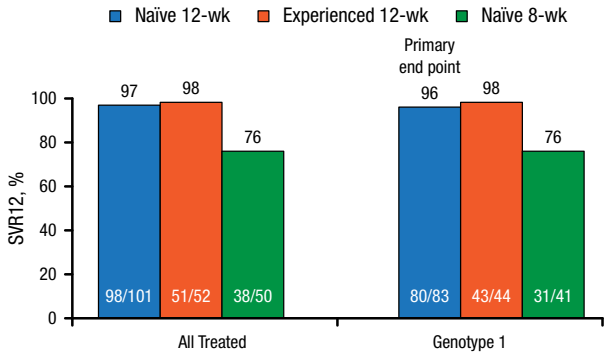
Figure 1. ALLY 2 Results: SVR12 (Intention to Treat) by Treatment Group



SVR12, sustained virologic response for 12 wk.

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for 12 weeks, and 70% (7/10) when treated for 8 weeks. Treatments did not compromise HIV control, as indicated by the unwavering mean CD4 count and continued HIV virologic suppression throughout the treatment period.

The frequency of serious adverse events was low, occurring in 1.0%, 5.8%, and 0.0% of the naïve/12-week, experienced/12-week, and naïve/8-week arms, respectively. The adverse events commonly comprised fatigue, nausea, headache, and diarrhea. One death occurred after stopping study treatment in the 8-week arm as a result of treatment-unrelated cardiac arrest.

ALLY 2 provides evidence of the efficacy and safety of the DCV + SOF combination in patients coinfected with HIV/HCV, whether or not they had been treated before for HCV. The treatment benefit does not come at the expense of compromised treatment of HIV infection.

TURANDOT: Monoclonal Antibody Effective and Safe in Relieving UC Symptoms

Written by Brian Hoyle

The randomized placebo-controlled double-blind TURANDOT trial [NCT01620255] substantiated the efficacy and safety of a monoclonal antibody that blocks white blood cell adhesion to gut mucosa in the treatment of moderate to severe ulcerative colitis (UC).

As explained by Walter Reinisch, MD, McMaster University Health Centre, Hamilton, Ontario, Canada, inflammatory bowel disease features translocation of white blood cells into the gut mucosa. An important part of this translocation involves the binding of the α4β7 integrin on some white blood cells to the mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) receptor on endothelial cells [Feagan BG et al. *N Engl J Med.* 2013; Sandborn WJ et al. *N Engl J Med.* 2013]. Blocking this binding may be beneficial in inflammatory bowel disease. The fully humanized monoclonal antibody PF-00547659 (PF) targets immunoglobulin G2 MAdCAM-1. The antibody does not hamper the immune function of the central nervous system and does not cross-react with vascular cell adhesion protein 1.

In the TURANDOT trial, 357 patients with moderate to severe UC were randomized to subcutaneously delivered placebo or 7.5-, 22.5-, 75-, or 225-mg doses of PF. Doses were given at 0, 4, and 8 weeks in the 12-week trial, with subsequent 24-month follow-up or enrollment in an open-label extension phase. The researchers reported here on the 12-week treatment.

Patients were aged 18 to 65 years, with biopsy-confirmed UC, Mayo endoscopy subscore ≥ 2, active disease beyond the rectum, Mayo score ≥ 6, and failure on or intolerance to ≥ 1 conventional therapy. Exclusion criteria included enteric infection, use of parenteral steroids with a dose of prednisone equivalent > 20 mg, recent biologic therapy, and any history of anti-integrin therapy. The primary efficacy end point was the proportion of patients in clinical remission at week 12, defined as a total Mayo score ≤ 2 points with no individual subscore > 1 point. There were also several secondary efficacy end points, including the proportion of patients with a clinical response at week 12, defined as a decrease in total Mayo score by ≥ 3 points and ≥ 30% decrease in subscore for rectal bleeding of ≥ 1 point or absolute subscore of ≤ 1.

Baseline demographic and clinical characteristics in the 5 arms were comparable. The primary efficacy end point was met, with improved remission in all PF arms compared with placebo at week 12 and with the differences for 7.5, 22.5, and 75 mg of PF being significant when compared with placebo (all $P < .05$; Table 1).

In secondary responses, improvements in clinical response at week 12 for all PF doses (7.5 mg, 38.0%;

Table 1. Primary Efficacy End Point Results: Clinical Remission at Week 12

PF-00547659 Dose, mg	Remission Rate in mITT Population[a], %
0 (placebo)	2.7
7.5	11.3*
22.5	16.7*
75	15.5*
225	5.7

mITT, modified intention to treat.

[a]All subjects randomized and who received at least 1 dose of randomized treatment.

*$P < .05$ vs placebo.

22.5 mg, 54.2%; 75 mg, 45.1%; 225 mg, 50.0%) were significantly improved (all $P<.05$) compared with placebo (28.8%). All doses of PF resulted in rates of mucosal healing (endoscopy subscore ≤ 1 point; 7.5 mg, 15.5%; 22.5 mg, 27.8%; 75 mg, 25.4%; 225 mg, 14.3%) that exceeded the rate in the placebo arm (8.2%), with the improvements for 22.5 and 75 mg of PF being significant (both $P<.05$). These trends in improvement were evident both in treatment-naïve and treatment-experienced patients.

