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Randomised clinical trial: First-line infliximab biosimilar is cost-effective compared to conventional treatment in paediatric Crohn's disease

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Summary

Background: Data on cost-effectiveness of first-line infliximab in paediatric patients with Crohn's disease are limited. Since biologics are increasingly prescribed and accompanied by high costs, this knowledge gap needs to be addressed.

Aim: To investigate the cost-effectiveness of first-line infliximab compared to conventional treatment in children with moderate-to-severe Crohn's disease.

Methods: We included patients from the Top-down Infliximab Study in Kids with Crohn's disease randomised controlled trial. Children with newly diagnosed

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moderate-to-severe Crohn's disease were treated with azathioprine maintenance and either five induction infliximab (biosimilar) infusions or conventional induction treatment (exclusive enteral nutrition or corticosteroids). Direct healthcare consumption and costs were obtained per patient until week 104. This included data on outpatient hospital visits, hospital admissions, drug costs, endoscopies and surgeries. The primary health outcome was the odds ratio of being in clinical remission (weighted paediatric Crohn's disease activity index<12.5) during 104 weeks.

Results: We included 89 patients (44 in the first-line infliximab group and 45 in the conventional treatment group). Mean direct healthcare costs per patient were €36,784 for first-line infliximab treatment and €36,874 for conventional treatment over 2 years ($p=0.981$). The odds ratio of first-line infliximab versus conventional treatment to be in clinical remission over 104 weeks was 1.56 (95%CI 1.03–2.35, $p=0.036$).

Conclusions: First-line infliximab treatment resulted in higher odds of being in clinical remission without being more expensive, making it the dominant strategy over conventional treatment in the first 2 years after diagnosis in children with moderate-to-severe Crohn's disease.

Trial registration number: NCT02517684.

1 | INTRODUCTION

Crohn's disease is a chronic immune-mediated disease that can affect the entire gastro-intestinal tract.[1] Paediatric patients with Crohn's disease are more likely to experience a severe disease course and to develop complications, such as strictures of fistulas, compared to adult patients with Crohn's disease.[2] Effective treatment from diagnosis onwards is required for disease control and to reduce the risk of complications. Infliximab is an important therapeutic option in the management of paediatric patients with Crohn's disease, and may be administered as first-line infliximab or as part of step-up therapy.[3] The TISKids study showed that first-line infliximab induction treatment (five infliximab infusions) combined with azathioprine is more effective in achieving and maintaining clinical remission without treatment escalation at week 52 compared to conventional induction treatment (exclusive enteral nutrition or prednisolone) combined with azathioprine in children with moderate-to-severe Crohn's disease.[4]

However, as infliximab is an expensive drug, a potential disadvantage of first-line infliximab therapy may be a substantial increase in healthcare costs. This is especially relevant to consider, given the significant increase in the use of anti-tumour necrosis factor (TNF) over the past decades.[5] Only a limited number of studies reported on the cost-effectiveness of early intervention with infliximab compared to conventional treatment in children with Crohn's disease. One study conducted in children with Crohn's disease showed that early intervention with Remicade® (€988 per 100 mg vial of infliximab), the originator of infliximab, was not only more effective but also more costly (with an incremental cost of Canadian $31,112) compared to conventional treatment.[6] However, another study performed in children with Crohn's disease, demonstrated that early anti-TNF treatment was more effective than late anti-TNF, with similar costs.[7] Despite the relatively high costs of infliximab, it has to be taken into account that the introduction of biosimilars (such as Inflectra® [CT-P13]) led to a decrease in the price of infliximab and a substantial reduction in healthcare costs of inflammatory bowel disease (IBD).[8] A study in Scotland reported that utilisation of biosimilars increased to 91% in 2019, and another study showed that biosimilar use led to a reduction of 38% in healthcare costs.[9,10]

