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Contrast-enhanced ultrasonography with SonoVue after infliximab therapy in Crohn's disease

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Abstract. – The introduction of biological treatments like monoclonal anti TNF-α antibodies (infliximab®), is changing the clinical history of Crohn's disease (CD). The effects of these therapies are monitored emplying clinical indexes of active disease, laboratory parameters, endoscopy and histology, and also with imaging techniques.

A new ultrasound contrast agent, SonoVue® (Bracco SpA, Milano, Italy), is opening new perspectives in the study of microvasculature of several organs. Aim of this study is to evaluate by SonoVue enhanced ultrasonography (US) the occurrence of modifications in bowel wall microvasculature of CD patients and to correlate them with parameters of disease activity and to follow up the findings during infliximab therapy.

After performing a basal color-doppler ultrasonography, the study of the affected bowel loop is performed after i.v. injection of SonoVue and the enhancement is evaluated on a qualitative basis.

We report on the preliminary results obtained in twenty patients, eight of which have been treated with three infusions of infliximab (induction cycle) and evaluated at baseline and after the treatment. While at baseline we describe a positive correlation of SonoVue enhancement of the affected bowel loop with CRP, α1-glycoprotein and white blood cell number, after infliximab treatment in 6/8 cases a definite improvement was detected.

Ultrasonographic evaluation of the changes of bowel wall enhancement after i.v. SonoVue during infliximab therapy might represent an useful, not invasive and relatively low cost imaging modality for the clinical monitoring of activity of small bowel Crohn's disease.

Key Words:

Crohn's disease, Infliximab, SonoVue, Ultrasonography.

Introduction

The recent introduction of the so called "biological therapy", and particularly of monoclonal anti TNF-α antibody (infliximab), is changing the clinical history of Crohn's disease.

These therapies, highly efficacious but expensive and not free of adverse effects, produce results that need to be monitored not only with clinical indexes of active disease (e.g. CDAI) or laboratory parameters, endoscopy and histology, but also with imaging techniques.

In particular, the diagnostic evaluation of bowel wall thickening and of strictures in small bowel Crohn's disease is a crucial step both in the early assessment and in the follow up of these patients.

Conventional radiology of the small bowel (small bowel barium enteroclysis or small bowel follow-through) is certainly able to identify strictures, but gives only few and indirect informations about bowel wall thickening and its characteristics.

Bowel wall thickening can be "inflammatory", according to the Vienna classification of Crohn's disease[1] and possibly susceptible of improvement with pharmacological treatment or chronic "fibrotic", susceptible, in case of critical lumen stenosis, only of surgical therapy.

Indeed, CT and MR, also when performed with enteroclysis, can better study bowel thickenings and extraluminal complications, but the proposed parameters defining disease activity (enhancement, bowel wall stratification or target sign, etc.)[2] need to be adequate-

ly validated. These techniques, furthermore, are costly and not suitable for the follow-up of patients during therapy with biological agents.

Bowel wall sonography has been employed both in the diagnostics and follow up of small bowel Crohn's disease[3]. Color-power-Doppler analysis[4], also performed with contrast-enhancement[5] can also be employed to evaluate disease activity as well as the examination of flow parameters in the mesenteric arteries[6,7].

New contrast-enhancement media have been introduced in the ultrasonographic practice, such as SonoVue® (Bracco SpA, Milano, Italy)[8], which is opening new perspectives in the study of microvasculature of several organs. It is based on sulphur-hexafluoride microbubbles (SF6) which dissolve in the blood with an average lifetime of 12 minutes and is eliminated trough breathing.

Bowel wall inflammation induced microvasculature activation and angiogenesis are the basis for the enhanced visualization of inflamed bowel walls evidenced by imaging methods employing intravenous contrast agents. In particular, for what concerns patients treated with infliximab, a rapid mucosal improvement has been documented by endoscopy as well as the disappearence of infiltrating inflammatory cells[9] in the responding patients after few drug infusions. By analogy, a modification in bowel wall microvasculature can be assumed after infliximab therapy, in parallel with what has been described both in the skin and synovium in psoriasis[10].

