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Biologics in inflammatory bowel disease: what are the data?

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Abstract

Background: Over the last decade, biologics have gained an important place for the treatment of moderate to severe inflammatory bowel disease (IBD), and many randomized control trials have evaluated their efficacy.

Aim: The goal of this review is to analyze the results of these trials and to highlight the evidence and indications emerging from these studies for their implementation in the management of IBD patients.

Methods: A PubMed search was realized to screen high-quality clinical trials studying biologic agents currently available in clinics for the treatment of IBD. Words used were: ''infliximab,'' ''adalimumab,'' ''certolizumab,'' ''golimumab,'' ''natalizumab,'' ''vedolizumab,'' ''ustekinumab,'' ''azathioprine,'' ''methotrexate,'' ''Crohn's disease,'' and ''ulcerative colitis.''

Results: In Crohn's disease, studies supporting induction and maintenance therapies were documented for infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and ustekinumab. Infliximab, adalimumab, and certolizumab have evidences for fistulizing Crohn's disease and only infliximab and adalimumab have evidences for mucosal healing. In ulcerative colitis, studies supporting induction, maintenance, and mucosal healing were found with infliximab, adalimumab, golimumab, and vedolizumab. Only infliximab was associated with evidences for combination therapy with thiopurine and acute severe colitis in ulcerative colitis.

Conclusion: Management with biologics in IBD patients is well validated by high-quality clinical trials.

Keywords

Inflammatory bowel disease, Crohn's disease, ulcerative colitis, biologics, clinical trials

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Introduction

Treatment of Crohn's disease with an anti-tumor necrosis factor (anti-TNF) chimeric monoclonal antibody was first reported in 1993 in a case report by Derkx et al.[1] In 1995, the same Amsterdam group published the results of their open trial done in 10 patients unresponsive to usual therapy;[2] one infliximab (then called cA2) infusion normalized the Crohn's disease activity index (CDAI) and healed the colonic ulcerations in eight of them for an average period of four months. In 1997, the first randomized control trial confirming the therapeutic effect of infliximab on Crohn's disease was published by Targan et al.[3] Infliximab was approved for treatment of Crohn's disease by the US Food and Drug Administration in August 1998.

Over the last decade, biologics have gained an important place for the treatment of moderate to severe inflammatory bowel disease (IBD), and many randomized control trials have evaluated their efficacy. The goal of this review is to analyze the results of these trials and to highlight the evidence and indications emerging from these studies for their implementation in the management of IBD patients.

Methods

A PubMed search was realized to screen trials studying biologic agents currently available in clinics for the

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treatment of IBD and a promising biologic, i.e. ustekinumab, was also included. The last search was undertaken on September 2014. Words used were: "infliximab," "adalimumab," "certolizumab," "golimumab," "natalizumab," "vedolizumab," "ustekinumab," "azathioprine," "methotrexate," "Crohn's disease," and "ulcerative colitis." Only high-quality randomized control trials were considered in our review with possible exceptions if randomized control trials were not available for a particular subject.

In Crohn's disease, outcomes of interest were: induction therapy, maintenance therapy, fistulizing Crohn's disease, mucosal healing, combination treatment with thiopurine or methotrexate, and rescue therapy (known as treatment efficacy in patients who failed previous biologics treatment). In ulcerative colitis, outcomes of interest were: induction therapy, maintenance therapy, mucosal healing, combination treatment with thiopurine or methotrexate, and acute severe colitis.

Results

Crohn's disease

A summary of biologics trials evidences in Crohn's disease is provided in Table 1 (see also Table 3 for details of administration and dosage of biologics in treating IBD).

- **Anti-TNF alpha**

a) Infliximab

Induction. In 1997, Targan et al. reported that infliximab induced a positive clinical response (defined as a 70 points CDAI reduction from baseline) in Crohn's disease.[3] A positive response at 4 weeks was obtained in 81% of patients treated with infliximab (5 mg/kg IV), 50% of patients (10 mg/kg IV), 64% of patients (20 mg/kg IV) compared to 17% for the placebo group ($p \leq 0.001$ for all).

Clinical remission off steroids was studied by Lemann et al. in patients refractory to thiopurine and steroids (for more than 6 months).[4] Infliximab 5 mg/kg IV at weeks 0, 2, and 6 was compared to placebo. Clinical remission off steroids was achieved in 64% with infliximab compared to 34% with placebo at week 12 ($p = 0.03$) in the failure stratum.