To the best of our knowledge, no cost-effectiveness analysis has been conducted based on a randomised controlled trial comparing first-line infliximab (biosimilar, Inflectra®) and conventional treatment in paediatric patients with Crohn's disease. This knowledge gap is important to address as in today's healthcare landscape, new treatments are increasingly required to represent efficient spending of public resources. Based on the results of the TISKids study, this study aimed to investigate the cost-effectiveness of first-line infliximab compared to conventional treatment in children with moderate-to-severe Crohn's disease. We hypothesised that first-line infliximab would be more expensive, but also more effective and therefore cost-effective compared to conventional treatment.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This study was protocolised as an ancillary analysis of the TISKids study. The TISKids study is a multicentre, randomised controlled

trial performed in 12 hospitals in three European countries (the Netherlands, Croatia and Finland). The trial included patients aged 3–17 years, with newly diagnosed, untreated active Crohn's disease (weighted paediatric Crohn's disease activity index [wPCDAI] >40). Further details of the TISKids study design have been previously published.[4,11] Compared to the results of the TISKids study that have been published so far, this cost-effectiveness analysis extends the follow-up period to 2 years. Exclusion criteria in this secondary analysis were patients with severe conditions requiring intensive treatment unrelated to Crohn's disease, as this would likely create bias unrelated to IBD treatment, and patients included in centres outside the Netherlands since it was not feasible to obtain healthcare costs for these patients.

2.2 | Randomisation and intervention

Patients were randomly assigned to treatment with first-line infliximab or conventional treatment. The patients in the first-line infliximab group received a total of five intravenous infliximab infusions of 5 mg/kg, at weeks 0, 2 and 6, followed by two maintenance infusions at weeks 14 and 22, after which infliximab was ceased. Patients were treated with Inflectra® (CT-P13), an infliximab biosimilar. The patients in the conventional treatment group received standard induction treatment with either exclusive enteral nutrition (polymeric formula for 6–8 weeks, after which normal diet was gradually reintroduced within 2–3 weeks) or oral prednisolone (for 4 weeks 1 mg/kg daily with a maximum of 40 mg, followed by tapering down of 5 mg per week until stop). In all patients, treatment was combined with oral azathioprine as maintenance treatment (2–3 mg/kg, once daily; Figure 1). Treatment could be intensified according to the physician's discretion in patients without response, loss of response or intolerance to treatment.

2.3 | Economic analysis

The economic analysis was a cost-effectiveness analysis of first-line infliximab compared to conventional treatment for Crohn's disease, executed from a healthcare perspective. The time horizon of the analysis was the first 104 weeks of follow-up after start of induction treatment. Given this relatively short timeframe, discounting of future costs and health outcomes was not applied. Established methods for economic evaluations in healthcare were used.[12,13] The economic evaluation was reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (Table S1).[14]

2.4 | Resource use and costs

Data on healthcare use were collected until week 104. These data were obtained from the electronic medical records of each patient. Healthcare use was captured for hospital admissions, visits to the outpatient clinic, consultations by telephone, daycare infusion unit, peer-to-peer consultations, visits to the emergency department, laboratory tests, diagnostic radiology, endoscopies and surgeries. Use of medication was retrieved from an electronic data capture system (Castor Electronic Data Capture) in which study data, including changes in medication, were registered.[15] The number of infliximab infusions and vials was additionally verified by data from the pharmacy or data from the patient's medical record. Consultations with healthcare providers outside of the treating hospital, such as general practitioners or physiotherapists, were not included since we expected these costs to have a minimal effect on the total costs. Only direct healthcare costs were included. Non-medical costs and indirect costs (e.g. travel costs to the hospital) were not assessed.

