planned. As we recently witnessed with the intravenous administration of TGN1412, designed to activate regulatory T cells for the treatment of leukaemia and autoimmune diseases such as rheumatoid arthritis, six volunteers were hospitalised, four of whom suffered major organ failure. The patients' conditions was described as ''cytokine release syndrome'' which occurs when activated T cells produce a systemic inflammatory response.

Could the violent reaction to the monoclonal antibody be avoided with oral administration? Ochi et al's recent report may offer an answer. They observed that oral was as effective as intravenous administration of anti-CD3 in reversing established experimental autoimmune encephalomyelitis.[1]

While traditionally administered intravenously, when anti-CD3 was administered orally it was found to be effective and to have fewer side effects. Because antibodies are not well absorbed in the gastrointestinal tract, they do not enter the bloodstream where they might otherwise stimulate circulating T cells to release the proinflammatory cytokines that are often associated with adverse events.

In many ways, similar to TGN1412, anti-CD3 also interacts with a subset of regulatory T cells on administration with the intent to suppress autoimmunity. On ingestion, anti-CD3 was found to survive passage through the gastrointestinal tract functionally intact, and was subsequently taken up into the Peyer's path in the luminal wall of the small intestine. There, anti-CD3 initiated a cascade of events outside of the gastrointestinal tract, leading to activation of regulatory T cells. These newly activated T cells migrated via the bloodstream to distal lymph nodes of autoimmune inflammation and suppressed the pathogenic T cells contributing to disease.

This complex cascade of events all began with ingestion of antibodies. Anti-CD3 survived the long passage through the harsh gut environment to find the appropriate portal in the small intestine to trigger the cascade of events. This outcome has significant implications that will likely reach beyond experimental encephalomyelitis and extend to other autoimmune inflammatory conditions found both locally within the gastrointestinal tract and systemically.

It is therefore somewhat surprising that of the 18 approved monoclonal antibodies, only one is administered outside of the bloodstream. Furthermore, there do not appear to be any monoclonals or therapeutic antibodies in late stage clinical trials intended for oral administration.

Chatenoud's opening comments in a review on oral administration of anti-CD3 reminds us that modern medicine continues to work under the assumption that therapeutic proteins, such as antibodies, are simply ineffective when administrated orally because of degradation in the digestive tract. Unfortunately, this prevailing assumption is carried over to both development and clinical practice where we continue to design and administer such biotherapeutics intravenously.[2]

Have we created a biopharmaceutical industry that is dependent on the needle to deliver biologicals? We currently live in an era of protein design, molecular targeting, and humanising therapeutic proteins to overcome potential side effects associated with intravenously administration.

The fact remains, however, that not only do antibodies survive pancreatic enzymes and low pH environments, they retain functionality after passage through the gastrointestinal tract of both infants and adults.[3 4] Animal models have demonstrated that orally delivered antibodies prevented rotavirus and cholera infections. Also, multiple human clinical trials have demonstrated that oral delivery of bovine antibodies were extremely effective in preventing rotavirus, enterogenic *E coli*, shigella infection, and necrotising enterocolitis.[4]

It is interesting to note that antibodies and other beneficial biologicals such as cytokine cocktails have been delivered in mother's milk for eons and have evolved to survive the harsh gut environment, ensuring their arrival to the mucosal lining of the gastrointestinal tract. These naturally occurring biologicals afford protection against a number of gastrointestinal pathogens, including rotavirus, *E coli*, shigella, *Crytosporidium, C difficile*, and *H pylori*, among others. They also protect us against a number of inflammatory bowel conditions, including ulcerative colitis, Crohn's disease, non-steroidal anti-inflammatory drug induced gut injury, and chemotherapy induced mucositis.[5 6]

In light of the clinical outcome of TGN1412, these recent observations about anti-CD3 should provoke a rethinking of the needle for many promising biologicals. Also, in the case of dose escalation of fontolizumab in future trials, flu-like symptoms and chills may be nonexistent with even more encouraging outcomes with oral administration.

