R E V I E W

A medicoeconomic review of early intervention with biologic agents in the treatment of inflammatory bowel diseases

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Abstract: The treatment of inflammatory bowel disease with standard therapy fails to control the disease in many patients. Biologic therapy has an increasing role in altering the natural history of Crohn's disease and ulcerative colitis, and is improving patient prognosis. However, indications for treatment and issues with drug costs and value for money remain unclear. Also, when to perform early intervention with biologic agents is at present unclear. We performed an extensive literature search and review to address these issues. The biologics provide better care for many patients. The choice of biologic agent, the indications for its use, the switch between agents, and the considerations of cost are outlined, with a view to guiding the treating physician in managing these cases. Outstanding issues and anticipated future developments are defined.

Keywords: biologic therapy, ulcerative colitis, Crohn's disease, cost-effectiveness

Introduction

Inflammatory bowel disease (IBD) comprises three entities: ulcerative colitis (UC), Crohn's disease (CD), and "inflammatory bowel disease – unclassified" (IBD-U).[1] In a recent large European incidence study, IBD-U accounted for 11% of all IBD cases.[2] The etiology of IBD is unknown, but the incidence is generally increasing, particularly in Asia, where IBD was rare in the past. UC is a disease of the colon and rectum; ileal involvement is rare. The inflammation involves the mucosa; deeper penetration is uncommon. CD is a transmural disease of the small or large bowel or of both in various combinations; occasionally, more proximal involvement is seen. CD can occur as inflammatory, stricturing, and penetrating (fistulous) disease, and the pattern can change with time from purely inflammation to the more complicated phenotypes. The course of UC and CD is variable among patients, but an overall pattern has been modeled mathematically for CD.[3] It is estimated that some 50% of patients will have active disease at any point in time.[4] All these diseases are incurable; they last a lifetime, can have considerable morbidity, and often require "heavy" medication and surgery. There are considerable impairments of social functioning and the ability to learn and work. Procreativity is affected. The health care burden of these diseases is immense and is increasing.

The current treatment of IBD is complex and consists of nutritional and psycho-sociological support, pharmacotherapy, and surgery where specifically indicated. Standard or conventional therapy includes 5-aminosalicylic acid, corticosteroids, and immunomodulators.[5] In recent years, biologic agents have been introduced for use in CD and UC patients who failed conventional therapy in the "step-up" approach (standard therapy given first, and biologics for the failures of standard therapy) and

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as a first-line agent for CD patients with fistulae.[6] In selected CD patients without a fistula, the use of biologics de novo has been tested in what has been dubbed the "step-down" or "top-down" approach.[7] Biologic treatments have changed the entire concept of the management of IBD since they yield a high rate of induction and maintenance of deep mucosal (or histological) healing, which has become the major end point of therapy in the modern approach. The attainment of mucosal healing with the biologic agents may, for the first time, lead to a change in the natural course of disease by decreasing irreversible bowel damage and avoiding surgery.[8] Introduction of biologic therapy within 30 days of diagnosis (with or without prior standard therapy) has been defined as "early biologic intervention".

This review will examine the present role of biologics in the acute treatment of IBD and their cost-effectiveness; drug trials and economic models of the biologics will be examined in detail. Although consideration of side effects (some are quite serious) remains very important, the major factor limiting the use of biologics is their exorbitant acquisition price.[9] Therefore, the place of expensive biologic therapy in the developing world will be considered as well.

Materials and methods

English language peer-reviewed articles published through March 31, 2014 were obtained by an extensive search in PubMed, EMBASE, the Cochrane Library, and others, and from references contained in the solicited articles, beginning in the year 1990, using search terms such as: "ulcerative colitis", "Crohn's disease", "indeterminate colitis", "IBD-unclassified", "economics", "cost", "cost-effectiveness", "cost savings", "incremental cost-effectiveness ratio (ICER)", "quality-adjusted life-years (QALYs)", and the names of the various biologic agents with proven or apparent clinical use. We also used the Tufts Medical Center Cost-Effectiveness Analysis Registry to search for relevant economic evaluations. Drugs in development and biosimilars were not considered, since their cost and clinical benefit, and therefore their economic benefit, are yet unknown. For clinical evaluations we reviewed original research articles, reviews, and technical reports pertaining to adult patients. Economic studies of interest included cost-effectiveness analyses (CEAs) of biologic agents presenting a cost per QALY ICER and were either CEAs using patient-level data (ie, conducted alongside a clinical study or clinical trial) or decision analytic models. We excluded review, editorial, and methodological articles, and CEAs that measured health outcomes in units other than QALYs, as well as analyses

published prior to 2007. We excluded CEAs not examining biologic drugs or comparing biologics with immunosuppressants in the absence of a placebo arm. We also searched ClinicalTrials.gov using the terms "ulcerative colitis", "Crohn's disease", and "cost" to identify ongoing economic studies conducted alongside a clinical trial.

For each relevant CEA we present a description of the intervention, its comparator, the target population, the study perspective, the time horizon used for the analysis, and the ICERs as presented in the Tufts Medical Center Cost-Effectiveness Analysis Registry. CEAs may present more than one ICER, eg, when more than two interventions (eg, drugs) are compared, when various doses or treatment duration of the same drug are examined, and for different target populations in which the intervention is used. As studies were performed in various countries, using different currencies and reference years for costs, we converted all ICERs to US dollars using the relevant exchange factor and inflated to 2013 values using the US Consumer Price Index. Based on commonly accepted practice, an intervention with an ICER <$50,000/QALY (approximately the US gross domestic product [GDP] per capita) was deemed to be highly cost-effective, a ratio of $50,000–$100,000/QALY was considered cost-effective, and an ICER >$100,000 suggested that the intervention was not cost-effective.