Data on resource use were combined with unit prices to calculate the healthcare costs for each patient. Unit prices were provided by the participating hospitals. Four of 10 hospitals (one academic and three non-academic) were willing to disclose their cost prices. The calculations of cost prices were based on the average cost prices of these four hospitals, with a distinction between academic and non-academic hospitals. When cost prices could not be determined using this method (5% of reported units), the cost prices were coupled to any cost price irrespective of the distinction between academic and non-academic hospitals, or prices were based on tariffs of the Dutch HealthCare Authority.[16] Medication prices, for example, of infliximab could differ strongly due to dependence on agreements with health insurers. Therefore, costs of medications were based on standard medication prices[17,18] (Table S2). The price of infliximab was set at €470.82 per vial of 100 mg based on the price of 2020.[18] Cost prices were based on prices determined in the period between 2015 and 2020. All costs were provided in Euros (€).

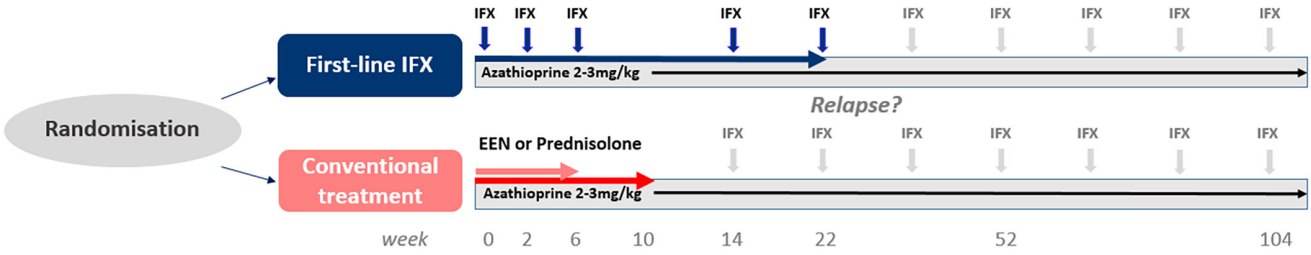

FIGURE 1 Study design. EEN, exclusive enteral nutrition; IFX, Infliximab.

2.5 | Data collection

Study visits were conducted at weeks 0, 6, 10, 14, 22, 52 and 104. At each visit, a clinical disease activity score (wPCDAI, CDAI at week 104 if patient was >18 years old or Physician Global Assessment (PGA) in case no wPCDAI or CDAI was available), changes in treatment and adverse events were recorded. Faecal calprotectin levels were obtained prior to treatment and at weeks 10, 52 and 104. Faecal calprotectin levels in the first 52 weeks were centrally assessed using the ELISA (CALPRO) assay. When faecal calprotectin samples were missing, levels determined in the local hospital at this time point were used. Faecal calprotectin levels at 104 weeks were all determined in the local hospitals. Disease-specific quality of life was obtained with the IMPACT-III questionnaire in patients at weeks 0, 14 and 52.[19,20] The questionnaire was not available at 104 weeks. The questionnaire consists of 35 items encompassing six domains: bowel symptoms, systemic symptoms, emotional functioning, social functioning, body image and treatment/interventions. The summary score ranges from 0 to 100, with a higher score indicating a higher quality of life.

2.6 | Effectiveness

For this trial-based economic evaluation, the primary health outcome was the odds of being in clinical remission over 2 years. Clinical remission was defined as a wPCDAI score <12.5, a CDAI score <150 or remission classified by the PGA.[21,22] Additionally, the proportion of patients in clinical remission at each visit and the number of times clinical remission was achieved during the 7 visits over 104 weeks were evaluated.

Secondary outcomes at 104 weeks included:

- Relapse rate.
- Odds of being in biochemical remission (faecal calprotectin <100 μg/g).
- Time to additional or (re)start of anti-TNF treatment.
- Proportion of patients requiring Crohn's disease-related surgery (such as peri-anal surgery or an ileocecal resection).
- Disease-specific quality of life (only available until 52 weeks).

