spontaneous bowel movements (CSBMs) per week during the last week of therapy. Secondary endpoints included mean number of CSBMs per week, mean increase in CSBMs from baseline, weekly average responder rates over the entire 4 weeks of therapy (using a definition of $\geq$3 CSBMs per week plus an increase in 1 CSBM from baseline), and colonic transit time. Quality-of-life data were also collected using validated instruments. This was a noninferiority trial, designed to test the hypothesis that PEG would not be appreciably worse than prucalopride for the treatment of CIC, using a margin of 20% to define noninferiority. If the lower limit of the 97.5% confidence interval lay completely above this margin, then noninferiority (or equivalence between the 2 treatments) was concluded.

In total, 240 CIC patients were enrolled, with 120 in each of the treatment arms. Compliance with therapy in both arms was >99%. In the intention-to-treat analysis, the proportion of patients with $\geq$3 CSBMs in the last week of therapy was higher among those receiving PEG compared with prucalopride (66.7% vs 56.9%), with a lower limit of the 97.5% confidence interval of –3.1%, confirming noninferiority. In the secondary endpoints, PEG was significantly superior to prucalopride when mean number of CSBMs or mean increase in CSBMs was examined, and also when the weekly average responder rate was considered (58.3% vs 35.3%; $P < .001$). Colonic transit time was similarly, and significantly, reduced from baseline in both groups. Quality of life was comparable between the 2 treatment arms, and total numbers of adverse events were similar, although rates of headache, vomiting, and abdominal pain were numerically higher among those assigned to prucalopride.

Comment. The medical management of CIC is suboptimal. Patients report high levels of dissatisfaction with conventional therapies such as laxatives (Aliment Pharmacol Ther 2007;25:599–608). As a result, novel agents such as prucalopride, lubiprostone, and linaclotide continue to be developed. Because of the lack of a gold standard therapy for CIC, new drugs are often tested against placebo. A meta-analysis of RCTs demonstrated superior efficacy of all these therapies over placebo. (Gut 2011;60:209–218) However, in this meta-analysis osmotic and stimulant laxatives were also superior to placebo for the treatment of CIC, with a number needed to treat of 3. Despite this, evidence-based management guidelines are conflicting in their recommendations for the use of laxatives in CIC (Am J Gastroenterol 2005;100:936–971; Gastroenterology 2013;144:218–238). It should be pointed out that no trials of stool softeners were identified by the authors of this meta-analysis.

The authors of this RCT concluded that PEG was at least as effective as, and better tolerated than, prucalopride. In fact, PEG was noninferior to, and in many of the secondary analyses actually demonstrated significant benefits over, prucalopride. This is perhaps surprising given that, in Europe, prucalopride is generally used for individuals with CIC who have already failed $\geq$1 laxative. As a result, these data have important implications for clinical practice, although in the United States, where prucalopride is not approved by the Food and Drug Administration for the treatment of CIC, this may be of less relevance.

However, there are some limitations of the study. First, patients were recruited from a single center in Eastern Europe. Whether these findings are generalizable to other populations is therefore uncertain. Second, the fact that the study was conducted in a controlled environment, with standardized food and fluid intake, also limits the applicability of the results to routine clinical practice. Third, the primary endpoint was not one endorsed by the Food and Drug Administration, with CSBM response rates during the last week of therapy used to confirm efficacy, rather than using a threshold number of weeks where CSBM criteria were achieved during treatment to define response. However, the secondary endpoint of weekly average responder rates reported by the authors approximated this type of endpoint.

These findings, taken together with those from the aforementioned meta-analysis demonstrating that both osmotic and stimulant laxatives are effective for the treatment of CIC (Gut 2011;60:209–218), call into question the design of future RCTs in CIC. It is probably unethical to continue to test new therapies against placebo, when other, effective treatments for CIC exist. New therapies, which are often expensive, should probably have to demonstrate that they are at least as effective as conventional laxatives before being approved for use in routine clinical practice. With respect to prucalopride, although the results of this trial are important, other head-to-head trials are needed to assess whether the findings hold true in a setting that more closely resembles usual care.

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BACTERIAL TRANSLOCATION INFLUENCES THE RESPONSE TO BIOLOGICAL THERAPY IN CROHN'S DISEASE

Gutiérrez A, Scharl M, Sempere L, et al. **Genetic susceptibility to increased bacterial translocation influences the response to biological therapy in patients with Crohn's disease. Gut 2013 Feb 1 [Epub ahead of print].**

The etiology of Crohn's disease (CD) remains unknown, although it is generally accepted that CD results from a combination of dysfunctional immune responses on a background of susceptible genetics and environmental factors. Until recently, *NOD2* (nucleotide-binding

oligomerization domain-containing protein 2) was the only gene associated with CD susceptibility encoding for an intracellular receptor that recognized muramyl dipeptide (MDP), a component of bacterial cell walls (Nature 2001;411:599–603 and 411:603–607). The subsequent use of genome-wide association studies have substantially increased the number of CD genetic risk loci including *ATG16L1* implicating defective autophagy, a process required for the degradation of cell organelles and intracellular microorganisms, in the etiology of CD (Nat Genet 2007;39:207–211). Since then, mechanistic studies have implicated defective handling of luminal bacteria in the pathogenesis of CD. This is highlighted by studies that have investigated an autophagy-dependent antibacterial pathway in response to MDP requiring *NOD2* and *ATG16L1* interactions. CD-associated mutations in these genes result in impaired MDP autophagy mediated killing of intracellular bacteria in intestinal epithelial cells (Gastroenterology 2010;139:1630–1641). However, despite these successes, translating these findings to impact on CD treatments has proven difficult.