Results
Mode of action of anti-tumor necrosis-α agents

The biologic agents can be classified by their primary mode of action (Table 1). Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine thought to contribute to mucosal inflammation in the intestines in CD and UC through a variety of mechanisms, including disruption of the mucosal barrier,

Table 1 Common biologic treatments for inflammatory bowel diseases

Class	Drugs	Current indications
Anti-TNF-α monoclonal antibodies	Infliximab	CD, UC
	Adalimumab	CD, UC
	Golimumab	UC, CD*
	Certolizumab	CD
Inhibition of leukocyte trafficking	Natalizumab	CD
	Vedolizumab	UC, CD
	Etrolizumab*	UC
T-cell depletion	Ustekinumab*	CD

Notes: *In trials, not yet approved for general use. Biosimilars of infliximab are not considered in this review.
Abbreviations: TNF, tumor necrosis factor; CD, Crohn's disease; UC, ulcerative colitis.

promotion of apoptosis of intestinal epithelial cells, and induction of intestinal chemokine secretion.[10] Monoclonal antibodies (mAbs) (immunoglobulins [Ig]) have been developed to specifically target transmembrane and soluble TNF-α molecules.

Three anti-TNF-α mAbs are US Food and Drug Administration (FDA)-approved for use in CD: infliximab (IFX), adalimumab (ADA), and certolizumab pegol (CZP). IFX and ADA are also approved in Europe. IFX and, more recently, ADA are approved for use in UC in the US and Europe; golimumab is now licensed in the US for use in UC. IFX is a chimeric IgG (75% human, 25% murine) mAb given intravenously. ADA is a fully humanized recombinant mAb injected subcutaneously. CZP is a pegylated, recombinant, fully humanized, antigen-binding fragment of a TNF mAb with less immunogenic potential. Like ADA, it is injected subcutaneously. Following a loading dose at onset of treatment, these agents have a linear relationship between the dose administered and the resulting plasma concentration achieved. The median half-life is shorter for IFX (7.7–9.5 days) than for ADA or CZP (2 weeks or more). These antibodies, being exogenous proteins introduced into the human host, are immunogenic, and their half-life is particularly affected by the presence of anti-TNF-α antibodies in the serum. Measurement of trough drug concentration and of antidrug antibody levels has become essential for monitoring patients on these therapies. There appears to be some correlation between IFX or ADA trough levels and the expected therapeutic response, but this has been difficult to demonstrate for CZP. With all agents, drug efficacy diminishes over time, the so-called secondary nonresponse. This failure rate may be lessened by adding azathioprine (AZA) to the therapeutic regime. An important consideration is that a certain percentage of naïve patients will be refractory to anti-TNF-α therapy from the outset, the so-called primary nonresponse. Since the armamentarium of approved biologic agents in most countries is limited to IFX and ADA, it is essential to optimize treatment with the first agent before making a change to the second drug.

Efficacy of anti-TNF-α medication in CD

This topic was the subject of two recent reviews. Ford et al[11] performed a meta-analysis of the efficacy of biologic therapies in IBD. Induction of remission rates in CD (drop of Crohn's Disease Activity Index [CDAI] to 150 or lower) for IFX (at weeks 10–12), ADA (at week 4), and CZP (at weeks 6–12) in CD was 45.3%, 24.2%, and 24.7%, respectively. Kawalec et al[12] carried out a meta-analysis of 18

randomized controlled trials and one clinical controlled trial, double-blinded and using a parallel group design, of induction (4 weeks of therapy) therapy with three anti-TNF-α agents in CD patients.[13–26] Remission in moderate-to-severe nonfistulizing and fistulizing CD was based on a drop of the CDAI to 150 or less. IFX was tested in five trials, and ADA and CZP were each tested in six. There were two studies of IFX versus ADA. All three agents were statistically more effective than placebo for induction of remission at week 4, with overall odds ratios (ORs) favoring the intervention as against placebo. Rates of fistula closure were also evaluated in two studies, showing >50% reduction in the number of fistulas with IFX or ADA versus placebo.

In looking specifically at the effect of early intervention with biologic agents, it is important to examine remission rates achievable in the short term (Table 2). The 14 studies shown examined the effects of ADA, CZP, IFX, natalizumab, golimumab, and, in two cases, IFX combined with AZA in placebo-controlled trials in patients with CD and UC. The patients had all failed standard therapy prior to randomization to biologic therapy or placebo, and the CD patients included a wide spectrum of disease manifestations, some with fistulae. The timeframe was 4–8 weeks for most studies, and remission in CD was defined by standard drop of activity indices. IFX and ADA were significantly better than placebo in inducing remission in CD patients, but it was more difficult to show similar efficacy for CZP. In one study, natalizumab was effective only in CD patients with an elevated C-reactive protein level. In the single top-down study of D'Haens et al,[20] IFX was given with AZA at the onset of treatment and had a better steroid-sparing effect than a step-up regimen where IFX was added as a last resort. Taken together, these ten studies show that it is possible to achieve remission in CD patients within a short time span at rates of about 30% in CD treated with ADA, IFX, or natalizumab. Stidham et al[27] performed a systematic review with network meta-analysis of trials of IFX, ADA, and CZP against placebo as comparator in CD patients. They found that there was no evidence of clinical superiority among these anti-TNF-α agents, although ADA was better than CZP for induction of remission. It is now evident that combination therapy using anti-TNF-α together with an immunomodulator gives higher remission rates than either agent alone in CD[23] and UC.[18] To date, there is no trial of early intervention with biologic agents where, for example, IFX or ADA is given at diagnosis for CD patients deemed to be at risk for serious forms of disease, to determine whether the long-term outcome will be better than early introduction of biologics when standard therapy was to no avail. Scheduled

