Infliximab in inflammatory bowel disease

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Konstantinos Papamichael*, Steve Lin*, Matthew Moore*, Garyfallia Papaioannou*, Lindsey Sattler* and Adam S. Cheifetz*

Abstract: Anti-tumor necrosis factor (TNF) therapy has revolutionized the medical treatment of the inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis. Twenty years ago, infliximab became the first anti-TNF agent approved for IBD. Data from randomized controlled trials, large observational cohort studies, postmarketing registries, and meta-analyses show that infliximab is a very effective treatment for moderate to severe IBD with a good safety profile. Infliximab has been also used to treat pouchitis following an ileal pouch–anal anastomosis (IPAA) after restorative proctocolectomy and to prevent postoperative recurrence following an ileocolonic resection for CD with good results. Nevertheless, up to 30% of patients show no clinical benefit following induction and up to 50% lose response over time. Both these unwanted outcomes can be largely explained by inadequate drug concentrations and frequently by the development of antibodies to infliximab. Loss of response can be managed efficiently and often prevented by applying therapeutic drug monitoring. Recently, the first biosimilars of infliximab have been approved and are utilized in clinical practice with comparable efficacy and safety with the originator. This review will mainly focus on the efficacy of infliximab in IBD.

Keywords: anti-TNF therapy, biosimilar, Crohn's disease, therapeutic drug monitoring, ulcerative colitis

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Correspondence to:
Konstantinos Papamichael
Center for Inflammatory Bowel Disease, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA
kpapamic@bidmc.harvard.edu

Steve Lin
Matthew Moore
Lindsey Sattler
Adam S. Cheifetz
Center for Inflammatory Bowel Diseases, Division of Gastroenterology, Beth-Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Garyfallia Papaioannou
North Florida Regional Medical Center, Internal Medicine Residency Program, University of Central Florida, College of Medicine, Gainesville, FL, USA

*equal contribution

Introduction

Inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are chronic, relapsing inflammatory disorders of the gastrointestinal (GI) tract.[1,2] CD can involve any part of the GI tract from the mouth to the anus and is characterized by a noncontinuous, transmural mucosal inflammation, whereas UC causes a continuous, mucosal inflammation of the colon starting in the rectum.[1,2] Medical treatment for IBD typically targets inflammatory mediators and include aminosalicylates, corticosteroids, immunomodulators (IMMs), such as thiopurines and methotrexate, and biological therapies including anti-tumor necrosis factor (TNF) therapies.[1,2]

Infliximab, a chimeric monoclonal IgG1 antibody against TNF, was the first biologic approved for the treatment of moderate to severe IBD 20 years ago. Infliximab has a half-life of approximately 14 days, is administered intravenously (iv) by weight-based dosing and is typically dosed every 4–8 weeks following an initial loading period (0–2–6 weeks).[3] Data from randomized controlled trials (RCTs) (Table 1), large observational cohort studies, post-marketing registries and meta-analyses show that infliximab is very effective at treating IBD.[4–29] However, up to 30% of patients show no clinical benefit after induction phase [primary nonresponse (PNR)] and up to 50% have to discontinue therapy, either for secondary loss of response (SLR) or a serious adverse event (SAE), such as infusion reaction, infection and malignancy.[4–29] Both PNR and SLR can be largely explained by low or undetectable concentrations due to increased nonimmune clearance and/or immunogenicity, defined as the development of antibodies to infliximab.[30,31] Many association studies have demonstrated a relation between infliximab trough concentrations and objective therapeutic outcomes in IBD, especially during maintenance treatment (Table 2).[32–44] Therapeutic drug

Table 1. Data from randomized controlled trials regarding efficacy and safety of infliximab in inflammatory bowel disease.

N	Follow up (weeks)	Medication	Clinical response (%)	SAE (%)	Serious infection (%)	Infusion reaction (%)	Reference
A. Crohn's disease							
108	12	Placebo ($n = 25$)	12	NR	NR	NR	Targan *et al.*[4]
		IFX 5 mg/kg ($n = 27$)	48			NR	
		IFX 10 mg/kg ($n = 28$)	29			NR	
		IFX 20 mg/kg ($n = 28$)	46			NR	
94	18	Placebo ($n = 31$)	26	NR	NR	NR	Present *et al.*[5]
		IFX 5 mg/kg ($n = 31$)	68			NR	
		IFX 10 mg/kg ($n = 32$)	56			NR	
335	54	Placebo ($n = 110$)	21[a]	29	4	9	Hanauer *et al.*[6]
		IFX 5 mg/kg ($n = 113$)	39[a]	28	4	23	
		IFX 10 mg/kg ($n = 112$)	45[a]	22	3	19	
195	54	Placebo ($n = 99$)	23	23	6	17	Sands *et al.*[7]
		IFX 5 mg/kg ($n = 96$)	46	14	3	16	
113	54	Thiopurines+placebo ($n = 56$)	22[b]	5	NR	0	Lemann *et al.*[8]
		Thiopurines+IFX 5 mg/kg ($n = 57$)	38[b]	5	NR	4	
508	30	AZA 2.5 mg/kg ($n = 170$)	30[b]	27	6	6	Colombel *et al.*[9]
		IFX 5 mg/kg ($n = 169$)	44[b]	18	5	17	
		AZA 2.5 mg/kg + IFX 5 mg/kg ($n = 169$)	57[b]	15	4	5	
B. Ulcerative colitis							
364	54	Placebo ($n = 121$)	20	26	4	11	Rutgeerts *et al.*[10]
		IFX 5 mg/kg ($n = 121$)	55	22	3	10	
		IFX 10 mg/kg ($n = 122$)	54	24	7	12	
364	30	Placebo ($n = 123$)	26	20	1	8	Rutgeerts *et al.*[10]
		IFX 5 mg/kg ($n = 121$)	47	12	2	12	
		IFX 10 mg/kg ($n = 120$)	60	9	3	12	