In the current study, the authors' investigate how *NOD2*/*ATG16L1* variants in patients with CD may affect the efficacy of anti-tumor necrosis factor (TNF)-α antibody therapies. This was based on the authors previous observations that patients with CD and variants of *NOD2* respond inappropriately to bacterial genomic fragments (bactDNA) in the blood (Inflamm Bowel Dis 2011;17: 1641–1650). The latter is likely to be a marker of bacterial translocation from the gut to the systemic circulation.

The authors recruited a cohort of patients with an established diagnosis of CD (n = 179) who were followed for 6 months, and a separate cohort of unmatched controls (n = 25). At recruitment blood samples were taken to determine the *NOD2/ATG16L1* genotype and bactDNA distribution in the patients with CD. There was no difference in the distribution of *NOD2* and *ATG16L1* wild-type (wt) and variant (var) genotypes between patients with active (CD activity index >150) and remitting disease (CD activity index <150).

Of the 179 patients with CD, 51 (29%) had bactDNA in their blood samples. BactDNA was absent in the blood of controls. A greater proportion of the CD patients with active disease (44.2%) had bactDNA than those with remitting disease (23.5%; $P = .01$). Bacterial DNA of *Staphylococcus aureus*, *Klebsiella pneumonia*, *Streptococcus pneumonia*, and *Enterococcus faecalis* was identified. Using a multivariate analysis the presence of bactDNA was significantly and independently related to CD activity (odds ratio [OR], 7.4; 95% confidence interval [CI], 1.69–32.60; $P = .008$). BactDNA was also the only independent factor associated with clinical relapse of CD at 6 months (OR, 5.1; 95% CI, 1.7–14.9; $P = .003$). However, although single and double gene variants for *NOD2* and *ATG16L1* were significantly associated with the presence of bactDNA (*varNOD2/wtATG16L1*: OR, 4.8 [95% CI, 1.1–13.3; $P = .03$]; *wtNOD2/varATG16L1*: OR, 2.4 [95% CI, 1.46–4.5; $P = .05$]; *varNOD2/varATG16L1*: OR, 12.7 [95% CI, 4.2–37.8; $P = .001$]), none of these gene variants were directly associated with CD activity ($P = .19$). Together these results suggest that NOD2 and ATG16L variants may influence CD indirectly via their effects on immune response against bacteria.

To determine whether *NOD2*/ATG16L1 genotypes and the presence of bactDNA in the serum of patients with CD affected immune responses, serum TNF-α, interferon-γ, and interleukin-12 were measured. Irrespective of genotype, the presence of bactDNA in patients with CD led to a significant increase in all cytokines measured compared with those without bactDNA ($P < .01$). CD patients with bactDNA and a *varNOD2* genotype, either in isolation or combined with the *varATG16L1* genotype, showed a further, significant increase in serum cytokine levels compared with *wtNOD2* genotype subgroups ($P < .01$). Double variant *NOD2/ATG16L1* genotypes and the presence of bactDNA led to the highest serum cytokine levels. Despite the excess secretion of proinflammatory cytokines, neutrophils from patients with CD and *varNOD2/wtATG16L1* or *varNOD2/varATG16L1* genotypes had significantly decreased phagocytic activity of fluorochrome-labeled *E coli*. Similarly, the bactericidal activities of neutrophils in the same genotypes were significantly reduced. These differences were not a consequence of any ongoing treatments for CD as decreased phagocytic and bactericidal activities were observed in healthy controls with the same genotypes. Together, these data show that CD patients have impaired innate immune responses against bacteria despite increased cytokine responses.

Given the elevated amounts of TNF-α secreted by CD patients with var*NOD2*/wtATG16L1 or *varNOD2/varATG16L1* genotypes in the presence of bactDNA, the authors evaluated the impact of this on anti–TNF-α therapy. Of the 179 patients, 52 were on anti–TNF-α therapy at recruitment. A greater percentage of those with var*NOD2/wtATG16L1*, or *varNOD2/varATG16L1* genotypes were noted to be receiving an intensified schedule of anti–TNF-α, that is, an increased dose/increased frequency. Similarly, a greater percentage of those on anti–TNF-α treatment with bactDNA present were on an intensified anti–TNF-α regime compared with those without bactDNA. However, neither of these findings were significant. Yet in those without antibodies against anti–TNF-α, serum-free anti–TNF-α levels were significantly reduced in those with *varNOD2/wtATG16L1* and *varNOD2/varATG16L1* genotypes when compared with their respective *wtNOD2* subgroup ($P < .01$). This was despite an increased number of these patients having an intensified regimen of anti–TNF-α. The presence of bactDNA further decreased the levels of free-serum anti–TNF-α. The authors speculate that the reduced serum concentration of free anti–TNF-α was owing to an increased rate of the consumption of the free antibody by the increased rate of TNF-α secretion in patients with bactDNA and variant NOD2.

Finally, in vitro assays were used to further assess the lower serum-free anti–TNF-α levels observed in the *varNOD2/wtATG16L1* and *varNOD2/varATG16L1* genotypes. Before