A relapse was defined as an increase in the wPCDAI score >17.5, or a total wPCDAI score >40 after response (wPCDAI decrease of <17.5) was achieved. This was assessed at each study visit until week 52. Additionally, physicians reported at week 104 if the patient experienced one or more relapses between weeks 52 and 104. Furthermore, intensification of treatment due to a Crohn's disease flare was considered a relapse.

Additional anti-TNF treatment was defined as the start of infliximab or adalimumab in the conventional treatment group. Within the first-line infliximab group, additional anti-TNF treatment was defined as either an (1) increase in the infliximab dose, (2) shortening of the infliximab treatment interval and (3) continuation or restart of infliximab or start of adalimumab after the standard five infusions.

2.7 | Cost-effectiveness

For the scenario of improved effects with higher costs, we planned to calculate incremental cost-effectiveness ratios (ICERs) to determine the cost-effectiveness of first-line infliximab. The a priori planned ICERs were expressed as incremental costs per additional patient in clinical remission over 104 weeks and as incremental costs per quality-adjusted life year (QALY) gained during 104 weeks. To calculate QALYs, health utilities were taken from a study by Bashir et al., who presented utilities of 0.810 and 0.694 for inactive and active disease, respectively (based on the wPCDAI).[23] ICERs were not calculated if one treatment strategy dominated the other (i.e. had lower or similar costs and greater effects).

2.8 | Statistical analysis

Data were analysed based on the treatment (first-line infliximab or conventional treatment) that was initiated. Categorical data were analysed by the Chi-squared test or the Fisher exact test. Continuous variables were compared by either the independent *T*-test or the Mann–Whitney *U*-test dependent on the normal distribution of the data. Total costs were provided both as median and mean, as the mean is the most informative measure of the total costs. The effect size of differences between costs was calculated by Cohen's *d* for standardised mean differences and by the rank biserial coefficient for standardised median differences.

Sensitivity analyses were performed to check the robustness of the results. To this aim, we performed the cost calculations by varying the costs of infliximab and varying the prices of daycare admissions in non-academic hospitals and recurrent consultations with paediatric gastroenterologists in non-academic hospitals by +100% and −50%. These prices were selected as these units were frequently registered, costs were relatively high and the prices of daycare and recurrent consultations with paediatric gastroenterologists that were provided separately by the three non-academic hospitals had distinct variation.

Missing wPCDAI and CDAI scores (19%) at weeks 0, 6, 10, 14, 22, 52 and 104 were imputed based on the eight variables within the wPCDAI or CDAI score, assigned treatment group, time to evaluation of wPCDAI, faecal calprotectin levels and regular IBD lab (CRP, haemoglobin, haematocrit, leukocytes, thrombocytes, ESR and albumin). In case the entire wPCDAI score was missing because the patient missed a visit (4%), the score was not imputed. Missing faecal calprotectin levels (19%) were imputed based on wPCDAI or CDAI scores, assigned treatment group, time to evaluation of faecal calprotectin level and regular IBD lab. Analysis of the results from the different imputed datasets were pooled using the standard formulas of multiple imputations.

To calculate the number of QALYs, the time difference in years was calculated between each visit, and multiplied by 0.810 if the patient was in remission, or by 0.694 if the patient had active disease. If a patient was in remission, but a relapse occurred before the next study visit, the time between the first visit and relapse was multiplied by 0.810, and the time between relapse and the next study visit by 0.694.[23] A linear regression model was fit with QALY as dependent

variable and treatment group (first-line infliximab or conventional treatment) as independent variable.

A generalised estimating equation model was fit to assess the odds of being in clinical remission over 2 years, in which the assigned treatment was included as predictor and the autoregressive covariance structure was assumed. The same analysis was performed to calculate the OR of being in biochemical remission. Event-free probabilities over the follow-up period for the time to additional or (re)start anti-TNF treatment use were calculated using the Kaplan–Meier method, and the log-rank test was used to test for difference between first-line infliximab and conventional treatment. The number of relapses and the number of times clinical remission was achieved were analysed using a Poisson regression-based model. The IMPACT-III scores were examined using a linear mixed model. All statistical testing was two sided and significant at the 0.05 level. Imputations were performed using IBM SPSS Statistics 25.0 (IBM Corp, Armonk, NY) and calculations were performed using R version 4.1.3. R packages which have been used for performing these calculations have been cited in Methods S1.