Maintenance. In 2002, Hanauer et al. published the results of the ACCENT 1 study.[5] They observed, in patients responding to an induction therapy with infliximab, that clinical remission (defined as a CDAI score <150) was achieved in 39% of these patients at week 30 with the anti-TNF maintenance regimen (5 mg/kg IV every 8 weeks) as compared to 21% in the placebo group ($p = 0.003$). At week 54, the median time to loss of response was 38 weeks in the infliximab group and 19 weeks in the placebo group ($p = 0.002$).

Episodic compared to regular treatments was studied by Rutgeerts et al.,[6] who compared patients given infliximab regularly every 8 weeks or receiving episodic infusions as needed by clinical symptoms. Scheduled strategy was associated with a higher rate of clinical remission (defined as a CDAI score < 150) and of clinical response (defined as a 70 points reduction in CDAI

Table 1. Biologics trials evidences in Crohn's disease

	Induction	Maintenance	Fistulizing	Mucosal healing	Combination thiopurine	Combination methotrexate	Rescue[a]
Anti-TNF alpha							
Infliximab	+	+	+	+	+	−	NA
Adalimumab	+	+	+	+	+/−	NA	+
Certolizumab	+	+	+	#	NA	NA	+
Golimumab	NA	NA	NA	NA	NA	NA	NA
Anti-integrin							
Natalizumab	+	+	NA	NA	NA	NA	NA
Vedolizumab	+	+	NA	NA	NA	NA	+
Others							
Ustekinumab (phase IIb)	+	+	NA	NA	NA	NA	+

[a]Efficacy of the treatment in patients who have failed previous biologics treatment.
NA: Study is not available.
+: Study is available with a positive outcome.
−: Study is available with a negative outcome.
+/−: Retrospective studies.
#: Study with a positive outcome but not comparing with placebo.

and 25% from baseline) compared to episodic strategy ($p < 0.05$ for both) from week 10 to 30.

Fistulizing. The ACCENT II trial was published in 2004 by Sands et al.[7] In patients with at least one abdominal or perianal fistula, the closure of fistulae at 54 weeks was higher in the infliximab group (5 mg/kg IV at weeks 0, 2, and 6 and then every 8 weeks) than in the placebo group (36% compared to 19% of patients; $p = 0.009$).

Mucosal healing. The SONIC trial published in in 2010 by Colombel et al. showed that,[8] at week 26, mucosal healing of colon and/or ileum was reached in 43.9% of patients submitted to a combination therapy with infliximab (5 mg/kg IV at weeks 0, 2, and 6 and every 8 weeks) and azathioprine (2.5 mg/kg po daily), in 30.1% of patients in the infliximab monotherapy group ($p = 0.06$ compared to combo group), and in only 16.5% of those receiving azathioprine monotherapy ($p < 0.001$ and $p = 0.02$, respectively).

Combination therapy with thiopurine. The SONIC trial revealed the beneficial effect of the combination therapy (infliximab and azathioprine (AZA)) in patients with moderate to severe Crohn's disease and naive to biologics.[8] Clinical remission (CDAI < 150) at week 26 was achieved in 56.8% of patients in the combination group, in 44.4% of those recruited in the infliximab monotherapy group ($p = 0.02$), and in 30.0% of those under AZA monotherapy ($p < 0.001$). At 50 weeks (trial extension), clinical remission persisted in 54.7% under AZA monotherapy compared to 66.0% under monotherapy with infliximab ($p = 0.09$). In the combination group, clinical remission was obtained in 74.1% of patients ($p = 0.005$ compared to AZA monotherapy; NS compared to infliximab monotherapy).

Combination therapy with methotrexate. Recently in 2014, Feagan et al. reported that a combination therapy with infliximab (5 mg/kg IV) and subcutaneous methotrexate (10 mg/kg at weeks 0–2, 20 mg/week at weeks 3–4, and 25 mg/week from week 5 through week 50) was not better than infliximab monotherapy to reduce treatment failure at 50 weeks (30.6% compared to 29.8%; NS).[9]

Rescue. No trial has been carried out on infliximab as a rescue treatment in Crohn's disease.

b) Adalimumab

Induction. In 2006, the CLASSIC I trial published by Hanauer et al. involved anti-TNF naïve patients.[10] Adalimumab induction therapy (160 mg sc at week 0 and 80 mg sc at week 2) induced clinical remission (CDAI score < 150) in 36 % of patients compared placebo in 12%, at week 4 ($p = 0.001$). Clinical response (defined as a 70 points reduction from baseline) at week 4 was 59% in the adalimumab group compared to 37% for placebo ($p = 0.007$).