Table 1. (Continued)

N	Follow up (weeks)	Medication	Clinical response (%)	SAE (%)	Serious infection (%)	Infusion reaction (%)	Reference
115	14	Cyclosporine[c] ($n = 58$)	40[d]	16	4	NR	Laharie *et al.*[11]
		IFX 5 mg/kg ($n = 57$)	46[d]	25	5	NR	
123	30	Placebo ($n = 41$)	63	10	0	5	Jiang *et al.*[13]
		IFX 3.5 mg/kg ($n = 41$)	66	5	0	5	
		IFX 5 mg/kg ($n = 41$)	27	7	2	7	

[a]Clinical remission at week 30.
[b]Corticosteroid-free clinical remission.
[c]2 mg/kg per day for 1 week, followed by oral drug until day 98.
[d]Lack of treatment failure.
IFX, infliximab; AZA, azathioprine; NR, not reported; SAE, serious adverse event.

monitoring (TDM), defined as the assessment of drug concentration and antidrug antibodies, has proven to be effective for optimizing infliximab therapy and has also been associated with favorable long-term therapeutic outcomes.[43,45–54]

Recently, the first biosimilars of infliximab have been utilized in IBD clinical practice[55–63] based on extrapolation of results of large RCT in ankylosing spondylitis[64] and rheumatoid arthritis.[65] Data from large observational cohort studies in IBD show that the infliximab biosimilar CT-P13 has comparable efficacy and safety with the originator (Table 3).[55–63] This review will mainly focus on the efficacy of infliximab in IBD based on RCT, large observational studies, postmarketing registries, and meta-analyses.

Infliximab and CD

RCTs

Efficacy and safety data from RCT of infliximab in CD is depicted in Table 1A. In the first double-blind, placebo-controlled RCT, patients with moderate to severe CD were randomly assigned to receive a single intravenous infusion of either placebo or infliximab in a dose of 5, 10, and 20 mg/kg. The primary outcome was clinical response defined as a reduction of ⩾70 in the score on the Crohn's Disease Activity Index (CDAI) at 4 weeks that was not accompanied by a change in any concomitant medications. At 4 weeks, 81%, 50%, and 64% of the patients given 5, 10, and 20 mg/kg, had a clinical response as compared with 17% of patients in the placebo group ($p < 0.001$ for the comparison of the infliximab group as a whole with placebo). Moreover, clinical remission (CDAI<150) was achieved by 33% of patients treated with infliximab as opposed to only 4% of the patients given placebo ($p = 0.005$). The rates of adverse effects were similar in the groups.[4]

In a placebo-controlled RCT patients with CD who had draining abdominal or perianal fistulas of at least 3 months' duration were randomly assigned to receive placebo, 5 or 10 mg/kg of infliximab at weeks 0, 2, and 6. The primary outcome was a reduction of ⩾50% from baseline in the number of draining fistulas observed at two or more consecutive study visits. A secondary end-point was closure of all fistulas. Primary outcome was met in 68% and 56% in the infliximab group (5 and 10 mg/kg, respectively) compared with 26% in the placebo group ($p = 0.002$ and $p = 0.02$, respectively). Closure of all fistulas occurred in 55% and 38% in the infliximab groups (5 and 10 mg/kg, respectively) compared with 13% in the placebo group ($p = 0.001$ and $p = 0.04$, respectively). For patients treated with infliximab, the most common adverse events were headache, abscess, upper respiratory tract infection, and fatigue.[5]

In the landmark ACCENT I [A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's

Table 2. Serum maintenance infliximab concentration thresholds associated with objective therapeutic outcomes in inflammatory bowel disease.

