From historical perspectives to modern therapy: a review of current and future biological treatments for Crohn's disease

Charles W. Randall, John A. Vizuite, Nicholas Martinez, John J. Alvarez, Karthik V. Garapati, Mazyar Malakouti and Carlo M. Taboada

Ther Adv Gastroenterol

2015, Vol. 8(3) 143–159

DOI: 10.1177/
1756283X15576462

© The Author(s), 2015.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Crohn's disease (CD) is a debilitating, systemic inflammatory disorder with both gastrointestinal and extraintestinal manifestations. Its existence predates modern medicine, but its precise etiology remains incompletely understood. Most authorities suggest a multifactorial pathogenesis owing to a mixture of genetic disorders, immunologic dysregulation, microbiota disequilibrium and environmental influences. Of these factors, the overactive immunologic response seen in CD appears to be the most promising target of medical therapy. Biological agents comprise a relatively new class of drugs that can induce and maintain remission in moderate to severe CD, as well as in ulcerative colitis. This review will provide an overview of CD, its history, clinical features, pathophysiology, and treatment options focusing on current and future biological agents with an emphasis on drug development, dosage and administration.

Keywords: Crohn's Disease, Inflammatory Bowel Disease, biologics, anti-TNF

Historical perspectives

The earliest descriptions of what was thought to be Crohn's disease (CD) date back to the 1700s. In 1761 and 1769, the Italian physician-scientist Giovanni Morgagni reported several patients demonstrating symptoms suggestive of CD [Kirsner, 1988]. These affected individuals had increased stool frequency, bloody bowel movements, intermittent fever and abdominal discomfort. One patient was determined on autopsy to have experienced an ileal perforation. His records even described bowel ulceration and large mesenteric nodes, classic features of what we now know as CD [Aufses, 2001]. Over the next 200 years, many other case reports with findings consistent with CD were described in the literature. It was not until 1932 that Bernard Crohn and colleagues at Mount Sinai University published the landmark article in the *Journal of the American Medical Association* describing regional ileitis in 14 patients with distinctively similar clinical and pathological findings [Crohn *et al.* 1932]. Interestingly, one of the investigators, A.A. Berg who provided the surgical expertise in the cases declined to put his

name on the article. Authorship was assigned alphabetically, so had Dr Berg been included in the authorship, it is quite possible that the eponym 'Crohn's disease' would never have come to pass. The following year, Harris and colleagues published an article discussing regional ileitis calling it 'Crohn's' and subsequent publications followed suit in associating the disease entity known as regional ileitis with Dr Crohn [Harris *et al.* 1933].

Between 1930 and 1960, a growing body of literature both expanded and refined the modern definition of CD. The term 'regional ileitis' was no longer acceptable as multiple cases described disease in the duodenum, stomach, esophagus and oral cavity. It was during this era that researchers also began to distinguish between ulcerative colitis (UC) and CD. In 1960, Lockhart-Mummery and Moroson took on the task of differentiating granulomatous ileitis with involvement of the colon from UC by defining the pathologic criteria needed to definitively diagnose each disease entity [Lockhart-Mummery and Moroson, 1960]. The

Correspondence to:
John A. Vizuite, MD, MPH
University of Texas Health
Science Center – San
Antonio, 7703 Floyd Curl
Dr, San Antonio, TX 78229,
USA
johnvizuite@gmail.com

Charles W. Randall, MD
Carlo M. Taboada, MD
Gastroenterology
Research of San Antonio,
San Antonio, TX, USA

Nicholas Martinez, MD
John J. Alvarez, MD, MPH
Karthik V. Garapati, MD
Mazyar Malakouti, MD
University of Texas Health
Science Center – San
Antonio, San Antonio,
TX, USA

works of the Mount Sinai team, along with other investigators previously mentioned, brought CD to the attention of the scientific world. Further notoriety occurred in 1956 when President Dwight D. Eisenhower was rushed to surgery with documented disease. During this era, few treatments beyond surgery were available to manage the complications of CD. The ensuing decades brought increased research efforts focusing on the pathophysiology of CD as well as investigation of novel therapies.

Epidemiology

The incidence of CD varies geographically, but has been shown to be the highest in North America, Europe and the UK. In North America, the prevalence of CD is 144–198 cases per 100,000 persons, with incidence rates ranging from 3 to 14 new cases per 100,000 person-years [Loftus *et al.* 2002]. The age of onset is typically between the ages of 15 to 30, with a small group of patients between the ages of 60 and 80 with late-onset disease [Friedman and Blumberg, 2012]. In general, there is a greater distribution of younger patients in CD compared with UC, with pediatric patients comprising up to 20% of cases [Cosnes *et al.* 2011]. Most studies suggest a trend toward a younger age of onset over time [Shivananda *et al.* 1996; Foster and Jacobsen, 2013]. There is a slightly higher predominance among female patients, though this may vary by population. Historically, the risk of acquiring CD was most closely associated with the Ashkenazi population of Jews, but in Israel where the population also includes Sephardic and African Jews, the prevalence of CD does not appear to be higher than any other part of the world. In general, the incidence of CD is most common among Caucasians, followed by African-Americans, Hispanics and Asians, although it appears as though Crohn's is increasing among all ethnic groups [Ng *et al.* 2013].

Clinical presentation

CD is a chronic systemic illness that primarily affects the gastrointestinal tract. Its natural course is marked by episodes of increased clinical symptoms (flares) interspersed with periods of quiescence. CD flares manifest with increased frequency of bowel movements, diarrhea, achy or crampy abdominal pain, bleeding, weight loss and fevers. Ulcers on the tongue, gums and oral cavity are infrequent but well-described manifestations

of CD. Chronically, nutritional deficiencies often develop due to small bowel malabsorption. As CD is marked by transmural inflammation, strictures, fissures, abscesses or fistulas may occur throughout the gastrointestinal (GI) tract [Friedman and Blumberg, 2012].

Classically, endoscopic findings include 'skip lesions', where inflamed segments alternate with normal mucosa. This pattern of alternating ulceration and edema has been termed 'cobblestoning'. Approximately one half of all patients have involvement of the ileum and proximal colon; 30% have disease restricted to the ileum; and 20% have disease involving only the colon [Hart and Ng, 2011]. Involvement of just the jejunum, duodenum, stomach or esophagus is less common. Chronic and untreated CD may lead to fibrostenosis or fistulae [Rankin *et al.* 1979]. Inflammation of the subserosa, mesenteric and adipose tissue along with wall thinning of the ileocecal region may lead to microperforations or frank perforations in approximately 1–2% of patients [Greenstein *et al.* 1987]. In the past, up to 70% of patients underwent at least one abdominal surgery for CD during their lifetime with approximately 1 in 4 requiring an ileostomy [Rutgeerts *et al.* 1990; Burisch *et al.* 2013].

The main feature of CD is transmural inflammation. Patchy areas of inflammation are noted primarily within the lamina propria and are composed of elevated populations of lymphocytes and plasma cells. In active disease, neutrophilic inflammation may be present, leading to aphthoid ulcers, crypt irregularity and microabscesses. Chronic inflammation leads to crypt architectural distortion, which may be helpful in distinguishing CD from transient colitis. Additionally, loose aggregations of macrophages can form noncaseating granulomas, which are considered pathognomonic for CD but are seen in less than 15% of cases [Friedman and Blumberg, 2012].

Extraintestinal manifestations are observed in approximately 30% of patients with CD and are thought to be immune mediated though a clear link has not been established [Das, 1999]. Rheumatologic manifestations include arthritis, ankylosing spondylitis and sacroiliitis. Dermatologic findings may present as pyoderma gangrenosum, erythema nodosum and Sweet's syndrome. Additional associations such as uveitis, episcleritis, hepatobiliary disease and thromboembolic phenomena, though uncommon, occur at a rate higher

than the general population. Occasionally, extraintestinal features can be the presenting signs or primary symptoms in patients with CD, as they do not always correlate with endoscopic disease activity [Ardizzone *et al.* 2008].

Pathophysiology

The etiology of CD is still incompletely understood. The general consensus among the scientific community is that the development of CD is dependent upon multiple factors involving a dysfunctional immune system with an exaggerated inflammatory response to common antigens and commensal enteric bacteria in a genetically susceptible individual [Sartor, 2006]. Environmental factors are felt to serve as a catalyst in the initiation and reactivation of the disease state. The complex interaction between these factors has made it difficult to decipher which is most influential in disease expression.

Gene expression has a clear role in the development of CD. The relative risk of disease is elevated in first-degree relatives, higher still in dizygotic twins and highest among monozygotes [Cosnes *et al.* 2011; Baumgart and Sandborn, 2012]. With advances in DNA analysis and sequencing, more than 160 inflammatory bowel disease (IBD) associated genes have been identified, at least 70 of which are specific to CD [Zhang and Li, 2014]. The first susceptibility gene to be associated with CD was the NOD2/CARD15/IBD1 [Hugot *et al.* 2001; Ogura *et al.* 2001]. Mutations in this gene have been associated with a 40-fold increased likelihood of developing severe ileal CD [Xavier and Podolsky, 2007]. NOD2 is expressed in macrophages and is a necessary component used for bacterial recognition. Binding of bacterial antigen in the normal host leads to activation of nuclear factor (NF) κ B *via* NOD2. NF- κ B is an important stimulus for the pro-inflammatory cascade. The mechanism of action of a NOD2 in the pathogenesis of CD is not entirely understood, but it is thought that cells demonstrating dysfunction are unable to effectively clear bacteria or downregulate the innate immune response to bacterial antigen stimulation [Salim and Sonderholm, 2011]. Other gene mutations have now been recognized to play roles in autophagy and leukocyte migration in the regulation of adaptive immunity and thus the regulatory cytokines [Zhang and Li, 2014].

