

## Colitis associated with biological agents

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Received: September 24, 2011 Revised: February 9, 2012  
Accepted: February 16, 2012  
Published online: April 28, 2012

### Abstract

In the past, there has been considerable focus on a host of drugs and chemicals that may produce colonic toxicity. Now, a variety of new biological monoclonal antibody agents, usually administered by infusion, have appeared in the clinical realm over the last decade or so to treat different chronic inflammatory or malignant disorders. For some of these agents, adverse effects have been documented, including apparently new forms of immune-mediated inflammatory bowel disease. In some, only limited symptoms have been recorded, but in others, severe colitis with serious complications, such as bowel perforation has been recorded. In others, adverse effects may have a direct vascular or ischemic basis, while other intestinal effects may be related to a superimposed infection. Some new onset cases of ulcerative colitis or Crohn's disease may also be attributed to the same agents used to treat these diseases, or be responsible for disease exacerbation. Dramatic and well documented side effects have been observed with ipilimumab, a humanized monoclonal antibody developed to reduce and overcome cytotoxic T-lymphocyte antigen 4, a key negative feedback regulator of the T-cell anti-tumor response. This agent has frequently been used in the treatment of different malignancies, notably, malignant melanoma. Side effects with this agent occur in up to 40% and these are believed to be largely immune-mediated. One of these is a form of enterocolitis that may be severe, and occa-

sionally, fatal. Other agents include rituximab (an anti-CD20 monoclonal antibody), bevacizumab (a monoclonal antibody against the vascular endothelial growth factor) and anti-tumor necrosis factor agents, including infliximab, adalimumab and etanercept.

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**Key words:** Biological agents; Colitis; Crohn's disease; Inflammatory bowel disease; Infliximab; Ipilimumab; Rituximab; Ulcerative colitis

**Peer reviewers:** Ole Haagen Nielsen, Professor, Department of Gastroenterology, Herlev Hospital, University of Copenhagen, Herlev Ringvej 75, 2730 Herlev DK, Denmark; Ian C Lawrance, Professor, Medicine and Pharmacology, University of Western Australia, Level 5 T block, Fremantle Hospital, Fremantle 6160, Australia

Freeman HJ. Colitis associated with biological agents. *World J Gastroenterol* 2012; 18(16): 1871-1874 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v18/i16/1871.htm> DOI: <http://dx.doi.org/10.3748/wjg.v18.i16.1871>

### INTRODUCTION

Different patterns of inflammatory disease involving the small and large intestine have been historically recognized over the past century or so, and their features are well detailed in clinical textbooks especially focused on inflammatory bowel diseases. Crohn's disease, for example, is recognized as a pattern of inflammatory disease that may involve any site along the length of the gastrointestinal tract, usually in a segmental or focal distribution, typically with transmural involvement, and frequently, granulomas may be demonstrated. Ulcerative colitis has been traditionally defined by its colonic distribution, a more continuous pattern of mucosal involvement extending proximally within the colon from the rectum for variable distances. In reality, however, clinical and pathological overlap may occur frequently, and in many patients, precise differentiation of these different forms of chronic

inflammatory disease based on these descriptive parameters may not be so precise.

In the past, a variety of drugs have been used to control the inflammatory process in these disorders and improve quality of life. In addition, a host of biological agents have also emerged in recent years to treat a number of chronic inflammatory disorders, including Crohn's disease and ulcerative colitis, as well as a lengthening list of malignant disorders. Some of these biological agents have also been associated with the appearance of novel forms of colonic inflammatory disease, often severe and potentially fatal, as well as apparent paradoxical intestinal complications, including the *de novo* appearance or worsening of an underlying or unrecognized intestinal inflammatory disorder that may, in themselves, lead to serious complications.

Although a number of administered drugs and chemicals causing colonic toxicity have been enumerated elsewhere and reviewed in detail during the past 3 decades<sup>[1-3]</sup>, this review focuses on newer agents, largely administered by the parenteral route, that interfere with key regulatory biological molecules. These include ipilimumab, rituximab, bevacizumab and a number of anti-tumor necrosis factor agents.