Table 2 Remission rates for biologic therapy in CD and UC patients in a short timeframe

Disease	Intervention	Cohort size	Timeframe (weeks)	Remission (%)	P	Reference
CD	ADA	76	4	36	0.001	Hanauer et al[13]
	Placebo	74		12		
CD	ADA	159	4	21	0.001	Sandborn et al[14]
	Placebo	166		7		
CD	CZP	215	6	32	0.174	Sandborn et al[15]
	Placebo	223		25		
CD	CZP various	23	4	47.1	0.041	Winter et al[16]
	Placebo	24		16		
CD (with fistula)	CZP	24	6	12	NS	Schreiber et al[17]
	Placebo	15		10		
CD	IFX	169	6	29.6	<0.001 vs AZA	Colombel et al[18]
	IFX + AZA	169		32.5	<0.001 vs AZA	
	AZA	170		14.1		
CD	IFX	27	4	33	0.002	Targan et al[19]
	Placebo	25		4		
CD	IFX + AZA	67	14	64	0.001	D'Haens et al[20]
	Step-up to IFX	66		34		
CD	Natalizumab	259	8	26	0.002	Targan et al[21]
	Placebo	280		16		
CD (with raised CRP)	Natalizumab	526	10	40	<0.05	Sandborn et al[22]
	Placebo	134		28		
UC	IFX	121	8	33.9	<0.001	Rutgeerts et al[23]
	Placebo	123		5.7		
UC	ADA	130	8	18.5	<0.03	Reinisch et al[24]
	Placebo	130		9.2		
UC	ADA	142	8	15.6	0.019	Sandborn et al[25]
	Placebo	152		9.3		
UC	Golimumab 400mg/200mg	257	6	17.9	<0.001 vs placebo	Sandborn et al[26]
	Golimumab 200mg/100mg	253		17.8	<0.001 vs placebo	
	Placebo	251		6.4		

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; ADA, adalimumab; CZP, certolizumab pegol; NS, not significant; IFX, infliximab; AZA, azathioprine; CRP, C-reactive protein; vs, versus.

biologic therapy in CD is more effective in achieving mucosal healing than episodic treatment.[28]

Of note, Schnitzler et al[29] showed that at a median time of 6.7 months (interquartile range 1.4–24.6) after the start of IFX therapy in a CD cohort, there was mucosal healing noted in 68% of 183 initial responders, with 83 patients (45.4%) having complete healing and 41 (22.4%) having partial healing. Scheduled IFX treatment from the start resulted in mucosal healing more frequently than episodic treatment. The annual risk for loss of response to IFX averages about 13% per patient-year of treatment,[30] and for ADA the corresponding estimate is 20.3%.[31] When CD patients lose response after two anti-TNF-α agents, it is still possible that a third drug of the same class may be beneficial.[32]

Efficacy of anti-TNF-α medication in UC

The first anti-TNF-α agent approved for use in UC treatment was IFX. In the Active Ulcerative Colitis Trials (ACT) 1 and 2,

patients with moderate-to-severe active UC treated with IFX were more likely to have a clinical response at week 8 than those receiving placebo.[23] Over 60% of patients on IFX (5 mg/kg and 10 mg/kg dosages) had a clinical response by week 8 versus 37% for placebo. Mucosal healing was significantly increased in the IFX group compared with placebo. In UC, the remission rates were reported by Ford et al[11] as 57.1% for IFX (at weeks 6–12) and 17% for ADA (at week 6).

It has been shown more recently that newer anti-TNF-α agents ADA[24,25] and golimumab[26] are also effective in induction of remission in patients with extensive UC. In an 8-week placebo-controlled study, 186 patients (resistant to steroids and immunomodulator therapy, anti-TNF-naïve) were given ADA (160 mg at week 0, 80 mg at week 2, and 40 mg at weeks 4 and 6 or 80 mg at week 0 and 40 mg at weeks 2, 4, and 6) or placebo. At week 8 there was a significantly higher remission rate with ADA 160/80/40 than with placebo, 18.5% versus 9.2%, but no difference with the

80/40 regime.[24] Table 2 summarizes the early remission rates of four placebo-controlled trials of biologic therapy in UC patients. Remission rates in UC at 8 weeks were 36% with IFX and half that rate with ADA. The remission rate in UC patients treated with golimumab resembled that achievable with ADA. These data are important when early introduction of biologic therapy in UC is considered. It would appear that IFX is the drug of choice for initial biologic therapy, since it has the higher remission rate. As was found with CD, the combination of IFX with an immunomodulator in UC patients gives better results than IFX alone.[33] Lv et al[34] have meta-analyzed eight trials (2,122 patients) receiving TNF-α blockers (IFX in seven studies, ADA in one study) or placebo for severe UC through 2012. There was clinical benefit for IFX or ADA as compared with placebo in terms of an increased frequency of clinical remission ($P<0.00001$), steroid-free remission ($P=0.01$), and endoscopic remission ($P<0.00001$). In three trials there was a reported decreased rate of colectomy ($P=0.03$).