An overactive innate and acquired cellular immune response has been observed in CD.

Several potential inciting sources have been proposed, including alterations in gut flora, repeated exposure to external dietary antigens or other fomites [Podolsky, 2002]. The functional integrity of the intestinal mucosa is the first line of defense in a normal individual. Patients with CD, likely as a result of genetic mutations, demonstrate decreased mucin production and leaky tight junctions between cells, thus allowing for increased permeability and excess of antigens to the lamina propria [Xavier and Podolsky, 2007]. Normal tolerance to commensal bacteria within the intestinal lumen is attributed to a down regulation of toll-like receptors (TLRs), membrane proteins expressed on the cells of the innate immune system (neutrophils, macrophages, dendritic cells). It has been postulated that in addition to leaky tight junctions, the ability to regulate tolerance is lost in CD, leading to persistent, unregulated response to enteric bacteria [Baumgart and Sandborn, 2012].

Under normal circumstances, inflammation within the intestinal mucosa is regulated with the balance of pro-inflammatory and anti-inflammatory mediators. In CD there is an excess of pro-inflammatory cytokines, primarily interleukin (IL) 12 and interferon (IFN) γ as a result of increased Th1 CD4+ lymphocytes [Santor, 2006]. These cells act to perpetuate the inflammatory response by secreting IFN γ , tumor necrosis factor (TNF) α , IL-17 and IL-22 [Andoh *et al.* 2008]. Furthermore, studies have shown that mucosal T cells have an extended lifecycle due to failure to undergo apoptosis. This impaired regulatory mechanism results in a continued presence of the cells in the mucosa leading to the development of the lesions seen in CD [Bandzar *et al.* 2013].

Interesting research has come through epidemiological studies concerning environmental factors and alterations in the intestinal microbiota. Some of this interest has been spurred by an increasing incidence of CD in certain immigrant populations, especially those from South Asia and Latin American countries [Loftus *et al.* 2002; Foster and Jacobson, 2013]. Higher socioeconomic status and an urban environment have been found to be associated with CD. These associations may indicate certain risk factors within industrialized societies that may play a role in the pathophysiology of CD and IBD in general. Potential risk factors that have been implicated in the development of CD include a Western diet, vitamin D deficiency and oral contraceptives [Longo *et al.* 2012]. Smoking

is another well-established factor associated with a twofold increase risk of CD compared to non-smokers [Loftus *et al.* 2002]. Various factors include dietary changes, GI infections leading to dysbiosis, and use of antibiotics can affect normal intestinal flora. Increased numbers of bacterial flora with diminished diversity in a susceptible genotype has been shown in animal models to contribute to the pathogenesis of CD [Sartor, 2006; Salim and Soderholm, 2011]. There has not been any research implicating one organism over another in the development of CD; however, colonization with *Feacalibacterium prausnitzii* appears to have a protective role [Sokol *et al.* 2013].

Therapy

There is no cure for CD, but once a diagnosis is made, the goal of treatment is to induce and sustain remission with the use of lifelong pharmacotherapy. It is widely believed that reducing chronic inflammation and achieving sustained remission prevents many of the crippling consequences of CD. Options for treatment are chosen based upon disease location, extent and risk for complications such as fibrostenosis or penetrating disease. Single or combination therapy of aminosalicylates, corticosteroids, immunomodulators and biological agents may be utilized. Aminosalicylates have a limited role in CD and are generally used in mild disease restricted to the colon [Sandborn and Feagan, 2003]. Corticosteroids are a poor choice for long-term management. In addition to carrying an undesirable side effect profile, no study to date has demonstrated long-term efficacy or a decreased/delayed need for surgery. Thus systemic corticosteroids should be reserved for induction of remission in the setting of disease flares, but other options may be as effective [Randall *et al.* 2012]. Immunomodulators such as azathioprine, mercaptopurine (6-MP) and methotrexate have played a major role in CD for over 30 years. They have been shown to maintain remission in some patients, but have a slow onset of action and may present adverse side effects including bone marrow suppression, liver toxicity, pancreatitis, opportunistic infections, and skin cancer and lymphoma [Bouhnik *et al.* 1996].

This paper focuses on the development and use of biological agents. In 1985, Beutler and associates hypothesized that TNF, a pro-inflammatory cytokine, played a significant role in endotoxin mediated shock [Beutler *et al.* 1985]. To confirm the hypothesis they treated mice with various

doses of lipopolysaccharide (LPS), a potent inducer of inflammation, while passively immunizing the treatment arm with a highly specific polyclonal rabbit antiserum directed against TNF. From this model they were able to show that the median lethal dose of LPS in animals treated with immune serum was significantly higher than the lethal dose for control mice treated with no immunity serum. This study led other labs to use transgenic mice with altered expression of the hTNF gene [Keffer *et al.* 1991]. They were able to prove that TNF played a significant role in the pathogenesis of inflammatory arthritis in mice. Moreover, they showed that monoclonal antibody administered to the arthritic mice effectively treated and prevented the development of polyarthritis. Other articles at that time showed increases in concentrations of TNF could be found in tissue inflammation, specifically rheumatoid synovial membranes and, interestingly, in the mucosa and lamina propria of patients with CD [MacDonald *et al.* 1990; Feldman and Maini, 2001].

The first human trial was conducted for rheumatoid arthritis patients using a chimeric mouse/human monoclonal antibody directed toward TNF α . Elliot and his group demonstrated a significant clinical improvement in rheumatoid patients treated with an anti-TNF antibody [Elliot *et al.* 1993]. Shortly afterward, the same beneficial effect was demonstrated for the first time in CD [Van Dulleme *et al.* 1995]. They found that 8 of 10 patients treated with a single dose of chimeric monoclonal antibody experienced normalization of CD activity index (CDAI) scores and healing of ulcerations on colonoscopy within 4 weeks. The effectiveness of biologics has since been demonstrated in diseases such as systemic sclerosis, systemic lupus erythematosus and vasculitis [Rosman *et al.* 2013]. Conversely, biologics can paradoxically induce other autoimmune processes such as lupus, vasculitis, sarcoidosis and psoriasis [Perez-Alvarez *et al.* 2013]. Overall, a large series of published studies have shown that biologics are relatively safe and efficacious compared with other modalities. We now turn our attention to specific drugs used to treat CD.

Infliximab

Infliximab is a chimeric immunoglobulin G1 (IgG1) monoclonal antibody made of 75% human and 25% murine sequences with high affinity to TNF α . In 1998, it was the first biological therapy approved by the US Food and Drug

Administration (FDA) for the treatment of CD. The endoscopic and histologic disease activity in Crohn's colitis is significantly decreased after treatment of patients with infliximab [D'Haens *et al.* 1999]. The drug is given as an infusion and distributed primarily within the vascular compartment with a half-life of 7.7–9.5 days. The approved induction doses for infliximab for moderate to severe disease activity is 5 mg/kg at weeks 0, 2 and 6. This is followed by maintenance therapy at 5 mg/kg every 8 weeks in patients who respond during the induction phase. This method is superior to single-dose therapy. This strategy has also been shown to be efficacious in patients with fistulizing disease [Sands *et al.* 2004a; Lichtenstein *et al.* 2005].

The efficacy of infliximab for the treatment of CD has been noted in numerous studies, the largest and most comprehensive of these being ACCENT 1 [Hanauer *et al.* 2002]. It examined single and multiple dosing strategies in patients with moderate to severe nonfistulizing CD for at least 3 months. Patients receiving therapy with 5-aminosalicylic acid (5-ASA) agents, steroids, azathioprine or 6-MP were eligible to participate. A total of 573 patients with a CDAI score of at least 220 received 5 mg/kg of infliximab at week 0. After evaluation of response at week 2, patients were divided into 3 groups. Group I received placebo infusions at weeks 2 and 6, then every 8 weeks thereafter until week 46. Group II received 5mg/kg at weeks 2 and 6, followed by 5 mg/kg every 8 weeks. Group 3 received 5 mg/kg at weeks 2 and 6, followed by 10 mg every 8 weeks. Overall, 335 of 573 (58%) patients had a clinical response at 2 weeks. At week 30, 21% (23 of 110) of the patients in group I were in clinical remission compared with 39% (44 of 113) in group II and 45% (50 of 112) in group III, suggesting remission is largely a product of continued treatment. After 54 weeks, the median duration response was 19 weeks for patients in group I compared with 38 weeks and 50 weeks in groups II and III, respectively. In patients with initial clinical remission, maintenance of remission occurred in only 14% in the single-dose group compared with 28% in group II and 38% in group III. Secondary analyses revealed that patients receiving scheduled infliximab had fewer CD related hospitalizations (23% *versus* 38%) and surgeries (3 *versus* 7%) compared with those who received only a single dose.

