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Interleukin-6 is associated with steroid resistance and reflects disease activity in severe pediatric ulcerative colitis

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Abstract

Background and aim: Approximately one third of patients with acute severe ulcerative colitis (ASC) will fail intravenous corticosteroids (IVCS). Predicting response to IVCS to initiate early salvage therapy remains challenging. The aim of this study was to evaluate the role of serum inflammatory cytokines in ASC and determine their predictive utility with IVCS treatment failure.
Methods: This preplanned ancillary study, part of the prospective multicenter OSCI study, evaluated pediatric ASC in North America. Serum samples were obtained from 79 children admitted for ASC on the third day of IVCS treatment. Twenty-three (29%) patients required second-line therapy. ELISA-based cytokine arrays were used [TNF-α, IFN-γ, interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, and IL-17], selected based on a systematic literature search.
Results: In univariate analysis, only IL-6 was significantly different between responders and non-responders (P=0.003). The risk for IVCS failure increased by 40% per each pg/mL increase in IL-6

Abbreviations: ASC, acute severe ulcerative colitis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GR, glucocortocoid receptor; IFN, interferon; IL, interleukin; IBD, inflammatory bowel diseases; IQR, interquartile range; IVCS, intravenous corticosteroids; OR, odds ratio; PGA, physician global assessment; PUCAI, Pediatric UC Activity Index; T_H, T-helper; TNF, tumor necrosis factor; UC, ulcerative colitis.

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level. Factor analysis found IL-6 to be associated with IL-17, suggesting involvement of the T-helper (T_H)17 pathway. In a multivariate analysis, disease activity [judged by the Pediatric UC Activity Index (PUCAI)] assumed all the association with the treatment outcome while IL-6 was no longer significant ($P=0.32$; PUCAI score $P<0.001$).

Conclusions: While IL-6 strongly predicted IVCS failure, it likely reflects disease activity and not direct interference with corticosteroid pathway. Nonetheless, IL-6 levels may have a role in predicting IVCS response in severe pediatric UC for treatment decision-making or potentially in medical intervention by virtue of anti-IL-6 antibodies in severe UC.

1. Introduction

Treatment of acute severe ulcerative colitis (ASC) often requires admission to hospital for use of intravenous corticosteroids (IVCS),[1] which has been the mainstay of treatment for decades.[2,3] However, as documented in a systematic review of cohort studies, one third of adult patients hospitalized with ASC fail to respond to such therapy,[4] and even more in children.[1] Several measures predict response to IVCS and thus facilitate timely introduction of salvage therapy (i.e., infliximab, cyclosporine, tacrolimus, or colectomy), such as clinical response [reflected in the Pediatric Ulcerative Colitis (UC) Activity Index (PUCAI)], laboratory markers, and changes in the microbiome.[3–10] However, it remains unclear why some patients respond rapidly to corticosteroids while others do not.

Cytokines are small signaling molecules with critical roles in inflammation.[11] Cytokines first released in response to inflammatory triggers include interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α, which activate a second wave of pro-inflammatory transcription factors to produce other cytokines.[12] IL-6 is a central cytokine released mainly from monocytes, macrophages, and T-cells during acute and chronic inflammation. Although this pleiotropic cytokine is related to many biological processes the roles relevant to human inflammatory bowel diseases (IBD) mainly relate to stimulation of additional pro-inflammatory cytokines, proteases, and adhesion molecules, anti-apoptotic effects, and regulation of T-cell differentiation.[13–15]

Changes in cytokines are well documented in UC and may persist even during disease remission.[16] Studies highlight the complex involvement of cytokines in UC and provide the rationale for understanding the interplay between cytokines and response to steroid therapy in severe UC. We aimed to evaluate the role of inflammatory cytokines in the serum of children with ASC and to determine their association with corticosteroid failure. We hypothesized that specific serum cytokines, measured at the third day of IVCS treatment, can differentiate those who will fail to respond to the medication and require further salvage therapy.

2. Materials and methods

2.1. Study design

This is a preplanned ancillary study performed as part of the large prospective multicenter OSCI study, which evaluated pediatric ASC in North America.[10] Explicit clinical, demographic, and outcome data were prospectively collected at admission, at multiple time-points during the admission, and at discharge of children admitted for IVCS treatment of ASC. The main goal of the OSCI study was to identify clinical and laboratory predictors of non-response to IVCS treatment. Samples of serum, obtained at the third day of corticosteroid therapy were linked to the phenotypic database, and used here to evaluate the association of inflammatory cytokines with steroid resistance. Day 3 of IVCS treatment was chosen to differentiate responders from non-responders as the longer one waits the larger the differences between those who are improving and those left unchanged and since this time provides a balance between the predictive power and timely clinical feasibility.[17] The work was approved by the appropriate ethical committees related to the institutions in which it was performed and that subjects gave informed consent to the work.

2.2. Patients

All patients with available serum at the time of the array analysis were included. To determine the association of cytokines with steroid failure, patients were categorized as *steroid-responsive* or *steroid-refractory* depending on the need for second line therapy (anti-TNF therapy, calcineurin inhibitors, or colectomy) prior to hospital discharge. Because physician factors may influence decision to institute second-line therapy, patients were further categorized into more homogenous extreme groups. *Stringent-failure*, was defined as a combination of at least moderate disease activity on the fifth day of steroid therapy (PUCAI>65) *and* the need for second line therapy by discharge and *stringent-response* was considered with no more than mild disease activity (PUCAI<35) on the fifth steroid day *and* discharge without the need for second line therapy. While PUCAI>65 does not include laboratory measures of severity, it has been validated as a measure of severity and predictor of response.[3]

2.3. Serum cytokine profiling

Serum was separated immediately after collection and shipped to the central study laboratory within 24 h, where it was stored in −80 °C for subsequent analysis. A total of 12 relevant cytokines were determined using a human T_H1/T_H2 multiplex cytokine array panel [for TNF-α, interferon (IFN)-γ,