Laharie et al[35] performed the only study that compared rescue IFX and cyclosporine treatments for severe UC (n=115); both drugs were effective, and no difference was found in mucosal healing ($P=0.85$), colectomy frequency ($P=0.60$), or serious adverse events (SAEs) ($P=0.23$). Given these impressive findings, cyclosporine is no longer considered the rescue therapy of first choice in fulminant UC. Considering UC patients failing rescue therapy and then going to colectomy, there is no consensus in the literature as to whether anti-TNF-α therapies can increase the risk of postoperative complications, so this consideration cannot detract from the possible benefit of giving IFX to these very sick patients. There are no reports of early biologic intervention in UC, but the results of short-term therapy with biologics shown in Table 2 can be taken as an indication of the likely response to early interventional biologic treatment.

Stidham et al[36] reported a network meta-analysis of the efficacy of three anti-TNF-α agents for the treatment of UC, based on a selection of six trials for induction response. This meta-analysis demonstrated that, compared with placebo, IFX, ADA, and golimumab were all effective for the induction of remission in UC, and that no single agent was statistically superior to the others for the end points of induction of remission ($P=0.071$) or response ($P=0.025$), although there was a trend in favor of IFX.

Non-anti-TNF agents in IBD

Approximately a third of patients fail treatment with TNF-α antagonists, and up to 40% of patients who initially benefit subsequently lose response over time. Accordingly, new therapeutic approaches are being developed. The cytokines interleukin (IL)-12 and IL-23 play a key role in T helper cell and innate lymphocyte cell differentiation and expansion. They are composed of a shared p40 chain, which pairs with a p35 or a p19 chain to form IL-12 and IL-23, respectively. Genome-wide association studies have indicated that variants of the gene encoding the IL-23 receptor, as well as the locus harboring the gene encoding the p40 chain, confer a genetic risk for developing CD. Ustekinumab is a fully human IgG1-κ mAb to the p40 subunit shared by IL-12 and IL-23, and has demonstrated clinical benefit (but not clinical remission) over placebo in a large Phase IIb dose-finding trial in moderate-to-severe CD patients who had failed anti-TNF-α therapy.[37] Forty percent of treated patients (ustekinumab 6 mg/kg) reached the 6-week primary end point with clinical response of a >100 point decrease of the baseline CDAI, as compared with 24% for placebo ($P=0.005$). Mucosal healing was impossible to assess because of small sample sizes. There were important safety concerns with ustekinumab. The potential place of this agent in the paradigm of treatments of CD is not known as yet, nor do we comprehend its possible role in anti-TNF-α-naïve patients.

Lobatón et al[38] have reviewed the drugs targeting the a4b1, a4b7, or aEb7 integrins as well as the ICAM-1 and MAdCAM-1 addressins and the chemokine receptor 9. These drugs reduce intestinal inflammation by preventing T-lymphocyte homing in the gut. Vedolizumab, an a4b7 antibody that produces gut-selective blockade of lymphocyte trafficking, has now completed Phase III trials with very positive results Sandborn et al[39] conducted a large, Phase III, randomized, double-blind, placebo-controlled trial of vedolizumab (300 mg intravenously at times 0 and 2 weeks) in moderate to severely active CD patients; 15% of patients entered clinical remission at week 6 versus 7% on placebo – a significant difference. These low response rates were attributed to confounding factors.[42] In active UC, vedolizumab was at least twice as effective as placebo in inducing remission at 6 weeks, 47% versus 26% ($P<0.001$).[41] Vedolizumab has a slower onset of action than the anti-TNF-α agents and a longer half-life. Further work is needed to determine its exact place in the algorithm of early biologic intervention for IBD treatment. It could serve as a second-line biologic for patients failing anti-TNF-α drugs within a time span of 4–8 weeks. It could be a first-line medication in subsets of patients yet to be defined, and in those persons with contraindications to anti-TNF-α drugs, such as those with multiple sclerosis. Finally, the effect of this therapy in perianal disease and

extraintestinal manifestations needs to be investigated. The FDA approval of vedolizumab (to be marketed as Entyvio) for use in refractory CD and UC in May 2014 is a positive step forward, and we await the outcomes of this treatment in large cohorts of difficult patients.

Etrolizumab is a humanized mAb that selectively binds the β7 subunit of the heterodimeric integrins α4β7 and αEβ7. In a Phase II trial in patients with moderate-to-severe UC refractory to standard therapy (and anti-TNF-naïve), etrolizumab given subcutaneously over 8 weeks produced rather modest rates of remission by 10 weeks compared with placebo, which was quite ineffective.[41] This agent is one of several that are in Phase II or III clinical trials in UC. For this agent, it is premature to make conclusions or recommendations.

Natalizumab is a recombinant, humanized, IgG4 mAb to α4 integrin. Natalizumab blocks both α-4 B1 integrin (VCAM-1) and α-4 B7 integrin (MAdCAM-1) interactions; it inhibits leukocyte adhesion and migration into inflamed tissue (bowel and other). It has been shown to be an efficacious agent for induction of remission in patients with CD who failed anti-TNF-α agents. A retrospective case review of 69 CD patients (failures of standard as well as two anti-TNF-α therapies) treated with natalizumab at six sites in Massachusetts, USA, showed that 69% had a partial or complete clinical response.[42] This rate is similar to that described with IFX.[25] Natalizumab has been described as more effective in nonpenetrating CD disease.[43] The great fear with the use

of natalizumab is the occurrence of progressive multifocal leukoencephalopathy. Accordingly, the use of this agent has been severely restricted to those CD patients resistant to all other forms of therapy, and its place in the armamentarium of anti-IBD drugs is still unclear.