Fecal calprotectin declined in all treatment groups relative to placebo, with the decline being less rapid in the 7.5-mg PF arm. PF doses >7.5 mg suppressed soluble MAdCAM-1 by >90%. Adverse events were comparable in type and prevalence in the 5 study arms.

The TURANDOT trial met its primary and secondary end points, with no safety issues. Increased remission of symptoms was evident in patients with moderate to severe UC who had failed ≥ 1 treatment before trial enrollment, with the 22.5-mg dose giving the best response.

Naldemedine Effective at Relieving Opioid-Induced Constipation

Written by Brian Hoyle

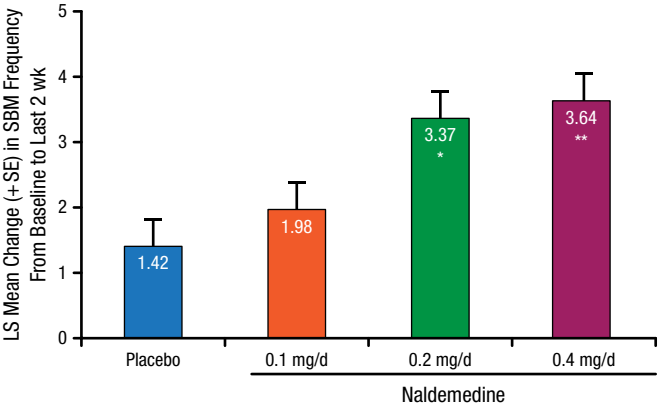
As described by Lynn Webster, MD, PRA Health Sciences, Salt Lake City, Utah, USA, a phase 2b, randomized, double-blind, placebo-controlled study revealed the benefit of naldemedine in easing constipation due to opioids given for relief of chronic noncancer pain.

The use of opioids for relief of noncancer pain has increased substantially over the last 20 years [Chou R et al. *J Pain*. 2009], but opioids can often result in constipation. Laxatives are a common recourse, but evidence for their effectiveness is scant and, in many patients, they do not provide satisfactory relief [Camilleri M et al. *Neurogastroenterol Motil*. 2014].

This trial evaluated naldemedine, a peripherally acting μ-opioid receptor antagonist that has been developed specifically for the relief of opioid-induced constipation. Patients meeting the enrollment criteria (n = 244) were randomized 1:1:1:1 (n = 61 for each group) to placebo or naldemedine 0.1, 0.2, or 0.4 mg/day. The primary efficacy end point was the mean change in the frequency of spontaneous bowel movements (SBMs) from the last 2 weeks of screening to the last 2 weeks of the up-to 28-day treatment period. Safety was also assessed.

Reported results represented patients in the modified intention-to-treat population who were assessed at least once (naldemedine 0.1 mg/d [n = 61], 0.2 mg/d [n = 59], and 0.4 mg/d [n = 57]). Patients in each of the 4 study arms were comparable at baseline in terms of age, sex, body mass index, weekly frequency of SBMs, and daily opioid dose. Naldemedine was rapidly absorbed and displayed a half-life that was compatible with once-daily use.

Figure 1. Primary Efficacy End Point



Modified intention-to-treat population: all randomized patients who received study drug had ≥ 1 postdose primary efficacy assessment completed.

LS, least squares; SBM, spontaneous bowel movement.

*P = .0014 vs placebo; **P = .0003 vs placebo and P = .6657 vs 0.2 mg (analysis of covariance with treatment group as a term and baseline value as a covariate).

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In the primary efficacy end point, naldemedine 0.2 and 0.4 mg/d produced significant differences in SBMs (3.37 and 3.64) compared with placebo (1.42; $P = .0014$ and $P = .0003$, respectively). Improvement was also evident for naldemedine 0.1 mg/d (1.98), but it was not significantly different from the placebo arm (Figure 1).

A similar pattern was apparent for the secondary end point of SBM response rate (39.3%, 52.5%, 71.2%, and 66.7% for placebo, naldemedine 0.1, 0.2, and 0.4 mg/day, respectively; $P = .0005$ and $P = .003$ for naldemedine 0.2 and 0.4 mg/d, respectively). SBM frequency was significantly increased by naldemedine 0.2 and 0.4 mg/d by the first week of treatment and maintained through week 4 ($P < .005$ for both doses). Analyses of other secondary end points, such as relief of abdominal bloating and abdominal discomfort, as well as patient satisfaction, favored naldemedine, especially at 0.2 and 0.4 mg/d.

Treatment-emergent adverse events that developed occurred with similar frequency in the 4 trial arms. The incidence of gastrointestinal adverse events was greater in patients who were randomized to naldemedine (13.1%, 21.3%, 25.0%, and 34.4% in placebo and naldemedine 0.1, 0.2, and 0.4 mg/d, respectively).

Naldemedine treatment did not compromise the effectiveness of opioid pain relief, with no changes evident in pain scores or evidence of opioid withdrawal. The patterns over the 4-week trial were very similar in all 4 trial arms.