A milestone in screening for adherent-invasive E. coli colonization in patients with Crohn's disease?

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EDITORIAL

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Crohn's disease (CD) is chronic relapsing inflammatory bowel disease, resulting from an inappropriate and ongoing activation of the mucosal immune system driven by the presence of an altered intestinal microbiota in a genetically predisposed patient. CD is associated with an intestinal dysbiosis characterized by an overall loss of diversity, a decrease in Firmicutes (such as *Faecalibacterium prausnitzii*[1]) and an increase in Enterobacteriaceae (such as adherent-invasive *Escherichia coli* [AIEC][2]). Current therapeutic strategies in CD aim at inhibiting the over-activated immune system and largely ignore the microbial component of the pathogenesis. Targeting the gut microbiota and in particular restoring its balance is a promising therapeutic strategy. In this line, small case series, uncontrolled studies and a single randomized controlled trial suggest a beneficial effect of faecal microbiota transplantation in CD.[3] Alternatively, strategies aiming at supplementing with anti-inflammatory commensal bacteria such as *F. prausnitzii* or at targeting AIEC in patients with CD could pave the way to personalised and likely more effective treatments. Several clinical trials are currently investigating the efficacy of AIEC-targeting strategies in CD including the use of phage (NCT03808103), antibiotics cocktail (NCT0262007), or anti-adhesive molecules (NCT03709628). Prevalence of AIEC in the ileal mucosa ranges from 21% to 63% in CD patients, versus 0% to 19% in healthy controls.[4] Therapeutic approaches targeting AIEC therefore require the identification of AIEC-positive patients, who could be more likely to benefit from these strategies, but the current method to screen patients for AIEC colonisation is a practical limitation. Indeed, up to now, the only way to identify AIEC strains relies on functional assays examining bacterial abilities to adhere to and to invade intestinal epithelial cells and to survive within macrophages.[5] This approach is invasive and time consuming, requiring a colonoscopy to take ileal biopsies, bacterial isolation, and complex in vitro assays. Although molecular approaches and genomic sequencing have identified genes associated with AIEC-host cells interaction, a specific and widely distributed molecular AIEC marker is still missing.[6] In 2018, a classification algorithm based on AIEC-associated single nucleotide polymorphisms (SNP) was designed within a Spanish strains collection as a potential molecular tool to classify AIEC/non-AIEC, with high accuracy (84%).[7] However, its accuracy was significantly reduced when *E. coli* strains from different cohorts were included, indicating that this tool is not robust enough to identify AIEC.[8] A multicentre international study, called "molecular biomarkers and Adherent and Invasive *Escherichia coli* detection study in CD patients" (MOBIDIC), evaluated the relationship between non-invasive biomarkers and AIEC detection in intestinal biopsies of patients with CD in order to develop a predictive algorithm of AIEC carriage, but the results of this trial have yet to be released (NCT02882841).

In this issue of UEG Journal, Buisson et al. identified faster and less invasive methods to detect AIEC colonisation in patients with ileal CD enrolled in a French multicentre prospective study.[9] Samples from saliva, blood, stools, and ileal biopsies were collected in 102 CD patients. Using multivariate analysis, the authors did not identify any clinical factor associated with AIEC colonisation, especially no relationship between disease activity and AIEC colonisation. They showed that the number of total *E. coli* associated to ileal mucosa and the global invasive ability of these strains could be faster alterative tests for AIEC screening. Although stool sampling was representing a convenient and intuitive candidate for non-invasive screening of AIEC-positive patients, no correlation between ileal AIEC colonisation and the number of faecal total *E. coli* or the global invasive properties of these bacteria was observed. In contrast, using indirect ELISA method on whole bacteria, the authors showed that the level of anti-total *E. coli* antibodies (AEcAb) was higher in sera from AIEC-positive patients compared to those from AIEC-negative patients. As blood puncture is more readily accepted by patients than a colonoscopy with biopsies, AEcAb level could therefore be an attractive, rapid and less invasive biomarker to identify AIEC-positive patients. Further investigations are needed to confirm these results in different cohorts and to identify immune-dominant antigens in AIEC bacteria to develop a more selective test. Immune reactivity against *E. coli* antigens such as I2, outer membrane protein OmpC and flagellin, has been described in CD[10] and these antigens might represent good candidates.

The results obtained in the study of Buisson and collaborators are important to clinicians and to patients. Although the tools highlighted in this work do not constitute non-invasive diagnosis tools,

they should facilitate the selection and recruitment of AIEC-positive patients, who have therefore a better chance of responding to AIEC-targeting treatment.

KEYWORDS

adherent-invasive *E. coli*, AIEC-positive patients, anti-*E. coli* antibodies, Crohn's disease

CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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