2.9 | Ethics and registration

Permission was obtained from the Medical Ethics Review Board of Erasmus Medical Center and the other participating centres. All patients (and if required also the parents) provided informed consent. This trial is registered in the European Clinical Trials Register under the EudraCT number 2014-005702-37.

3 | RESULTS

3.1 | Participants

From April 2015 to November 2018, 100 patients were included in the TISKids randomised controlled trial.[4] Eighty-nine of these 100 patients were included in the cost-effectiveness analysis (Figure 2). Two patients were excluded because of withdrawal of consent after randomisation, and one patient was excluded due to a later diagnosis of Ulcerative colitis. Six patients were excluded because they were included in a centre outside of the Netherlands. Two other patients were excluded due to (non-IBD related) conditions (neurological impairment and pregnancy, respectively). Forty-four patients were treated with first-line infliximab and 45 patients were treated with conventional treatment. Patient characteristics were not significantly different between the two treatment groups at baseline (Table 1).

3.2 | Costs

The total mean costs per patient in the first-line infliximab group were €36,784 (SD €18,464), which were not significantly different from those in the conventional treatment group (€36,874 [SD €17,851], $p = 0.981$; Table 2). Neither were the total median costs significantly different between the two treatment groups (Table 2). Cost prices per unit and distribution of costs are shown in Table S3 and Figure S1 respectively.

An overview of costs per category is depicted in Figure 3 and Table S4. Infliximab costs accounted for the highest costs in both treatment groups and roughly made up one-third of the total mean costs over 2 years. Mean infliximab costs were €14,595 (SD €9874) per patient in the first-line infliximab group and €12,388 (SD €10,475) per patient in the conventional treatment group, which was not significantly different ($p = 0.309$). Additionally, this is reflected by the similar median number of infliximab infusions per patient given to the first-line infliximab group (10.0 [5.0–13.0]) and conventional treatment group (9.0 [0.0–13.0]) after 2 years ($p = 0.313$). Mean costs of infliximab, daycare infusion unit, endoscopies and other costs were numerically higher in the first-line infliximab group compared to conventional treatment. The mean costs of the other categories, including hospital days and gastroenterology consultations, were numerically higher than the conventional treatment. Only costs for consultations with other specialists were significantly higher in the conventional treatment group. Adalimumab was administered to five patients of the conventional treatment group, with mean adalimumab costs of €9195 (SD €3529).

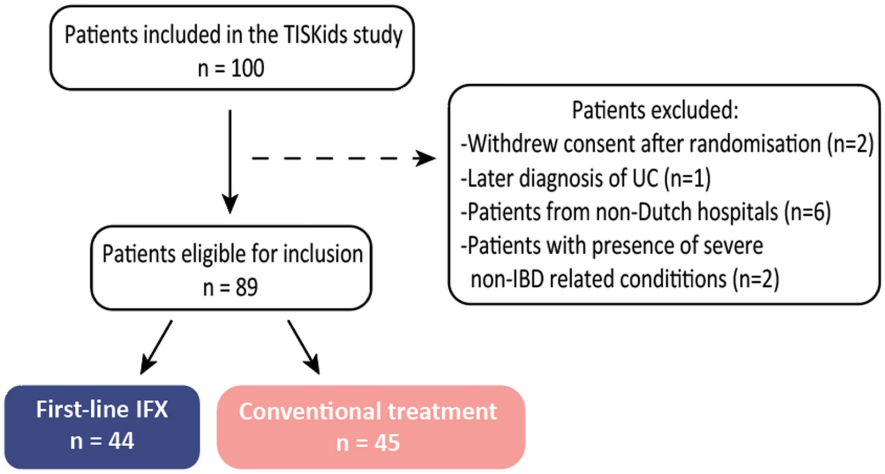

FIGURE 2 Trial profile. Flow chart of selection of patients for the cost-effectiveness analysis. IBD, inflammatory bowel disease; IFX, infliximab; UC, ulcerative colitis.