IBD type	Threshold (μg/mL)	Therapeutic outcome	TDM assay	Ref.
CD	>2.8	Normal CRP (≤5 mg/l)	HMSA	Vande Casteele *et al.*[32]
CD	≥2.2	Normal CRP (≤5 mg/l)	HMSA / ELISA	Papamichael *et al.*[33]
CD	≥9.7	Endoscopic remission	HMSA / ELISA	Papamichael *et al.*[33]
CD	≥9.8	Histologic remission	HMSA / ELISA	Papamichael *et al.*[33]
CD	>0.6	Normal CRP (≤0.3 mg/dl)	ELISA	Imaeda *et al.*[34]
CD	>1.1	Normal FC (<300 μg/g)	ELISA	Imaeda *et al.*[34]
CD	>4	Mucosal healing	ELISA	Imaeda *et al.*[34]
CD	>2.7	Mucosal healing	ELISA	Morita *et al.*[35]
CD	>3.4	Normal CRP (≤5 mg/l)	ELISA	Ward *et al.*[36]
CD	>5.7	Normal FC (<59 μg/g)	ELISA	Ward *et al.*[36]
CD	>10.1	Fistula healing	HMSA	Yarur *et al.*[37]
CD	>10.1	Mucosal healing	HMSA	Yarur *et al.*[37]
UC	>3	Normal FC (<250 mg/g)	ELISA	Magro *et al.*[38]
UC	>3	Mucosal healing	ELISA	Magro *et al.*[38]
UC	≥7.5	Endoscopic healing	HMSA / ELISA	Papamichael *et al.*[39]
UC	≥10.5	Histologic healing	HMSA / ELISA	Papamichael *et al.*[39]
CD/UC	>6.8	Normal CRP (≤5 mg/l)	ELISA	Ungar *et al.*[40]
CD/UC	>5	Mucosal healing	ELISA	Ungar *et al.*[40]
CD/UC	>7.3	Normal FC (<250 mg/g)	ELISA	Huang *et al.*[41]
CD/UC	>8.3	Mucosal healing	HMSA	Yarur *et al.*[42]
CD/UC	<4.6	IBD-related hospitalization	HMSA	Yarur *et al.*[42]
CD/UC	<6.3	Serious infusion reaction	HMSA / ELISA	Papamichael *et al.*[43]
CD/UC	>5.4	Endoscopic remission	ELISA	van Hoeve *et al.*[44]

ELISA, enzyme-linked immunosorbent assay; HMSA, homogeneous mobility shift assay; CRP, C-reactive protein; FC, fecal calprotectin; TDM, therapeutic drug monitoring; CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease.

Disease] trial patients with a CDAI score of at least 220 received a 5 mg/kg iv infusion of infliximab at week 0. After assessment of response at week 2 patients were randomly assigned to receive placebo (group I), 5 mg/kg (group II), or 10 mg/kg infliximab (group III) at weeks 2 and 6 and then every 8 weeks thereafter until week 46. Primary outcomes were the proportion of patients who responded at week 2 and were in remission (CDAI <150) at week 30 and the time to loss of response up to week 54 in patients who responded. A total of 58% of patients responded to a single infusion of infliximab

Table 3. Data from large observational cohort studies for the infliximab biosimilar CT-P13 in inflammatory bowel disease.

IBD type	*N*	Follow up (weeks)	Clinical response (%)	SAE (%)	Serious infection (%)	Infusion reaction (%)	Reference
CD/UC	126/84	30	67/80	NR	0	7	Gecse *et al.*[55]
CD/UC	32/42	54	88/100	5	3	3	Jung *et al.*[56]
CD/UC	209/144	54	65/50	NR	0	9	Gonczi *et al.*[57]
CD/UC	173/14	54	71	NR	NR	7	Ratnakumaran *et al.*[58]
UC	63	14	83	0	0	0	Farkas *et al.*[59]

IBD, inflammatory bowel disease; CD, ulcerative colitis; UC, ulcerative colitis; NR, not reported; SAE, serious adverse events.

within 2 weeks. At week 30, 21% of group I patients were in remission compared with 39% of group II ($p = 0.003$) and 45% of group III ($p = 0.0002$) patients. Thus, patients in groups II and III combined were more likely to sustain clinical remission than patients in group I [odds ratio (OR) 2.7, 95% confidence interval (CI) 1.6–4.6]. Throughout the 54-week trial, the median time to loss of response was 38 weeks [interquartile range (IQR) 15 to >54) and more than 54 weeks (IQR 21 to >54) for groups II and III, respectively, compared with 19 weeks (IQR 10–45) for group I ($p = 0.002$ and $p = 0.0002$, respectively). The incidence of serious infections was similar across treatment groups.

The ACCENT II [A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long Term Treatment of Patients With Fistulizing Crohn's Disease] trial included patients with one or more draining abdominal or perianal fistulas of at least 3 months' duration. Patients received 5 mg/kg of infliximab iv on weeks 0, 2, and 6. A total of 195 patients who had a response at weeks 10 and 14 and 87 patients who had no response (defined as a lack of a reduction from a baseline CDAI ⩾220 by at least 25% and 70 points) were then randomly assigned to receive placebo or 5 mg/kg of infliximab every 8 weeks and were followed to week 54. The primary outcome was time to loss of response. Time to loss of response was significantly longer for patients on infliximab maintenance therapy than for those who received placebo (>40 weeks *versus* 14 weeks, $p < 0.001$). At week 54, complete absence of draining fistulas was achieved in 36% of patients receiving infliximab compared to 19% of patients in the placebo group ($p = 0.009$). The most common SAE was worsening of CD.[7]