The ACCENT II trial focused on patients with fistulizing disease [Sands *et al.* 2004b]. This study

was a multicenter, double-blind, randomized, placebo-controlled trial designed to evaluate the efficacy of infliximab maintenance therapy in 306 adult patients with 1 or more draining abdominal or perianal fistula of at least 3 months' duration. All patients received an initial loading dose of infliximab at 5 mg/kg at weeks 0, 2 and 6. Patients were then randomly assigned to two groups. Patients in group I received 5 mg/kg every 8 weeks whereas patients in group II received placebo on the same schedule. If patients failed therapy at any point, those in group I had their dose increased to from 5mg/kg to 10 mg/kg or from 0 mg/kg to 5 mg/kg in the case of placebo. A total of 195 patients (64%) had response by week 14, defined as a reduction in number of open or draining fistulas. Among responders, those placed on maintenance therapy had significant fewer hospitalizations, surgeries and procedures compared with placebo. The duration of closure was longer with infliximab using the 5 mg/kg maintenance dose every 8 weeks compared with placebo. In short, infliximab is superior to placebo with respect to induction of remission, maintaining response and fistula closure.

If patients develop symptom recurrence between 8-week infusion intervals due to anti-infliximab antibody formation, one approach is to decrease the intervals between infusions as frequently as every 4 weeks and/or increase the infliximab dose to 10 mg/kg [Targan *et al.* 1997]. This approach is effective in some but not all patients, and studies suggest that the measurement of both infliximab antibodies as well as drug levels is more likely to be beneficial in achieving an optimal therapeutic drug concentration. It is more cost-effective than simple dose escalation [Ford *et al.* 2011].

Longitudinal cohort studies have demonstrated that up to 50% of patients who achieve remission on infliximab will eventually relapse if the drug is discontinued compared with 35% of those on maintenance therapy [Vaughn *et al.* 2010]. Moreover, if a patient responds well to infliximab, they should be continued on it rather than switching to another biologic [Van Assche *et al.* 2012].

The SONIC study showed that patients with moderate to severe disease who were treated with infliximab at standard induction and maintenance doses plus azathioprine were more likely to have a glucocorticosteroid-free clinical remission than those on monotherapy with either infliximab alone or azathioprine (2.5 mg/kg) alone. The

combination therapy group had 56.8% in remission at week 26 compared with 44.4% on infliximab only and 30% on azathioprine monotherapy [Colombel *et al.* 2010].

Continuation of therapy during pregnancy as well as for mothers nursing is often necessary. Maternal antibodies cross the placenta at any time through passive diffusion, but active transport begins in the second trimester, with the highest fetal concentration in the third trimester near-term [Mahadevan *et al.* 2013]. Infliximab is able to cross the placenta but its exact timing is unknown [Mahadevan *et al.* 2011]. The clinical significance of infliximab in the newborn is unclear, but is theoretically concerning because of potential increased infection risk or reduced response to vaccinations [Cheent *et al.* 2010]. It is suggested that infliximab be discontinued 8–10 weeks before the estimated date of delivery in women with inactive IBD. Therapy can then be resumed following delivery [Zelinkova *et al.* 2013]. For active CD during pregnancy, infliximab may be continued up to birth [Van Assche *et al.* 2010]. Infliximab is compatible with breastfeeding since only a small amount is excreted in human milk and is poorly absorbed orally; it thus has low potential to reach detectable levels in the newborn [Ben-Horin *et al.* 2011; Gawron *et al.* 2013].

Patients with bowel obstruction from Crohn's related strictures warrant special consideration. Some concern has been raised suggesting that a rapid reduction in inflammation from infliximab use may promote scarring and lead to stenosis, strictures or obstruction. Data from the Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry included 3179 patients and noted that patients with more aggressive disease are more likely to receive infliximab, creating a selection bias [Lichtenstein *et al.* 2006]. After adjustment, factors associated with stricturing disease include disease duration, severity, ileal involvement and, ironically, corticosteroid use.

Smoking appears to be a modifiable risk factor in the course of treatment. In a study of 100 patients at the Cleveland Clinic, nonsmokers with mucosal involvement only demonstrated a significantly higher initial response to infliximab compared with active smokers (73% *versus* 22%) at 3 months [Parsi *et al.* 2002]. Interestingly, concomitant use of immunomodulators increased the response rate in smokers to 39%. A prolonged response was significantly more likely in nonsmokers

compared with smokers (59% *versus* 6%). Fistulizing disease appeared to blunt the response to infliximab regardless of smoking activity.

Like all biologics, infliximab is associated with adverse events including increased risk of infections, malignancy, infusion reactions, autoimmunity, heart failure and demyelinating diseases. However, in clinical practice, the overall incidence is quite low. Most adverse reactions to infliximab are acute, occurring between 1 and 14 days after initiation of treatment. Acute reactions often are true allergies and can cause hypotension, bronchospasm, wheezing or urticaria [Cheifetz and Mayer, 2005]. Infusion reactions were evaluated in a study of 165 consecutive patients who received a total of 479 infusions of infliximab [Vultaggio *et al.* 2010]. In this study, 16 patients (10%) experienced at least one infusion reaction; 3.1% were judged mild, 1.2% moderate and only 1% severe. Delayed infusion reactions which may represent mild type two reactions were similar to serum sickness in terms of time of onset in association with skin rash, fever, diffuse joint pain, myalgias and fatigue. A variety of methods are helpful in preventing infliximab infusion reactions. These strategies include giving diphenhydramine at doses of 25–50 mg along with acetaminophen 650 mg 90 minutes before the infusion. Alternatively, a second-generation, nonsedating antihistamine can be given for 5 days before the infusion. The method of giving a test rate of 10 ml/hour, followed by an increase infusion rate as tolerated every 15 minutes until the usual rate of 125 ml/hour is reached, can be employed. If a patient has a history of anaphylaxis reaction after infliximab, then prednisone 50 mg every 8 hours should be given over the 24 hours before the infusion in addition to diphenhydramine and acetaminophen [Cheifetz *et al.* 2003].

Adalimumab

Adalimumab is a recombinant, human monoclonal IgG1 anti-TNF antibody. It is injected subcutaneously usually into the thigh or lower abdomen. Following a single 40 mg dose it reaches maximum serum concentration in 131 ± 56 hours. Its elimination half-life ranges from 10 to 20 days [Lichtenstein *et al.* 2008]. Adalimumab was FDA approved for the treatment of moderate to severe CD in 2007.

The CLASSIC I trial was a double-blinded, randomized, placebo-controlled, dose ranging trial of

adalimumab for induction therapy [Hanauer *et al.* 2006]. A total of 299 TNF-antagonist naïve patients with moderate to severe CD were randomly assigned to receive 1 of 4 induction regimens at weeks 0 and 2. At week 4, remission rates (defined as a CDAI score <220) were as follows: placebo, 12%; adalimumab 40 mg/20 mg, 18%; 80 mg/40 mg, 24%; and 160 mg/80 mg, 36%. These results illustrated a linear dose response to induction therapy with adalimumab. The two highest dose groups had significantly lower average CDAI scores than the placebo group. Some of these patients experienced results as early as week 1. Patients receiving the highest induction dose (160 mg/80 mg) were 3 times more likely to achieve remission than the placebo group, not to mention that they were significantly more likely to decrease their CDAI score by at least 100 points. Despite its short duration, this study demonstrated that an induction dose of adalimumab followed by a second dose at week 2 led to remission in anti-TNF naïve patients with moderate to severe CD.

The CLASSIC II trial examined the long-term efficacy and safety of maintenance therapy with adalimumab [Sandborn *et al.* 2007b]. A total of 276 of 299 eligible patients from CLASSIC I enrolled. All patients received open label adalimumab 40 mg at weeks 0 and again at week 2. At week 4, the 55 patients who were in remission were re-randomized into 3 treatment arms: placebo; 40mg adalimumab weekly; and 40mg adalimumab every other week. The remaining patients represented more difficult to treat disease and were placed in an open label cohort where they received 40mg adalimumab every other week. Patients in either group could have their treatment frequency increased in the case of a flare. The primary endpoint was maintenance of remission as defined by a CDAI < 150 at the end of 56 weeks. In the randomized groups, a significant difference was observed between placebo therapy (44% in remission) *versus* either treatment group (79 and 83%; $p < 0.05$). Overall, 65% (132/204) achieved a 100 point response and 46% (93/204) were in remission by week 56. CLASSIC II demonstrates that both weekly and every other week adalimumab is a more effective long-term maintenance therapy for moderate to severe CD than placebo.