In 2012, Watanabe et al. studied adalimumab induction in Japanese patients.[11] They demonstrated that adalimumab induction therapy (160/80 mg sc or 80/40 mg sc at week 0 and 2) induced clinical remission (CDAI score < 150) at week 4 in 33% and 18%, respectively, compared to 13% with placebo. Clinical response rate (defined as a 70 points reduction from baseline) at week 4 was 70% in the adalimumab 160/80 group, 59% in the adalimumab 80/40 group compared to 30% with placebo ($p = 0.0062$ and NS respectively).

Maintenance. In 2007, Colombel et al. in the CHARM trial confirmed the effect of adalimumab maintenance therapy (40 mg sc every other week (eow)) in patients responding to an induction dose.[12] The adalimumab maintenance group achieved a remission rate (CDAI score < 150) of 40% and 36% at weeks 26 and 56, respectively, compared to a remission seen in only 17% and 12% of patients treated with placebo (both $p < 0.001$). Steroid-free clinical remission occurred in 35% and 29% in the adalimumab maintenance group at 26 and 52 weeks, respectively, compared to 3% and 6% in the placebo group (both $p < 0.001$).

Watanabe et al. observed that,[11] in clinical responders at week 4 with adalimumab induction monotherapy, maintenance with adalimumab 40 mg sc every two weeks had a higher rate of remission at week 52 compared to placebo ($p < 0.05$).

Fistulizing. In the CHARM study,[12] complete closure of fistulas was achieved in 30% and 33% of patients on adalimumab (combined adalimumab groups) at 26 and 56 weeks, respectively; in comparison, a positive response was seen in only 13% and 13% patients on placebo ($p = 0.043$ and $p = 0.016$, respectively).

Mucosal healing. In the EXTEND trial published in 2012 by Rutgeerts et al.,[13] all patients had an induction with adalimumab 160 mg sc at week 0 and 80 mg sc at week 2. Mucosal healing of the ileocolonic mucosa (defined as absence of mucosal ulcerations) was obtained at week 12 and 52 in 27% and 24% of patients under adalimumab maintenance therapy (40mg sc eow) and in 13% and 0% of patients without maintenance treatment ($p = 0.056$ and $p < 0.001$).

Combination therapy with thiopurine or methotrexate. Results are less conclusive for the combination treatment with adalimumab than with infliximab. No study compared the adalimumab with methotrexate. One retrospective study, published by Reenaers et al. in 2012,[14] suggested a positive effect of a thiopurine-adalimumab combination therapy (86% of patients had no disease flare in the first 6 months in the combination group compared to 64% with adalimumab monotherapy ($p = 0.02$)). Another retrospective study,

which was published in 2013 by Ishida et al.,[15] demonstrated that, at week 24, a combination therapy with adalimumab and azathioprine induced a higher rate of clinical remission (defined as a CDAI <150) compared to adalimumab monotherapy ($p = 0.046$).

Rescue. The GAIN trial, published in 2007 by Sandborn et al.,[16] confirmed the efficacy of adalimumab (160 mg sc at week 0 and 80 mg sc at week 2) to induce remission (CDAI < 150) in patients who had symptoms despite infliximab treatment (134 patients) or who were unable to tolerate infliximab (190 patients). Remission at week 4 with adalimumab was achieved in 21% of patients (compared to 7% with placebo; $p < 0.001$). No difference was found between patients with previous loss of response to infliximab or intolerant to infliximab. Clinical response at week 4 (defined as a 70 points reduction from baseline) occurred in 52% with adalimumab compared to 34% with placebo ($p = 0.001$).

c) Certolizumab

Induction. In 2007, Sandborn et al. published the PRECISE I trial where they studied the effect of an induction treatment with certolizumab (400 mg sc at weeks 0, 2, and 4 and then every 4 weeks) in patients with moderate to severe Crohn's disease (and CRP higher than 10 mg/L).[17] At week 6, 37% of patients had responded (baseline CDAI score decrease >100 points) to certolizumab, and 26% to placebo ($p = 0.04$). At week 26, a positive response was still present in 22% of patients on certolizumab and in 12% on placebo ($p = 0.05$).

Maintenance. The PRECISE II trial, reported by Schreiber et al. in 2007,[18] studied maintenance therapy after a successful induction with certolizumab. At week 26, 62% of patients maintained their response (CDAI score decrease > 100 points from baseline) in the certolizumab group (400 mg sc every 4 weeks), compared to only 34% with placebo ($p < 0.001$); clinical remission (CDAI ≤ 150) was superior with certolizumab (48% compared to 29% ($p < 0.001$)).