The landmark randomized double-blind SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn Disease) trial, evaluated the efficacy of infliximab monotherapy, azathioprine monotherapy, and the two drugs combined in 508 adults with moderate-to-severe CD who had not undergone previous immunosuppressive or biologic therapy. Patients were randomly assigned to receive 5 mg/kg infliximab, 2.5 mg azathioprine, or combination therapy with the two drugs. At week 26, patients receiving combination therapy achieved a higher rate of corticosteroid-free clinical remission than infliximab (56.8 *versus* 44.4%, $p = 0.02$) or azathioprine monotherapy (56.8% *versus* 30%, $p < 0.001$). Combination therapy was also better in terms of mucosal healing when compared with either infliximab (43.9 *versus* 30.1%, $p = 0.06$) or azathioprine monotherapy (43.9 *versus* 16.5%, $p < 0.001$). Through week 50, the incidence of adverse events was similar among the three groups. However, infusion reactions occurred in only 5% of patients in the combination therapy group compared with 16.6% in the infliximab group ($p < 0.001$).[9]

Large observational cohort studies

Large observational cohort studies as compared with RCT more typically reflect real-life clinical

practice and have longer follow up. These studies show that infliximab is generally safe and effective for treating CD. One sizable observational cohort single-center study of 614 patients who were followed for a median of 55 (IQR: 27–83) months showed that only 10.9% of patients had PNR and 63.4% of the initial responders had sustained clinical benefit defined as a lasting control of the disease activity during follow up with persistent improvement of the symptoms. However, approximately half of the initial responders required dose optimization [shorten of infusion (19.7%), increase of the dose to 10 mg/kg and/or a re-induction (26.3%) or an increase of the dose plus a reduction of the interval (3.8%)]. Overall, 4% of patients had a SAE with the most common being infusion reactions. Five patients had serious infections necessitating infliximab discontinuation.[14]

Another substantial observational study from the same center showed that SAE were similar between a group of 734 infliximab-treated patients and a control group of 666 patients (13 *versus* 19%, $p = 0.45$, respectively). The infliximab and the control group also had similar rates of serious infections [1.6 *versus* 1.1/100 patient-years (PY), respectively] and mortality (0.3 *versus* 0.2/100PY, respectively). Concomitant treatment with steroids was the only independent risk factor for infections in patients treated with infliximab (OR 2.7, 95% CI 1.2–6.1, $p = 0.018$). The most commonly observed systemic side effects were skin eruptions, including psoriasiform lesions, which occurred in 20% of patients.[15]

In another retrospective, single-center cohort study of 261 CD patients who responded to infliximab and were treated with scheduled infliximab maintenance therapy, the median time on drug was 2.4 (IQR 1.4–4.7) years and 24.9% of patients experienced infliximab failure. During the study period, 62.5% of patients underwent infliximab optimization with a median time to first dose optimization of 41 [21–92] weeks. Disease duration $\geqslant$1 year [hazard ratio (HR) 2.5, 95% CI 1.2–5.2), $p = 0.02$), L1 disease location (HR 2, 95% CI 1.1–3.5, $p = 0.02$), prior anti-TNF use (HR 2.3, 95% CI 1.1–4.8, $p = 0.03$), hemoglobin $<$13.5 g/dl (HR 2.3, 95% CI 1.2–4.4, $p = 0.02$), not using TDM (HR 8, 95% CI 4.1–15.6, $p < 0.001$, and dose optimization within first year (HR 3.7, 95% CI 2.1–6.6), $p < 0.001$] were independent predictors of infliximab failure-free survival.[16]

In a recent retrospective, single-center cohort study of 351 CD patients treated with infliximab the overall mean persistence of first-line treatment was 3.6 [standard deviation (SD) 3.1] years. In multivariate Cox regression, female gender (HR 2.1, 95% CI 1.4–3.3, $p < 0.001$) and body mass index (BMI) $\geqslant$23.4 (HR 1.7, 95% CI 1.1–2.7, $p = 0.034$) were the only factors independently associated with persistence of first-line treatment with infliximab.[17]

Registries and meta-analyses

The TREAT (Crohn's Therapy, Resource, Evaluation, and Assessment Tool) registry, a prospective cohort study examining long-term outcomes of CD treatments in community and academic settings, included patients receiving either infliximab ($n = 3400$, 20,971PY) or other treatments ($n = 2833$, 14,806PY) from July 1999 through March 2012.[18] The final analysis of this registry showed that serious infection rates were higher for infliximab-treated than other-treatments-only patients (2.15 *versus* 0.86/100PY), yielding an unadjusted relative risk of 2.46 (95% CI 1.8–3.4); pneumonia occurred most frequently. Age, use of prednisone, narcotic analgesics, or infliximab; moderate/severe disease; colonic disease; and disease duration at enrolment independently predicted serious infection. Mortality (0.57 *versus* 0.67/100PY, respectively) and malignancy rates (0.69 *versus* 0.71/100PY, respectively) were generally similar between patients treated with infliximab and those receiving other-treatments-only.[18] Age ($p < 0.001$), ileal disease ($p = 0.050$), prednisone use ($p < 0.001$), and narcotic analgesic use ($p = 0.016$) were independently associated with mortality.[18]

