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REVIEW

Infliximab use in patients with Crohn's disease: quality of life, costs and resource use

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KEYWORDS

Crohn's disease, infliximab

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract which primarily affects young adults, with the highest incidence rates reported from Northern Europe, the United Kingdom and North America ranging from 6.9 to 15.6 cases per 100.000 person-years.[1] The course of disease is characterised by episodes of remission and flare-up. The impact on the physical, social, as well as the emotional well-being of patients is substantial and the disease profoundly decreases the quality of life (QoL).[2-4]

The treatment of CD is unsatisfactory, since none of the existing treatments such as aminosalicylates, corticosteroids, immunosuppressive drugs or surgery are curative. Although these treatments have a positive effect on most patients, there is a high incidence of relapse and particularly morbidity from side effects.

Infliximab (Remicade®), a monoclonal antibody directed against tumour necrosis factor-alpha (TNF-α), was introduced in 1998 and has revolutionised treatment. It is indicated for fistulising CD and the treatment of moderately to severely active luminal CD resistant to conventional therapy.[5,6] The initial response rates for these indications are 61 to 69% and 58 to 65%, respectively.[7-10] An infusion of 5 mg/kg infliximab can be given as induction treatment at week 0, 2 and 6, or as maintenance treatment every eight weeks after induction treatment. Maintenance therapy sustains fistula closure, clinical remission and clinical response significantly more than induction treatment only. This implicates an additional therapeutic option for patients previously thought to be refractory to therapy.[7-10]

Although the efficacy of infliximab treatment in CD patients is proven, prescription of infliximab is hampered in daily practice due to its costs (the Netherlands: up to € 14,000 yearly) and the funding system (such as in the Netherlands, Belgium, Canada and the USA).

In general, CD has an expensive course of disease, since diagnosis is at an early age and life expectancy is normal. Annual direct medical costs for CD patients are predominantly caused by surgery and other inpatient services, such as hospitalisation, resulting in 81% of the costs, whereas medications only account for 10% of the costs. All other costs are produced by initial diagnostic workups, outpatient services and long-term complications.[11,12] Annual costs for CD patients per year are difficult to obtain since costs depend on the natural course of the disease. Feagan *et al*. estimated annual costs varying from US $ 6,277 to $ 37,135 by employing different disease severity groups.[13] Remarkable is the fact that only 2% of the CD patients generate 28.9% of the total costs.[11]

Unemployment, disability compensation, compromising of professional career, lost time from work and early retirement are indirect non-medical costs of CD which are difficult to assess but account for high costs to society.[14] An average of 25% of patients with moderate to severe luminal CD in the USA, Europe, Canada and Israel received disability compensation, 39% were unemployed with only 14% of them feeling well enough to work.[15] A Swedish study, which used Swedish national registry data to calculate costs for both ulcerative colitis and CD, reported annual indirect costs at US $ 58.4 million for 40,000 patients, which is a twofold higher than the direct costs.[16] Remission of CD increases employment and is associated with a reduced number of hospitalisations and operations, as well as a normalised QoL.[17] Because infliximab can induce and sustain remission in most patients with refractory and fistulising CD, the most severe type of the disease, this strategy could be cost-effective despite its costs.

The aim of this review is to critically appraise the cost-utility and cost-effectiveness of infliximab in patients with CD by summarising all available evidence with respect to the effect of infliximab on QoL, medical costs and use of resources.

MATERIALS AND METHODS

Literature search

A search in MEDLINE and EMBASE was performed combining different synonyms for CD and QoL, as well as for costs and resource use (*table 1*). No limits were added and the search was run until July 2005. Additionally, we searched the Cochrane Library 2005 and reference lists of relevant systematic reviews and randomised controlled trials (RCT) for articles missed by the computer-based search strategy.

Study selection criteria

Studies in which the efficacy of infliximab was evaluated in adult patients with moderate to severe active luminal or fistulising CD were selected for this review. The outcome of the QoL had to be described with the Inflammatory Bowel Disease Questionnaire (IBDQ) or the SF-36 Health Survey (SF-36). The IBDQ is a disease-specific questionnaire which contains 32 items concerning bowel, systemic, emotional and social subjects and correlates significantly with the Crohn's Disease Activity Index.[18,19] Total IBDQ scores range from 32 to 224, corresponding to a very poor and perfect QoL, respectively. The SF-36 is a generic QoL evaluation which contains two summary measures, the physical component summary (PCS) and the mental component summary (MCS), with a mean summary score of 50 and a standard deviation of 10 for the general population.[20] Previous studies have shown no[21] or only a weak correlation[22] between the SF-36 and the IBDQ.