The CHARM trial was designed to assess the efficacy of adalimumab in maintaining remission in treatment-responsive patients. A total of 854

patients received open label induction therapy of 80 mg at week 0, followed by 40 mg at week 2 [Colombel *et al.* 2007]. Of these patients, 778 (91%) experienced a decrease of greater than or equal to 70 points in their CDAI by week 4. These patients were then randomized to receive 40 mg of adalimumab every other week, 40 mg weekly, or placebo through week 56. Again, patients in the placebo group with disease flares could be started on every other week treatment, while patients in the biweekly group were changed to weekly dosing. Wholly unresponsive patients were withdrawn from the study. At week 26, remission rates (CDAI < 150) were 17%, 40% and 47% in the placebo, biweekly and weekly groups, respectively. At week 56, rates declined slightly to 12%, 36% and 41%, respectively, but were significantly better in both treatment groups. No significant benefit was noted in group dosed weekly *versus* every other week and thus standard adalimumab dosing is every 2 weeks. Overall, participants in the treatment arms were noted to have decreased hospitalizations and Crohn's related surgeries, along with improvement in quality of life. The CHARM trial demonstrated adalimumab is an effective tool in the treatment of CD.

The GAIN trial extended the body of literature by assessing efficacy of adalimumab induction therapy in patients with prior infliximab exposure [Sandborn *et al.* 2007c]. A total of 325 patients with persistent symptoms were randomized to adalimumab 160 mg at week 0 and 80 mg at week 2 *versus* placebo. At week 4, 21% of the patients in the treatment group *versus* 7% of the placebo group achieved remission (CDAI < 150). Response (CDAI decrease of at least 70 points) was seen in 52% of the treatment group *versus* 34% of the placebo group. The results of this trial provided patients who had lost response or experienced side effects with infliximab another option.

Clinical signs and symptoms of active CD often correlate with mucosal activity. The EXTEND trial specifically examined the effect of adalimumab for inducing and maintaining mucosal healing in patients with CD [Rutgeerts *et al.* 2012]. A total of 135 patients with moderate to severe CD and evidence of mucosal activity on colonoscopy received induction therapy with open label adalimumab 160 mg at week 0 and 80 mg at week 2. At week 8, clinical responders, defined by a decrease in CDAI of at least 70 points, were randomized to receive maintenance

therapy of 40 mg every other week or placebo for 52 weeks. After 8 weeks, patients with flares or were unresponsive to therapy received open label 40 mg every other week and then 40 mg weekly as indicated. Colonoscopies were performed at weeks 0, 12 and 52. At 12 weeks, 27% of patients in the treatment group had mucosal healing compared with only 13% in the placebo group. At 52 weeks, mucosal healing rates were 24% and 0%, respectively. Thus, patients treated with adalimumab are more likely to achieve mucosal healing in the short and long term.

The optimal induction dose of adalimumab is 160 mg at week 0 followed by 80 mg in 2 weeks. A subsequent maintenance dose of 40 mg every other week is used for those who respond to induction. Some patients may require escalation to 40 mg weekly to maintain response [Lichtenstein *et al.* 2009]. Dose frequency escalation has been cited as a concern and some studies by Bultman and colleagues noted that over one-third of patients are dose escalated within a median of 5 months [Bultman *et al.* 2012]. A meta-analysis of 39 studies noted an average percentage of loss of response as high as 18% with a yearly risk of over 20% per patient year. Despite the need for dose escalation, it appears that decreasing the interval to weekly injections can lead to successful outcomes [Billioud *et al.* 2011].

In general, adalimumab is well tolerated with local injection site reactions including erythema, itching, pain and swelling among the more common reactions affecting 12–20%. Other common side effects include headaches and nausea as well as upper respiratory tract infections (17%). Serious infections occur at a rate of 1.42–6.7 events per 100 patient years [Burmester *et al.* 2013]. Since adalimumab is a fully human antibody, its potential for immunogenicity is quite low with the CLASSIC I and II trials showing only 0.7% and 2.6%, respectively, developing antibodies.

Certolizumab

Certolizumab pegol represents the third anti-TNF antibody for the treatment of CD. It was FDA approved in 2007 and, like adalimumab, is a human anti-TNF monoclonal antibody. Unlike the previous agents discussed, certolizumab is pegylated, meaning that a polyethylene glycol polymer is attached to the Fab' fragment, extending its half-life. Advantages of certolizumab include a

reduction in dose interval to every 4 weeks, administration through subcutaneous injection and decreased host immune response due to the absence of the Fc' portion of the antibody. Certolizumab therapy begins with 400 mg doses at weeks 0, 2 and 4, followed by 400 mg every 4 weeks for maintenance therapy [Schreiber *et al.* 2005].

PRECISE I, a multi-center, randomized, placebo-controlled trial, was the first to examine certolizumab induction therapy for moderate to severe CD [Sandborn *et al.* 2007a]. This study employed an intention-to-treat analysis and, unlike the studies on adalimumab, it defined response as a drop in the CDAI of at least 100 points rather than 70. At 6 weeks following induction, the response rate in the treatment arm was 35% *versus* 27% in the placebo arm ($p < 0.02$). There was no difference in the remission rates (CDAI < 150) at any point in the study ($p = 0.17$).

The PRECISE II trial demonstrated efficacy of certolizumab for maintenance therapy compared with placebo [Schreiber *et al.* 2007]. In this study, 668 patients were treated with certolizumab for induction therapy at weeks 0, 2 and 4. A total of 428 (64%) of them showed initial response as defined by a CDAI drop of 100 points or more by week 6 and were then randomized to receive placebo or certolizumab every 4 weeks. At week 26, 63% of patients in the treatment arm demonstrated response compared with 36% in the placebo arm. A secondary endpoint examined remission rates at week 26, and 48% of those in the treatment arm were in remission compared with 29% in the placebo group. There was no difference in benefit for patients with high (>10 mg/dl) or low (<10 mg/dl) C-reactive protein. Superiority over placebo was noted whether or not patients were taking concomitant corticosteroids or immunomodulators, or had previously taken infliximab. The disparity in 6-week response rates between PRECISE I and II (35% *versus* 64%) is not entirely understood, but may be explained in part by the high dropout rate in PRECISE I. The results of PRECISE II show that patients responsive to induction have favorable results on maintenance therapy and up to one half will be in remission at 6 months.

Patients who completed all 26 weeks of PRECISE II were offered ongoing maintenance therapy for an additional year in an open label prospective trial known as PRECISE III [Lichtenstein *et al.*

2010]. The primary outcome was to compare response and remission rates for patients receiving interrupted therapy (the placebo group from PRECISE II) *versus* continuous therapy (the treatment group from PRECISE II). In this trial the Harvey–Bradshaw index (HBI), a simplified scale of clinical disease activity was used instead of the CDAI. PRECISE III was designed to more closely reflect clinical situations faced by physicians where therapy may be interrupted for various reasons. A modest benefit of continuous over interrupted therapy was demonstrated. Patients who responded well (HBI decrease >3 points) by week 26 did well regardless of whether therapy was continuous or interrupted at both week 52 (74.4% *versus* 79.7%, respectively) and week 80 (66.1% *versus* 63.3%). PRECISE III followed patients for 7 years, with data continuing to show long-term efficacy and safety [Sandborn *et al.* 2014].

With the use of biologicals, the situation occasionally arises where a patient may lose response. This problem was addressed in the previous discussions on infliximab and adalimumab. The PRECISE IV trial, an open label extension trial, was designed to answer this question in patients taking certolizumab. In this study, patients who responded to initial therapy but relapsed at any point were offered inclusion into PRECISE IV [Sandborn *et al.* 2010b]. A total of 124 of the 168 patients meeting this criterion enrolled: 75 (61%) from the interrupted arm (group A); and 49 (39%) from the continuous arm (group B). Patients from Group A received standard induction of certolizumab at weeks 0, 2 and 4, while those from group B received an additional 400 mg called a ‘recapture dose’ at a 2-week interval between maintenance doses. Response rates were similar in both groups at 4 weeks. By 52 weeks, response rates were also similar with 37% in group A and 41% in group B. Remission rates were 36% and 35% in each group at one year.

Patients who have previously failed infliximab present a special situation. Using certolizumab, Sandborn and colleagues were able to induce response in 334 of 539 patients (62%) at week 6 and 212 (39%) at week 26 [Sandborn *et al.* 2010a]. Some of these patients were observed to enter remission. Clinicians should be aware that patients with prior exposure to any biologic agent generally have more limited response and remission rates compared with naïve patients. In general, plasma levels of are not monitored for certolizumab; however, one study demonstrated a

significant relationship between improved endoscopic mucosal healing and plasma levels of drug after 8 weeks of therapy [Colombel *et al.* 2014].

The side effect profile of certolizumab is generally acceptable and well tolerated. Less than 2% of patients experience an injection site reaction. As with all anti-TNF antibodies, certolizumab carries an increased risk of infection including reactivation of tuberculosis as well as opportunistic infections. A review of biologic therapies administered for the treatment of rheumatoid arthritis found an increased risk of infection [odds ratio (OR) 4.75 (1.52–18.65)] and hospitalizations [OR 1.57 (1.06–2.32)] but not overall adverse events [OR 1.17 (0.71–1.95)] with certolizumab compared with controls [Singh *et al.* 2011]. In studies of certolizumab for CD, there has not been an increased incidence of malignancy including leukemia, lymphoma or solid tumors in comparison with the general population. There have been three reported cases of lymphoma in all patients treated with certolizumab [Lichtenstein *et al.* 2012; Sandborn *et al.* 2014]. A more recent meta-analysis of this agent used alone for the treatment of CD included the major trials listed above and found no difference in toxicity related to treatment across the course of therapy [Da *et al.* 2013]. The most common reported adverse events include upper respiratory tract infections (20% *versus* 13% placebo), urinary tract infection (7% *versus* 6% placebo) and arthralgias (6% *versus* 4%).