On these basis we decided to evaluate by Sonovue enhanced ultrasonography the occurrence of modifications in bowel wall microvasculature of Crohn's disease patients, to correlate them with parameters of disease activity and to follow up the findings during infliximab therapy.

Methods

A prospective comparative study is performed on a consecutive series of Crohn's disease patients, with established diagnosis or during the diagnostic work up. Informed consent is obtained from the patients before entering the protocol. Patients undergoing infliximab therapy are studied before treatment, after the third infusion (induction cycle) and, if responders and subjected to maintenance, at 6 and 12 months of treatment.

Ultrasound Examination

Ultrasound examination is performed by a iU22 ultrasound scanner (Philips Medical Systems SpA, Milano, Italy), following a overnight fasting. Patients are examined in supine position, using the 8-4 MHz convex transducer head, with subsequent detailed analysis with linear high frequency heads.

All patients are subjected to a preliminary conventional ultrasound examination, aimed to the study of the bowel wall, to define the echographic findings of Crohn's disease: bowel wall thickness, length of affected tract(s), maintenance or disappearance of the normal bowel wall stratification, bowel wall stiffness, abnormalities of peristaltic movements. Furthermore, the presence of complications is assessed: strictures, fistulas, abscesses, regional lymphadenopathies.

In order to complete the analysis, a Sonovue enhanced sonography is performed. The contrast media is injected i.v. as a bolus of 4.8 ml and the degree of enhancement is recorded, as compared to a unaffected bowel segment. The following parameters are registered: peak time, shoulder width, time extent of the enhancement. In this preliminary study we evaluated only the subjective evaluation of bowel wall ehancement after i.v. Sonovue injection. It was graded as 0 = absent, 1= mild, 2 = intense, 3 = intense and prolonged.

Clinical Study

For each patient the following parameters are recorded at the entrance in the protocol and during the follow up: phenotype according to Vienna classification, CDAI, concomitant therapies, white blood cells number, ESR, CRP, α1 acid glycoprotein, fibrinogen.

Statistical Analysis

Correlations were analysed by Spearman's rank correlation test and group differences by Student's t test for paired samples.

Results

We report the preliminary results obtained in 20 patients affected with at least one small bowel localization of Crohn's disease.

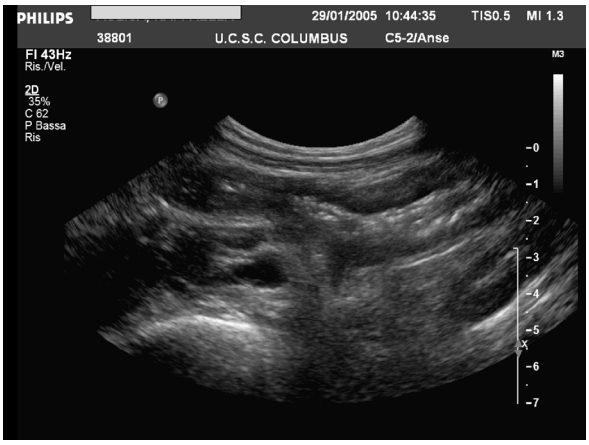

Figure 1. SonoVue enhanced bowel wall ultrasonography: active Crohn's disease before infliximab therapy.

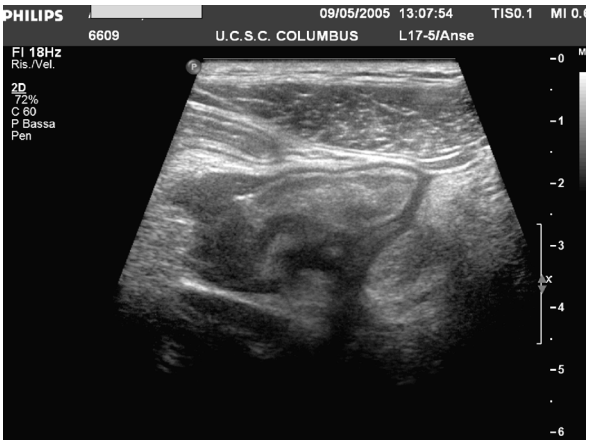

Figure 3. SonoVue enhanced bowel wall ultrasonography: active Crohn's disease with fistula.

