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ORIGINAL ARTICLE

Clinical and endoscopic features of responders and non-responders to adsorptive leucocytapheresis: A report based on 120 patients with active ulcerative colitis

Caractéristiques cliniques et endoscopiques des sujets répondeurs et non répondeurs à la leucophérèse : un rapport basé sur 120 patients ayant une colite ulcéreuse

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Abstract
Background and Objective. — Elevated/activated myeloid leucocytes, like the CD14(+)CD16(+) monocytes are sources of TNF-α, and therefore, selective depletion of these cells by granulocyte/monocyte (GM) adsorption (GMA) should promote remission or enhance drug efficacy. However, studies in ulcerative colitis (UC) reported contrasting efficacy, from an 85% to statistically insignificant level. We investigated patients' demography in responders and non-responders.
Methods. — In 120 UC patients, 61 steroid naive and 59 steroid dependent, we looked for entry clinical or endoscopic features to identify responders (or non-responders) to GMA. Patients received up to an 11 Adacolumn GMA sessions over 12 weeks. Patients were clinically and endoscopically evaluated, allowing each patient to serve as her/his own control. Immunohistochemistry on colonic biopsies was to reveal the impact of GMA on leucocyte infiltration of the mucosa.

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Results. — Entry average clinical activity index (CAI) was 12.6, 10—16. An 80 of 120 patients responded (CAI $\leq$ 4); 45 steroid naïve (73.8%) and 35 steroid dependent (59.3%). Over 900 biopsies were processed. Infiltrating leucocytes were overwhelmingly polymorphonuclear and macrophages around and within crypt abscesses. There was a marked reduction of infiltrating leucocytes in responders. Most non-responders had extensive colonic lesions with virtually no mucosal tissue left at the lesions.
Conclusions. — Steroid naïve patients with short duration of UC were the best responders, while patients with deep colonic lesions and extensive loss of the mucosal tissue were non-responders.

Introduction

Ulcerative colitis (UC) together with Crohn's disease (CD) are the major phenotypes of chronic inflammatory bowel disease (IBD) that has a relapsing-remitting feature. Relapses are manifested as increased inflammatory activity and symptoms. The latter include abdominal discomfort, diarrhoea, fever, and weight loss [1,2]. During a relapse, patients with IBD are treated with drugs like corticosteroids, 5-aminosalicylates (5-ASA), azathioprine, 6-mercatopurines, methotrexate, cyclosporine, biologics, notably infliximab (IFX), and antibiotics (in some patients), with surgery being a common option if drug therapy fails and severe IBD continues [1—5].

However, recently, the efficacy of IFX has validated the role of inflammatory cytokines like tumour necrosis factor (TNF)-α in the immunopathogensis of IBD. Further, patients with IBD often present with elevated or activated leucocytes of myeloid lineage (granulocytes, monocytes) and during active disease, vast numbers of these cells are seen in the colonic mucosa in patients with UC [2,6,7]. Myeloid leucocytes, like the CD14(+)CD16(+) monocytes are major sources of TNF-α [8—10], and it could be valid to say that selective depletion of myeloid leucocytes by granulocyte and monocyte (GM) adsorption (GMA) should alleviate inflammation and promote remission or at least enhance the efficacy of pharmacologics. However, clinical studies in patients with UC have reported unmatched efficacy outcomes, ranging from an 85% [11] to a statistically insignificant level [12], indicating that certain subpopulations of patients benefit from GMA while others not so; could this reflect different demographic features (Discussion)?

In light of the afore reviewed background, the Adacolumn medical device has been developed for selective depletion of excess and activated leucocytes [13], which are suspected to promote IBD [14—16], and in the past few years, a large number of authors have reported on the clinical efficacy of GMA [17—28]. Further, in spite of the very poor clinical trial outcome in one study [12], treatment of IBD by GMA has been expanding in Europe and in Japan, unimaginable if, in fact, GMA therapy was not associated with clinical efficacy and in our view being without steroid sparing effect [17]. Our view is that GMA will remain as a non-pharmacologic strategy to treat IBD, very much favoured by patients for its safety profile. The major focus of this investigation was to identify patient demographic factors, which could label a patient a responder, or otherwise a non-responder to GMA. We found patients with the first UC episode and short duration of disease being the best responders, while patients with deep-colonic lesions and extensive loss of the mucosal tissue as unlikely responders.

Methods

Objectives

In view of the inherent diversity of demographic factors in patients with UC together with the aforementioned inconsistent clinical efficacy reports, in this investigation, we were interested to find patient background factor(s), which could be markers of clinical response (or lack of response) to the Adacolumn GMA. As the treatment cost with this medical device is very expensive, this work was expected to benefit cost-saving endeavours as well.

Patients' demography at entry

One hundred and twenty consecutive patients, 57 male and 63 female with moderate to severe UC, average clinical activity index (CAI) 12.6, range 10—16 [30] were included (Table 1). Patients' average age was 45.8 years, range 11—84 years. Of the 120 patients, 61 were steroid-naïve, and 59 steroid-dependent as defined by Hanai et al. [18,28]. The extent of UC was total colitis in 68 patients

Table 1 Main baseline demographic features of the 120 patients with active ulcerative colitis (UC) who received Adacolumn granulocyte and monocyte adsorption (GMA) therapy.

Demography	Measurement
Number of patients	120
Mean age (range), years	45.8 (11—84)
Gender (male/female)	57/63
Use of corticosteroid	
Steroid-naïve	61
Steroid-dependent	59
Location of lesion	
Total colitis	68
Left-sided colitis	52
Clinical activity index, average (range) according to Rachmilewitz [30]	12.6 (10—17)