Certolizumab represents an additional option for patients choosing anti-TNF antibodies to treat CD. It offers a convenience of subcutaneous injections with 4-week dosing intervals and has a safety and efficacy profile compatible with other agents. An important observation is that it is effective with or without simultaneous use of corticosteroids or immunomodulators, and induces mucosal healing.

Natalizumab

Natalizumab is an FDA approved biological agent for the treatment of moderate-to-severe CD and relapsing/remitting multiple sclerosis. It is a recombinant, humanized, monoclonal IgG4 antibody that inhibits the adhesion and subsequent migration of leukocytes into inflamed intestinal mucosa, thereby reducing inflammation. Specifically, natalizumab inhibits the binding of MAdCAM-1 to integrin $\alpha4/\beta1$ and VCAM-1

binding to $\alpha 4/\beta 1$ through the competitive inhibition of the $\alpha 4$ integrin chain [Gordon *et al.* 2001; Villablanca *et al.* 2011]. It is administered as a 300 mg intravenous infusion once every 4 weeks over 1 hour and does not require induction. Patients should be monitored for up to 1 hour postinfusion for acute reactions.

The first large trial of natalizumab included 248 patients with moderate to severe CD, randomized into one of 4 arms with the endpoint of remission (CDAI < 150) at 6 weeks [Ghosh *et al.* 2003]. The four arms included placebo, natalizumab (3mg/kg) at week 0 only, natalizumab (3mg/kg) at weeks 0 and 4, and natalizumab (6mg/kg) at weeks 0 and 4. Remission rates at 6 weeks were as follows: placebo 27%; 3 mg/kg natalizumab at week 0, 29%; natalizumab at weeks 0 and 4, 44%; in patients receiving 2 high dose infusions, 35%. Response rates at week 12 and were 43%, 50%, 61% and 65% ($p = 0.018$), respectively. The study was criticized for high response rates in the placebo group. However, as in most IBD studies, patients in the placebo group were able to continue 5-ASA compounds, oral corticosteroids and azathioprine or 6-MP or a combination of those agents.

Larger trials of natalizumab such as ENACT-1 and ENACT-2 extended the window of observation to 10 weeks and 36 weeks, respectively [Sandborn *et al.* 2005; Targan *et al.* 2007]. In ENACT-1, 905 patients (724 in the treatment arm) were randomized to receive 300 mg natalizumab at weeks, 0, 4 and 8. Response (defined as a decreased of at least 70 CDAI points) at 10 weeks in the treatment arm was 56% *versus* 49% in the placebo arm ($p = 0.05$). In ENACT-2, the 339 patients who had a response to therapy in ENACT-1 were randomized to continue 300 mg of natalizumab *versus* placebo every 4 weeks through 56 weeks. At 36 weeks, response compared with placebo was 61% *versus* 28% ($p < 0.001$) and remission rates were 44% *versus* 26% ($p = 0.003$).

The ENCORE trial added more weight of data for natalizumab by randomizing 509 patients with moderate to severe CD to receive 300 mg of natalizumab or placebo every 4 weeks [Targan *et al.* 2007]. The primary endpoint was a response defined as a >70 point decrease in CDAI at weeks 8 through 12. The secondary endpoint was sustained remission (CDAI < 150) at both 8 and 12 weeks. The response rate was 48% in the treat-

ment arm *versus* 32% in the placebo arm ($p = 0.001$). Remission rates were 26% and 16% in the treatment and placebo arms, respectively ($p = 0.002$).

Given its unique mechanism of action to other biologic agents, natalizumab has the potential to be used concurrently with other biologic agents. Sands and colleagues evaluated the safety and tolerability of simultaneous treatment with natalizumab and infliximab [Sands *et al.* 2007]. In this study patients who had been previously treated with at least 8 weeks of infliximab at 5mg/kg were randomized in a 2:1 fashion to receive natalizumab 300 mg every 4 weeks ($n = 52$) *versus* placebo plus infliximab. The primary endpoint was short-term safety and tolerability. Secondary endpoints included efficacy, health-related quality of life, and inflammatory markers. There was no significant difference in adverse events associated with each arm: 92% in the dual therapy group and 100% in the infliximab plus placebo group experienced side effects. The most common adverse events were headache, exacerbation of CD, nausea and nasopharyngitis. The mean decrease in the CDAI was 37.7 points in the dual therapy arm compared with an increase by 3.5 points in the monotherapy group ($p = 0.08$).

A Cochrane review of natalizumab therapy including the above four trials concluded its effectiveness for induction of clinical response and remission in patients with moderate to severe CD [MacDonald and MacDonald, 2007]. The number needed to treat (NNT) to gain response with a single infusion was 17; if two infusions were given, the NNT decreased to 10. The NNT for response and remission following three infusions was 12 and 10, respectively, at 12 weeks. Another systematic review showed that failure to achieve remission occurred in 65.4% of patients receiving natalizumab at weeks 2 to 12 compared with 77.3% of patients receiving placebo [Ford *et al.* 2011]. Moreover, both studies found a similar incidence of side effects with natalizumab and placebo therapy.

Another report found that 69% of patients with extensive ileocolonic disease who had failed prior conventional immunosuppressants and *at least* two anti-TNF agents exhibited at least partial response (a decrease in HBI by ≥ 3 points) to natalizumab [Ananthakrishnan *et al.* 2012]. Juillerat and colleagues noted a 46% clinical

response (HBI decrease ≥ 3 points) and a 56% cumulative probability of achieving remission (HBI < 4) within one year [Juillerat *et al.* 2013]. Other efficacy studies have examined a clinical response as defined above, the ability to decrease steroid requirements and mucosal healing [Kane *et al.* 2012; Sakuraba *et al.* 2013a]. Observations at 1 year found 42% of patients demonstrating a clinical response and 50% enjoying a reduction in steroids [Sakuraba *et al.* 2013b]. Mucosal healing was reported in 42.3% following a mean of 14.1 months of therapy. It is important to remember that the majority of participants in these studies had failed immunomodulators and anti-TNF agents.

The potential for developing progressive multifocal leukoencephalopathy (PML) has limited the widespread use of natalizumab outside centers of excellence. Although rare, it is often fatal and there is no successful treatment. It seems to be more prevalent in patients with multiple sclerosis (MS) than in those treated for CD. A meta-analysis of 99,571 patients with MS found 212 cases of PML (2.1 cases per 1000 patients) [Kleinschmidt-DeMasters and Tyler, 2005]. Patients at highest risk for PML include those with antibodies to the John Cunningham (JC) virus, prior use of immunosuppressants, received natalizumab for >2 years, female sex (70.5%) and patients beyond 40 years of age (Van Assche *et al.* 2005; Bloomgren *et al.* 2012). A more recent paper has shown the number of MS patients with PML to be 319 [Verbeeck *et al.* 2008]. If a clinician decides to use natalizumab, the patient must undergo screening for anti-JC antibodies and enroll in the safety follow-up program, CD-TOUCH.

Vedolizumab

Vedolizumab is a recombinant humanized, anti- α -4/ β -7 integrin monoclonal antibody. To exit the intravascular compartment and invade affected mucosa, leukocytes must adhere to vascular endothelium and exit the blood stream through diapedesis. The three families of molecules that aid in the leukocyte adhesion to the endothelial wall are selectins (expressed on both the leukocyte and endothelium), integrins (expressed on the leukocyte cell wall) and immunoglobulins (primarily found on the endothelium) [Van Deventer, 1990].

α -4/ β -7 Integrin is relatively specific to the gastrointestinal tract and does not bind to the more ubiquitous α -4/ β -1 integrin found in brain and other tissue, and should thus theoretically

decrease the risk of PML associated with natalizumab. Following a small concept study that suggested a dose-dependent response to vedolizumab, the major trial preceding FDA approval was GEMINI 2 [Feagan *et al.* 2008].

In GEMINI 2, 368 patients with moderate to severe CD who had failed at least one conventional therapy exhibited increased rates of inducing remission with 300 mg intravenous (IV) vedolizumab at weeks 0 and 2 compared with placebo (15.6% *versus* 6.8%, $p = 0.02$) at 6 weeks [Sandborn *et al.* 2013]. A difference in response rates in this group was not seen. A second open label arm of 747 patients demonstrated similar response and remission rates (34.4% and 17.7%, respectively). Patients from both arms who responded to induction therapy were then randomized to vedolizumab every 8 weeks, every 4 weeks, or placebo for 52 weeks. At the conclusion of the study, 39% of patients in the 8-week group and 36.4% in the 4-week group were in remission, compared with 21.6% in the placebo group ($p = 0.001$ and $p = 0.004$, respectively). Secondary endpoints including CDAI response and steroid-free remission were significantly greater in the vedolizumab groups as compared with placebo but durable remission (defined as CDAI < 150 points during $\geq 80\%$ of the study) was similar among all 3 arms. No cases of PML were observed in this trial, nor have any been reported since. If vedolizumab presented the same increased risk of PML as natalizumab, we would expect to have seen at least four cases reported at the present time. Serious side effects were more common in the vedolizumab groups compared with placebo (24.4% *versus* 15.3%). Though continued observational data registries will shed further light onto both efficacy and safety over the coming years, vedolizumab is a welcome addition to our arsenal against CD.