Costs had to be described by direct financial medical costs or resource use. Another, indirect, tool for assessing costs is a Markov model. Markov models are theoretical models and estimate long-term costs by combining time spent in different distinct health states (e.g. remission, mild, drug dependence, surgery) and the calculated costs. The proportion of time spent in each health state and its costs has to be determined retrospectively.[23] The validity of a such model is critically dependent on the underlying assumptions and on the reliability of the data input. Because infliximab has only been available since 1998 and long-term effects have not been published, cost estimates are commonly based upon unpublished industry models. We question the validity of these estimations and do not consider clinical conclusions drawn from Markov models based on these data to be feasible.

Validity assessment and data abstraction

Only RCTs and clinical cohort studies were included. Three independent reviewers selected potentially relevant references based on title, abstract and keywords. From articles for which disagreement existed, full texts were obtained and in all of these cases consensus was reached at a later stage.

The number of patients, similarity of treated groups, blinding of patients and physicians, randomisation, setting, follow-up, dropout rate and intention-to-treat analysis were used as criteria to evaluate the selected studies.[24] Quality of evidence was assigned based on regulations formulated elsewhere, in decreasing value from meta-analysis, RCTs, nonrandomised (observational) comparative cohort study, nonrandomised historical cohort studies to case series.[25] If publications were based on the same study population the most relevant reference was selected. Furthermore, we corresponded with some authors to obtain missing data.[21,22,26,27]

Table 1. *Search strategy MEDLINE and EMBASE*

#	Terms	Number of articles	
		MEDLINE	EMBASE
1	Search ("Crohn Disease"[MeSH] OR "Inflammatory Bowel Diseases"[MeSH]) OR Crohn's disease[Title/Abstract] OR crohn disease[Title/Abstract] OR Inflammatory bowel disease[Title/Abstract]	39,071	96,822
2	Search "infliximab"[Substance Name] OR infliximab[Title/Abstract] OR remicade[Title/Abstract]	1976	4822
3	Search "Value of Life"[MeSH Terms] OR "Quality of Life"[MeSH Terms] OR "Quality Adjusted Life Years"[MeSH] [Terms] OR "Health status indicators"[MeSH Terms]) OR "Value of Life"[Title/Abstract] OR "quality of life"[Title/Abstract] OR "quality adjusted life years"[Title/Abstract] OR "health status indicators"[Title/Abstract]))	141,171	229,820
4	Search #1 AND #2 AND #3	88	125[§]
5	Search "Costs and Cost Analysis"[MeSH]) OR cost of illness[Title/Abstract] OR surger*[Title/Abstract]) OR hospitalizations[Title/Abstract] OR "Resource use"[Title/Abstract] OR "Patient Care"[MeSH]	839,489	409,638[†]
6	Search #1 AND #2 AND #5	86	143

[§]**Limits: English, human;** [†]**without surger*** **and hospitalizations.**

RESULTS

Characteristics of selected studies

Quality of life

In total 88 and 125 potential relevant references were found in MEDLINE and EMBASE, respectively (*table 1*). Of all these references only five RCT and two cohort studies met the inclusion criteria and were considered suitable for evaluation in this review.[10,21,22,28-31] These articles all turned up in both search strategies. The publication by Targan *et al*. was added after searching the Cochrane Library.[10] Two of the RCTs, those by Rutgeerts *et al*. and Feagan *et al*., were based on the same patient population (ACCENT I).[22,29] Since Feagan *et al*. specifically described the QoL while Rutgeerts *et al*. focussed on the effects on resource use, these trials were selected for their different endpoints. Three other RCTs, from Targan *et al*., Lichtenstein *et al*. and Rutgeerts *et al*., were based on the same cohort of patients as well.[10,28,31] The publication by Lichtenstein *et al*. described the QoL most specifically and was selected for this purpose. Thus, four studies were eventually used for our assessment (*table 2*).

The publications by Lichtenstein *et al*. and Feagan *et al*. are both double-blinded, multicentre RCTs supported by the manufacturer of infliximab. With a follow-up time of 54 weeks, Feagan *et al*. compared infliximab maintenance treatment with placebo in patients responding to a single 5 mg/kg infliximab infusion at week 0. Participants in the study had had moderately to severely active CD for at least three months. After 14 weeks patients were able to cross over to a 5 mg/kg infliximab regimen and their results were carried forward. QoL was assessed, with the IBDQ and SF-36. Results from the responders were used for the assessment of the QoL.