TABLE 1 Baseline characteristics per treatment group.

	FL-IFX ($n=44$)	Conventional treatment ($n=45$)
Age at diagnosis (years)	15.2 (12.8–16.3)	14.2 (12.0–16.1)
Male sex (*n*)	20 (45%)	24 (53%)
Height (cm)	167.3 (156.0–175.1)	161.0 (146.5–169.5)
Height for age (SDS)	−0.18 (−0.89–0.76)	−0.55 (−1.08–0.13)
Weight (kg)	49.0 (34.8–57.1)	45.0 (33.2–54.6)
wPCDAI	58.8 (47.5–68.8)	60.0 (50.0–72.5)
CRP (mg/L)	29.5 (10.3–46.3)	36.0 (22.0–57.0)
ESR (mm/h)	34.0 (26.7–46.0)	32.5 (22.0–62.5)[a]
Alb (g/L)	37.0 (32.1–40.0)[a]	35.0 (29.2–38.8)[b]
Leucocytes, 10^9/L	8.4 (7.5–11.1)	9.1 (6.7–11.6)
SES-CD	15.0 (9.0–21.0)	15.0 (8.0–19)
Faecal calprotectin (μg/g)	1112.1 (904.1–1622.5)[b]	1084.9 (595.7–1467.7)[b]
Paris classification		
Age at diagnosis (years)		
<10	5 (11%)	7 (16%)
10–17	34 (77%)	35 (78%)
17–40	5 (11%)	3 (7%)
Disease location		
L1	12 (27%)	11 (24%)
L2	10 (23%)	12 (27%)
L3	21 (48%)	22 (49%)
Isolated L4	1 (2%)	0
Upper disease location		
No upper GI	24 (54%)	23 (51%)
L4a	18 (4%)	20 (44%)
L4b	2 (5%)	2 (4%)
Disease behaviour		
B1	42 (95%)	39 (87%)
B2	2 (5%)	6 (13.3%)
B3	0	0
B2B3	0	0
Start treatment within academic hospital	34 (77%)	31 (69%)

Note: Data are presented as *n* (%) or median (IQR).

Abbreviations: Alb, albumin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FL-IFX, first-line infliximab; SDS, standard deviation score; SES-CD, Simple Endoscopic Score for Crohn's Disease (range 0–60); wPCDAI, weighted paediatric Crohn's disease activity index (range 0–125).

[a]1 missing data point.

[b]>1 missing data point.

From the sensitivity analysis, it appeared that when the cost prices for infliximab, non-academic prices of daycare admissions or recurrent consultations with paediatric gastroenterologist were halved or doubled, the difference in total mean costs per patient remained similar between first-line infliximab and conventional treatment (Figure S2 and Table S5).

3.3 | Effectiveness

First-line infliximab-treated patients were on average 1.5 times more likely to be in clinical remission compared to patients in the conventional treatment group (OR 1.56 [95% CI 1.03–2.35], $p=0.036$; Table 3). At each study visit after start of treatment, a higher proportion of patients in the first-line infliximab group was in clinical remission compared to the conventional treatment group until week 104 (Table 3).