Fistulizing. Schreiber et al. reported that after 26 weeks of treatment with certolizumab (400 mg sc every 4 weeks) total fistulas closure (95% anal fistulas) was obtained in 36% of patients (compared to 17% with placebo ($p = 0.038$)).[19]

Mucosal healing. In the MUSIC trial,[20] a significant decrease in the mean score of Crohn's disease endoscopic index (CDEIS potential score: 0–44) from baseline was observed at week 10 (from 14.5 at week 0 to 8.8 at week 10; $p < 0.001$). This was considered as a clinically significant response (defined as a reduction of 5 points in CDEIS score). At week 54, endoscopic remission (CDEIS score < 6) was seen in 27% of patients; mucosal healing (no ulcers at colonoscopy) was achieved in only 8% of patients. No control group was available for comparison.

Combination therapy with thiopurine or methotrexate. No study is available.

Rescue. In 2010, the WELCOME study, published by Sandborn et al.,[21] reported the effect of an open-label induction treatment with certolizumab (400 mg sc at weeks 0, 2, and 4) in patients with moderate to severe Crohn's disease and secondary non-responders to infliximab. At week 6, a clinical response (CDAI score decrease > 100 points from baseline) was achieved in 62% of patients. In these patients, the response was maintained after 26 weeks in 39.9% and 36.6 % of patients treated with certolizumab switch for every 4 and 2 weeks respectively.

d) Golimumab.

No study has been published on the treatment of Crohn's disease with golimumab.

- **Anti-integrins**

a) Natalizumab (anti-alpha 4 integrin)

Induction. The first trial was done by Ghosh et al. in 2003 on 248 patients receiving natalizumab at 0 and 4 weeks at the following IV doses: 0-0 mg/kg, 3-0 mg/kg, 3-3 mg/kg, or 6-6 mg/kg.[22] Remission rate (CDAI < 150) at week 6 was 27%, 29% (NS), 44% ($p = 0.03$), and 31 % (NS) of patients respectively. Response rate (>70 points decrease from baseline CDAI) at week 6 was 38%, 59% ($p = 0.022$), 71% ($p < 0.001$), and 57% ($p = 0.039$) of patients.

Sandborn et al. found,[23] in the ENACT I trial published in 2005, that natalizumab induction (300 mg IV at weeks 0, 4, and 8) was no better than placebo to induce a clinical response (>70 points decrease from baseline CDAI score) (56% compared to 49% of patients; $p = 0.05$) or to achieve clinical remission (CDAI < 150) (37% compared to 30%; $p = 0.12$) at week 10. A sub-analysis demonstrated that in patients with an elevated C-reactive protein (CRP), the treatment group with natalizumab achieved a higher response rate (58%) and a higher remission rate (40%) than placebo (45%, $p < 0.05$; 28%, $p < 0.05$ respectively).

In the ENCORE trial published by Targan et al. in 2007,[24] moderate to severe Crohn's disease patients defined as a CDAI score of 220–450 and with an elevated CRP received natalizumab 0 or 300 mg IV at weeks 0, 4, and 8. At week 4, the clinical response (>70 points decrease from baseline CDAI score) was more frequent in the natalizumab group

(51% compared to 37% of patients; $p = 0.001$). Patients with a positive response at week 8 persisting at week 12 were statistically more numerous in the natalizumab group than in placebo group (48% compared to 32%; $p < 0.001$). Sustained remission (CDAI < 150) was achieved at weeks 8 through 12 with natalizumab in 26% of patients (compared to 16% with placebo; p=0.002). The difference in the results between ENACT I and ENCORE can be explained by the inclusion of only elevated CRP patients in the ENCORE trial.[23,24]

Maintenance. In the ENACT II trial,[23] maintenance of response (>70 points decrease from baseline CDAI score) at week 36 and 60 was evaluated in responders after induction therapy (300 mg IV at weeks 0, 4 and 8 at week 10 in ENACT I trial). Response was maintained in 61% (week 36) and 54% (week 60) of patients under natalizumab treatment (300 mg every 4 weeks) compared to 28% and 20%, respectively, with placebo (p < 0.001 for both). Remission was maintained in 44% and 39% of patients under natalizumab treatment compared to 26% and 15% in the placebo group ($p = 0.003$ and $p < 0.001$, respectively). Serious adverse events occurred in the natalizumab maintenance group and as well as in the placebo group after the induction therapy with natalizumab; one patient of this trial died from multifocal leukoencephalopathy.

