Editorial

Swallowing anti-TNFα in Ulcerative Colitis: Potentially More Gain Than Pain

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The introduction of anti-tumour necrosis factor α (TNFα) monoclonal antibodies in the late 1990s led to major advances in the management of outpatients with symptoms and endoscopic evidence of active ulcerative colitis (UC), despite ongoing treatment with conventional therapy. Infliximab, adalimumab and the more recently introduced golimumab are effective for inducing and maintaining clinical and endoscopic remission in both pivotal trials and practice. Although these drugs are generally well tolerated, serious adverse events can occur because they cause systemic immunosuppression. Anti-TNFα-related safety concerns, such as opportunistic infections, autoimmunity, lymphoma/malignancies, demyelinating disease and congestive heart failure, limit their appeal to some patients. Moreover, a significant proportion of patients lose response over time and the development of immunogenicity, associated with the presence of anti-drug antibodies (ADAs), is an important determinant.

In this issue of the Journal of Crohn’s and Colitis, two companion papers report on the safety, pharmacokinetics, immunogenicity, preliminary efficacy and colonic tissue activity of AVX-470 in patients with active UC. AVX-470 is an oral formulation of polyclonal immunoglobulin (Ig) purified from the colostrum of cows immunized with recombinant human TNF. In the study by Harris et al., 36 adult patients with moderate to severe active UC were randomized to receive either daily ascending oral doses (0.2, 1.6 or 3.5 g/d) of AVX-470 or matching placebo for 4 weeks. The primary endpoint of this first-in-human trial was safety; pharmacokinetics and immunogenicity were assessed as secondary, while efficacy and pharmacodynamics were evaluated as exploratory endpoints. AVX-470 was well tolerated, with similar adverse events experienced across groups. In particular, neither adverse events of special interest nor opportunistic infections and allergic reactions were reported. Although baseline bovine Ig was detected in the serum and stool of some patients, indicative of routine dietary intake of dairy products, patients given AVX-470 did not show any significant increase after exposure. Likewise, a dose-dependent increase in bovine Ig with TNF-binding capacity in stool was observed. AVX-470 did not appear capable of inducing human anti-bovine antibodies (HABAs) and no change in HABA background levels was observed.

Polyclonal bovine antibodies are high molecular weight molecules stable to intestinal degradation and therefore suitable for oral delivery. They are poorly absorbed into the systemic circulation and neither this study nor others have revealed systemic absorption or safety concerns, even when administered to immunocompromised subjects. It is notable that this first-in-human study on the safety, pharmacokinetic and immunogenicity preliminary profiles of AVX-470 shows very low systemic absorption, no evidence of induction of immunogenicity and a dose-dependent appearance in stool. This could translate into gut-specific anti-TNFα activity, with a low risk of systemic immunosuppression and a low risk of ADA generation with associated loss of response to treatment. The question, then, is whether applying anti-TNF therapy to the mucosal surface will work.

Exploratory efficacy endpoints showed a higher proportion of patients with clinical response (defined as reduction of at least 3 points on the total Mayo score and an overall decrease of at least 30%, plus a decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 1 or less, at Week 4 relative to baseline) in the pooled AVX-470 groups compared with placebo. Furthermore, a greater proportion of patients receiving the highest dose of AVX-470 (3.5 g/d) reached clinical (14.3%) and endoscopic (14.3%) remission (defined respectively as a total Mayo score ≤2 and no subscore >1) than those on placebo (0%). The study is also one of the first to compare the Mayo Clinic endoscopic subscore and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) in the evaluation of endoscopic activity. Greater improvement in endoscopic activity, as assessed by the UCEIS, was detected in the highest AVX-470 dose group compared with placebo, interestingly with more change observed in the proximal than in the distal colon. Other thoughts arise from the endoscopic findings. It was recently reported that, in patients with active UC, the UCEIS more accurately reflected early endoscopic change after induction with tacrolimus than the Mayo Clinic endoscopic subscore. This needs to be ratified, because there is as yet unpublished evidence that this may not be the case with mesalazine. In the current study this comparison was not performed, probably because the small sample size would have made it difficult to make reliable statistical comparisons. The reported
proximal-to-distal gradient of endoscopic improvement over 4 weeks is an intriguing finding and probably implies that mucosal healing is not a field effect. It has not been previously described and raises the question whether full colonoscopy would better assess disease outcome than flexible sigmoidoscopy, both in therapeutic trials and clinical practice. Apart from centrally read endoscopy, biomarker analysis showed dose-proportional changes in serum C-reactive protein and interleukin-6 (IL6) levels. These preliminary results suggest a trend in favour of clinical efficacy of AVX-470 in the treatment of patients with active UC.