There were significantly less relapses within 104 weeks in the first-line infliximab group compared to the conventional treatment group (incidence rate ratio 0.64, 95% CI 0.43–0.96, $p=0.032$; Table 3). Furthermore, the OR of being in biochemical remission was 1.93 (95% CI 1.09–3.44, $p=0.025$) times higher compared to conventional treatment groups on average over 2 years (Table 3). After 2 years, 26/44 (59%) patients in the first-line infliximab group (11/26 patients continued infliximab after five infusions and 15/26 patients stopped infliximab after five infusions but restarted), while 34/45 (76%) patients in the conventional treatment group received additional anti-TNF treatment ($p=0.098$). The median time to additional anti-TNF treatment was significantly longer in the first-line infliximab group (median 71 weeks [95% CI 56–n/a weeks]) in comparison with the conventional treatment group (median 32 weeks [95% CI 20–58 weeks]), $p=0.017$ (Figure 4). Additionally, 2/44 (5%) patients in the first-line infliximab group were in need of IBD-related surgery compared to 7/45 (16%) in the conventional treatment group ($p=0.157$; Table 3). After 1 year, in 81/89 (91%) patients, at least one measurement was available on disease-specific quality of life. Quality-of-life scores in the first-line infliximab group and conventional group were similar ($p=0.722$) over 52 weeks and in both groups significantly higher than at baseline (Table 3). In the first-line infliximab group, the score increased with 17.7 points at week 52 compared to baseline ($p<0.001$), and an increase of 18.0 points was seen in the conventional treatment group ($p<0.001$).

3.4 | Cost-effectiveness

To assess the cost-effectiveness of a new treatment strategy, an ICER can be calculated, which depicts the extra cost per unit of outcome obtained. In this study, costs between the treatment groups were identical, whereas first-line infliximab was clinically more effective in terms of the number of patients who achieved clinical remission over 2 years. Therefore, first-line infliximab may be considered the dominant therapy. Accordingly, calculation of an ICER was not necessary. Taking QALYs as outcome measure, there was no significant difference between the first-line infliximab group (pooled mean number of QALYs 1.51) and the conventional treatment group (pooled mean number of QALYs 1.52; the

TABLE 2 Mean (SD) and median (IQR) costs per treatment group 104 weeks after the start of treatment.

	FL-IFX ($n=44$)	Conventional treatment ($n=45$)	Standardised difference	p-value
Total costs				
Mean (SD)	€36,784 (€18,464)	€36,874 (€17,851)	0.01	0.981
Median (IQR)	€32,645 (€24,506–€44,257)	€37,190 (€25,796–€44,710)	0.04	0.746
IFX costs				
Mean (SD)	€14,595 (€9874)	€12,388 (€10,475)	0.22	0.309
Median (IQR)	€12,241 (€7062–€19,892)	€11,771 (€0–€19,774)	−0.11	0.353

Note: Costs were not normally distributed, but total costs were provided both as median and mean, as the mean is more representative of the total costs.

Abbreviations: FL-IFX, first-line infliximab; IQR, interquartile range; SD, standard deviation.