## IPILIMUMAB-INDUCED COLITIS

A relatively novel strategy has emerged in cancer treatment in recent years to induce tumor regression and prolong patient survival involving control and reduction of the effect of specific immune regulatory molecules, such as the cytotoxic T-lymphocyte antigen 4 (CTLA-4). Ipilimumab is a fully human monoclonal antibody that has been developed to reduce and overcome cytotoxic CTLA-4, a key negative regulator of the T-cell anti-tumor immune response. In recent years, evidence has appeared showing tumor regression with prolonged time to progression in melanoma patients treated with CTLA-4 antibodies<sup>[4,5]</sup>. Ipilimumab plus dacarbazine showed improved survival in malignant melanoma compared to dacarbazine alone, a drug most frequently compared with new agents in randomized treatment trials on melanoma<sup>[5]</sup>. In addition to melanoma, prolonged effects with ipilimumab have been noted in other malignancies including ovarian cancer<sup>[6]</sup>, prostate cancer<sup>[7]</sup> and renal cell cancer<sup>[8]</sup>. Inhibition of CTLA-4 with this antibody is also associated with characteristic side effects in an estimated 40%<sup>[4]</sup>. These are believed to be largely immune-mediated and include an ever-lengthening list of adverse effects such as dermatitis, endocrinopathies, particularly hypophysitis, uveitis, nephritis, inflammatory myopathies, hepatitis, and diarrhea or colitis<sup>[9,10]</sup>. Similar immune-related adverse events may result from another monoclonal CTLA-4 antibody, tremelimumab, used for the treatment of metastatic melanoma<sup>[11]</sup>.

Colonic toxicity has been recorded in about 20% and appears to occur relatively rapidly after administration of ipilimumab, sometimes within days marked by the onset of abdominal cramping pain and profuse diarrhea, often bloody<sup>[9,12]</sup>. In others with few or mild symptoms, colitis could still be present since only those with more severe

symptoms were recorded<sup>[12]</sup>. Up to 5% of patients may suffer a fatal outcome attributed to a significant complication, a protracted clinical course or failure of prompt treatment, sometimes related to limited compliance<sup>[12]</sup>. Colonoscopy and ileoscopy as well as upper endoscopy with duodenal biopsies have documented both small bowel and colonic inflammatory changes. In some, a diffuse, but non-specific colitis may occur, in the absence of any detectable infectious agent, while in others, the inflammatory process may be patchy or segmental in distribution. The appearances may not be distinguishable by endoscopy from other forms of inflammatory bowel disease. Endoscopic biopsies may show a non-specific acute and chronic inflammatory infiltrate, including cryptitis as well as crypt abscess formation. Colon biopsy samples show a colitis that has an abundant T-cell infiltrate<sup>[13]</sup>. Granulomatous inflammation has not been recorded.

Treatment for this enterocolitis largely based upon supportive measures, specifically, fluid and electrolyte replenishment and, sometimes, parenteral nutrition. In addition, the colitis has often been treated with intravenous high dose steroids (or oral budesonide) and, if the response to steroids fails or has been limited, infusions of infliximab have been used<sup>[14,15]</sup>. If no response for the colitis is evident, diverting ileostomy or partial/complete colectomy has been recommended. The incidence of life-threatening colon perforation has been recorded at 4 in 700 cases with doses of ipilimumab of 3 mg/kg or more (i.e., less than 1%). Even during treatment with steroids or infliximab for the colitis, the anti-tumor response for metastatic melanoma still appears to be sustained. In a recent study of ipilimumab with dacarbazine for previously untreated metastatic melanoma, rates of intestinal adverse events were reported to be lower, while the rates of altered liver chemistry test changes were higher<sup>[5]</sup>.

## RITUXIMAB-ASSOCIATED COLITIS

Rituximab is an anti-CD20 monoclonal antibody that has been used in the management of nephrotic syndrome in children and adults<sup>[16-18]</sup> as well as a form of B-cell targeted therapy in rheumatoid arthritis<sup>[19,20]</sup>. It appears to result in depletion of systemic as well as intestinal B cell populations. Although the agent appears to be efficacious, adverse effects have been noted in about 27% of children treated with rituximab for refractory nephrotic syndrome<sup>[21]</sup>. Some of the reported adverse effects have included fever and chills, mucocutaneous reactions, fatal infusion reactions, progressive multifocal leukoencephalopathy, and bowel perforation<sup>[18,22]</sup>. New onset ulcerative colitis<sup>[23]</sup> and an exacerbation of previously documented colitis have been recorded<sup>[24]</sup>. In a later report, it was hypothesized that a severe colitis that developed after rituximab therapy may have been related to an infectious torovirus agent<sup>[22]</sup>.

