Endoscopic Findings during the Early Induction Phase of Infliximab Therapy may Predict its Efficacy for Refractory Ulcerative Colitis

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Abstract

Background and Aims: Infliximab (IFX) is one of the most potent and effective treatments for steroid- or immunomodulator-refractory ulcerative colitis (UC). We evaluated the early efficacy of IFX, based on endoscopic findings, and also attempted to define endoscopic findings predictive of IFX efficacy.

Methods: Nine patients were treated with IFX induction therapy at weeks 0, 2, and 6. Early efficacy was evaluated, using endoscopic and clinical findings, at week 1 (n=9) and again at weeks 3 (n=3) or 7 (n=4). Efficacy was evaluated using the Mayo, Schroeder, and Rachmilewitz endoscopic (RES) scores.

Results: At week 1, 8 of 9 (89%) patients showed a clinical response, and 11% (1 of 9) experienced clinical remission. The mean Mayo score was significantly decreased at week 1 (10 ± 1.2 at baseline vs. 5.6 ± 1.9 at week 1, p<0.001). By week 7, 63% of patients (5 of 8) achieved clinical remission and mucosal healing. We used the RESs at week 1 to evaluate the endoscopic findings and to detect marker(s) predictive of remission. We found that week 1 endoscopic findings of “vascular pattern,” “vulnerability of mucosa,” and “mucosal damage” were predictive. Additionally, C-reactive protein levels at weeks 1 and 6 were positive (>0.3 mg/dl) in the non-remission group, but were negative in the remission group.

Conclusions: Week 1 endoscopic epic tÕWeekaÈnd

Mucosal damage (mucus, fibrin, erosion, ulcer)	None	0
	Slight	2
	Pronounced	4

Table 3: Rachmilewitz Endoscopic Score (19). Rachmilewitz endoscopic score (RES) can range from 0 to 12, with higher scores indicating increased disease severity. Mucosal healing is defined as a total RES of ≤4 points.

Although large, deep ulcerations were detected before the initial IFX treatment, almost all lesions showed improvement at week 1 (Figure 2). The deep, extensive ulcerations and diffuse mucosal edema were markedly improved 1 week after the first IFX infusion (Figure 3). Regenerating epithelium was also broadly detected at week 1 (Figures 3c and 3d).

Case	Age, Sex	Concomitant medications	Disease extension	Schroeder Baseline	Schroeder Week 1	Schroeder Week 3 (or 4)	Schroeder Week 7
1	63y.o., M	5-ASA, AZA, PSL	total	2	1		

Non-Remission group	6	62y.o., M	2	2	2	2		2	4
	7	62y.o., M	2	2	2	1		2	4
	8	54y.o., M	2	2	2	2	2	2	4
		Mean SD	2.0 ± 0	2.0 ± 0	2 ± 0	1.7 ± 0.5	3.3 ± 0.9	2.0 ± 0	4.0
		Mean ± SD (n=8)	2 ± 0	1.8 ± 0.6	2 ± 0	1.4 ±	3.0 ± 1.0	1.5 ± 0.9	3.8 ± 0.7
t-TEST (n=8)			p=0.35		p=0.01		p=0.02		p=0.01

	Case	Age, Sex	Pre	Week 1	Week 6
Remission group	1	63y.o., M	0.31	0.34	0.04
	2	62y.o., F	0.23	0.04	0.04
	3	30y.o., M	0.98	0.04	0.04
	4	32y.o., M	0.29	0.06	1.02
	5	66y.o., F	1.32	0.07	0.22
		Mean ± SD	0.63 ± 0.44	0.1 ± 0.12	0.27 ± 0.38
Non-Remission group	6	62y.o., M	5.02	2.66	5.41
	7	62y.o., M	1.27	0.09	1.35
	8	54y.o., M	5.21	4.18	4.62
		Mean ± SD	3.8 ± 1.8	2.3 ± 1.7	3.8 ± 1.8

Table 7: CRP during clinical course.

Safety

One patient had a persistent fever (>39°C), without any symptoms of infection, for 10 days following the first IFX infusion. Since a delayed infusion reaction to IFX could not be excluded, this patient did not receive a second IFX infusion. The other patients received IFX without any specific adverse effects during the induction and maintenance phases.

Discussion

In this study, patients with moderate-to-severe, active UC that was refractory to initial treatment showed clinical responses or remission, based on their Mayo scores, within 1 week of starting IFX induction therapy. Endoscopic remission rates indicated that IFX efficacy was prompt and required only 1 IFX infusion for most patients. Similar to the ACT 1 and 2 studies (13), our data also showed that clinical remission was evident in 56% of the patients by week 7.

Our previous experience indicated that a single IFX infusion worked extremely well for UC patients; therefore, this study focused on the endoscopic findings during the early phase of treatment. Specifically, the first post-treatment colonoscopy, 1 week after the first IFX infusion, was performed to evaluate the detailed endoscopic changes that had occurred, i.e., the extent of damaged colonic mucosal recovery. The endoscopic findings describing the RESs for "vascular pattern", "mucosal vulnerability", and "mucosal damage" demonstrated significant improvement within the first week. Because a single IFX infusion resulted in these dramatic endoscopic findings, IFX is considered one of the most potent induction therapies for UC, as it is for CD. A single infusion, however, appeared to be insufficient to result in "granulation scattering" improvement, which did not show recovery until after the second or third infusion. Laharie et al. showed that the initial IFX infusion works as well as intravenous cyclosporine therapy within the first week [17]. Our data also showed that IFX efficacy can be evaluated, using colonoscopy, 1 week after the first IFX infusion.

However, 22% of the treated patients, with a week 1 Schroeder endoscopy score of 3, did not exhibit clinical responses or mucosal healing at week 7. Although some of the patients had a clinical response at week 1, they had not achieved clinical remission by week 7. In the remission group, 5 of the 6 patients achieved "vascular pattern" improvements at week 1, but only 1 of 3 patients achieved this finding in the non-remission group. Therefore, we believe that if "vascular pattern", "mucosal vulnerability", and "mucosal damage" improvements can be determined using the RES (with a particular focus on "vascular pattern") at week 1, the patients may have a greater likelihood of achieving clinical remission during the induction phase.

Identifying a predictive marker for patients who experience a significant positive response to IFX remains difficult. Our results suggest that endoscopic findings at week 1 may be reliable predictors of an IFX response in patients with UC. CRP levels are generally recognized as useful predictive markers of CD and UC activity [20–22]. In this study, CRP was positive at weeks 1 and 6 in the non-remission group and negative (CRP

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