Role of fecal B-cell activating factor (BAFF) as a new non-invasive marker in evaluation of Ulcerative colitis patients

THESIS

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List of Contents

List of Tables

List of Tables cont...

List of Figures

ABSTRACT

Background: Ulcerative colitis is a chronic inflammatory disease of the colon, that is characterised by attacks of remission and exacerbations, The diagnosis is suspected clinically and confirmed through endoscopic biopsy, it needs to be followed up and assessed by non-invasive biomarkers, one of these biomarkers is fecal calprotectin. Recently B cell-activating factor (BAFF), a new biomarker, has been proposed to be a regulator of B cell and T cell immune responses and be associated with inflammatory processes in autoimmunity and B cell malignancies.

Aim: To investigate the role of faecal BAFF in monitoring activity of Ulcerative Colitis.

Patients and methods: 50 Egyptian patients with ulcerative colitis were divided into 2 groups: group 1 including 40 patients with active UC and group 2 including 10 patients with inactive UC, disease activity was measured according to the Mayo activity scoring index, fecal BAFF and fecal Calprotectin were measured for all subjectcs using ELISA.

Results: Fecal BAFF was significantly increased in patients with active UC (group 1) in comparison with inactive UC patients (group 2) with mean value of 2.69 ± 0.48, 1.63 ± 0.25, respectively, p value < 0.001. And that the cut-off value of 120 mg/l indicating the presence of active disease, with a sensitivity of 92% and a specificity of 100%. In comparison with fecal Calprotectin, fecal BAFF is more sensitive and specific for monitoring activity of UC patients.

Conclusion: Correlations of faecal BAFF to Mayo activity scoring index were both higher than that of faecal calprotectin, implying that faecal BAFF could be a good indicator for overall evaluation of mucosal inflammation combining severity and extent. So, faecal BAFF has a better performance as compared with faecal calprotectin in evaluation of intestinal inflammation in UC. Faecal BAFF is a simple and non-invasive marker that can be helpful for differentiating active UC from inactive disease and a good guide for mucosal inflammation.

Keywords: Ulcerative colitis, Fecal BAFF, Fecal Calprotectin, Inflammatory Bowel Disease.

INTRODUCTION

Ulcerative colitis (UC) is a chronic, idiopathic, inflammatory bowel disease that causes inflammation and ulcers in the colonic mucosa. Assessment of intestinal inflammation in UC is crucial and still remains a difficult challenge for the clinician. Although endoscopic modalities with biopsy sampling seem to be the most reliable method for estimating disease severity, they are invasive and costly. Apart from endoscopic interventions, disease severity can be assessed using both laboratory studies and non-invasive imaging tests ***(Cakal et al., 2009)***.

C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBCs), acid glycoprotein, platelet count and albumin are in common use but have only modest accuracy in reflecting UC disease activity. Therefore, adjunctive use of additional serum markers that will be more sensitive and specific for determination of disease activity and achieving diagnostic accuracy is strongly needed in daily clinical practice ***(Yüksel et al., 2009)***.

B cell-activating factor, a member of the tumor necrosis factor (TNF) superfamily predominantly produced by myeloid cells (monocytes, macrophages, dendritic cells) and neutrophils, is critical for the maintenance of normal B-cell development and homeostasis ***(Krumbholz M. et al., 2013).***

Dysregulated expression and/or function of B-cell activating factor (BAFF) has been demonstrated to be associated with several autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (SS) and B cell malignancies ***(Lester et al., 2009)***.

AIM OF THE WORK

The aim of this study is to investigate the role of fecal B-cell activating factor (BAFF) in monitoring activity and severity of Ulcerative Colitis.

ULCERATIVE COLITIS

I. Definition:

Ulcerative colitis (UC) is a chronic relapsing disease characterized by diffuse mucosal inflammation limited to the colon. It involves the rectum in about 95 % of cases and may extend proximally in a symmetrical, circumferential, and uninterrupted pattern to involve parts or all of the large intestine. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus ***(Cakal et al., 2009).***

II. Epidemiology:

Worldwide, UC is more common than Crohn's disease. Both diseases are more common in the industrialized world, particularly North America and Western Europe, although the incidence is increasing in Asia. The overall incidence is reported as 1.2 to 20.3 cases per 100,000 persons per year, with a prevalence of 7.6 to 245 cases per 100,000 per year ***(Danese and Fiocchi, 2011).***

III. Etiology:

The exact pathogenesis of UC is unknown, although there are a number of genetic and environmental factors that have been found to increase the risk of the disease. A current hypothesis suggests that primary dysregulation of the mucosal immune system leads to an excessive immunologic response to normal micro flora ***(Strober et al., 2007).*** It can be considered as an inappropriate inflammatory response to the gut contents in genetically predisposed individuals ***(Abraham and Cho, 2009).***