## BEVACIZUMAB-ASSOCIATED COLONIC ULCERATION

Bevacizumab is a humanized monoclonal antibody against

the vascular endothelial growth factor receptor. This antibody has shown promise in the treatment of recurrent and metastatic colorectal cancer as well as metastatic non-small cell lung cancer. The agent has also been used to treat other malignancies, including ovarian cancer. Several mechanisms of action have been proposed, including an ability to restrict or deprive tumors of their neovascularity required to permit tumor progression and growth.

A number of cases have now been reported describing bowel perforation following bevacizumab treatment<sup>[25-29]</sup>. There also appears to be an especially increased risk of leakage at anastomotic suture sites following surgery for either ulcerative colitis or colorectal cancer<sup>[26]</sup>. In some, delayed anastomotic complications have been observed, some more than 1 year after surgery. Some hypothesized risk factors included anastomotic leakage during the original operative procedure or prior pre-operative pelvic irradiation<sup>[27]</sup>. Other mechanisms that have been recorded include an ischemic pathogenesis with anastomotic perforation after a partial colectomy<sup>[28]</sup> or more diffuse perforation associated with histological evidence of ischemia in a patient with non-small cell lung cancer<sup>[29]</sup>.

## ANTI-TUMOR NECROSIS FACTOR ADVERSE EVENTS

Most intriguing is the recent increased recognition of paradoxical adverse events following therapy with anti-tumor necrosis factor. In selected patients with inflammatory bowel disease, improved symptoms and mucosal changes may result. Similar treatment effects have been recorded for different agents including the chimeric monoclonal agent, infliximab, along with more humanized forms, such as adalimumab. Interestingly, in some treated with these agents for other disorders, in particular spondyloarthropathies or rheumatoid arthritis, so-called “paradoxical” adverse effects have been recorded, including flares or new onset inflammatory bowel disease<sup>[30]</sup>. Initially, in this early evaluation, intestinal effects appeared to occur more often with etanercept than either of the monoclonal antibody agents<sup>[30]</sup>. Later, however, other effects appeared to develop during arthritis treatment, particularly the skin disorder, *pyoderma gangrenosum*<sup>[31,32]</sup>. Later, new onset ulcerative colitis was initially recorded during infliximab treatment<sup>[33]</sup> as well as adalimumab<sup>[34]</sup>. Similar cases of new onset inflammatory bowel disease, specifically, Crohn’s disease have also been recorded usually after etanercept therapy administered for spondyloarthropathy (as opposed to Crohn’s disease where etanercept has not been effective)<sup>[35-39]</sup>. Some have suggested that the *de novo* appearance of inflammatory bowel disease following anti-tumor necrosis factor therapy may simply be related to “unmasking” of an underlying inflammatory disease process<sup>[40]</sup>. Others have documented a superimposed infectious agent<sup>[41,42]</sup>. A large retrospective study concluded that paradoxical adverse events of anti-tumor necrosis factor therapy may occur, but none were agent specific<sup>[43]</sup>.

## CONCLUSION

Several intestinal, particularly colonic complications have been recorded with the emerging armamentarium of monoclonal antibody agents used in the management of different inflammatory or malignant disorders. For some, immune-mediated adverse events may occur regularly, while for others, a complication may be rare and the mechanism not so evident. The precise frequency of colonic complications after treatment with these agents has been difficult to determine. In large part, this has been related to the clinical focus being largely directed to the most severely symptomatic cases. Although selected patients treated for either ulcerative colitis or Crohn’s disease with these biological agents has increased over the past decade, in retrospect, it may be that some labeled as “refractory” or not responsive to these agents may simply have been made worse. Published clinical trials may not always detail a failed therapeutic event as an adverse event. Future awareness of the possible adverse intestinal effects of monoclonal agents may be important.

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