Fistulizing. No trial is available.

Mucosal healing. No trial is available.

Combination therapy with thiopurine or methotrexate. No study is available.

Rescue. No trial is available.

b) Vedolizumab (anti-alpha 4 beta 7 integrin)

Induction. In the GEMINI II trial, reported in 2013 by Sandborn et al.,[25] studied vedolizumab as an induction therapy (300 mg IV at weeks 0 and 2) for moderate to severe Crohn's disease. At week 6, the vedolizumab group achieved clinical remission (CDAI score ≤ 150) in 14.5% of patients as compared to 6.8% in the placebo group ($p = 0.02$). Clinical response (>100 points decrease from baseline CDAI score) was seen in 31.4% of patients who received vedolizumab and in 25.7% of those under placebo (p = 0.23).

Maintenance. In the same GEMINI II study,[25] among patients who responded to the initial induction therapy, maintenance treatment with vedolizumab 300 mg IV every 8 or 4 weeks provided clinical remission (CDAI ≤ 150) at week 52 in 39.0% and 36.4% of patients, respectively, compared to 21.6 % with placebo ($p < 0.001$ (every 8 weeks) and $p = 0.004$ (every 4 weeks)).

Fistulizing. No trial is available.

Mucosal healing. No trial is available.

Combination therapy with thiopurine or methotrexate. No study is available.

Rescue. In 2014, Sands et al. studied vedolizumab treatment in patients with a previous anti-TNF alpha failure.[26] Clinical remission (CDAI score ≤ 150) at weeks 6 and 10 was obtained in the vedolizumab group (300 mg IV at weeks 0, 2, and 6) by, respectively, 15.2% and 26.6% of patients compared to 12.1% and 12.1% with placebo ($p = 0.433$ and $p = 0.001$). Clinical response (>100 points decrease from baseline CDAI) was seen in 39.2% and 46.8% of patients in the vedolizumab group (compared to 22.3% and 24.8% with placebo ($p = 0.001$ and $p < 0.0001$)).

- **Others**

a) Ustekinumab (anti Il-12 and Il-23) (Phase III trial is ongoing)

Induction. No data are available with this agent in biologic naive patients. In the phase IIb CERTIFI trial published in 2012 by Sandborn et al.,[27] primary or secondary non-responders to an anti-TNF drug were given an induction therapy with ustekinumab. Clinical response (decrease > 100 points from baseline CDAI score) at week 6 was achieved in 36.6%, 34.1%, and 39.7% of patients receiving an IV dose of 1, 3, or 6 mg/kg, respectively, and in only 23.5% of those treated with placebo ($p = 0.02$, $p = 0.06$, and $p = 0.005$, respectively).

Maintenance. In the same study,[27] prolonged with patients who had responded to the initial induction regimen, 69.4% of patients under ustekinumab maintenance treatment (90 mg sc at weeks 8 and 16) maintained their response at week 22, as compared to 42.5% in those randomized to receive placebo ($p < 0.05$)

Fistulizing. No trial is available.

Mucosal healing. No trial is available.

Combination therapy with thiopurine. No study is available.

Rescue. Patients from the CERTIFI trial (discussed above) were primary or secondary anti-TNF alpha non-responders.[27]

Ulcerative colitis

Details of biologics trials evidences in ulcerative colitis are summarized in Table 2 and (see also Table 3 for details of administration and dosage of biologics in treating IBD).

Most ulcerative colitis trials used the Mayo score as an activity index.[28] The Mayo score includes 4 subscores: stool frequency (0–3), rectal bleeding (0–3), physician's global assessment (0–3), and endoscopy findings (0–3) for a total of 12 possible points.

Table 2. Biologics trials evidences in ulcerative colitis

		Induction	Maintenance	Mucosal healing	Combination thiopurine	Combination methotrexate	Acute severe colitis
Anti-TNF alpha							
	Infliximab	+	+	+	+	NA	+
	Adalimumab	+	+	+	NA	NA	NA
	Certolizumab	NA	NA	NA	NA	NA	NA
	Golimumab	+	+	+	NA	NA	NA
Anti-integrin							
	Natalizumab	NA	NA	NA	NA	NA	NA
	Vedolizumab	+	+	+	NA	NA	NA
Others							
	Ustekinumab	NA	NA	NA	NA	NA	NA

NA: Study is not available.
+: Study is available with a positive outcome.
−: Study is available with a negative outcome.

