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Distinct fatigue trajectories in active IBD: clinical predictors and treatment-linked improvements independent of inflammation

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Background: Fatigue is one of the most debilitating and persistent symptoms in inflammatory bowel disease (IBD), often remaining despite adequate control of intestinal inflammation. Current treatments insufficiently address this burden, underscoring the need to better characterise its course and determinants [1]. The study aimed to identify distinct fatigue trajectories in patients with active IBD, and to determine clinical and psychological predictors of fatigue improvement over one year.

Methods: Data were derived from a large prospective cohort within the 3TR consortium, including 207 patients with active endoscopic ulcerative colitis (UC) or Crohn's disease (CD), recruited at 2 large referral centres. Assessments were performed at baseline, week 6 and 1 year after treatment initiation. Fatigue (FACIT-F), mental health (SF-36, mental component summary) and inflammatory markers (faecal calprotectin [FC] and C-reactive protein [CRP]) were collected at each visit. Latent class growth analysis (LCGA) was used to identify fatigue trajectory clusters based on intercepts and slopes of individual patients. Mixed-effects models tested the influence of advanced IBD treatment, baseline inflammation and mental health on fatigue changes.

Results: LCGA identified three distinct trajectories differing in fatigue severity ($p < 0.001$) at baseline with mild (FACIT-F = 45.4), moderate (FACIT-F = 28.6) and severe (FACIT-F = 11) fatigue, with the majority (72.9%) of patients with active IBD in our cohort experiencing moderate-to-severe levels that often persist up to 1 year. The quadratic slopes over time did not significantly differ between the groups ($p > 0.05$), although patients with mild or moderate fatigue improved significantly, particularly in the first 6 weeks ($p < 0.01$), whereas those with severe baseline fatigue showed minimal change ($p = 0.51$; Figure 2A) [2]. Treatment with upadacitinib ($p < 0.001$), infliximab ($p < 0.001$) and vedolizumab ($p < 0.05$) was associated with greater fatigue improvement, while risankizumab ($p = 0.07$) and ustekinumab ($p = 0.15$) was not, despite similar baseline levels of fatigue (Figure 2B). Baseline mental health problems predicted worse initial fatigue, but greater improvement over time ($p < 0.05$; Figure 2C). Neither FC nor CRP at baseline were significantly associated with fatigue changes ($p = 0.53$).

Conclusion: LCGA identified three distinct fatigue trajectories, where the evolution appeared largely independent of baseline inflammatory activity. Improvement in fatigue was more strongly associated with specific advanced therapies and baseline mental health problems than baseline inflammatory markers. The differences between biologics classes are seen in a non-randomized setting and should lead to randomized controlled comparisons between interventions.

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OVERVIEW OF PATIENT CHARACTERISTICS (N=207)		
Diagnosis	**UC**	**CD**
Age		
18-24	14 (13.6%)	21 (20.2%)
25-29	17 (16.5%)	15 (14.4%)
30-39	33 (32%)	18 (17.3%)
40-49	13 (12.6%)	17 (16.6%)
50-59	10 (9.7%)	21 (20.2%)
60-69	11 (10.7%)	7 (6.7%)
70+	5 (4.6%)	5 (4.8%)
Gender		
Female	41 (39.8%)	55 (52.9%)
Male	62 (60.2%)	49 (47.1%)
Medication initiated at baseline because of active disease (SES-CD ≥ 4, Mayo ≥ 2 or FC > 150 µg/g)		
Infliximab	29 (28.2%)	26 (25%)
Risankizumab	/	30 (28.9%)
Upadacitinib	17 (16.5%)	12 (11.5%)
Ustekinumab	11 (10.7%)	15 (14.4%)
Vedolizumab	26 (25.2%)	16 (15.4%)
Other	20 (19.4%)	5 (4.8%)
Disease status after 1 year		
Active	37 (35.9%)	43 (41.4%)
Unknown	18 (17.5%)	22 (21.2%)
Remission	48 (46.6%)	39 (37.5%)

Figure 1. Table with overview of patient characteristics (n=207)