One pooled analysis of infliximab RCT in CD showed that the incidence of malignancy (excluding nonmelanoma skin cancers) (0.49 *versus* 1.61/100PY), respectively) and mortality (0.24 *versus* 0.8/100PY, respectively) were similar for infliximab and placebo.[19] A recent systematic review of RCT published between January 1980 and May 2016 examining efficacy of biological or IMM therapy in IBD performed direct comparisons of pooled proportions of hospitalization and surgery. In CD, anti-TNF significantly reduced hospitalization (OR 0.46, 95% CI 0.36–0.6) and surgery (OR 0.23, 95% CI 0.13–0.42) compared with placebo. There were no statistically significant differences in the

pairwise comparisons between active treatments.[20] A recent systematic review and network meta-analysis assessed comparative efficacy (induction and maintenance of clinical remission) and safety (SAEs and infections) of biological therapy in patients with moderate–severe CD using surface under the cumulative ranking (SUCRA) probabilities. In biologic-naïve patients, infliximab was ranked highest for induction of clinical remission (SUCRA 0.93). In patients with response to induction therapy, adalimumab (SUCRA 0.97) and infliximab (SUCRA 0.68) were ranked highest for maintenance of remission. Ustekinumab had lowest risk of SAE (SUCRA 0.72) and infection (SUCRA 0.71; along with infliximab, SUCRA 0.83) in maintenance trials.[66]

Infliximab and UC

RCTs

Data from RCT of infliximab in UC is depicted in Table 1B. The landmark RCTs ACT 1 and ACT 2 (Active Ulcerative Colitis Trials 1 and 2) evaluated the efficacy of infliximab for induction and maintenance therapy in adults with moderate to severe UC. In each study, 364 patients with moderate-to-severe active UC despite treatment with concurrent medications received placebo or 5 or 10 mg/kg of infliximab at weeks 0, 2, and 6 and then every 8 weeks through week 46 (in ACT 1) or week 22 (in ACT 2). The primary outcome for both studies was clinical response defined as a decrease in the Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute rectal-bleeding subscore of 0 or 1. In ACT 1, more patients who received 5 mg or 10 mg of infliximab had a clinical response at week 54 (45 and 44%, respectively) than did those who received placebo (20%, $p < 0.001$ for both comparisons). In both studies, patients who received infliximab were more likely to have a clinical response at week 30 ($p \leqslant 0.002$ for all comparisons). In ACT 1, SAE were comparable between the infliximab and the placebo groups, whereas in ACT 2, SAE were more common in the placebo compared with the infliximab groups.[10]

In a small RCT, patients with fulminant or severe to moderately severe UC were randomized to receive either infliximab as a rescue therapy or placebo. The primary outcome was colectomy or death 3 months after randomization. Seven out of 24 patients in the infliximab group and 14/21 in the placebo group had a colectomy (OR 4.9, 95% CI 1.4–17, $p = 0.017$). No patient died.[21]

In a parallel, open-label RCT, patients who had an acute severe flare of UC (defined by a Lichtiger score >10 points) and had been given an unsuccessful course of high-dose iv steroids received either iv cyclosporine (2 mg/kg per day for 1 week, followed by oral drug until day 98) or infliximab (5 mg/kg on days 0, 14, and 42). Primary outcome was treatment failure defined as absence of a clinical response at day 7, a relapse between day 7 and day 98, absence of steroid-free remission at day 98, a SAE leading to treatment interruption, colectomy, or death. Treatment failure occurred in 35 (60%) patients given ciclosporin and 31 (54%) given infliximab (absolute risk difference 6%, 95% CI –7 to 19, $p = 0.52$). Overall, 16% patients given cyclosporine and 25% given infliximab had a SAE, with worsening of UC being the most frequent.[11] Long-term outcome of these patients showed that the colectomy-free survival rates (95%CI) at 5 years were 61.5% (48.7–74.2%) in patients who received cyclosporine and 65.1% (52.4–77.8%) in those who received infliximab ($p = 0.97$).[12]

Large observational cohort studies

A retrospective study of 7227 patients from the British Columbia Ministry of Health database from 2001 to 2010 evaluated whether treatment with infliximab decreased colectomy rates. Patients in a pre-infliximab era (2003–2004) were compared with patients from a post-infliximab era (2008–2009). Infliximab was shown to decrease colectomy rates from 9.97% to 8.88% ($p = 0.03$) for all patients with UC. However, for patients with severe UC (having received steroids during study period), there was no significant difference in colectomy rates (9.97 *versus* 11.14%; $p = 0.18$).[22]

Another retrospective multicenter study that included 191 adult patients with UC who received at least one infliximab infusion showed that 18.8% of patients underwent colectomy over a median follow-up time of 18 (IQR: 8–32) months. Predictors of colectomy were no clinical response after infliximab induction (HR 7, 95%