In Table 3 we have summarized the current clinical approaches to the use of biologic medications in CD and UC patients.

Economic considerations: the cost of biologic treatments

In the prebiologic era (for practical purposes, just over 15 years ago), the cost of treating CD and UC was driven strongly by charges for hospitalization and surgery.[44–51] With the advent of biologic therapy, this situation has changed completely, and it is now the cost of biologic agents that accounts for the main expenditure in treating these patients.[52–56] The use of biologic agents actually increases the cost of managing patients, at least in the short term, since their acquisition costs are high.

In the absence of long-term follow-up of patient cohorts to determine health care costs and savings after biologic therapy, cost studies and economic evaluations have been carried out using decision analytic models of hypothetical patients. These models are based on assumptions of changes in health status and make use of quality of life assessments (ie, utility weights) as reported in the literature. Since clinical reports vary greatly in their methodology, and CD and UC

Table 3 Paradigm: use of biologics in inflammatory bowel disease

Clinical scenario	Step-up first-line therapy	Step-up second-line therapy	Early biologic therapy	Stopping rule (possible)
Mild first attack, CD or UC	Standard*	Immunosuppression**	Usually not indicated	Single attack with remission and mucosal healing in patient unwilling to continue medication
Severe first or subsequent attack, CD or UC	Accelerated standard	Rapid introduction of biologic	Indicated in high-risk patients***	None
Fistulous and perianal CD	Standard, biologic in selected cases	Biologic	Indicated	None
CD, short strictures	Endoscopic/surgical dilatation	Requires maintenance therapy (likely azathioprine)	Indicated if there is evidence of acute inflammation	None
UC, strictures	Surgery	None	Not indicated	After panproctocolectomy in absence of pouchitis
Postoperative CD	Continue the immunomodulator or biologic used preoperatively	Biologic (of same or another class)		Not advised

Notes: *5-aminosalicylic acid (in UC), corticosteroids (consider budesonide in CD), consider MMX preparations; **azathioprine or 6-mercaptopurine preferred; ***refers to factors indicating a poor prognosis, such as onset in children or young adults, extensive disease and/or extraintestinal manifestations at presentation, terminal ileum location, stricturing and/or penetrating behavior, genetic/serological markers, and family history of inflammatory bowel disease. In every case, it is necessary to fit the treatment paradigm to the specific needs of the particular patient, including patient preferences and the availability and cost of medications.
Abbreviations: CD, Crohn's disease; MMX, Multi-Matrix System; UC, ulcerative colitis.

are diseases with a broad and varying clinical spectrum, there will be large disparities between various models. Herein follows a review of a few pertinent studies, with the objective of determining the economic impact of the use of biologics. As health care budgets become more restricted in all countries with the passage of time, CEAs are increasingly being used to inform coverage and reimbursement decisions in many countries. These analyses have been used recently to assess whether new biologic agents are cost-effective and provide "good value for money". Using the Tufts Medical Center Cost-Effectiveness Analysis Registry,[57] we identified 38 publications reporting on interventions for CD and UC, of which 13 examined biologic agents (ten for CD and three for UC). The results from these analyses are presented in Tables 4 and 5, pertaining to CD[58–67] and UC,[68–70] respectively.

The cost-effectiveness in CD of IFX, ADA, certolizumab, and natalizumab was assessed in ten studies conducted in the US (N=4), the UK (N=4), Canada (N=1), and Italy (N=1). ICERs varied widely. Some of the treatment regimens were both more effective and cost-saving, while others were associated with very high ICERs. The evaluations varied widely in regard to patient characteristics, regimens compared, and product dosing. For example, Tang et al[60] suggested that ADA was cost-saving when compared with natalizumab but was not cost-effective when compared with certolizumab. ADA and IFX seem to be cost-effective treatment options in various patients and countries. However, induction therapy followed by maintenance therapy is not cost-effective regardless of the drug used.[61] The cost-effectiveness of biologic agents for treating patients with UC has been assessed in three studies from the UK and Canada. When compared with usual care, treating moderate to severely acute UC patients with IFX seems to be cost-effective. However, an assessment of a sequential therapy of IFX and ADA in refractory UC patients suggests that this treatment modality does not provide good value for money.