Lichtenstein *et al*. compared placebo and single doses of infliximab (5, 10 and 20 mg/kg) in patients with a diagnosis of luminal CD. The initial follow-up time was four weeks. For the present analysis only the results of the 5 mg/kg subgroup were used since this dosage is commonly administered in daily practice.

Cadahia *et al*. and Van Balkom *et al*. both published cohort studies in which parameters of QoL following infliximab use were compared with baseline data (*table 2*). Cadahia *et al*. included only patients with fistulising CD, while Van Balkom *et al*. included patients with fistulising as well as luminal disease. The study by Van Balkom *et al*. was supported by the manufacturer.

The quality of evidence of the RCT by Feagan *et al*. was considered to be the highest followed by the RCT by Lichtenstein *et al*. and the cohort studies by Van Balkom *et al*. and Cadahia *et al*.[32]

Table 2. *Overview of papers assessing the clinical outcome and the quality of life*

	Quality of evidence	Country (centres)	Indication (number of patients)	Inclusion criteria	Exclusion criteria	Intervention (n)	Comparator (n)	Primary outcome	Secondary outcome	Period of follow-up
Feagan (2003)	RCT (ACCENT I)	North America, Europe, Israel (55)	Luminal CD (335)	CDAI 220-400 responding to infliximab	+	Infliximab week 0, 2, 6 and every 8 weeks: 5 mg/kg (113) 10 mg/kg (112)	Infliximab week 0 (110)	Clinical remission Time to loss of response	HRQOL: SF-36 and IBDQ	54 weeks
Lichtenstein (2002)	RCT	North America, Europe (18)	Luminal CD (108)	CDAI 220-400	+	Infliximab week 0: 5 mg/kg (27) 10 mg/kg (28) 20 mg/kg (28)	Placebo week 0 (25)	Clinical response	HRQOL: IBDQ	4 weeks
Van Balkom (2002)	Cohort study	The Netherlands (5)	Fistulising and luminal CD (56)	CDAI ≥200	+	Infliximab week 0 for luminal CD and week 0, 2, 6 for fistulising CD	Baseline week 0	HRQOL: IBDQ	-	8-10 weeks
Cadahia (2004)	Cohort study	Spain (1)	Fistulising CD (25)	Single or multiple draining abdominal or perianal fistulas	+	Infliximab week 0, 2, 6	Baseline week 0	Clinical response	HRQOL: SF-36 and IBDQ	10 weeks

+ = Well described; - = not described; RCT = randomised controlled trial; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; HRQOL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; SF-36 = SF-36 Health Survey.

Costs and resource use

Of the 86 and 143 references found by MEDLINE and EMBASE, only three studies met the inclusion criteria and were selected for evaluation of costs and resource use in this particular category of patients treated with infliximab (*table 1*).[26,27,29] The Cochrane Library search did not yield additional studies. Two RCTs, the ACCENT I by Rutgeerts *et al.* and the ACCENT II by Lichtenstein *et al.*, presented data on the effect of infliximab on the number of hospitalisations, hospitalised days and operations with a high quality of evidence. Both are large RCTs in which patients with luminal and fistulising disease, respectively, were enrolled. In these trials, maintenance use of infliximab was compared with placebo, after infliximab induction of remission with a follow-up time of 54 weeks. Both studies were supported by the manufacturer. Rubenstein *et al.* retrospectively compared resource use before and after infliximab administration in the same cohort of patients. Since most patients had severely active CD in the period preceding infliximab use, data were averaged over a timeframe of three years, allowing for a more accurate estimation of healthcare resource use. No studies were found comparing the direct medical costs or indirect costs in CD patients treated with infliximab *vs* conventional drugs (*table 3*).

All studies selected for this review were carried out in university hospitals. Patients were at least 18 years of age and had no severe infections. Infliximab was administered in a dose of 5 mg/kg.