- ***Environmental***

Cigarette smoking has a protective effect against UC, and cessation of cigarette smoking has been associated with an increased risk of developing the disease ***(Ng SC et al., 2013).*** However, given the complications associated with cigarette smoking, patient should be counseled to stop smoking. The role of diet has been evaluated in numerous studies, but no specific diet has been consistently linked to an increased risk of UC ***(Hart et al., 2008).***

Bacterial infection has been proposed as a possible cause, for example, the presence of Shigella or Shigella-like toxin and Yersinia has been investigated as a possible cause of UC, whereas Clostridium difficle toxin has been associated with disease exacerbation. A similar role has

been suggested for Salmonella infection, perhaps associated with a diminished protective activity of the mucus **(*Martinez et al., 2014).***

Patients who used nonsteroidal anti-inflammatory drugs for at least 15 days were at an increased risk of developing IBD especially those taking higher doses for a longer time were at the highest risk ***(Ananthakrishnan et al., 2012)***. Antibiotic exposure, particularly to tetracyclines, is also associated with a higher risk of UC. Other risk factors may include hormone replacement therapy and oral contraceptives ***(Khalili et al., 2012).***

- ***Genetic***

Although family history portends an increased risk, only 10% to 25% of patients with IBD have a first-degree relative with the disease. Ulcerative colitis is more common in patients of Jewish origin compared with non-Jews and is less frequently seen in African Americans or Hispanics ***(Ng et al., 2013)***. Genetic risk factors are still being elucidated. HLA-DqA1 variants appear most strongly associated with UC. Other genetic pathways involve epithelial barrier function, such as CHD1 and LAMB1, and those that encode cytokines and inflammatory markers, such as TNFRSF15, TNFRSF9, IL1R2 and IL7R ***(Ventham et al., 2013).***

IV. Pathology:

Ulcerative colitis (UC) is usually limited to the colon. Typically, inflammation begins at the rectum and continuously involves all or part of the colon. The transition to normal areas may be either abrupt or gradual, and it may occur anywhere from the rectum to the cecum. Some cases only involve the rectum, often called ulcerative proctitis. Less commonly, isolated or discontinuous proximal segments of disease may be identified at presentation, also called patch colitis. Similarly, the appendix may be involved in a discontinuous fashion, sparing all or part of the cecum ***(Heuschen et al., 2001).***

1- Classic gross findings

In classic ulcerative colitis, the mucosal changes characteristic of UC, consisting of loss of the typical vascular pattern, granularity, friability, and ulceration ***(Simpson and Papadakis, 2008).*** These changes typically involve the distal rectum, both endoscopically and histologically and proceed proximally in a symmetric, continuous, and circumferential pattern to involve all or part of the colon. The ulcers are typically broad-based and may be linear or geographic; blood, pus, or mucus may overlie the mucosa ***(Robert et al., 2004)***.

An effective biopsy strategy is critical for correct diagnosis of ulcerative colitis (UC), with providing appropriate clinical details. Without clinical information, the pathologist may misinterpret biopsy or resection findings, particularly in patients who have received previous medical or surgical treatment. For instance, steroid enemas may eliminate the distal colonic and rectal inflammation so that these areas may appear normal in the specimen ***(Yantiss and Odze, 2009).*** Such patients may appear to have right-side disease that, in association with backwash ileitis, may lead to the incorrect diagnosis of Crohn disease. Oral treatment with anti-inflammatory drugs may also quiet the inflammation and give rise to areas where the colitis heals, altering the distribution pattern and creating discontinuous areas of involvement that mimic Crohn's disease. Pediatric patients may also show no evidence of rectal involvement at their initial presentation with ulcerative colitis ***(Roberts et al., 2007).***

2- Histologic changes

- ***Early stage disease***

Not all the microscopic features found in UC are observed in early stage disease; only about 20% of patients show crypt distortion within 2 weeks of the first symptoms of colitis. The distinction from infectious colitis [acute self-limiting colitis], which is characterized by preserved crypt

architecture and acute inflammation, is therefore a major concern ***(Swan et al., 2002).***

Basal plasmacytosis is the earliest diagnostic feature with the highest predictive value for the diagnosis of ulcerative colitis. Preserved crypt architecture and the absence of a transmucosal inflammatory cell infiltrate do not rule out ulcerative colitis at an early stage. Repeat biopsies after an interval may help to solve differential diagnostic problems and establish a definitive diagnosis by showing additional features ***(Swan et al., 2002).***

Focal or diffuse basal plasmacytosis has been recognized as the earliest feature with the highest predictive value for UC diagnosis. It can be identified in 38% of patients within 2 weeks after symptoms presentation. During this period, the distribution pattern of basal plasmacytosis is focal, but may eventually change into a diffuse pattern throughout the disease course. Widespread mucosal or crypt architectural distortion, mucosal atrophy, and an irregular or villous mucosal surface appear later during the evolution of disease [at least 4 weeks after presentation] ***(Roberts et al., 2007).***

- ***Established disease***

The microscopic diagnosis of ulcerative colitis is based upon the combination of widespread crypt architectural distortion and mucosal atrophy, and a diffuse transmucosal inflammatory infiltrate with basal