Treat to Target: A Proposed New Paradigm for the Management of Crohn's Disease.

Guillaume Bouguen, Barrett G. Levesque, Brian G. Feagan, Arthur Kavanaugh, Laurent Peyrin-Biroulet, Jean-Frederic Colombel, Stephen B. Hanauer, William J. Sandborn

Supplemental material: Alternative targets

Assessment of intestinal inflammation by non-invasive imaging techniques, especially magnetic resonance enterography (MRE), is attractive given the opportunity to reduce discomfort, and complications relative to ileocolonoscopy. Furthermore MRE avoids the radiation exposure associated with computed tomography.(1) The overall sensitivity of MRE for the detection of disease activity is 80% (95% CI 77–83%) and specificity is 89% (95% CI 93–96%).(2) However long-term data regarding the outcomes of patients stratified by disease activity based on MRE assessment are, for the most part, lacking.(3) In a recently published abstract, in which 27 patients were assessed before and after treatment with either corticosteroids or adalimumab, the magnitude of reduction in a MRE activity index closely paralleled improvement in CDEIS scores.(3)

Since both ileocolonoscopy and MRE are costly, their repeated use to monitor patients for the presence of intestinal inflammation is constrained. Considerable attention has been placed on the development of surrogate markers of mucosal disease activity such as fecal biomarkers or CRP. Data showing a relationship between fecal biomarkers (calprotectin or lactoferrin) and clinically meaningful events are sparse necessitating further validation.(4–6) Elevated concentrations of CRP correlate well with both endoscopic and histologic evidence of inflammation. In contrast a poor correlation exists between CRP concentrations and symptoms.(7,8) A prospectivelongitudinalstudy that evaluated 101 patients with CD showed that CRP was reproducible and reliable, CRP concentrations decreased as the disease went into clinical remission.(9) A higher rate of clinical relapse was observed in patients with a persistently elevated CRP. However, up to one third of patients with intestinal inflammation do not have an elevated CRP concentration.(9–11) In several studies assessing biologics such as TNF antagonists or ustekinumab, normalization of CRP concentrations reflected objective evidence of decreased inflammation and increased the likelihood of sustained remission on maintenance therapy or the likelihood of clinical relapse in case of a persistently elevated CRP.(12–14) In the ACCENT 1, 75% of patients with normalization of the CRP (<0.5mg/dL) at week 22 maintained remission over the study period.(15) Thus, changes in CRP concentrations provide useful information in monitoring response to treatment and the risk of further relapse in the two third of CD patients who have a raised CRP concentration in the presence of active disease.(9)

References

1. Peloquin JM, Pardi DS, Sandborn WJ, *et al.* Diagnostic ionizing radiation exposure in a population-based cohort of patients with inflammatory bowel disease. Am. J. Gastroenterol. 2008;103:2015–2022.

2. Panés J, Bouzas R, Chaparro M, *et al.* Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment. Pharmacol. Ther. 2011;34:125–145.

3. Ordás I, Rimola J, Ripolles T, *et al.*Accuracy of MRI to Assess Therapeutic Responses and Mucosal Healing in Crohn's Disease. Gastroenterology 2011;140:S–73.[cited 2013 Mar 1]

4. Gisbert JP, Bermejo F, Pérez-Calle J-L, *et al.* Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm. BowelDis. 2009;15:1190–1198.

5. Sipponen T, Kärkkäinen P, Savilahti E, *et al.*Correlation of faecalcalprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings.Aliment. Pharmacol. Ther. 2008;28:1221–1229.

6. Sipponen T, Savilahti E, Kärkkäinen P, *et al.*Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease.Inflamm. Bowel Dis. 2008;14:1392–1398.

7. Solem CA, Loftus EV Jr, Tremaine WJ, *et al.* Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm. Bowel Dis. 2005;11:707–712.

8. Jones J, Loftus EV Jr, Panaccione R, *et al.* Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. Clin.Gastroenterol.Hepatol. Off. Clin. Pr. J. Am. Gastroenterol. Assoc. 2008;6:1218–1224.

9. Boirivant M, Leoni M, Tariciotti D, *et al.* The clinical significance of serum C reactive protein levels in Crohn's disease. Results of a prospective longitudinal study. J. Clin. Gastroenterol. 1988;10:401–405.

10. Koelewijn CL, Schwartz MP, Samsom M, *et al.* C-reactive protein levels during a relapse of Crohn's disease are associated with the clinical course of the disease. World J. Gastroenterol. WJG 2008;14:85–89.

11. Denis M-A, Reenaers C, Fontaine F, *et al.* Assessment of endoscopic activity index and biological inflammatory markers in clinically active Crohn's disease with normal C-reactive protein serum level. Inflamm. Bowel Dis. 2007;13:1100–1105.

12. Jürgens M, Mahachie John JM, Cleynen I, *et al.* Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. Clin.Gastroenterol.Hepatol. Off. Clin. Pr. J. Am. Gastroenterol. Assoc. 2011;9:421–427.e1.

13. Toedter GP, Blank M, Lang Y, *et al.* Relationship of C-reactive protein with clinical response after therapy with ustekinumab in Crohn's disease. Am. J. Gastroenterol. 2009;104:2768–2773.

14. Vermeire S, Assche G Van, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut 2006;55:426–431.

15. Reinisch W, Wang Y, Oddens BJ, *et al.* C-reactive protein, an indicator for maintained response or remission to infliximab in patients with Crohn's disease: a post-hoc analysis from ACCENT I. Aliment. Pharmacol. Ther. 2012;35:568–576.