Quality of life

All studies showed a significant improvement in the QoL of CD patients following administration of infliximab (*table 4*). A significant short-term improvement in the IBDQ was shown by Lichtenstein *et al.*, Van Balkom *et al.* and Cadahia *et al.* In addition, Feagan *et al.* concluded that maintenance treatment with infliximab induced a significantly longer improvement in the QoL. Measurement of the QoL using the SF-36 resulted in a significant improvement as well. Cadahia *et al.* reported an overall improvement in the PCS after four and ten weeks ($p<0.05$), as did Feagan *et al.* after ten and 54 weeks. The MCS did not significantly change in the trial by Cahadia *et al.* Feagan *et al.* only showed a significant increase in the MCS after 54 weeks in the 10 mg/kg infliximab group, $p<0.05$. Overall, the individual

Table 3. *Overview of papers assessing resource use*

	Quality of evidence	Country (centres)	Use of infliximab	Indication (number of patients)	Inclusion criteria	Exclusion criteria	Intervention (n)	Comparator (n)	Primary outcome	Secondary outcome	Period of follow-up
Lichtenstein (2005)	RCT (ACCENT II)	North America, Europe, Israel (45)	Clinical trial	Fistulising CD (282)	Single or multiple perianal/ entero-cutaneous draining fistulas	+	Infliximab week 0, 2, 6 and every 8 weeks (143)	Infliximab week 0, 2, 6 (139)	Time to loss of response	Hospitalisations Hospitalised days Operations Procedures Safety	54 weeks
Rutgeerts (2004)	RCT (ACCENT I)	North America, Europe, Israel (55)	Clinical trial	Luminal CD (573)	CDAI: 220-400 >3 months	+	Infliximab week 0, 2, 6 and every 8 weeks: 5 mg/kg (192) 10 mg/kg (193)	Infliximab week 0 (188)	Study treatment Efficacy	HRQOL: IBDQ Steroid sparing Mucosal healing Hospitalisations Operations Safety	54 weeks
Rubenstein (2002)	Cohort study with a pre and post test	USA (1)	Daily care	Luminal and fistulising CD (79)	>1 year data available before and after infliximab use	-	Infliximab week 0 for luminal CD and week 0, 2, 6 for fistulising CD	Treatment before infliximab use	Hospitalisations Hospitalised days Operations Procedures	Endoscopies Emergency room visits Radiology Parenteral nutrition	1-3 years retrospective + 1 year prospective

+ = Well described; - = not described; RCT = randomised controlled trial; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; HRQL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; SF-36 = SF-36 Health Survey.

scales of the SF-36 demonstrated greater improvement in scales relevant to the physical aspects of health as opposed to psychological measures.

Cost and resource use

The results are given in *table 5*. The ACCENT I and II studies described the differences in resource use in patients treated with infliximab for induction and for maintenance use only as a secondary endpoint.[26,29] In both studies a significant reduction in the number of hospitalisations and operations in patients in the maintenance treatment arm was found. In the ACCENT II study, maintenance treatment was shown to result in fewer days in hospital in patients responding to infliximab. They also reported a decrease of 18.9 to 8.6% in patients hospitalised in the maintenance group (follow-up period 54 weeks, p<0.05).[26] Moreover, a significant reduction in major operations, such as fistula excision and anal fistulotomy was shown (13 *vs* 2 per 100 patients, p<0.05). The cohort study by Rubenstein *et al*. showed a significant decrease of 59% in patients with fistulising CD in the number of hospital admissions (p<0.05), a decrease in all surgery of 38% (p<0.01) and a trend towards a reduction in hospitalised days. Additionally, a significant reduction in the number of endoscopies, emergency room visits, radiology exams and gastroenterology outpatient visits was noted (43, 66, 12 and 20% in all patients, respectively).[27]

DISCUSSION

In this review we appraised all the available evidence about the QoL and costs of infliximab use in CD patients. We performed a systematic search and evaluated all relevant articles. However, the number of appropriate, high-quality articles is limited. Four and three publications with respect to the QoL and costs, respectively, were considered suitable for evaluation. Of all studies, only the RCT by Lichtenstein *et al*. compared the use of infliximab *vs* placebo.[31] The other studies compared the effect of infliximab within one study population or maintenance *vs* induction treatment.

Table 4. *Results of articles assessing the quality of life, presented in descending quality of evidence*

	Crohn' s Disease Activity Index		Inflammatory Bowel Disease Questionnaire	
Feagan (2003)	**Week 0**	**Week 54**	**Week 0**	**Week 54**
	Single dose: 298 ± 50	254 ± 132	Single dose: 129 ± 27	138 ± 41
	Maintenance: 309 ± 52	201 ± 122*	Maintenance: 130 ± 25	152 ± 43§
Lichtenstein# (2002)	**Week 0**	**Week 4**	**Week 0**	**Week 4**
	Placebo: 288 ± 54	271 ± 82	Placebo: 128 ± 29	133 ± 28
	Infliximab: 312 ± 56	166 ± 76§	Infliximab: 122 ± 29	168 ± 36§
Van Balkom (2002)	**Week 0**	**Week 4 and 10**	**Week 0**	**Week 4 and 10**
	Active CD: 311 ± 83.4	133.32 ± 110.6	Active CD: 117.5 ± 17.7	168.7 ± 31.8§
	Fistulising CD: 203 ± 131.0	131.0 ± 120.3	Fistulising CD: 151.8 ± 33.9	179.3 ± 25.5†
Cadahia## (2004)	**Week 0**	**Week 10**	**Week 0**	**Week 10**
	Active CD 220.5 ± 79.0	110.9 ± 61.2**	Active CD 174.6 ± 45.7	209.5 ± 35.6