Table 3. Route of administration and dosage of biologics in inflammatory bowel disease

	Mechanism	Route of administration	Induction Dose (interval)	Maintenance Dose (interval)
Infliximab	Anti-TNF alpha	IV	5 mg/kg (w0-2-6)	5 mg/kg (e8w)
Adalimumab	Anti-TNF alpha	SC	160 mg (w0), 80 mg (w2)	40 mg (e2w)
Certolizumab	Anti-TNF alpha	SC	400 mg (w0-2-4)	400 mg (e4w)
Golimumab	Anti-TNF alpha	SC	200 mg (w0), 100 mg (w2)	50–100 mg (e4w)
Natalizumab	Anti integrin alpha 4	IV	300 mg (w0-4-8)	300 mg (e4w)
Vedolizumab	Anti integrin alpha 4/beta 7	IV	300 mg (w0-2-6)	300 mg (e8w)
Ustekinumab	Anti Il12/Il23	IV/SC	ND	ND

w: week, e: every, ND: not determined

Clinical response is defined as a decrease of at least 3 points and at least 30% of the Mayo score, accompanied with a rectal bleeding subscore decrease of at least 1 point and an absolute rectal bleeding subscore of 0 or 1; *clinical remission* as a Mayo score of 2 or less and no subscore more than 1; and *mucosal healing* as absolute Mayo endoscopy subscore of 0 or 1.

- **Anti-TNF alpha**

a) Infliximab

Induction. The first results on the effect of biologics as an induction treatment for ulcerative colitis were published in 2005 (ACT I and ACT II trials) by Rutgeerts et al.[29] They studied the clinical response obtained at 8 weeks, to infliximab given at weeks 0, 2, and 6 in patients with moderate to severe ulcerative colitis (Mayo score 6–12). The number of patients improved by infliximab 5 or 10 mg/kg IV was clearly superior to the response observed with placebo: ACT I (done in Belgium): 69.4% ($p < 0.001$) and 61.5% of patients ($p < 0.001$), respectively, compared to placebo 37.2%; and ACT II (done in the United States): 64.5% ($p < 0.001$) and 69.2% of patients ($p < 0.001$) compared to 29.3% in the placebo group. Remission rate at week 8 was: ACT I: 38.8% ($p < 0.001$) and 32% ($p = 0.002$) compared to placebo 14.9%; ACT II: 33.9% ($p < 0.001$) and 27.5% ($p < 0.001$) compared to placebo 5.7%.

Maintenance. The ACT I and ACT II trials looked at the capacity of infliximab (administered every 8 weeks) to maintain response in patients who responded to induction treatment.[29] At week 30, the effect of maintenance therapy with infliximab was clearly superior to the results obtained with placebo: ACT I: 48.8% and 45.9% of patients in the 5 and 10 mg/kg IV groups, respectively, were maintained in clinical response compared to 23.1% in the placebo group ($p < 0.001$ for both); ACT II: 41.3% ($p < 0.001$) and 53.3% ($p < 0.001$), respectively, compared to placebo 15.4%. Sustained clinical remission was also superior with infliximab: ACT I: 23.1% ($p = 0.001$) and 26.2%

($p < 0.001$), respectively, compared to placebo 8.3%; ACT II: 14.9% ($p < 0.001$) and 22.5% ($p < 0.001$), respectively, compared to placebo 2.4%. Similar results were found at week 54 (sustained clinical response at weeks 8, 30, and 54) in ACT I: 38.8% and 36.9% of patients in the 5 and 10 mg/kg IV groups, respectively, were maintained in clinical response compared to 14.0% in the placebo group ($p < 0.001$ for both). Sustained clinical remission was also superior with infliximab 19.8% ($p = 0.002$) and 20.5% ($p = 0.002$), respectively, compared to placebo 6.6%.

Mucosal healing. The ACT I and ACT II trials confirmed the superiority of infliximab to provide colonic mucosal healing at week 8.[29] In ACT I, 62% of patients in the 5 mg/kg IV infliximab group and 59% in the 10 mg/kg IV group had mucosal healing compared to placebo 33.9% ($p < 0.001$). Similar results were found in the ACT II trial.

Combination with thiopurine. Combination therapy with infliximab and azathioprine was analyzed in the SUCCESS trial by Panaccione et al. in 2014.[30] Corticosteroid-free clinical remission at week 16 was obtained by 39.7% of patients treated with the combination regimen (infliximab 5 mg/kg IV at weeks 0, 2, 6, and 14 and azathioprine 2.5 mg/kg PO daily), compared to 22.1% with infliximab monotherapy ($p = 0.017$), and 23.7% under azathioprine monotherapy ($p = 0.032$).

