Proteomic analyses do not reveal subclinical inflammation in fatigued patients with quiescent Inflammatory Bowel Disease

Bourgonje, Arno R.; Wichers, Sietse J.; Hu, Shixian; van Dullemen, Hendrik M.; Visschedijk, Marijn C.; Faber, Klaas Nico; Festen, Eleonora A. M.; Dijkstra, Gerard; Samsom, Janneke N.; Weersma, Rinse K.

Published in:
Journal of Crohn's and Colitis

DOI:
10.1093/ecco-jcc/jjab232.364

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
SARS-CoV-2 to prevent hospitalization, mechanical ventilation, and death. However, IMS may adversely affect vaccination, raising concerns as to how vulnerable these patients are to break through COVID-19 infections. Thus, we aimed to assess the proportion of IBD patients who despite complete vaccination developed COVID-19, as well as the course of the infection.

**Methods:** This study was an initiative of the Hellenic Group for the study of IBD which involved seven IBD referral Centers. Patients attending these Centers who reported a COVID-19 infection at least 3 weeks after vaccination completion were asked to complete an on-line anonymous questionnaire which included patient demographics and IBD clinical and therapeutic data, a detailed vaccination history, and the course and outcome of COVID-19, especially the need for hospitalization, oxygen supply, and admission to ICU. In patients with grave outcome information was sought by family members.

**Results:** On estimate, 2940 patients reported full vaccination (Pfizer vaccine) in the 7 centers. Between 1<sup>st</sup> May 2021 and 30<sup>th</sup> October 2021, 46 (1.5%) fully vaccinated IBD patients reported COVID-19 infection [25 male, 32 CD, 14 UC, mean (SD) age 40.8 (13.7) years, mean (SD) IBD duration mean, 11.2 (10.8) years]. Five patients were receiving 5-ASAs, 2 corticosteroids, 5 azathioprine/methotrexate, 23 anti-TNFs as monotherapy and 3 in combination with azathioprine/methotrexate, and 1 with corticosteroids, 3 vedolizumab and 1 each ustekinumab, tofacitinib and rizankinumab at the time of COVID-19 diagnosis; one patient was receiving no treatment. IBD was in remission in 37/46 patients (80.4%). Comorbidities were seen in 21 patients (thyroid disease 11; diabetes mellitus 2; hypertension 2; psoriasis 1; prior breast cancer 1; spondyloarthropathy 2; dyslipidemia 1; and PSC 1 patient). The mean (SD) time between last vaccination dose and infection was 3.2 (1.4) months. Overall, 40 (86.9%) patients reported mild constitutional and respiratory symptoms, 4 (8.7%) were asymptomatic and only 2 patients (4.3%) required hospitalization which was uneventful in both. None needed high flow oxygen supply or ICU admission, and none reported symptoms of long COVID. No deaths were reported by patient relatives. IBD medications were stopped in 21 patients (45.6%) during the COVID-19 infection.

**Conclusion:** A minority of fully vaccinated IBD vaccinated patients developed COVID-19 which was relatively mild and uneventful. These results reinforce the importance of vaccination especially in vulnerable populations.

---

**P237**

**Proteomic analyses do not reveal subclinical inflammation in fatigued patients with quiescent Inflammatory Bowel Disease**

A.R. Bourgonje<sup>1</sup>, S.J. Wichers<sup>1</sup>, S. Hu<sup>1,2</sup>, H.M. van Dullemen<sup>1</sup>, M.C. Visschedijk<sup>1</sup>, K.N. Faber<sup>1</sup>, E.A.M. Festen<sup>1</sup>, G. Dijkstra<sup>1</sup>, J.N. Samsom<sup>1</sup>, R.K. Weersma<sup>1</sup>, L.M. Spekhorst<sup>1,4</sup>

<sup>1</sup>University of Groningen- University Medical Center Groningen, Gastroenterology and Hepatology, Groningen, The Netherlands, <sup>2</sup>University of Groningen- University Medical Center Groningen, Genetics, Groningen, The Netherlands, <sup>3</sup>Easmus University Medical Center, Pediatrics- Division of Gastroenterology, Groningen, The Netherlands, <sup>4</sup>Medisch Spectrum Twente, Gastroenterology and Hepatology, Enschede, The Netherlands

**Background:** Fatigue is a common and clinically challenging symptom in patients with inflammatory bowel diseases (IBD). While fatigue occurs most often in patients with active disease, up to 50% of patients with quiescent disease still report significant fatigue of unknown aetiology. Here, we aimed to investigate whether fatigue in patients with quiescent IBD is reflected by circulating inflammatory proteins, that in turn might reflect ongoing subclinical inflammation.

**Methods:** Ninety-two (92) different inflammation-related proteins were measured in plasma of 350 patients with quiescent IBD (188 Crohn’s disease [CD]; 162 ulcerative colitis [UC]). Quiescent IBD was defined as clinical (Harvey-Bradshaw Index [HBI] <5) or Simple Clinical Colitis Activity Index [SCCAI] <2.5) and biochemical remission (C-reactive protein [CRP] <5 mg/L) at time of sampling. Fatigue severity was assessed on a visual analogue scale (VAS).