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A case of exacerbation of ulcerative colitis induced by combination therapy with PEG-interferon α-2b and ribavirin

A 55 year old man with chronic hepatitis C presented with diarrhoea and bloody stools in July 2003. Colonoscopic examination showed redness and oedematous mucosa in the rectum and ulcerative colitis was suspected. Biopsy of the lesion confirmed the diagnosis and treatment was initiated with mesalazine (5-ASA 2250 mg/day). However, he showed short term improvement and mesalazine was discontinued. He was treated with percutaneous radiofrequency ablation therapy (RFA)(Cool-tip) for adenomatous hyperplasia in S5 of the liver in December 2004. After providing consent to treatment with interferon (IFN), the patient underwent combination therapy with PEG-IFNα-2b (100 mg/week) and ribavirin (800 mg/day) for chronic hepatitis C. Liver biopsy and blood biochemistry revealed chronic active hepatitis C virus (HCV) F3/A2, genotype 1b, liver injury associated with HCV, aspartate aminotransferase (AST) 109 IU/l, alanine aminotransferase (ALT) 126 IU/l, and HCV RNA 3400.0 KIU/ml (by reverse transcription nested polymerase chain reaction, high range method).

One month after initiation of combination therapy, AST was 20 IU/l, ALT 24 IU/l, and transaminase levels were normal. However, 2.5 months after initiation of combination therapy, bloody diarrhoea was first observed and the incidence of bloody diarrhoea continually increased. Colonoscopic findings and biopsy specimens were compatible with active ulcerative colitis (fig 1A, B) and we confirmed the diagnosis of exacerbation of ulcerative colitis. We discontinued PEG-IFN

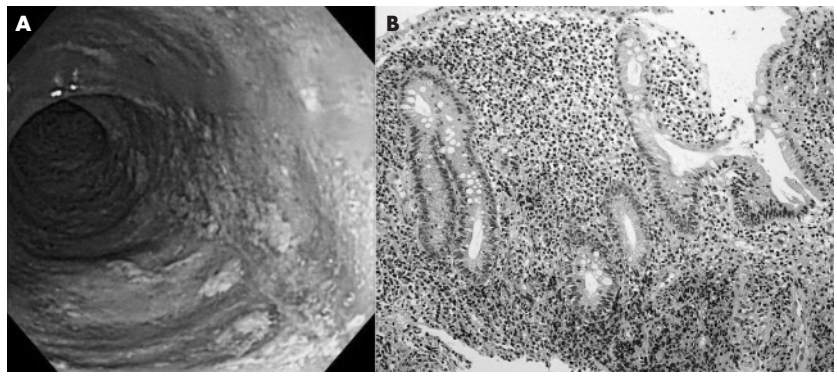

Figure 1 (A) Colonoscopic findings. Colonoscopic examination revealed the absence of vessel pattern, easy bleeding on contact, and oedema in the mucosa from the rectum to the descending colon in a continuous fashion. (B) Histological findings. Biopsy specimens from the colonic mucosa showed crypt abscess, decreased number of goblet cells, and marked infiltration of inflammatory cells. Haematoxylin-eosin, ×100.

Table 1 Reported cases of exacerbation of ulcerative colitis induced by interferon (IFN) therapy in Japana Centra Revuo Medicina (in Japan) and in MEDLINE