Combination with methotrexate. No trial is available

Severe acute colitis. This long-awaited information was published in 2012 in the *Lancet*. In severe acute ulcerative colitis refractory to intravenous corticosteroid, Laharie et al. found that infliximab was not inferior to ciclosporin as a rescue treatment to avoid colectomy.[31] A significant clinical response at day 7 was obtained in 86% patients who received an intravenous perfusion of ciclosporin 2 mg/kg/day for one week, and in 84% of those treated with one dose of IV infliximab 5 mg/kg on day 0 ($p = 0.76$). Total treatment failure at day 98 occurred in 60% patients in the ciclosporin group (induction treatment followed by oral drug until day 98) and in 54% of those receiving infliximab 5 mg/kg IV on days 14 and 42 ($p = 0.52$). Both group received AZA 2.0–2.5 mg/kg po at day 7 in patients with clinical response.

b) Adalimumab

Induction. The ULTRA I trial, published by Reinisch et al. in 2011,[32] studied the effect of an induction treatment with adalimumab (160/80 mg sc or 80/40 mg sc or placebo at weeks 0 and 2) in moderate to severe ulcerative colitis. Clinical remission at week 8 was achieved in 18.5% of patients in the 160/80 mg group, 10.0% in the 80/40 mg group, and 9.2% with placebo ($p = 0.031$ and $p = 0.833$, respectively). Clinical response and rate of mucosal healing at week 8 were not statistically significant among the three treatment groups.

The ULTRA-2 trial, published by Sandborn et al. in 2012,[33] studied induction therapy with adalimumab (160 mg sc at week 0, 80 mg sc at week 2, and 40 mg eow). The clinical remission rate at week 8 was 16.5% in the adalimumab group compared to 9.3% in the placebo group ($p = 0.019$). Clinical response at week 8 was 50.4% with adalimumab and 34.6% with placebo ($p < 0.005$).

In 2014, Suzuki et al. studied adalimumab induction therapy (160/80 mg sc or 80/40 mg sc at week 0 and 2) in Japanese patients with moderate to severe ulcerative colitis.[34] Clinical remission rates at week 8 were 10% and 14%, respectively, compared with placebo 11% (NS for both). Clinical response rates at week 8 were 50% and 43% compared to 35% with placebo ($p = 0.044$ and NS).

Maintenance. The ULTRA-2 trial also studied the effect of a maintenance treatment with adalimumab (40 mg sc eow).[33] Clinical remission at week 52 was documented in 17.3% of patients treated by adalimumab compared to 8.5% with placebo ($p = 0.004$). Clinical response at week 52 was seen in 30.2% of patients receiving adalimumab compared to 18.3% on placebo ($p < 0.05$).

Suzuki et al. evaluated adalimumab 40 mg sc every 2 weeks in Japanese patients after an induction therapy with adalimumab.[34] At week 52, clinical remission and clinical response were higher in the adalimumab group compared to placebo (23% compared to 7% ($p = 0.001$) and 31% compared to 18% ($p = 0.021$), respectively)

Mucosal healing. In the ULTRA-2 trial,[33] mucosal healing of colon mucosa at weeks 8 and 52 was obtained in 41.1% and 25.0% of patients treated with adalimumab and in 31.7% and 15.4% of those receiving placebo (both $p < 0.05$). Suzuki et al. also studied mucosal healing at 52 weeks with adalimumab treatment.[34] They found that the treatment group achieved 29% of mucosal healing compared to 16% with placebo ($p = 0.015$).

Combination with thiopurine or methotrexate. No trial is available.

Severe acute colitis. No trial is available.

c) Certolizumab

No trial is available.

d) Golimumab

Induction. The PURSUIT-SC trial, published by Sandborn et al.,[35] studied golimumab as an induction

therapy for patients with moderate to severe ulcerative colitis. Induction treatment with golimumab 200/100 mg sc or 400/200 mg sc at weeks 0 and 2 was compared to placebo. Clinical response at week 6 was detected in 51.0%, 54.9%, and 30.3% of patients, respectively, in each randomized group ($p < 0.0001$ for both active treatments). Clinical remission at week 6 was obtained in 17.8% and 17.9% of patients under golimumab treatment compared to 6.4% of those receiving placebo ($p < 0.0001$ for both).

