers less frequently discontinued treatment at one year after initiation (**Figure 1**).

Conclusion: Baseline levels of serum biomarkers for neutrophil activity (CPa9-HNE [serum calprotectin]) and mucosal damage (C1M, C3M, C4M, C4G, PRO-C4, and PRO-C3) could predict long-term response to VEDO in patients with CD. Therefore, these biomarkers could aid in early decision making concerning treatment with vedolizumab in patients with CD.

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Comparative efficacy of biologic therapies for inducing response and remission in fistulizing Crohn's disease; Systematic Review and Network Meta-analysis

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Background: The management of patients with fistulising Crohn's disease (CD) is challenging. Several biologics have been used for the treatment of fistulising CD over the last two decades. We aimed to compare the efficacy of biologic therapies in inducing response and remission in fistulising Crohn's disease.

Methods: Systematic searches were made of MEDLINE, EMBASE, Scopus, Cochrane Central databases for randomized controlled trials (RCTs) to November 2021 that assessed the efficacy of infliximab, adalimumab, certolizumab, vedolizumab, or ustekinumab against placebo or an active agent for induction of response or remission in adult Crohn's patients with fistulising disease. Primary outcome was proportion of patients with fistula response or remission as defined by each RCT. Pairwise treatment effects were estimated through a Bayesian random-effects network meta-analysis and reported as odds ratios (OR) with a 95% confidence interval (CI).

Results: Ten studies were included in the analysis. Main analysis showed that there was no statistical difference in inducting remission between infliximab, adalimumab, certolizumab, vedolizumab and ustekinumab. Anti-TNFs were superior to placebo in inducing response [OR= 0.51 (95% CI 0.35; 0.750] and remission [OR= 0.36 (95% CI 0.22; 0.58)]. Infliximab was superior to placebo in inducing response [OR= 0.36 (95% CI 0.17; 0.75)] and remission [OR=0.17 (95% CI 0.03; 0.87)]. Ustekinumab was superior to placebo in inducing response [OR=0.48 (95% CI 0.26; 0.860] but not remission [OR=0.50 (95% CI 0.13; 1.93)]. Vedolizumab was not superior to placebo in inducting remission [OR=0.32 (95% CI 0.04; 2.29)]. Certolizumab was not superior to placebo in inducting response [OR=0.78 (95% CI 0.40; 1.55)] or remission [OR= 0.78 (95% CI 0.40; 1.55)]. Infliximab was superior to adalimumab in inducting response [OR=0.24 (95% CI 0.06; 0.99)] but not remission [OR=0.31 (95% CI 0.04; 2.27)].

Conclusion: In patients with fistulising Crohn's disease, anti-TNFs are effective in inducing response and remission. Infliximab was superior to adalimumab in inducing response but not remission. No difference among various biologics was observed for inducing remission. These data highlight the need for dedicated studies to assess the efficacy of biologics in fistulising Crohn's disease.