Author, year, country	Age/ sex	Background	IFN	Period to exacerbation	Region of colitis	Therapy	Result
Mitoro 1993 Japan[1]	34M	Hepatitis C	IFN-α	23 days	R-A	Conservative	Reinjection of IFN under administration of SASP
Honda 1993 Japan[2]	50M	Hepatitis C	IFN-α	14 months	R-D	SASP	Exacerbation after readministration of IFN
Yasumori 1995 Japan[3]	42M	Hepatitis B	IFN-α	1 day	Total colon	Total colectomy	Death
Yamamoto 1995 Japan[4]	40M	Hepatitis C	IFN-α	5 months	R-S	SASP	Discontinuation of IFN
Usami 1999 Japan[5]	47M	Renal cancer	IFN-α,γ	12 months	R-A	Conservative	Discontinuation of IFN
Mavrogianni 2001 Greece[8]	29F	Hepatitis C	IFN-α	14 days	R	Mesalazine+steroid	Continuation of IFN under administration of mesalazine and steroid resulted in exacerbation of UC
Niki T 2001 Japan[6]	49M	Hepatitis C	IFN-α	2 months	Total colon	Mesalazine, steroid	Discontinuation of IFN
Awakawa 2002 Japan[7]	48M	Hepatitis C	IFN-β	7 days	R-A	Mesalazine	Discontinuation of IFN
Sprenger 2005 Austria[9]	54M	Hepatitis C	PEG-IFN-α + ribavirin	3.5 months	Total colon	Mesalazine+steroid	Discontinuation of PEG-IFN-α and ribavirin
Watanabe (2006) Japan (present study)	55M	Hepatitis C	PEG-IFN-α + ribavirin	2.5 months	R-D	Mesalazine+steroid	Discontinuation of PEG-IFN-α and ribavirin

R, rectum; S, sigmoid colon; D, descending colon; A, ascending colon; SASP, salazosulfapyridine; UC, ulcerative colitis.

and ribavirin in April 2005, and continued treatment for ulcerative colitis with continuous oral mesalazine and prednisolone. Despite discontinuation of PEG-IFN and ribavirin, the patient's symptoms did not change and he was hospitalised in May 2005. The patient improved following treatment for ulcerative colitis with mesalazine and steroid therapy. He was discharged on 3 June 2005 and was followed and observed as an outpatient.

We encountered a case of ulcerative colitis apparently caused by combination therapy of PEG-IFN and ribavirin for hepatitis C. A literature search using Japana Centra Revuo Medicina (keywords: interferon, ulcerative colitis; retrieval period: 1983–2006) found seven cases[1–7] of onset and exacerbation of ulcerative colitis caused by IFN therapy in Japan (table 1). Conversely, a literature search using MEDLINE (keywords: interferon, ulcerative colitis) found only three reports in English worldwide (Mitoro and colleagues,[1] Mavrogiannis and colleagues,[8] and Sprenger and colleagues) (table 1).[9] Moreover, only one of these cases described exacerbation of ulcerative colitis due to combination therapy with PEG-IFN and ribavirin.[9] Thus our patient is the second reported case to date.

As PEG-IFN can maintain higher blood levels than classical IFN, IFN may have a larger effect on the immune system. Furthermore, it has been reported that ribavirin alters the balance of Th1/Th2 and causes resistance to HCV by cellular immune processes.[10] Combination therapy with PEG-IFN and ribavirin may thus have more significant effects on immunomodulation than classical IFN treatment.

This is a case of chronic hepatitis C with adenomatous hyperplasia of the liver at the age of 55 years. Antiviral therapy for chronic hepatitis C after RFA for adenomatous hyperplasia might prevent future carcinogenesis in the liver. We conclude that the benefits of prevention of carcinogenesis in the liver by combination therapy with PEG-IFN and ribavirin supersede the risk of relapse and exacerbation of ulcerative colitis. Furthermore, we selected the combination therapy of PEG-IFN and ribavirin for antiviral therapy because the patient had HCV genotype 1 infection and high pretreatment viral burdens.

We expect the use of IFN, as an antiviral therapy for hepatitis C, to continue to increase. Changes to immune system regulation and specific adverse reactions such as ulcerative colitis associated with combination therapy may be expected to occur at a significantly higher frequency than with monotherapy IFN. Further discussion in needed on how to prevent adverse reactions with combination therapy.

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BOOK REVIEWS

Pocket Consultant Gastroenterology, 3rd edn

S Travis, T Ahmed, J Collier, et al. Oxford: Blackwell, 2005, £34.99, pp 488. ISBN 1405111925

''Things should be made as simple as possible, but not any simpler''
Albert Einstein

The aim of this revision was to update a book originally published in 1991, with the second edition appearing in 1998. The objective is clearly to produce a manageable distillate of the contemporary state of clinical