Maintenance. The PURSUIT-M trial,[36] published in 2014, evaluated maintenance therapy with golimumab in responders to induction therapy. Clinical response at week 54 was seen in 31.2% of patients randomized to placebo, and in 47.0% and 49.7% of those receiving golimumab 50 or 100 mg sc every 4 weeks ($p = 0.010$ and $p < 0.001$ compared to placebo). Sustained clinical remission at week 30 through 54 occurred in 23.2% (50 mg sc group) and 27.8% (100 mg sc group) compared to 15.6% with placebo (NS and $p = 0.004$, respectively). Corticosteroid-free remission at 54 weeks among those who received corticosteroids at baseline was statistically non-significant among the groups.

Mucosal healing. In the PURSUIT-SC trial,[35] colonic mucosal healing was observed at week 6 in 42.3% and 45.1% of patients included in the 200/100 or the 400/200 mg groups, and in 28.7% of those under placebo ($p = 0.014$ and $p < 0.0001$). In the PURSUIT-M trial, 41.7% (50 mg group) and 42.4% (100 mg group) of patients achieved mucosal healing at both weeks 30 and 54 compared to 26.6% with placebo ($p = 0.011$ and $p = 0.002$, respectively).

Combination with thiopurine or methotrexate. No trial is available.

Severe acute colitis. No trial is available.

- **Anti-integrin**

a) Natalizumab

No trial is available with natalizumab in ulcerative colitis.

b) Vedolizumab

Induction. The GEMINI I trial by Feagan et al. in 2013 studied vedolizumab as an induction treatment for moderate to severe ulcerative colitis.[37] At week 6, clinical response and clinical remission were superior in patients randomized to vedolizumab (300 mg IV at weeks 0 and 2) than placebo (47.1% and 16.9% of patients, respectively, compared to 25.5% ($p < 0.001$) and 5.4% ($p = 0.001$) with placebo).

Maintenance. GEMINI I also studied vedolizumab maintenance treatment (300 mg IV every 8 or 4 weeks) in responders to the induction therapy.[37] Clinical remission was achieved in 41.8% and 44.8% patients, respectively, at week 52, compared to placebo 15.9% ($p < 0.001$ for both). Durable clinical response (at both weeks 6 and 52) was achieved in 56.6% and 52.0% of vedolizumab treated patients, and in only 23.8% with placebo ($p < 0.001$ for both).

Mucosal healing. In the GEMINI I trial,[37] mucosal healing at week 52 was achieved in 51.6% and 56.0% of patients receiving vedolizumab 300 mg every 8 or 4 weeks compared to 19.8% with placebo ($p < 0.001$ for both).

Combination with thiopurine or methotrexate. No trial is available.

Severe acute colitis. No trial is available.

- **Others**

a) Ustekinumab

No trial is available with ustekinumab in ulcerative colitis.

Conclusion

This paper has reviewed the scientific evidence obtained on the use of the biologics currently available in clinical medicine for the treatment of IBD.

Biologics have revolutionized the treatment of IBD over the last 15 years. Classically, medical treatment of IBD relies on corticosteroids. Minor disease can sometimes respond to 5-ASAs, while cortico-resistance or cortico-dependence can benefit from immunosuppressive agents such as azathioprine, 6-mercaptopurine, methotrexate, or from surgery. Recent treatment involves anti-TNF agents that are very potent to control IBD; in fact, their therapeutic capacity is often revealed in patients not improved by classical treatments, and, even now, in many countries, their administration is restricted to patients unresponsive to classical pharmacotherapy with corticoids and/or immunosuppressive drugs. The safety profile of anti-TNFs appears reassuring enough to be used now not only for brief induction treatment, but also for chronic maintenance therapy. However, biologics are expensive drugs and this certainly represents a major limitation for their universal use in IBD patients. Debate is still ongoing on whether the therapeutic advantages of anti-TNFs (e.g. rapid and effective clinical response, mucosal healing, improved quality of life, reduced need for surgery, etc.) induces a cost-effective global socio-economic benefit. Data from high-quality clinical trials are essential to guide proper use of these medications in our clinical practice.

Our therapeutic arsenal can now benefit from many biological agents acting on different inflammatory pathways. Various formulations of anti-TNFs have been developed (infliximab, adalimumab, certozilumab, golimumab) and anti-integrins (natalizumab, vedolizumab) agents are now available. No doubt that, in the very near future, new molecules addressing different inflammatory pathways will be submitted to the jury of evidence-based medicine (EBM). Further studies will be needed soon to identify which drug should be preferred first. Combination therapy with biologics addressing various different pathways (e.g. anti-integrin plus anti Il12-Il23 or anti-TNF) can now be contemplated, and will have to be submitted to the expertise of EBM for the benefit and safety of our patients.

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Conflict of interest

None declared.

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