gastroenterology insights

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Editorial

Cytokines and Biologic Therapy in Patients with Inflammatory Bowel Diseases

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Inflammatory bowel diseases (IBD) are chronic inflammatory disorders, including Crohns' disease (CD) and ulcerative colitis (UC), both characterized by a clinical relapsing course and an immune-mediated pathogenesis [1–3]. Together with genetics, environmental factors, and intestinal barrier integrity [4], cytokines have been identified as key players in the pathological process responsible for the onset and progression of IBD [5,6].

Cytokines are a wide group of small, secreted proteins ranging from 5 to 20 kDa that are actively released by different cell types and able to induce specific effects on target cells. Cytokines can be characterized by pleiotropic activity (i.e., the ability of a cytokine to exert different cell responses) and redundancy (i.e., the ability of more cytokines to induce similar effects), which can synergize or antagonize each other [7]. Moreover, these proteins can induce cascade effects, stimulating the production of other cytokines [7]. Based on their binding to different receptors, cytokines can be broadly grouped into 6 families: interleukin (IL)-1 family (such as IL-1α, IL-1β, IL-18, and IL-33), class 1 cytokines, also known as hematopoietins (such as IL-2, IL-4, IL-6, IL-12, and IL-23), class 2 cytokines, also known as interferons (IFN) (such as IFN-α, IFN-β, IFN-γ, IL-10, and IL-22), tumor necrosis factor (TNF) family (such as TNF-α, TNF-β, and Fas), IL-17 family (such as IL-17A, IL-17B, IL-17C, IL-17D, and IL-17F), and chemokines (such as IL-8 and chemokines C–C motif ligand) [8].

Disruption of the cytokine network responsible for the maintenance of the homeostasis between epithelial cells of the intestinal barrier and cells of the innate and adaptative immune system, represents the early event that leads to the initiation and establishment of chronic inflammation in IBD [9]. Among pro-inflammatory cytokines, TNF-α is a pleiotropic cytokine produced by different immune and stromal cells that plays a key role in the pathogenesis of IBD; this cytokine induces angiogenesis and hypervascularization, elicits a cascade effect on macrophages leading to the synthesis of additional pro-inflammatory cytokines (i.e., IL-1, IL-6, and TNF), and promotes tissue damage and loss of intestinal barrier integrity [10]. The IL-12/23 pathway is involved in IBD pathogenesis through promoting a pathological Th1 and Th17 response [11], leading to the synthesis of additional pro-inflammatory cytokines that contribute both to the pro-inflammatory milieu and to neutrophil recruitment [11]. IL-6 is another pleiotropic pro-inflammatory cytokine, mainly produced by macrophages and dendritic cells that is indispensable for Th17 differentiation from naïve CD4+ T cells [5,12]; the synergic action with IL-1β induces T-cells resistant to apoptosis and promotes neutrophil recruitment [5]. Among anti-inflammatory cytokines, IL-10 is produced by almost all leukocytes and plays a crucial role in the maintenance of intestinal homeostasis, mainly counteracting IL-6 and TNF [13].

Given the relevance of cytokines in the pathogenesis of IBD, several therapeutic approaches have been developed in order to modulate cytokine signaling, including direct inhibition of cytokines or their receptors. In this regard, from 1990 to the present, various formulations of monoclonal antibodies directed towards pro-inflammatory cytokines have

Citation: Caviglia, G.P.; Ribaldone, D.G.; Nicolosi, A.; Pellicano, R. Cytokines and Biologic Therapy in Patients with Inflammatory Bowel Diseases. *Gastroenterol. Insights* **2021**, *12*, 443–445. https://doi.org/10.3390/gastroent12040042

Received: 28 November 2021
Accepted: 30 November 2021
Published: 1 December 2021

been progressively developed, with infliximab (IFX) (anti-TNF-α) being the first chimeric monoclonal antibody approved for IBD therapy (1998 in USA and 1999 in Europe) [1]. Subsequently, several novel and less immunogenic biologic drugs based on fully humanized monoclonal antibodies were developed and introduced in the therapy of IBD, including adalimumab (ADA) (anti-TNF-α), golimumab (anti-TNF-α), certolizumab pegol (anti-TNF-α), and ustekinumab (anti-IL12/23). Though anti-TNF drugs showed high efficacy for the treatment of IBD patients, more than 40% of moderate-to-severe IBD patients do not respond to anti-TNF-α, while 20% lose the initial response within a year [14]. Likely, the blockade of a single cytokine may lead to the establishment of compensatory pathways, ultimately leading to loss of response to targeted therapy.

In recent decades, serum cytokines have been investigated in patients with IBD as potential markers for the prediction of responses to biologic drugs. In patients with CD under maintenance therapy with IFX, baseline IL-6, IL-12, IL-23, and IL-17A circulating levels were significantly different between sustained and non-sustained responders [15]. In patients with UC, a panel of 17 serum cytokines was investigated for the prediction of the therapeutic efficacy of IFX. Remarkably, IL-6 values at 8 weeks of IFX therapy were significantly different between responders and non-responders to 26 weeks of treatment; IL-6, as a possible biomarker of response, showed good diagnostic accuracy with an area under the curve (AUC) value of 0.802 (cut-off = 0.71 pg/mL, sensitivity (Se) = 0.92 and specificity (Sp) = 0.71) [16]. More recently, Bertani and colleagues investigated a panel of cytokines including IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12, IL-17A, IL-23, and TNF-α for the prediction of clinical and endoscopic response in patients with UC treated with vedolizumab (VDZ) [17]. Overall, 12 patients (41.4%) achieved mucosal healing at the end of treatment; the outcome was associated with higher IL-6 and IL-8 values at baseline and with a significant decrease in IL-6 and IL-8 levels over the first 6 weeks [17]. The authors developed a nomogram based on baseline IL-6 and IL-8 values and their decline over the first 6 weeks of VDZ showed excellent diagnostic accuracy (AUC = 0.950, Se = 0.82 and Sp = 0.90) [17]. Similarly, they investigated the role of a panel of serum cytokines (IL-1β, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, IL-23, IL-33, IFN-γ, and TNF-α) at baseline and at 10 weeks of treatment as a possible predictor of clinical response to biologic therapy in patients with IBD (43 CD and 17 UC). In a multivariate analysis corrected for disease (CD or UC), type of biologic therapy, and disease activity, the reduction in serum IL-6 values from baseline to week 10 of treatment was the only predictor of clinical response at 12 months of therapy (odds ratio = 4.75, $p = 0.022$) [18].

Given the central role of cytokines in the pathogenesis of IBD (both those with intestinal and extra-intestinal localization [19]) and their increasing relevance as therapeutic targets, the number of studies evaluating the potential clinical role of circulating cytokines is steadily growing [20]. To date, promising results have been achieved, especially for circulating IL-6 during anti-TNF-α therapy. However, further multicenter prospective studies on large cohorts of patients are warranted to prove the clinical value of serum cytokines as reliable biomarkers for the management of patients with IBD undergoing biologic therapy.

Author Contributions: Conceptualization, G.P.C. and R.P.; investigation, G.P.C., A.N. and R.P.; resources, G.P.C., D.G.R. and R.P.; data curation, G.P.C. and A.N.; writing—original draft preparation, G.P.C. and A.N.; writing—review and editing, R.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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