CI 3.4–14.8), baseline C-reactive protein (CRP) >10 mg/l (HR 5.1, 95% CI 1.8–14.8), infliximab for acute severe UC (HR 3.4, 95% CI 1.5–7.8), and previous treatment with cyclosporine (HR 2.5; 95% CI 1.2–5.3).[23]

In an observational cohort study of 285 patients with refractory UC treated with infliximab, 61% of patients relapsed and 20% required colectomy during a median follow-up period of 5 years. Independent predictors of colectomy-free survival included short-term clinical response (OR 7.7, 95% CI 2.8–21.7; $p < 0.001$), mucosal healing (OR 4, 95% CI 1.2–14, $p = 0.028$), baseline CRP ⩽5 mg/l (OR 2.9, 95% CI 1.3–6.9, $p = 0.012$), and baseline albumin ⩾35 g/l (OR 3, 95% CI 1.1–8.2, $p = 0.029$). Based on serologic analysis of a subgroup of 112 patients, infliximab concentrations at week 14 > 2.5 μg/ml predicted relapse-free survival ($p < 0.001$) and colectomy-free survival ($p = 0.034$).[24]

In a recent retrospective, single-center cohort study of patients with UC treated with infliximab as a first-line therapy the mean duration of drug persistence was 3.4 (SD 3.5) years, compared with 2.0 (SD 1.7) years when infliximab was used as a second-line treatment.[25]

Registries and meta-analyses

A large multicenter registry from Spain (1989–2013) included 740 patients with steroid-refractory acute severe UC, receiving cyclosporine ($n = 377$), infliximab ($n = 131$), or sequential rescue therapy ($n = 63$). The cumulative colectomy rate was higher in the cyclosporine (24.1%) and sequential therapy (32.7%) than in the infliximab group (14.5%; $p = 0.01$) at 3 months and 5 years. There were no differences in mortality between cyclosporine (2.4%), infliximab (1.5%) and sequential therapy (0%; $p = 0.771$). However, the proportion of patients with SAE was lower in cyclosporine (15.4%) than in infliximab-treated patients (26.5%) or sequential therapy (33.4%; $p < 0.001$).[26]

The results of a network meta-analysis suggested that infliximab was more effective at inducing clinical response (OR 2.4, 95% CI 1.2–4.6) and mucosal healing (OR 2, 95% CI 1.1–3.6) than adalimumab.[27] Another metanalysis showed that anti-TNF significantly reduced hospitalization (OR 0.48, 95% CI 0.29–0.80) and surgery (OR 0.67, 95% CI 0.46–0.97) in UC when compared with placebo.[20] In a recent metanalysis, anti-TNF and anti-integrins were more effective than placebo for inducing and maintaining mucosal healing in UC. In network analysis, adalimumab therapy was inferior to infliximab and combination infliximab–azathioprine for inducing mucosal healing in UC. There was no statistically significant pairwise difference between vedolizumab and anti-TNF agents.[28] A systematic review with network meta-analysis to comparatively assess efficacy and harm of tofacitinib and biologics in adult patients not previously exposed to TNF antagonists showed that all treatments were superior to placebo. Indirect treatment comparisons showed that infliximab was better than adalimumab (OR 2, 95% CI 1.4–3) and golimumab (OR 1.7, 95% CI 1.1–2.6) in clinical response, better than adalimumab (OR 2.1, 95% CI 1.2–3.6) in clinical remission, and better than adalimumab (OR 1.9, 95% CI 1.3–2.8) and golimumab (OR 1.7, 95% CI 1.1–2.7) in mucosal healing. Nine studies ($n = 1776$) contributed maintenance data showing that all treatments had higher clinical efficacy than placebo.[29]

Infliximab biosimilars in IBD

In 2013, CT-P13 was the first biosimilar of infliximab approved by the European Medicines Agency for both adult and pediatric patients with IBD, based on extrapolation of results from ankylosing spondylitis[64] and rheumatoid arthritis.[65] Although there are already three infliximab biosimilars in the market, CT-P13 is the one that has the most published data including large observational cohort studies in IBD (Table 3). These studies show that the infliximab biosimilar has a comparable efficacy and safety profile with the originator.[55–63]

PROSIT-BIO (Prospective Observational Study of Patients with Inflammatory Bowel Disease Treated with Infliximab Biosimilar) included consecutive patients with IBD (CD, $n = 313$ and UC, $n = 234$) who were naive to anti-TNF therapy ($n = 311$), had a previous exposure to biologics ($n = 139$) or switched to CT-P13 ($n = 97$). Sixty-six (12.1%) SAEs were reported, 38 (6.9%) of them were infusion-related reactions. The biosimilar had to be stopped in 29 (5.3%) cases for severe infusion reactions (8 naïve, 19 previous

exposed, and 2 switch), and in another 16 patients (2.9%) for other SAEs.[60] In a prolonged follow up of the PROSIT-BIO study including 810 patients (452 with CD) SAEs leading to cessation of the biosimilar were reported in 12.7% subjects of whom 6.5% had a serious infusion reaction (significantly more frequent in patients pre-exposed to anti-TNF, $p = 0.017$).[61]