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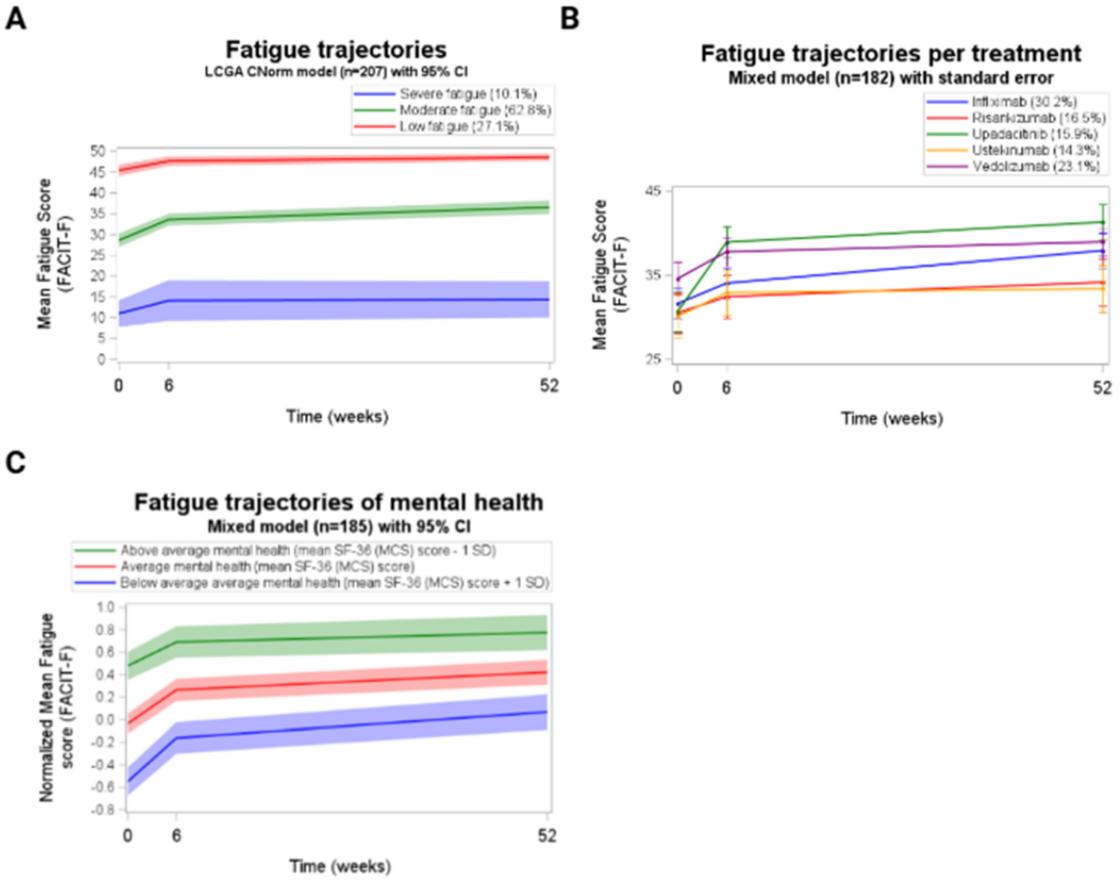

Figure 2 ***A****. LCGA identified three distinct fatigue trajectories with different baseline values (p<0.001) and similar quadratic slopes over time (p>0.05). There was a significant improvement in fatigue in the low (baseline FACIT-F = 45.4) and moderate (baseline FACIT-F = 28.6) fatigue groups, with a stronger improvement in the first 6 weeks (p's<0.01), but not in the severe fatigue (baseline FACIT-F = 11) group (p=0.51).* ***B****. Mixed model analysis revealed that treatment with infliximab (p<0.001), upadacitinib (p<0.001) and vedolizumab (p<0.05) at baseline was associated with improvements in fatigue, as opposed to treatment with risankizumab (p=0.07) and ustekinumab (p=0.15).* ***C****. Mixed model analysis showed that worse mental health at baseline was associated with worse fatigue, but greater improvement over time (p<0.05).*