Our review of economic evaluations has several limitations. Firstly, we did not evaluate the merit and accuracy of the data used for CEAs, nor did we assess the quality of modeling assumptions and the robustness of study findings. Results of CEAs may differ among countries even if the same target population, treatment, comparator, and treatment efficacy are used. This is mainly due to differences in the relative cost of the drugs, and differences in utilization of health care services and their price and charges. Secondly, results may also vary when different follow-up periods are applied, mainly because of the cost of the drug when a long maintenance treatment is applied. Studies using decision analytic models rather than patient-level data may use different assumptions on the target population, which may influence the results. For example, Saito et al[58] used a hypothetical cohort of 25-year-old men weighting 60 kg followed for 1 year, while Blackhouse et al[61] assumed a cohort of those aged 37 years weighing 73 kg and being followed for a period of 5 years. Moreover, although all CEAs presented in our review were conducted from a health care payer's perspective, analyses conducted from a broader societal perspective, considering also indirect costs to the patient, the caregivers, and society, may reach different conclusions. Thirdly, to allow comparison among studies, our review is limited to CEAs reporting a cost per QALY ratio. It is possible that economic evaluations of biologic agents for CD and UC have used other metrics. Finally, our economic review was limited to English language peer-reviewed literature indexed in MEDLINE and published from 2007 to 2014. We did not include health technology assessment reports generated by health technology assessment agencies such as the National Institute for Health and Care Excellence (in England). Of interest, the recent economic review by Tang et al[71] yielded similar conclusions regarding the reported studies of biologic agents used to treat CD, but they did not include analyses of biologic interventions for treating UC.

Given the great expense involved in treating IBD patients with biologic therapies, and noting the pivotal role of these agents in altering the natural history of disease and offering the chance to avoid serious complications and surgery, attention must be paid to the provision of these compounds in countries with limited resources. Indeed, biologic therapy is now available for many diseases, and this development will likely continue. Rogler et al[72] have reviewed this topic regarding IBD patients at length. Developing countries account for the majority of the world population, and IBD incidence has risen alarmingly in those populations as they become more Westernized. The health care systems in these countries will have difficulty affording such high-priced treatments. A dialogue was suggested as to how the IBD experience of the developed countries could be transferred to those countries with limited resources in order to best identify those patients with a prospect of a severe prognosis. Furthermore, joint involvement of the World Health Organization, the World Gastroenterology Organization, and the pharmaceutical industry is recommended. The World Gastroenterology Organization uses CEAs in making recommendations for the treatment of IBD in developing countries, and the World Health Organization has established threshold limits for intervention cost-effectiveness based on the GDP per region.

Table 4 Cost-effectiveness analyses of biologic agents for CD

Intervention, comparator, and target population	Country	Time horizon	Study perspective	ICER ($/QALY)	Reference
Combination therapy with IFX + AZA at 2.5 mg/kg daily versus IFX monotherapy (IV infusion 5 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter) in men aged 25 years with biologically naïve CD refractory to conventional non-anti-TNF-α therapy	UK	1 year	Health care payer	50,000	Saito et al[58]
Top-down strategy: induction treatment of combined immunosuppressive therapy with IFX (2.5 mg/kg/day) and if symptom exacerbation occurred, additional IFX infusions and methylprednisone (32 mg/day for 3 weeks followed by 4 mg/week dose tapering) prescribed versus step-up strategy: induction treatment of methylprednisone and if symptom exacerbation or relapse occurred, AZA and IFX were added to treatment in newly diagnosed patients with luminal CD	Italy	5 years	Health care payer	Cost-saving	Marchetti et al[59]
ADA versus CZP in US adult patients aged 35 years with moderate-to-severe CD who failed to respond to standard therapy	US	54 weeks	Health care payer	Cost-saving	Tang et al[60]
Natalizumab versus CZP in US adult patients aged 35 years with moderate-to-severe CD who failed to respond to standard therapy	US	54 weeks	Health care payer	300,000	Tang et al[60]
ADA versus natalizumab in US adult patients aged 35 years with moderate-to-severe CD who failed to respond to standard therapy	US	54 weeks	Health care payer	Cost-saving	Tang et al[60]
IFX versus natalizumab in US adult patients aged 35 years with moderate-to-severe CD who failed to respond to standard therapy	US	54 weeks	Health care payer	Cost-saving	Tang et al[60]
IFX versus CZP in US adult patients aged 35 years with moderate-to-severe CD who failed to respond to standard therapy	US	54 weeks	Health care payer	Cost-saving	Tang et al[60]
Induction therapy of IFX (5 mg/kg) infusions followed by maintenance therapy of IFX (5 mg/kg) infusions every 8 weeks versus induction therapy of ADA (160 mg) subcutaneous injections followed by maintenance therapy of ADA (40 mg) subcutaneous injections every 2 weeks in Canadian patients aged 37 years and weighing 73 kg	Canada	5 years	Health care payer	470,000	Blackhouse et al[61]
Induction therapy of IFX (5 mg/kg) infusions followed by maintenance therapy of IFX (5 mg/kg) infusions every 8 weeks versus usual care: variety of conventional non-anti-TNF-α treatments including corticosteroids and other immunosuppressants in Canadian patients aged 37 years with refractory CD	Canada	5 years	Health care payer	230,000	Blackhouse et al[61]
Induction therapy of ADA (160 mg) subcutaneous injections followed by maintenance therapy of ADA (40 mg) subcutaneous injections every 2 weeks versus usual care: variety of conventional non-anti-TNF-α treatments including corticosteroids and other immunosuppressants in Canadian patients aged 37 years and weighing 73 kg	Canada	5 years	Health care payer	200,000	Blackhouse et al[61]
CZP (400 mg) subcutaneously and continued on monthly maintenance therapy versus natalizumab (300 mg) intravenously every month in US patients aged 35 years with moderate-to-severe CD unresponsive to prior TNF-α antagonists	US	1 year	Health care payer	590,000	Ananthakrishnan et al[62]
ADA versus IFX in US patients with moderately to severely active CD	US	56 weeks	Health care payer	Cost-saving	Yu et al[63]

(Continued)

Table 4 (*Continued*)