In the accompanying paper by Hartman et al., colon biopsy samples collected from patients participating in the AVX-470 trial were analysed to explore local mechanisms of action of AVX-470. Preclinical studies in murine models of colitis (TNBS [2,4,6-trinitrobenzene sulphonic acid] or DSS [dextran sodium sulphate]) had shown that an oral murine TNF-specific surrogate antibody (AVX-470m) localized and penetrated into intestinal mucosa with a dose-dependent effect and minimal systemic exposure. In particular, treatment reduced local levels of TNF and TNF mRNA, inflammatory cytokines and endothelial activity. The antibody was not detected in the intestine of control mice, leading to the hypothesis that increased mucosal permeability, associated with intestinal inflammation, would enable antibody penetration principally into inflamed mucosal tissue.

Current anti-TNFα agents are parenterally administered and reach the intestinal mucosa after systemic distribution. Although serum and tissue anti-TNF levels show overall correlation, a higher rate of serum-to-tissue anti-TNF mismatch has been reported in patients with active disease, suggesting that high serum drug levels may not always translate into high tissue levels in mucosal areas of ongoing inflammation. In the current study of patients with active UC, baseline and Week 4 colonic biopsy samples were processed to characterize mucosal tissue distribution of bovine Ig and TNF to quantify expression of inflammatory markers across colonic regions and correlate with endoscopic activity. Immunohistochemical staining (IHC) detected bovine Ig in the lamina propria and in submucosal tissue of patients irrespective of endoscopic activity. By contrast, bovine Ig was not identified in normal colonic biopsies from subjects without inflammatory bowel disease (IBD). This finding is consistent with that reported in preclinical studies and suggests deep tissue penetration in patients with IBD, probably because of increased mucosal permeability even if patients have endoscopically normal mucosa. However, no histological evaluation was reported and further study, correlating bovine Ig intestinal tissue localization with both endoscopic and histological indices, is necessary to further understand the process.

The TNF protein level in colonic tissue was significantly decreased after exposure to AVX-470 and IHC quantitation of TNF significantly correlated with the baseline UCEIS, although after AVX-470 exposure there was an overall reduction in TNF levels in all colonic regions. The reduced levels of TNF correlated with clinical response only in AVX-470-exposed groups, further supporting a direct effect of the drug on its target in the intestinal mucosa.

Apart from the evaluation of tissue TNF and bovine Ig, the AVX470 study also examined epithelial apoptosis. After exposure to AVX-470, a reduction in intestinal epithelial cell (IEC) TUNEL (terminal deoxynucleotidyl transferase DUTP nick end labelling) staining was detected in all colonic regions, consistent with the decrease in IEC apoptosis accompanied by an increase in epithelial resistance, as previously reported after treatment with infliximab in Crohn’s disease. This suggests that a decrease in IEC apoptosis in patients with UC after oral anti-TNF therapy may represent a first-step epithelial barrier restitution and repair, potentially leading to mucosal healing.

The study also showed evidence for an AVX-470-mediated reduction in inflammatory processes downstream of TNF. Neutrophil myeloperoxidase IHC staining at baseline showed a significant distal-to-proximal colon gradient. After exposure to AVX-470 there was a substantial reduction in myeloperoxidase staining in both distal and proximal colonic segments. These changes correlated with TNF IHC scores. Similar results were obtained with macrophage CD68, IL-1β and T-cell CD3 IHC staining. Finally, reverse transcription–polymerase chain reaction (RT-PCR) analysis of inflammatory markers was internally consistent with the proximal-to-distal gradient in tissue inflammatory signals. Taken together, these results indicate that an AVX-470-mediated anti-inflammatory effect is consistent with earlier tissue biomarker analysis after infliximab exposure in patients with UC.

These are, of course, preliminary findings. What messages are there for the future therapy of UC? Oral therapy with an anti-TNFα agent for UC is practicable and has tissue responses that are associated with inhibition of TNFα. The oral anti-TNFα AVX-470 seems to be safe, without risk of systemic exposure and immunogenicity. There are efficacy signals consistent with local anti-TNF activity and this correlates with tissue biomarker expression and endoscopic activity in multiple colonic segments. Watch this space!

References