**Results:** None of the analysed plasma proteins were differentially abundant between mildly (1<sup>st</sup> quartile, Q1) or severely (4<sup>th</sup> quartile, Q4) fatigued patients with quiescent IBD.
Q4) fatigued patients under a false discovery rate of 10%. Considering nominal significance (P<0.05), however, leukemia inhibitory factor receptor (LIF-R) concentrations were inversely associated with severe fatigue, also after adjustment for confounding factors (P < 0.05) (Figure 1). Although solely LIF-R showed weak ability to discriminate between mild (Q1) and severe (Q4) fatigue (area under the curve [AUC]=0.61, 95% CI: 0.53–0.69, P<0.05), a combined set of the top seven (7) fatigue-associated proteins (LIF-R, vascular endothelial growth factor A [VEGF-A], glial-derived neurotrophic factor [GDNF], interleukin-20 receptor subunit alpha [IL-20RA], Delta and Notch-like epidermal growth factor-related receptor [DNER], T-cell surface glycoprotein CD5 [CD5], and extracellular newly identified receptor for advanced glycation end-products binding protein [EN-RAGE], also known as protein S100-A12, all P<0.10) was observed to have reasonable discriminative performance (AUC=0.82 [95% CI: 0.74–0.91], P<0.01).

Conclusion: Fatigue in patients with IBD is not clearly reflected by distinct circulating inflammatory protein signatures, which suggests that subclinical immune activation as defined by the studied panel of inflammatory proteins could not be detected. Reduced shedding of the LIF-R protein could be related to fatigue in IBD through modification of the oncostatin-M (OSM) signaling pathway, or through induction of pro-inflammatory phenotypes of T-cells, macrophages, or neural cells. Future studies are warranted to investigate other proteomic or metabolomic markers that may accurately reflect fatigue in quiescent IBD, which might represent alternative pathophysiological pathways.

P238
Symptom burden and indolent disease in newly diagnosed patients with ulcerative colitis and Crohn’s disease - a Copenhagen IBD Inception Cohort Study

M. Attauabi1,2,3, G.R. Madsen1, E. Bendtsen1, R. Wilkens1, J.E.K.F. Ilvemark2, K. Thede1, T. Boysen1, J.T. Bjerrum2, J.B. Seidelin1, J. Burisch1

1Copenhagen University Hospital- Hvidovre, Gastroint- Medical Section, Hvidovre, Denmark, 2Herlev Hospital- University of Copenhagen, Department of Gastroenterology and Hepatology, Herlev, Denmark, 3University of Copenhagen- Hvidovre Hospital, Copenhagen Center for Inflammatory Bowel Disease in Children- Adolescents and Adults, Hvidovre, Denmark

Background: The early course of ulcerative colitis (UC) and Crohn’s disease (CD) is difficult to predict, particularly regarding identifying patients for whom an indolent course might be expected. Therefore, we aimed to investigate the initial course of UC and CD and clinical predictors hereof in a generalizable population-based inception cohort.

Methods: We initiated a prospective population-based inception cohort of newly diagnosed patients with UC and CD between May 1st, 2021 and November 1st, 2021, according to the Copenhagen IBD Criteria within the geographical uptake area of Hvidovre University Hospital and Herlev University Hospital. All patients were examined systematically by IBD specialists at diagnosis using endoscopy, magnetic resonance (MR) enterography, and patient-reported measures including Simple Clinical Colitis Index (SCCAI) and Harvey-Bradshaw Index (HBI) for UC and CD, respectively. Indolent disease presentation was defined as the absence of UC or CD-related hospitalization, surgery, or decision to start steroid, immunomodulator, or biologic therapy within three months of follow-up. In addition, well-recognized predictors of long-term disease course of UC and CD were a priori defined and implemented in a univariate logistic model, and factors with a p-value smaller than 0.10 were included in the multivariate model.

Results: The study included 63 adult patients with UC and 50 with CD. At diagnosis, 23 (36.5%) and 13 (26.0%) patients with UC and CD were in clinical remission according to their SCCAI or HBI score, respectively (Table 1). The symptomatic disease burden is outlined in Table 2–3. Interestingly, well-recognized risk factors for the long-term disease course of UC and CD, including disease extent, behavior, baseline endoscopy, MR enterography, and serologic data, did not predict the initial disease course in a multivariable analysis (Table 4). However, C-reactive protein <10 mg/L were associated with an indolent course of UC (adjusted odds ratio=6.2 (95% confidence interval 1.3–38.9), p=0.03).

Conclusion: The preliminary data from the ongoing prospective population-based cohort study indicate that very heterogeneous disease course patterns might be experienced very early. As initial disease control is considered critical for long-term outcomes, this study highlights the inapplicability of long-term predictors for the short-term disease course. It emphasizes the need for further development of simple clinical tools or biomarkers for early patient stratification.