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Severe endoscopic lesions are not associated with more infliximab fecal loss in acute severe ulcerative colitis

ABSTRACT

Background: It has been observed that early infliximab (IFX) fecal excretion in patients with acute severe ulcerative colitis (ASUC) was associated with low treatment response.
Aim: The objective was to assess if severe endoscopic lesions (SEL) were associated with IFX loss in the stool as well as low IFX concentrations in plasma at day 1 and 2 in a cohort of patients admitted for ASUC.
Methods: Consecutive patients admitted for a steroid-refractory ASUC requiring IFX and who underwent flexible sigmoidoscopy before starting the drug were included in a case-control, prospective, two-center study. Cases were patients with SEL and controls those without SEL. Plasmatic and fecal IFX concentrations were measured at day 1 and 2.
Results: Among the 15 patients analyzed (10 men; median age: 49 years), 6 were cases harboring SEL at baseline. IFX was detected in the stool in 2/6 (33%) of cases and 4/9 (44%) of controls ($p = 1$) and no difference was observed between the two groups regarding plasmatic concentrations at day 1 or 2 ($p = 1$).
Conclusion: In ASUC, SEL were not associated with more loss of IFX in the stool or lower plasmatic levels. Early IFX pharmacokinetics in this setting does not seem related to endoscopic severity.

1. Introduction

Infliximab (IFX) is a chimeric anti-TNF with proven efficacy in both induction and maintenance of remission in ulcerative colitis (UC), as well as in patients with acute severe UC (ASUC) after intravenous prednisolone failure [1].

However, among UC patients treated with IFX, a primary failure is observed in 20–30% of them, and after 5 years of treatment, a disease relapse is seen in almost 60% of patients and in 20% a colectomy is needed [2]. Several mechanisms have been proposed to explain the primary non-response to IFX in UC. This could be related to inflammation driven by a TNF-alpha independent pathogenic pathway [3], an increased drug clearance resulting in inadequate exposure to the inflammatory burden [4], or an early fecal excretion of IFX as suggested in a cohort of 30 patients with severe colitis [5]. Interestingly, this later observational study did not demonstrate a relationship between IFX plasmatic concentrations and fecal loss of the drug.

Patients with ASUC may have severe endoscopic lesions (SEL) such as deep ulcerations and mucosal detachment. When present, these endoscopic characteristics are found in 89% of patients in the rectum or the sigmoid colon [6]. According to several retrospective studies [7], SEL can also be a predictive factor of colectomy. Nonetheless, the relationship between SEL and fecal excretion of IFX in ASUC remains unclear. To address this question, the aim of the present study was to search for an association between SEL and IFX levels in blood and stool samples in patients admitted for ASUC.

2. Patients and methods

We conducted a prospective, observational, two-center (Bordeaux and Saint-Etienne hospitals, France) case-control study. Consecutive patients admitted for ASUC (defined by the Truelove and Witts criteria [8]) were recruited between February 2015 and July 2016, after having undergone a flexible sigmoidoscopy, and before starting IFX consequently to steroid failure. IFX was started by a single 5 mg/kg infusion. After this initial infusion, patients were scheduled to receive a classical induction regimen which included three IFX infusions of 5 mg/kg at day 0, 14 and 42 followed by maintenance infusions. Treatment optimization was possible according to clinical need. All patients provided written informed consent. The study was approved by the French ethic committee (CNIL) on December 9, 2014. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki.

Eligible patients were at least 18 years old and had a diagnosis of UC based on the usual criteria [8]. Exclusion criteria were the following: pregnant or breastfeeding women, UC limited to the rectum (less than 15 cm above the anal verge), fulminant UC with an indication for immediate colectomy, usual contraindications to anti-TNF agents, prior anti-TNF exposure, a history of complete or partial colectomy. Patients receiving thiopurines at baseline could continue this treatment. Inclusion date (day 0) corresponded to the day of administration of the first IFX infusion.

Before inclusion, UC endoscopic activity was assessed by flexible sigmoidoscopy using endoscopic Mayo-score and UCEIS. Identification of SEL as defined by Carbonnel et al. [6] was performed during the same examination. SEL corresponded to deep ulcerations eroding the muscle layer, deep ulcerations not eroding the muscle layer

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Table 1
Patients' characteristics at baseline.

	Patients with SEL N = 6	Patients without SEL N = 9
Median Lichtiger score (range)	12.5 (7–14)	9 (2–18)
Median partial Mayo score (range)	8.5 (6–9)	7 (1–9)
Median endoscopic Mayo subscore (range)	3 (3–3)	2,9 (2–3)
Median UCEIS (range)	8 (7–8)	6 (5–8)
Median CRP value, mg/mL (range)	40.8 (13.9–90.7)	32.7 (1.6–193)
Median hemoglobin value, g/dL (range)	10.8 (9–13.5)	12.3 (10.3–15.2)
Median albumin value, g/L (range)	24.8 (19.6–27.6)	37.6 (24–42.8)

SEL: severe endoscopic lesions; CRP: C-reactive protein.
Absence of difference between the 2 groups.