Emerging therapies

Several other anti-TNF α agents have been evaluated for the treatment of CD including etanercept (inactivates TNF by binding to TNF p75 receptor protein), oncept (soluble p55 TNF receptor) and CDP571, but none have been found to be efficacious [Sandborn *et al.* 2001; Feagan *et al.* 2005; Rutgeerts *et al.* 2006].

All the agents discussed above attempt to calm or suppress inflammation. This strategy is also applied in many new molecules undergoing clinical study. Since inflammation occurs when

leukocytes migrate into areas of mucosal injury and release toxic cytokines, attention has been turned toward developing agents that either prevent the travel of leukocytes or bind specific cytokines. Those given the most attention include IL 6, 10, 11, 12, 17 and 23, and chemokine receptor antagonists. IL-12 research did not produce sufficient results [Mannon *et al.* 2004], but better outcomes have been observed with ustekinumab, a combined antibody directed at both IL-12 and IL-23 [Burakoff *et al.* 2006; Sandborn *et al.* 2008]. In the CERTIFI trial, ustekinumab demonstrated efficacy over placebo for response (69.4% *versus* 42.5%) and remission (41.7% *versus* 27.4%) at 22 weeks as maintenance therapy [Sandborn *et al.* 2012]. Notably, no significant benefit was noted for induction therapy in these 526 patients.

The other agent receiving some interest is tocilizumab, a humanized antibody directed toward IL-6. It has received FDA approval for rheumatoid arthritis and one pilot study for CD observed an 80% response rate to treatment compared with 31% in the placebo arm [Ito *et al.* 2004]. Further trials may be seen in the future.

The PROTECT-1 study group has been investigating the effectiveness of CCX282-B, an oral antagonist to CCR9, a chemokine that manages the migration and activation of leukocytes in the intestine [Bekker *et al.* 2007]. Promising *in vitro* studies led to a trial of CCX282-B in 436 patients for induction and maintenance [Keshav *et al.* 2009, 2013]. Despite equivocal initial response rates, at 52 weeks, 47% of patients receiving CCX282-B were in remission compared with 31% of the placebo group ($p = 0.01$). It should be mentioned that 26% of these patients had received one anti-TNF prior to screening and nearly 13% of the total group had failed one or more of these agents. With an increased understanding of CD pathophysiology, multiple exciting new agents are being developed in labs around the world each year.

Conclusion

Research from the past 20 years has given us the ability to alter the course of CD, a condition not only physically demanding, but one that carries a significant psychosocial impact. The anti-TNF α antagonists that are commercially available offer similar efficacy and safety profiles that are generally acceptable for a condition associated with such morbidity. Many major trials as well as

clinical experience have shown that as a class, biologicals can induce rapid response and remission rates. Additionally, patients who show benefit early in the course of treatment predictably do well over a prolonged period of time. Moreover, those who do not initially respond to a given agent are unlikely to improve with continued treatment and should be offered an alternative approach. In general, therapies directed toward the α/β integrins have a slower onset of action than the anti-TNF α antibodies, necessitating a degree of patience when deploying these drugs. Once thought to be a last resort, biological therapies are enjoying mainstream acceptance and are becoming conventional if not standard of care practice, although further research is needed [Lichtenstein *et al.* 2009]. Research is also underway exploring hypotheses that using biologicals early in the course of CD may offer higher response and remission rates. The future is bright with the advent of newer and potentially safer and more effective tools for CD as well as learning how to maximize the agents already at our disposal.

Conflict of interest statement

Dr. Randall receives research funding, speaking or consulting fees from: Abbvie, UCB, Janssen, Takeda, Salix, Prometheus, Amgen and Bristol-Meyers Squibb.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

- Ananthakrishnan, A., Hur, C. and Korzenik, R. (2012) Certolizumab pegol compared to natalizumab in patients with moderate to severe Crohn's disease: results of a decision analysis. *Dig Dis Sci* 57: 472–480.
- Andoh, A., Yagi, Y., Shioya, M., Nishida, A., Tsujikawa, T. and Fujiyama, Y. (2008) Mucosal cytokine network in inflammatory bowel disease. *World J Gastroenterol* 14: 5154.
- Ardizzone, S., Puttini, P., Cassinotti, A. and Porro, G. (2008) Extraintestinal manifestations of inflammatory bowel disease. *Digest Liver Dis* 40: 253–259.
- Aufses, A. Jr. (2001) The history of Crohn's disease. *Surg Clin N Am* 81: 1–11.
- Bandzar, S., Gupta, S. and Platt, M. (2013) Crohn's disease: a review of treatment options and current research. *Cell Immunol* 286: 45–52.

- Baumgart, D. and Sandborn, W. (2012) Crohn's disease. *Lancet* 380: 1590–1605.
- Bekker, P., Schreiber, S. and Keshav, S. (2007) PROTECT-1, prospective randomized oral therapy evaluation of CCX282-B (TRAFICET-EN) in Crohn's disease. *Gut* 56: A23.
- Ben-Horin, S., Yavzori, M., Kopylov, U., Picard, O., Fudim, E., Eliakim, R. *et al.* (2011) Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. *J Crohn's Colitis* 5: 555–558.
- Beutler, B., Milsark, I. and Cerami, A. (1985) Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. *Science* 229: 869–871.
- Billioud, V., Sandborn, W. and Peyrin-Biroulet, L. (2011) Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. *Am J Gastroenterol* 106: 674–684.
- Bloomgren, G., Richman, S., Hotermans, C., Subramanyam, M., Goelz, S., Natarajan, A. *et al.* (2012) Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Eng J Med* 366: 1870–1880.
- Bouhnik, Y., Scemama, G., Tai, R., Matuchansky, C., Rambaud, J., Lémann, M. *et al.* (1996) Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Lancet* 347: 215–219.
- Bultman, E., de Haar, C., van Liere-Baron, A., Verhoog, H., West, R., Kuipers, E. *et al.* (2012) Predictors of dose escalation of adalimumab in a prospective cohort of Crohn's disease patients. *Alim Pharm Ther* 35: 335–341.
- Burakoff, R., Barish, C., Riff, D., Pruitt, R., Chey, W., Farraye, F. *et al.* (2006) A phase 1/2A trial of STA 5326, an oral interleukin-12/23 inhibitor, in patients with active moderate to severe Crohn's disease. *Inflamm Bowel Dis* 12: 558–565.
- Burisch, J., Jess, T., Martinato, M. and Lakatos, P. (2013) The burden of inflammatory bowel disease in Europe. *J Crohns Colitis* 7: 322–337.
- Burmester, G., Panaccione, R., Gordon, K., McIlraith, M. and Lacerda, A. (2013) Adalimumab: Long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis* 72: 517–524.
- Cheent, K., Nolan, J., Shariq, S., Kiho, L., Pal, A. and Arnold, J. (2010). Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J Crohns Colitis* 4: 603–605.
- Cheifetz, A. and Mayer, L. (2005) Monoclonal antibodies, immunogenicity and associated infusion reactions. *Mt Sin J Med* 72: 250–256.
- Cheifetz, A., Smedley, M., Martin, S., Reiter, M., Leone, G., Mayer, L. *et al.* (2003) The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol* 98: 1315–1324.
- Colombel, J., Sandborn, W., Allez, M., Dupas, J., Dewit, O., D'Haens, G. *et al.* (2014) Association between plasma concentrations of certolizumab pegol and endoscopic outcomes of patients with Crohn's disease. *Clin Gastroenterol Hepatol* 12: 423–431.
- Colombel, J., Sandborn, W., Reinisch, W., Mantzaris, G., Kornbluth, A., Rachmilewitz, D. *et al.* (2010) Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Eng J Med* 362: 1383–1395.
- Colombel, J., Sandborn, W., Rutgeerts, P., Enns, R., Hanauer, S., Panaccione, R. *et al.* (2007) Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: The CHARM trial. *Gastroenterology* 132: 52–65.
- Cosnes, J., Gower-Rousseau, C., Seksik, P. and Cortot, A. (2011) Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 140: 1785–1794.
- Crohn, B., Ginzburg, L. and Oppenheimer, G. (1932) Regional ileitis: a pathologic and clinical entity. *JAMA* 99: 1323–1329.
- D'Haens, G., Van Deventer, S., Van Hogezaand, R., Chalmers, D., Kothe, C., Baert, F. *et al.* (1999) Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. *Gastroenterology* 116: 1029–1034.
- Da, W., Zhu, J., Wang, L. and Lu, Y. (2013) Efficacy and safety of certolizumab pegol for Crohn's disease: a systematic review and meta-analysis. *Adv Ther* 30: 541–553.
- Das, K. (1999) Relationship of extraintestinal involvements in inflammatory bowel disease (new insights into autoimmune pathogenesis). *Dig Dis Sci* 44: 1–13.
- Elliott, M., Maini, R., Feldmann, M., Long-Fox, A., Charles, P., Katsikis, P. *et al.* (1993) Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. *Arthritis Rheum* 36: 1681–1690.
- Feagan, B., Greenberg, G., Wild, G., Fedorak, R., Paré, P., McDonald, J. *et al.* (2008) Treatment of active Crohn's disease with MLN0002, a humanized antibody to the $\alpha 4\beta 7$ integrin. *Clin Gastroenterol Hepatol* 6: 1370–1377.