Intervention, comparator, and target population	Country	Time horizon	Study perspective	ICER ($/QALY)	Reference
ADA 2 years of treatment versus standard care in moderate to severely active CD patients in the UK	UK	60 years	Health care payer	23,000	Bodger et al[64]
ADA 1 year of treatment versus standard care in moderate to severely active CD patients in the UK	UK	60 years	Health care payer	16,000	Bodger et al[64]
IFX 2 years of treatment versus standard care in moderate to severely active CD patients in the UK	UK	60 years	Health care payer	48,000	Bodger et al[64]
IFX 1 year of treatment versus standard care in moderate to severely active CD patients in the UK	UK	60 years	Health care payer	51,000	Bodger et al[64]
ADA (every other week) maintenance treatment versus nonbiologic treatment, placebo (also doses of conventional, nonbiologic medications) in CD patients (in two randomized, double-blind placebo-controlled trails, CHARM and CLASSIC, lifetime model duration) (severe disease groups)	UK	1 year	Health care payer	14,000	Loftus et al[65]
ADA (every other week) maintenance treatment versus nonbiologic treatment, placebo (also doses of conventional, nonbiologic medications) in CD patients (in two randomized, double-blind placebo-controlled trails, CHARM and CLASSIC, lifetime model duration) (moderately severe disease groups)	UK	1 year	Health care payer	38,000	Loftus et al[65]
ADA (every other week) maintenance treatment versus nonbiologic treatment, placebo (also doses of conventional, nonbiologic medications) in CD patients (in two randomized, double-blind placebo-controlled trails, CHARM and CLASSIC, 56-week model duration) (moderately severe disease groups)	UK	1 year	Health care payer	72,000	Loftus et al[65]
ADA (every other week) maintenance treatment versus nonbiologic treatment, placebo (also doses of conventional, nonbiologic medications) in CD patients (in two randomized, double-blind placebo-controlled trails, CHARM and CLASSIC, 56-week base case model) (severe disease group)	UK	1 year	Health care payer	34,000	Loftus et al[65]
ADA (every other week) maintenance treatment versus nonbiologic treatment, placebo (also doses of conventional, nonbiologic medications) in CD patients (in two randomized, double-blind placebo-controlled trails, CHARM and CLASSIC, 56-week base case model) (severe disease group)	UK	1 year	Health care payer	34,000	Loftus et al[65]
Maintenance therapy with IFX (5 mg/kg) versus standard care without IFX in adult patients with fistulizing CD in the UK	UK	5 years	Health care payer	63,000	Linsday et al[66]
Maintenance therapy with IFX (5 mg/kg) versus standard care without IFX in adult patients with active luminal CD in the UK	UK	5 years	Health care payer	56,000	Linsday et al[66]
Dose escalation of IFX to 10 mg/kg versus IFX discontinued and ADA initiated with a 160 mg injection followed by a 80 mg dose 2 weeks later, maintenance of 40 mg every other week in CD patients who have lost response to standard dose (5 mg/kg) IFX therapy	US	1 year	Health care payer	380,000	Kaplan et al[67]

Notes: Study perspective: The study perspective is the viewpoint from which costs and benefits are calculated. All studies included in our review were conducted from a health care payer perspective and include only direct costs incurred by insurance companies (private or national health care service). Time horizon: The time horizon is the length of time in which resource use (eg, drug use, hospital admissions) are measured. ICER is calculated by dividing the incremental cost by the incremental QALYs gained of an intervention over the examined comparator. An ICER is not calculated when the intervention costs less (cost-saving) and is at least as effective as the comparator. In many of these cases, the intervention is considered "dominant" over the comparator, suggesting that it is both cost-saving and more effective.
Abbreviations: CD, Crohn's disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; IFX, infliximab; AZA, azathioprine; IV, intravenous; TNF, tumor necrosis factor; ADA, adalimumab; CZP, certolizumab pegol; CHARM, Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance; CLASSIC, CLinical assessment of Adalimumab Safety and efficacy Studied as Induction therapy in Crohn's disease.

Table 5 Cost-effectiveness analyses of biologic agents for UC

Intervention, comparator, and target population	Country	Time horizon	Study perspective	ICER ($/QALY)	Reference
IFX, includes first infusion of 5 mg/kg on the 4th day, with concomitant standard care comprising IV therapy for an additional 7 days during the hospital stay versus cyclosporine, includes infusion of 4 mg/kg on the 4th to 11th days, with concomitant standard care comprising IV therapy for an additional 7 days during the hospital stay in acute severe UC patients not responding to 72 hours of IV steroid therapy	UK	1 year	Health care payer	41,000	Punekar et al[68]
5 mg/kg and 10 mg/kg IFX + ADA versus usual care in Canadian patients diagnosed with refractory UC	Canada	5 years	Health care payer	590,000	Xie et al[69]
5 mg/kg IFX + ADA versus usual care in Canadian patients diagnosed with refractory UC	Canada	5 years	Health care payer	370,000	Xie et al[69]
IFX treatment 5 mg/kg, remission strategy versus standard care in patients with moderate-to-severe UC in the UK	UK	10 years	Health care payer	44,000	Tsai et al[70]
IFX treatment 5 mg/kg, responder strategy versus standard care in patients with moderate-to-severe UC in the UK	UK	10 years	Health care payer	62,000	Tsai et al[70]

Notes: Study perspective: The study perspective is the viewpoint from which costs and benefits are calculated. All studies included in our review were conducted from a health care payer perspective and include only direct costs incurred by insurance companies (private or national health care service). Time horizon: The time horizon is the length of time in which resource use (eg, drug use, hospital admissions) are measured. ICER is calculated by dividing the incremental cost by the incremental QALYs gained of an intervention over the examined comparator. An ICER is not calculated when the intervention costs less (cost-saving) and is at least as effective as the comparator. In many of these cases, the intervention is considered "dominant" over the comparator, suggesting that it is both cost-saving and more effective.
Abbreviations: UC, ulcerative colitis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; IFX, infliximab; IV, intravenous; ADA, adalimumab.