The landmark NOR-SWITCH trial (a randomized, double-blind, parallel-group study to evaluate the safety and efficacy of switching from innovator infliximab to biosimilar infliximab compared with continued treatment with innovator infliximab in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, UC, CD, and chronic plaque psoriasis) included 482 patients (CD, $n = 155$; UC, $n = 93$) who were followed for 52 weeks. Switching from infliximab originator to CT-P13 was not inferior to continued treatment in terms of disease worsening (30% *versus* 26%, respectively). The frequency of SAEs (9% *versus* 10%, respectively) and adverse events leading to discontinuation (3% *versus* 4%, respectively) were similar between patients switching from infliximab originator to CT-P13 and those who continued on the originator.[67]

A prospective study of 133 IBD patients (64% CD) most of whom were in remission or had only mild disease (CD 82%; UC 90%) demonstrated that after switching to infliximab biosimilar, 35 (26%) discontinued therapy within 12 months mostly due to subjective higher disease activity (9%) and adverse events (9.8%) including general malaise/fatigue, arthralgia, skin problems, and infusion reactions.[62] In another prospective observational cohort study of patients with IBD (CD, $n = 195$; UC, $n = 118$) who switched from infliximab originator to CT-P13 there were no significant changes in clinical disease activity, quality of life, drug trough concentrations, or proportion of patients in remission. Disease worsening rates were 14% for CD and 13.8% for UC; and 2.7% developed antidrug antibodies and 2.2% developed SAEs.[63]

A recent metanalysis of 24 studies and 1326 patients switching from infliximab originator to CT-P13 showed that disease control, defined as no worsening after switching, was maintained in most of the patients (weighted mean, 88%; 95% CI 86–89%).[68]

Infliximab in other specific IBD clinical scenarios

Pouchitis

Despite significant advances of medical therapy, up to 20–33% of patients with UC undergo surgery, with the majority of these patients having a total proctocolectomy and IPAA.[69–71] Both inflammatory and noninflammatory diseases can develop after IPAA formation, including pouchitis and CD of the pouch. In chronic and refractory cases of pouchitis, infliximab has recently shown to be effective.[69–73]

In a Belgian case series of 28 patients with IPAA with refractory luminal inflammation, 56% of patients showed sustained clinical response after a median follow-up period of 20 months.[72] In a retrospective, multicenter study of 35 patients with chronic, refractory pouchitis treated with infliximab 21%, 33%, and 27% achieved complete response and 63%, 33%, and 19% showed partial clinical response at weeks 8, 26, and 52, respectively.[70] A Canadian cohort of 42 patients with either chronic refractory pouchitis ($n = 26$) or CD after IPAA ($n = 16$) showed that 62.6% and 29.6% achieved a partial or complete clinical response, respectively.[69]

Most recently, a systematic review and meta-analysis of 313 patients on anti-TNF therapy (infliximab $n = 194$, adalimumab $n = 119$) demonstrated that the rates of short-term and long-term clinical remission were 0.50 (95% CI 0.37–0.63, $I^2 = 0.57$) and 0.52 (95% CI 0.39–0.65, $I^2 = 0.59$), respectively. The rate of remission after anti-TNF induction therapy seemed to be higher in CD-like complications of the pouch 0.64 (95% CI 0.5–0.77, $I^2 = 0.18$), compared with refractory pouchitis 0.10 (95% CI 0–0.35, $I^2 = 0$, $p = 0.06$), whereas less difference was seen during long-term maintenance therapy 0.57 (95% CI 0.43–0.71, $I^2 = 0.32$) and 0.37 (95% CI 0.14–0.62, $I^2 = 0.47$), respectively ($p = 0.57$).[73]

Infliximab for prophylaxis of postoperative recurrence after an ileocolonic resection for CD

Whereas proctocolectomy is considered curative in UC, clinical and endoscopic postoperative recurrence in CD can happen in the neoterminal ileum in as many as 90% of patients within 12 months of surgical resection and up to 50% of

patients can develop a recurrence of symptoms by 5 years.[74–79] Infliximab has been used with good results for prevention of clinical and endoscopic postoperative recurrence in CD.[75–79]

A small RCT was the first to investigate the role of infliximab for preventing postoperative recurrence in patients following an ileocolonic resection for CD. Patients were randomly assigned to receive infliximab or placebo. The primary outcome was the proportion of patients with endoscopic recurrence at 1 year. The rate of endoscopic recurrence at 1 year was significantly lower in the infliximab group (1/11, 9.1%) compared with the placebo group (11/13, 84.6%) ($p = 0.0006$).[79] In a prospective, open-label, long-term follow up of this study, patients were given the option to continue, stop, or start infliximab therapy. The primary endpoint was the time to endoscopic recurrence from the initial assignment to postoperative infliximab or placebo. Patients assigned to the infliximab group in the first year after surgery had a longer mean time to first endoscopic recurrence (1231 ± 747 days) than patients originally assigned to the placebo group (460 ± 121 days, $p = 0.003$).[77]