#Results are described from the 5 mg/kg subgroup, since infliximab is now prescribed in this dosage; ##Cadahia used a Spanish version of IBDQ validated from the 36-item version of Love *et al*.[63] *p<0.05; †p< 0.01; §p<0.001, **p<0.0001.

Table 5. *Results of the articles assessing resource use, presented in descending quality of evidence*

	Hospitalisations[a]		Hospitalised days[b]		Surgeries[a]	
	Control	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**
					All surgeries and procedures	
Lichtenstein (2005)#	All patients: 31	14*	2.4	0.8°	118	60†
	Responders: 31	11*	2.5	0.5*	126	65*
					CD-related intra-abdominal surgeries	
Rutgeerts (2004)	38	23*	-	-	7.5	2.6*
					Gastrointestinal surgeries	
	All: -	-	2.35	2.14$	0.28	0.18*
Rubenstein (2002)[c##]	Fistula : 0.46	0.19*	2.13	1.16$	0.39	0.14†
	Luminal: -	-	-	-	-	-

The results are shown as comparator versus intervention group for RCT and as difference for cohort studies. [a]The mean number per 100 patients; [b]the mean number of days hospitalised per patient; [c]the means per patient year. #Lichtenstein et al. divide their results in all patients and the responders of infliximab; ##Rubenstein *et al*. distinguish between fistulising and luminal Crohn's disease; *p<0.05; †p<0.01; ‡p<0.001; °not significant; $p=0.06.

Notably, only two studies were not financially supported by the pharmaceutical industry.[21,27] The results of both studies were in line with the studies supported by the manufacturer.[22,26,29-31]

A clear conclusion can be made with respect to QoL. All studies described a significant improvement in short-term and one study in long-term analyses. Another clear conclusion can be made concerning the use of resources: all studies showed a decrease in the number of operations and hospitalisations. Although it might be appealing to combine these two conclusions, the statement that infliximab use is cost-effective is premature. The available studies do not provide empirical evidence for this assumption: costs were not calculated and cost-effectiveness ratios were not constructed.

We chose to disregard Markov models, because reliable data to feed these models are currently not available. This is underscored by the wide range of costs per quality adjusted life years for infliximab *vs* alternative treatments in CD, calculated using Markov models in recent literature.[33-35]

Different reports and guidelines on the use and the cost-effectiveness of infliximab were recently published, highlighting the importance of this subject and the need for consensus. Notwithstanding the presumed high incremental costs, infliximab is considered a valuable therapeutic alternative in patients with refractory CD. For example, the National Institute for Clinical Excellence (NICE) in the UK recommended treatment with infliximab in patients with severe active luminal CD, refractory to other treatment or inappropriate for surgery, and for fistulising CD meeting aforementioned criteria.[36] NICE suggested that infliximab would be cost-effective when only used in patients with severe active CD, refractory to conventional treatment and inappropriate for surgery. The Canadian Coordinating Office for Health Technology Assessment did not support infliximab therapy for CD on the grounds of cost-effectiveness, but emphasised that indirect cost savings by attenuating productivity losses and the lack of therapeutic alternatives in a specific group of patients with severe, refractory CD justifies the use of infliximab.[37]

Until now, cost effectiveness has not been studied prospectively as a primary endpoint. We feel that this should be done and that the study design should include parameters of indirect costs. Since the majority of CD patients are younger than 65 years of age, the indirect costs are high because of unemployment allowances, sickness relief allowances and handicap-related income allowances of the CD.[11,12] We expect infliximab therapy to result in a considerable decrease in these costs, possibly rendering the drug cost effective in the long run. In conclusion, treatment with infliximab has been shown to be effective in terms of disease activity and QoL. Since cost-effectiveness has not been specifically studied, no definitive conclusions can be drawn regarding this subject. Although evidence regarding decreases in the number of operations and hospitalisations following infliximab therapy is accumulating, a straightforward, well-designed and prospective cost-effectiveness analysis is needed.

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