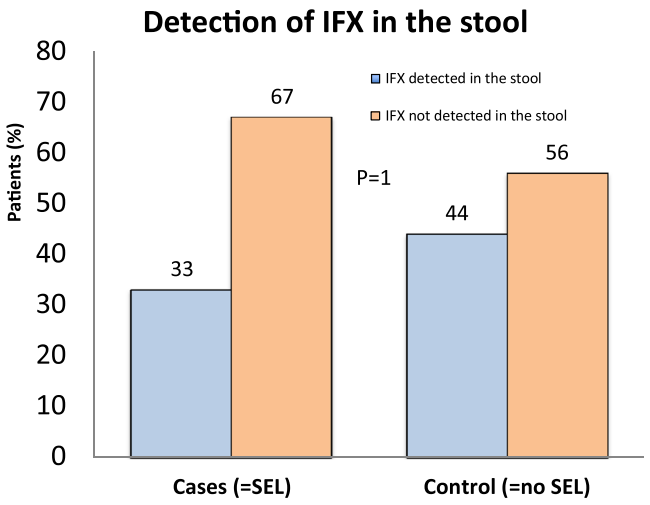

Fig. 1. Proportion of patients admitted for acute severe ulcerative colitis with or without severe endoscopic lesions having detectable infliximab in the stools at day 1 or 2.
IFX = infliximab; SEL = severe endoscopic lesions.

but involving more than one third of the mucosal area, and mucosal detachment on the edge of ulcerations. Cases were patients with SEL and the control group was composed of those without SEL.

IFX concentrations were measured in the blood and stool at inclusion and at day 1 and 2. Blood and fecal samples for IFX dosages were collected and frozen before a centralized analysis in the immunology laboratory of the Saint Etienne hospital. Plasmatic IFX levels were assessed using the Lisa-Tracker Premium Infliximab ELISA kit (Theradiag, France). Fecal sample were analyzed after protein extraction using CALEX tubes and Quantum blue extraction buffer (Buhlmann, Switzerland).

The primary objective of the study was to compare proportion of patients with detectable IFX in the stool at day 1 or 2 and the median IFX plasmatic concentrations at day 1 and 2 between cases and controls. Secondary objectives were to look for an association between (i) fecal levels of IFX and clinical response at day 7 (defined by a decrease in Mayo score ≥30% and ≥3 points compared to day 0 with a rectal bleeding sub score of 0 or 1), (ii) serum IFX levels and clinical response at day 7, (iii) fecal IFX levels and the colectomy rate at day 30 and 98.

Clinical, biological and endoscopic scores were expressed in medians and ranges. Continuous variables were compared with the Mann–Whitney–Wilcoxon. Categorical variables were compared with Fisher's exact test.

3. Results

Sixteen consecutive anti-TNF naive patients admitted for an ASUC (10 men, median age: 49 years) were recruited during the study period. At baseline, 2 patients were treated with azathioprine, both for 4 months. After exclusion of one patient with missing pharmacological data, data of 15 patients were analyzed: 6 with SEL at baseline (5 pancolitis; 1 left-side colitis) and 9 (6 pancolitis; 3 left-side colitis) without SEL. Their main characteristics are presented in Table 1.

At inclusion, no patients had detectable IFX in the plasma. At day 1 or 2, IFX was detectable in the stool in 2/6 (33%) cases and 4/9 (44%) controls (p = 1), Fig. 1. Median IFX stool concentrations in cases at day 1 and 2 were 0 μg/mL (range: 0–1) and 0 μg/mL (0–2.6); they were 0.1 μg/mL (0–3.5) and 0 μg/mL (0–2) in controls, respectively. No significant difference was observed between the two groups regarding these levels at day 1 (p = 1) or 2 (p = 1). All IFX plasmatic concentrations at day 1 and 2 except one were greater than the upper measurement limit (>16 μg/mL). Blood and stool concentrations for each patient are provided in Fig. 2. No correlation was found between blood and fecal IFX concentrations.

At day 7, 2/6 (33%) cases and 8/9 (89%) controls had responded to IFX (p = 0.08). This was observed in 4/6 (67%) patients with detectable IFX in the stool and 6/9 (67%) in patients with non-detectable levels of IFX in fecal samples (p = 1). No association was found between serum IFX levels and treatment response.

At day 98, 3/6 (50%) of cases – including one with detectable IFX in the stool at day 1 and 2 – and 1/9 (11%) of controls underwent colectomy (p = 0.6). Surgery was performed before day 30 in all operated patients.

4. Discussion

In a cohort of patients admitted for ASUC treated with IFX, pre-existing SEL was not associated with more drug loss in the stool or lower plasmatic concentrations during the two first days after administration than in patients without SEL. Therefore, such an observation does not support the use of increased doses of IFX in ASUC patients with deep ulcerations or mucosal detachment. Even though we observed a numerically higher percentage of responders in the group without SEL, this did not reach significance. This difference is probably simply due to the association of SEL to a more severe disease, but not to the SEL themselves.

Previous studies identified lower response to IFX in patients with severe UC as compared to those with a mild to moderate form of the disease [9]. This could be related to a rapid drug clearance as supposed by Ungar et al. [10] who have observed that IFX plasmatic concentrations at day 14 were lower in patients with ASUC as compared to others. Inflammatory burden and drug leakage in the stool are suspected to be the two main non-immune explanations for these findings [5,11]. Based on early pharmacokinetic measurements at day 1 and 2, we could not confirm the relationship between UC endoscopic severity and fecal IFX excretion. Our results highlight the complexity of the mechanisms involved in the pharmacokinetics of IFX in ASUC. The assumption that only a high inflammatory burden [9] or an increased drug clearance influencing fecal and blood levels of IFX is probably too simple.

Recently, two other explanations have been proposed. Firstly, Yarur et al. [12] suggested that local tissue inflammation characterized by a high amount of TNF may literally act as a sink for anti-TNF agents. Consequently patients with elevated drug concentrations in the blood could have an active form of disease because tissue levels of anti-TNF are insufficient to neutralize local TNF production. This

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