In another RCT, consecutive CD patients who underwent curative ileocolonic resection were randomized (1:1) to receive infliximab (standard induction and maintenance schedule) or azathioprine (2.5 mg/kg/day) for 1 year. Among patients treated with azathioprine, 4/10 (40%) had endoscopic recurrence compared to 1/11 (9%) in the infliximab group ($p = 0.14$). Eight out of 10 (80%) among those who received azathioprine had severe histological activity, whereas 2/11 (18%) in the infliximab group developed histological recurrence ($p = 0.008$).[76]

The landmark PREVENT trial (Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE® [infliximab] and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence) evaluated the efficacy of infliximab in preventing postoperative recurrence of CD in 297 patients at 104 sites worldwide from November 2010 through May 2012. Patients were randomly assigned (1:1) to groups given infliximab (5 mg/kg) or placebo every 8 weeks for 200 weeks. The primary outcome was clinical recurrence, defined as a composite outcome consisting of a CDAI >200 and a ⩾70-point increase from baseline, and endoscopic recurrence (Rutgeerts score ⩾i2) or development of a new or redraining fistula or abscess, before or at week 76. Endoscopic recurrence was a major secondary endpoint. Clinical recurrence was numerically less in the infliximab compared with the placebo group (12.9% *versus* 20%, respectively, $p = 0.097$). However, a significantly smaller proportion of patients in the infliximab group had endoscopic recurrence compared with the placebo group (30.6% *versus* 60%, respectively, $p < 0.001$).[77]

A recent systematic review and network meta-analysis including 571 patients and 5 treatment options (infliximab, adalimumab, thiopurines, mesalamine, and placebo) for prevention of endoscopic and clinical recurrence showed that either infliximab or adalimumab may be efficiently used in the postoperative prophylaxis of CD recurrence.[78]

TDM of infliximab in IBD

Several studies have shown that higher maintenance infliximab concentrations are associated with higher rates of objective therapeutic outcomes in IBD (Table 2).[32–44] Reactive TDM, defined as the evaluation of drug concentrations and antidrug antibodies in patients with PNR or SLR is currently emerging as the new standard of care for optimizing anti-TNF therapy in IBD.[80–82] Reactive TDM more efficiently directs care and is more cost-effective than empiric treatment optimization based only on symptoms.[45–52] Preliminary data suggest that proactive TDM, and dosing to a therapeutic drug concentration, is associated with improved long-term outcomes.[43,53,54,83] The landmark RCT TAXIT (Trough Concentration Adapted Infliximab Treatment) showed that infliximab proactive TDM was associated with less undetectable drug concentrations and relapse compared with clinically based dosing.[53] Moreover, proactive TDM of infliximab was associated with less treatment failure, need for IBD-related surgery or hospitalization, risk of antibodies to infliximab, and serious infusion reactions compared with reactive testing alone.[43] A recent multicenter retrospective study showed that proactive following reactive TDM of infliximab was also associated with greater drug survival and fewer IBD-related hospitalizations than reactive TDM alone.[54] Though most of the data for proactive TDM is

during the maintenance phase, it is probably most important during the induction phase when the disease is active and drug clearance is greatest. As noted above, drug concentrations need to be higher during induction and adequate drug concentrations during induction are associated with better short- and long-term outcomes. The RCT TAILORIX (Drug-concentration versus Symptom-driven Dose Adaptation of Infliximab in patients with active Crohn's disease) failed to reach its primary endpoint (sustained clinical remission with no endoscopic ulceration) probably due to several methodological issues concerning study design, the fact that <50% of the 'optimized' groups attained a drug concentration >3 μg/ml and that dosing changes were only made 8 weeks following TDM.[84] However, a recent *post hoc* analysis of this trial showed that higher infliximab concentrations during induction therapy at week 2 (⩾23.1 μg/ml) and 6 (⩾10 μg/ml) are associated with early endoscopic remission at week 12.[85] However, there are still some barriers when applying TDM in day to day clinical practice, including cost, the long lag time from sampling to results, the interpretation of the results, and defining the optimal drug concentration thresholds to target as these can vary depending on the therapeutic goal of interest, the IBD phenotype, and the TDM assay used (Table 2).[86,87] The application of point-of-care assays to rapidly measure infliximab concentrations could be the next step for maximizing the efficacy of TDM towards a faster and more accurate infliximab treatment optimization.[88]

Conclusion

Current evidence suggests that infliximab is very efficacious for the treatment of IBD. However, two decades following its introduction there are still issues concerning its optimal use and how to prevent drug discontinuation for PNR, SLR, and serious infusion reactions. TDM can help physician better understand and manage these unwanted outcomes, although several limitations still hinder widespread adoption of this clinical strategy.

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ORCID iD

Konstantinos Papamichael https://orcid.org/0000-0003-1497-0254

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