They were 15 males, 5 females, mean age 36 ± 13 (range 19-61). Patients' clinical behaviour according to the Vienna classification was as follows B1 (No = 4), B2 (No = 6), B2/B3 (No = 3), B3 (No = 7).

Eight patients were treated by infliximab at conventional dosage (5 mg/kg at week 0, 2, 6 and subsequent maintenance every eight weeks). We compared the grade of ultrasonographic enhancement after i.v. SonoVue (Figures 1, 3) with clinical and laboratory parameters and we detected by Spearman's rank correlation test positive correlations between bowel wall enhancement and CRP, α1-glycoprotein and white blood cell number (Table I).

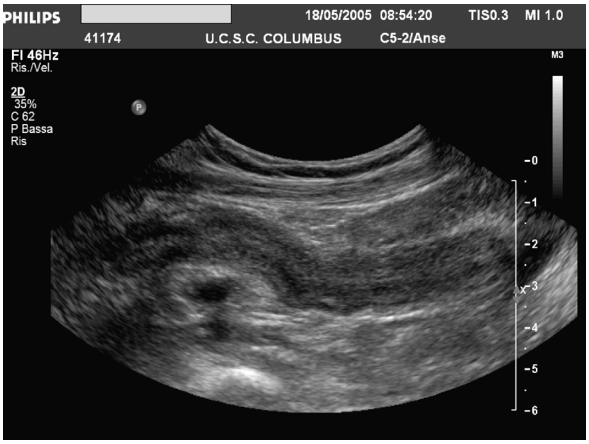

Figure 2. SonoVue enhanced bowel wall ultrasonography: same patient of Figure 1 after 3rd infliximab infusion.

Furthermore, we were able to compare Sonovue enhanced ultrasonography after 3 doses of infliximab with the pre-treatment examination in 8 patients: in 6/8 cases a definite improvement (reduction in the enhancement grade) was detected (Figures 2, 4).

Discussion

A limited experience exists in the literature, concerning the assessment of bowel wall vascularity in Crohn's disease by SonoVue enhanced ultrasonography. Robotti et al[11] have described a series of 52 patients in which the method partly agreed with clinical and laboratory testing and with color power Doppler. Successively, Kratzer et al[12] have described a method for quantitative determination of bowel wall vascularity in Crohn's disease, using SonoVue enhanced wideband harmonic imaging ultrasound and a dedicated software. However, they were unable to correlate their data to clinical ac-

Table I. SonoVue enhanced ultrasonography of bowel wall in Crohn's disease (Spearman's rank correlation test).

	R	p
Enhancement vs CRP	0.44	0.05
Enhancement vs α1-glycoprotein	0.60	0.006
Enhancement vs white blood cell number	0.52	0.017

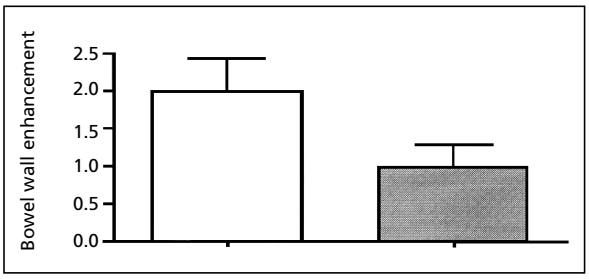

Figure 4. Baseline and post infliximab bowel wall enhancement after i.v. SonoVue ($p < 0.01$ by Student's t test for paired samples).

tivity indexes in their group of 21 patients, selected for the presence of bowel wall thickness of at least 5 mm.

Our preliminary results on baseline patients and after infliximab treatment are encouraging and indicate the need for further quantitative measurements of SonoVue ultrasonographic enhancement of bowel wall: this technique could be a useful, not expensive and not invasive tool in the monitoring of response to treatment with biological agents.

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