- Feagan, B., Sandborn, W., Baker, J., Cominelli, F., Sutherland, L., Elson, C. *et al.* (2005) A randomized, double-blind, placebo-controlled trial of CDP571, a humanized monoclonal antibody to tumour necrosis factor- α , in patients with corticosteroid-dependent Crohn's disease. *Alim Pharm Ther* 21: 373–384.
- Feldman, M. and Maini, R. (2001) Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? *Ann Rev Immunol* 19: 163–169.
- Ford, A., Sandborn, W., Khan, K., Hanauer, S., Talley, N. and Moayyedi, P. (2011) Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 106: 644–659.
- Foster, A. and Jacobson, K. (2013) Changing Incidence of inflammatory bowel disease: environmental influences and lessons learnt from the South Asia population. *Front Pediatr* 1: 1–7.
- Friedman, S. and Blumberg, R.S. (2012) Inflammatory bowel disease. In: Longo, D.L., Fauci, A.S., Kasper, D.L., Hauser, S.L., Jameson, J. and Loscalzo, J. (eds), *Harrison's Principles of Internal Medicine*, 18th edn. New York, NY: Mc-Graw Hill, pp. 2477–2495.
- Gawron, L., Hammond, C. and Ernst, L. (2013) perinatal pathologic examination of non-intact, second trimester fetal demise specimens: the value of standardization. *Arch Pathol Lab Med* 167: 326–331.
- Ghosh, S., Goldin, E., Gordon, F., Malchow, H., Rask-Madsen, J., Rutgeerts, P. *et al.* (2003) Natalizumab for active Crohn's disease. *N Engl J Med* 348: 24–32.
- Gordon, F., Lai, C., Hamilton, M., Allison, M., Srivastava, E., Fouweather, M. *et al.* (2001) A randomized placebo-controlled trial of a humanized monoclonal antibody to $\alpha 4$ integrin in active Crohn's disease. *Gastroenterology* 121: 268–274.
- Greenstein, A., Sachar, D., Mann, D., Lachman, P., Heimann, T. and Aufses, A Jr (1987) Spontaneous free perforation and perforated abscess in 30 patients with Crohn's disease. *Ann Surg* 205: 72–76.
- Hanauer, S., Feagan, B., Lichtenstein, G., Mayer, L., Schreiber, S., Colombel, J. *et al.* (2002) Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 359: 1541–1549.
- Hanauer, S., Sandborn, W., Rutgeerts, P., Fedorak, R., Lukas, M., MacIntosh, D. *et al.* (2006) Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC trial. *Gastroenterology* 130: 323–33.
- Harris, F., Bell, G. and Brunn, H. (1933) Chronic cicatrizing enteritis: regional ileitis (Crohn). A new surgical entity. *Surg Gynecol Obstet* 57: 637–645.
- Hart, A. and Ng, S. (2011) Crohn's disease. *Medicine* 39: 229–236.
- Hugot, J., Chamaillard, M., Zouali, H., Lesage, S., Cézard, J., Belaiche, J. *et al.* (2001) Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* 411: 599–603.
- Ito, H., Takazoe, M., Fukuda, Y., Hibi, T., Kusugami, K., Andoh, A. *et al.* (2004) A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 126: 989–996.
- Juillera, P., Wasan, S., Fowler, S., Friedman, S., Pabby, V., Coukas, J. *et al.* (2013) Efficacy and safety of natalizumab in Crohn's disease patients treated at 6 Boston academic hospitals. *Inflamm Bowel Dis* 19: 2457–2463.
- Kane, S., Horst, S., Sandborn, W., Becker, B., Neis, B., Moscarello, M. *et al.* (2012) Natalizumab for moderate to severe Crohn's disease in clinical practice: the Mayo Clinic Rochester experience. *Inflamm Bowel Dis* 18: 2203–2208.
- Keffer, J., Probert, L., Cazlaris, H., Georgopoulos, S., Kaslaris, E., Kioussis, D. *et al.* (1991) Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. *EMBO J* 10: 4025–4031.
- Keshav, S., Johnson, D., Bekker, P. and Schall, T. (2009) PROTECT-1 study demonstrated efficacy of the intestine-specific chemokine receptor antagonist CCX282-B (Traficet-EN) in treatment of patients with moderate to severe Crohn's disease. *Gastroenterology* 136: A65.
- Keshav, S., Vaňásek, T., Niv, Y., Petryka, R., Howaldt, S., Bafutto, M. *et al.* (2013) A randomized controlled trial of the efficacy and safety of CCX282-B, an orally-administered blocker of chemokine receptor CCR9, for patients with Crohn's disease. *PLoS One*, 8: e60094.
- Kirsner, J. (1988) Historical aspects of inflammatory bowel disease. *J Clin Gastroenterol* 10: 286–297.
- Kleinschmidt-DeMasters, B. and Tyler, K. (2005) Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med* 353: 369–374.
- Lichtenstein, G., Hanauer, S. and Sandborn, W. (2009) Practice Parameters Committee of American College of Gastroenterology; management of Crohn's disease in adults. *Am J Gastroenterol* 104: 465–483.
- Lichtenstein, G., Olson, A., Travers, S., Diamond, R., Chen, D., Pritchard, M. *et al.* (2006) Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. *Am J Gastroenterol* 101: 1030–1038.

- Lichtenstein, G., Panaccione, R. and Mallarkey, G. (2008) Efficacy and safety of adalimumab in crohn's disease. *Ther Adv Gastroenterol* 1: 43–50.
- Lichtenstein, G., Rutgeerts, P., Sandborn, W., Sands, B., Diamond, R., Blank, M. *et al.* (2012) A pooled analysis of infections, malignancy and mortality in infliximab-and immunomodulator-treated adult patients with inflammatory bowel disease. *Am J Gastroenterol* 107: 1051–1063.
- Lichtenstein, G., Thomsen, O., Schreiber, S., Lawrance, I., Hanauer, S., Bloomfield, R. *et al.* (2010) Continuous therapy with certolizumab pegol maintains remission of patients with Crohn's disease for up to 18 months. *Clin Gastroenterol Hepatol* 8: 600–609.
- Lichtenstein, G., Yan, S., Bala, M., Blank, M. and Sands, B. (2005) Infliximab maintenance treatment reduces hospitalizations, surgeries and procedures in fistulizing Crohn's disease. *Gastroenterology* 128: 862–869.
- Lockhart-Mummery, H. and Morson, B. (1960) Crohn's disease (regional enteritis) of the large intestine and its distinction from ulcerative colitis. *Gut* 1: 87–105.
- Loftus, E., Schoenfeld, P. and Sandborn, W. (2002) The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. *Alim Pharm Ther* 16: 51–60.
- MacDonald, J. and McDonald, J. (2007) Natalizumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 24 January 2007. DOI: 10.1002/14651858.CD006097.pub2.
- MacDonald, T., Hatchings, P., Choy, M., Munch, S. and Cooke, A. (1990) Tumor necrosis factor- α and interferon gamma production measured at the single cell level in normal and inflamed human intestine. *Clin Exp Immunol* 81: 301–305.
- Mahadevan, U., Cucchiara, S., Hyams, J., Steinwurz, F., Nuti, F., Travis, S. *et al.* (2011) The London position statement of the world congress of gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. *Am J Gastroenterol* 106: 214–223.
- Mahadevan, U., Wolf, D., Dubinsky, M., Cortot, A., Lee, S., Siegel, C. *et al.* (2013) Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 11: 286–292.
- Mannon, P., Fuss, I., Mayer, L., Elson, C., Sandborn, W., Present, D. *et al.* (2004) Anti-interleukin-12 antibody for active Crohn's disease. *N Engl J Med* 351: 2069–2079.
- Ng, S., Tang, W., Ching, J., Wong, M., Chow, C., Hui, A. *et al.* (2013) Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn's and colitis epidemiology study. *Gastroenterology* 145: 158–165.
- Ogura, Y., Bonen, D., Inohara, N., Nicolae, D., Chen, F., Ramos, R. *et al.* (2001) A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature* 411: 603–606.
- Parsi, M., Achkar, J., Richardson, S., Katz, J., Hammel, J., Lashner, B. *et al.* (2002) Predictors of response to infliximab in patients with Crohn's disease. *Gastroenterology* 123: 707–713.
- Perez-Alvarez, R., Pérez-de-Lis, M., Ramos-Casals, M. and BIOGEAS Study Group (2013) Biologics-induced autoimmune diseases. *Curr Opin Rheumatol* 25: 56–64.
- Podolsky, D. (2002) Inflammatory bowel disease. *N Engl J Med*. 347: 417–429.
- Randall, C., Vizuete, J., Wendorf, G., Ayyar, B. and Constantine, G. (2012) Current and emerging strategies in the management of Crohn's disease. *Best Pract Res Clin Gastroenterol* 26: 601–610.
- Rankin, G., Watts, H., Melnyk, C. and Kelley, M Jr. (1979) National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. *Gastroenterology* 77: 914–920.
- Rosman, Z., Shoenfeld, Y. and Zandman-Goddard, G. (2013) Biologic therapy for autoimmune diseases: an update. *BMC Med* 11: 88.
- Rutgeerts, P., Geboes, K., Vantrappen, G., Beyls, J., Kerremans, R. and Hiele, M. (1990) Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 99: 956–963.
- Rutgeerts, P., Sandborn, W., Fedorak, R., Rachmilewitz, D., Tarabar, D., Gibson, P. *et al.* (2006) Onercept for moderate-to-severe Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol* 4: 888–893.
- Rutgeerts, P., Van Assche, G., Sandborn, W., Wolf, D., Geboes, K., Colombel, J. *et al.* (2012) Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 142: 1102–1111.
- Sakuraba, A., Keyashian, K., Correia, C., Melek, J., Cohen, R., Hanauer, S. *et al.* (2013a) Natalizumab in Crohn's disease: results from a US tertiary inflammatory bowel disease center. *Inflamm Bowel Dis* 19: 621–626.
- Sakuraba, A., Annunziata, M., Cohen, R., Hanauer, S. and Rubin, D. (2013b) Mucosal healing is associated with improved long-term outcome of