Of importance, endemic diseases such as tuberculosis and intestinal parasites need to be excluded, and a trial of therapy may be indicated where differentiation from CD and UC is difficult or limited by lack of resources. Biologic therapy can also be harmful in persons with chronic hepatitis, a condition that is more common in developing nations, and in those with human immunodeficiency virus. There are particular ethical considerations regarding poorer countries that have no easy solutions.

Adverse effects of biologic therapies

As with all medications, it is important to consider the side effects reported with biologic therapies. The anti-TNF-α medications are usually well tolerated, but adverse events resulted in up to 15% of patients withdrawing from clinical trials. Injection site and infusion reactions were highest with IFX and lowest with CZP. Infusion reactions can be prevented in most cases by coadministration of hydrocortisone. Delayed hypersensitivity reactions are uncommon and can appear within a few days after treatment. Infections may be more common after anti-TNF-α administration, including activation of latent tuberculosis and hepatitis B. Proper screening procedures and immunizations are thus advised before biologics are prescribed. Malignancy after anti-TNF-α therapy is an important concern, particularly the rare hepatosplenic T-cell lymphoma in young men and non-melanotic skin cancer. A recent Cochrane review looked at SAEs, activation of tuberculosis, lymphoma, and congestive

cardiac failure after biologic therapy in a variety of diseases in the short term.[73] Of the anti-TNF-α agents, IFX had significantly more adverse events than placebo (OR 1.55, 95% confidence interval 1.01–2.35) and the largest number of patient withdrawals from drug trials (OR 2.34, 1.40–4.14) compared with the other biologics. CZP had the highest risk of serious infections (OR 4.75, 1.52–18.5) and SAEs (OR 1.57, 1.06–2.32). CZP had significantly more SAEs than ADA, and ADA more than golimumab. Lymphoma and cardiac failure were not more common after biologic therapy compared with control subjects. Natalizumab, as noted, has been associated with the onset of progressive multifocal leukoencephalopathy caused by the JC virus.[74] Other newer biologics had a reported 10% rate of adverse events. The issue of whether biologic agents increase perioperative morbidity remains an open question.

The patient's perspective

Patients seek clinical improvement and an increased quality of life, and are confused by new and unknown treatments. It is increasingly recognized that the patients must be given time to express their opinions about choice of therapy and related cost issues. The European Federation of Crohn's and Ulcerative Colitis Associations has studied the subject of patient–physician communication and found that nearly half of IBD patients do not initiate discussion of quality of life issues with their doctors.[75] We emphasize here the great importance of such discourse, particularly when biologic

therapy is considered, given both its cost and potential for adverse events, and endorse the federation's recommendation for a "prescription for information" personalized to the exact sociodemographic and clinical situation of the patient.

Conclusion

In clinical terms, the choice of a biologic agent in CD or UC seems now to depend on patient preference of route of administration and on availability (this latter depends principally on cost considerations). There is probably no difference of clinical efficacy between IFX and ADA, although this statement is based on indirect evidence and on a network meta-analysis from one research group. The place of other anti-TNF-α agents is less certain. The available non-anti-TNF agents will likely be used as second-line therapies, although there is no evidence for this statement. Clearly, better identification of subphenotypes of CD and UC is required to make these decisions. Regarding IBD-U, this is basically an unresearched entity, and choice of medication will continue to be empirical in the near future.

The introduction of biologic drugs has shifted the cost of treating IBD from hospitalizations and surgical procedures toward anti-TNF-α therapy. A recent study suggests that anti-TNF-α use was the main cost driver, accounting for 64% and 31% of the total cost in CD and UC, respectively.[58] The current high cost of these drugs remains a problem; current evidence suggests that biologic agents may be cost-effective for both CD and UC only under certain specific clinical scenarios. However, these interventions are not cost-saving, suggesting that savings in follow-up costs (for surgery, hospitalization) are not sufficient to offset the cost of the drugs. The number of CEAs published in recent years is rather limited, and it is very difficult to draw conclusions on their economic merit for all indications and target patients, particularly when dealing with diseases with protean manifestations, such as as UC and CD. Important factors such as length and frequency of treatment (ie, induction or maintenance treatment) with each drug, as well as switching among biologic drugs when the first employed agent was ineffective, should be further examined in economic evaluations. The progress of golimumab will be followed keenly both clinically and from the cost aspect. With the new availability of different classes of biologic agents such as vedolizumab, it will be interesting to follow the upcoming clinical and economic evaluations in large patient populations. The introduction of biosimilars in the coming years may improve the cost-effectiveness of biologic agents, due to expected price reductions. This is contingent upon the assumption that biosimilar drugs are as effective clinically as the original patented agents. Finally, the newer biologics undergoing clinical trials or still in the development stage will need to be assessed in the context of health economics.

Disclosure

The authors report no conflicts of interest in this work.

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