- maintenance therapy with natalizumab in Crohn's disease. *Inflamm Bowel Dis* 19: 2577–2583.
- Salim, S. and Soderholm, J. (2011) Importance of disrupted intestinal barrier in inflammatory bowel diseases. *Inflamm Bowel Dis* 17: 362–381.
- Sandborn, W., Abreu, M., D'Haens, G., Colombel, J., Vermeire, S., Mitchev, K. *et al.* (2010a) Certolizumab pegol in patients with moderate to severe Crohn's disease and secondary failure to infliximab. *Clin Gastroenterol Hepatol* 8: 688–695.
- Sandborn, W., Colombel, J., Enns, R., Feagan, B., Hanauer, S., Lawrance, I. *et al.* (2005) Natalizumab induction and maintenance therapy for Crohn's disease. *N Eng J Med* 353: 1912–1925.
- Sandborn, W. and Feagan, B. (2003) Review article: mild to moderate Crohn's disease – defining the basics for new treatment algorithm. *Alim Pharm Ther* 18: 263–277.
- Sandborn, W., Feagan, B., Fedorak, R., Scherl, E., Fleisher, M., Katz, S. *et al.* (2008) A randomized trial of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 135: 1130–1141.
- Sandborn, W., Feagan, B., Rutgeerts, P., Hanauer, S., Colombel, J., Sands, B. *et al.* (2013) Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Eng J Med* 369: 711–721.
- Sandborn, W., Feagan, B., Stoinov, S., Honiball, P., Rutgeerts, P., Mason, D. *et al.* (2007a) Certolizumab pegol for the treatment of Crohn's disease. *N Eng J Med* 357: 228–238.
- Sandborn, W., Gasink, C., Gao, L., Blank, M., Johanss, J., Guzzo, C. *et al.* (2012) Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Eng J Med* 367: 1519–1528.
- Sandborn, W., Hanauer, S., Katz, S., Safdi, M., Wolf, D., Baerg, R. *et al.* (2001) Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 121: 1088–1094.
- Sandborn, W., Hanauer, S., Rutgeerts, P., Fedorak, R., Lukas, M., MacIntosh, D. *et al.* (2007b) Adalimumab for maintenance treatment of Crohn's disease: Results of the CLASSIC II trial. *Gut* 56: 1232–1239.
- Sandborn, W., Lee, S., Randall, C., Gutierrez, A., Schwartz, D., Ambarkhane, S. *et al.* (2014) Long-term safety and efficacy of certolizumab pegol in the treatment of Crohn's disease: 7-year results from the PRECiSE 3 study. *Alim Pharm Ther* 40: 903–916.
- Sandborn, W., Rutgeerts, P., Enns, R., Hanauer, S., Colombel, J., Panaccione, R. *et al.* (2007c) Adalimumab induction therapy for crohn's disease previously treated with infliximab: A randomized trial. *Ann Int Med* 146: 829–838.
- Sandborn, W., Schreiber, S., Hanauer, S., Colombel, J., Bloomfield, R., Lichtenstein, G. *et al.* (2010b) Reinduction with certolizumab pegol in patients with relapsed Crohn's disease: results from the PRECiSE 4 Study. *Clin Gastroenterol Hepatol* 8: 696–702.
- Sands, B., Anderson, F., Bernstein, C., Chey, W., Feagan, B., Fedorak, R. *et al.* (2004a) Infliximab maintenance therapy for fistulizing Crohn's disease. *N Eng J Med* 350: 876–885.
- Sands, B., Blank, M., Patel, K. and Van Deventer, S. (2004b) Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. *Clin Gastroenterol Hepatol* 2: 912–920.
- Sands, B., Kozarek, R., Spainhour, J., Barish, C., Becker, S., Goldberg, L. *et al.* (2007) Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. *Inflamm Bowel Dis* 13: 2–11.
- Sartor, R. (2006) Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol* 3: 390–407.
- Schreiber, S., Khaliq-Kareemi, M., Lawrance, I., Thomsen, O., Hanauer, S., McColm, J. *et al.* (2007) Maintenance therapy with certolizumab pegol for Crohn's disease. *N Eng J Med* 357: 239–250.
- Schreiber, S., Rutgeerts, P., Fedorak, R., Khaliq-Kareemi, M., Kamm, M., Boivin, M. *et al.* (2005) A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology* 129: 807–818.
- Shivananda, S., Lennard-Jones, J., Logan, R., Fear, N., Price, A., Carpenter, L. *et al.* (1996) Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut* 39: 690–697.
- Singh, J., Wells, G., Christensen, R., Tanjong Ghogomu, E., Maxwell, L., MacDonald, J. *et al.* (2011) Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 16 February 2011. DOI: 10.1002/14651858.CD008794.pub2.
- Sokol, H., Seksik, P., Furet, J., Firmesse, O., Nion-Larmurier, I., Beaugerie, L. *et al.* (2009) Low counts of *Faecalibacterium prausnitzii* in colitis microbiota. *Inflamm Bowel Dis* 15: 1183–1189.
- Targan, S., Feagan, B., Fedorak, R., Lashner, B., Panaccione, R., Present, D. *et al.* (2007) Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. *Gastroenterology* 132: 1672–1683.

- Targan, S., Hanauer, S., van Deventer, S., Mayer, L., Present, D., Braakman, T. *et al.* (1997) A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. *N Eng J Med* 337: 1029–1036.
- Van Assche, G., Dignass, A., Reinisch, W., van der Woude, C., Sturm, A., De Vos, M. *et al.* (2010) The second European evidence-based consensus on the diagnosis and management of Crohn's disease: special situations. *J Crohns Colitis* 4: 63–101.
- Van Assche, G., Van Ranst, M., Sciot, R., Dubois, B., Vermeire, S., Noman, M. *et al.* (2005) Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Eng J Med* 353: 362–368.
- Van Assche, G., Vermeire, S., Ballet, V., Gabriels, F., Noman, M., D'Haens, G. *et al.* (2012) Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. *Gut* 61: 229–234.
- Van Deventer, S. (1999) Anti-TNF antibody treatment of Crohn's disease. *Ann Rheum Dis* 58: I114–I120.
- Van Dullemen, H., van Deventer, S., Hommes, D., Bijl, H., Jansen, J., Tytgat, G. *et al.* (1995) Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). *Gastroenterology* 109: 129–135.
- Verbeeck, J., Van Assche, G., Ryding, J., Wollants, E., Rans, K., Vermeire, S. *et al.* (2008) JC viral loads in patients with Crohn's disease treated with immunosuppression: can we screen for elevated risk of progressive multifocal leukoencephalopathy?. *Gut* 57: 1393–1397.
- Villablanca, E., Cassani, B., von Andrian, U. and Mora, J. (2011) Blocking lymphocyte localization to the gastrointestinal mucosa as a therapeutic strategy for inflammatory bowel diseases. *Gastroenterology* 140: 1776–1784.
- Vultaggio, A., Matucci, A., Nencini, F., Pratesi, S., Parronchi, P., Rossi, O. *et al.* (2010) Anti-infliximab IgE and non-IgE antibodies and induction of infusion-related severe anaphylactic reactions. *Allergy* 65: 657–661.
- Wagh, A., Garg, S., Matic, K., Gramlich, L., Wong, C., Sadowski, D. *et al.* (2010) Maintenance of clinical benefit in Crohn's disease patients after discontinuation of infliximab: long-term follow-up of a single centre cohort. *Alim Pharm Ther* 32: 1129–1134.
- Xavier, R. and Podolsky, D. (2007) Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 448: 427–434.
- Zelinkova, Z., van der Ent, C., Bruin, K., van Baalen, O., Vermeulen, H., Smalbraak, H. *et al.* (2013) Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. *Clin Gastroenterol Hepatol* 11: 318–321.
- Zhang, Y. and Li, Y. (2014) Inflammatory bowel disease: pathogenesis. *World J Gastroenterol* 20: 91.

Visit SAGE journals online
<http://tag.sagepub.com>

SAGE journals