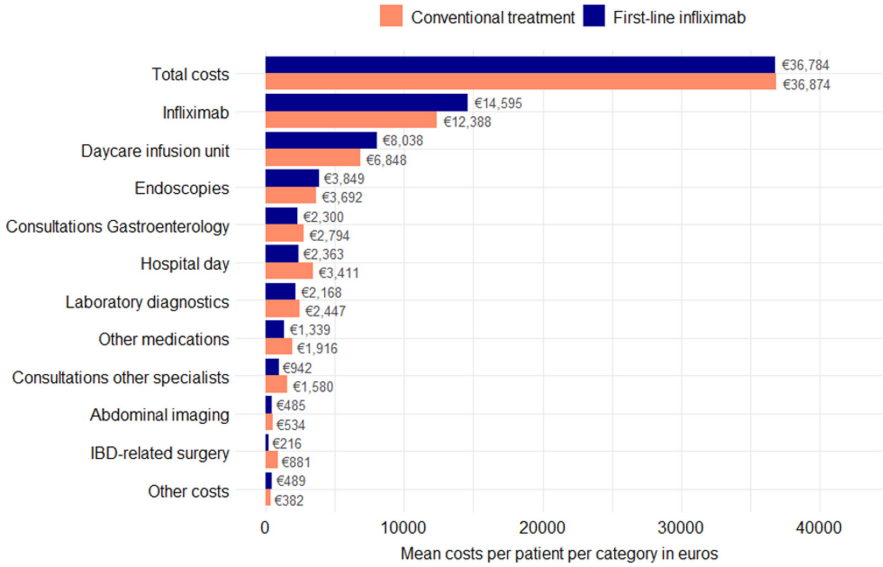

FIGURE 3 Mean costs (in euros) over 2 years per patient stratified by category. Costs have been shown per category and treatment group. Categories included *infliximab*, *daycare infusion unit* (daycare and administration of biological), *endoscopies* (gastroscopy, ileocolonoscopy and pathological analysis of biopsies), *consultation gastroenterology* (outpatients visits to the clinic or emergency department, consultation by telephone or email with (paediatric) gastroenterologist or nurse practitioner), *abdominal imaging* (MR enterography, abdominal ultrasound, abdominal X-ray and abdominal CT), *hospital admissions*, *laboratory diagnostics* (large variety of laboratory tests, including IBD related-lab and faecal calprotectin), *other medications* (see Table S2), *consultations other specialists* (consultations of dermatology, anaesthesiology, surgery, dietician, in-hospital physiotherapy, medical psychology and social work), *IBD-related surgery* (perianal surgery, ileocecal resection and drainage of intra-abdominal abscess) and *other costs* (including chest X-ray, bone mineral density measurement and non-IBD-related surgery costs).

estimated difference between first-line infliximab and conventional treatment was −0.008 [95% CI: −0.058 to 0.042], p = 0.75). As there was no difference in QALYs or costs between the groups, a calculation of the ICER was not required.

4 | DISCUSSION

This is the first randomised controlled trial providing insights into the cost-effectiveness of first-line infliximab in comparison with conventional treatment in children with Crohn's disease. First-line infliximab treatment resulted in higher odds of achieving clinical remission without incurring higher direct healthcare costs compared to conventional treatment, making first-line infliximab the dominant strategy for managing moderate-to-severe Crohn's disease in children during the first 2 years after diagnosis.

Although the introduction of biosimilars has strongly reduced the price of infliximab, high costs of infliximab in comparison with conventional treatment may form a counterargument to start treatment with first-line infliximab. Indeed, this study showed that infliximab was the major cost driver of treatment costs in both groups, as was reported before.[6,24] However, contrary to our expectations, this study found that total costs over 2 years were not significantly different between first-line infliximab and conventional treatment. This finding was robust for different prices of infliximab. There may be several explanations for this result. First, more patients in the conventional treatment group required additional anti-TNF treatment, and the time for additional biological was shorter for the conventional treatment group compared

TABLE 3 Results of primary and secondary outcome measurements during 104 weeks.

	FL-IFX ($n=44$)	Conventional treatment ($n=45$)	OR/IRR	p-value
Clinical remission (wPCDAI <12.5) (%)[a]				
Week 0	0%	0%	OR 1.56 [95% CI 1.03–2.35]	0.036
Week 6	49%	43%		
Week 10	54%	26%		
Week 14	59%	49%		
Week 22	72%	56%		
Week 52	66%	54%		
Week 104	77%	67%		
Total count of clinical remission	159	131		
Number of relapses (mean)	0.43 (95% CI 0.31–0.59)	0.67 (95% CI 0.52–0.86)	IRR 0.64 (95% CI 0.43–0.96)	0.032
Biochemical remission (fcal <100 μg/g) (%)				
Week 0	3%	0%	OR 1.93 (95% CI 1.09–3.44)	0.025
Week 10	28%	9%		
Week 52	30%	18%		
Week 104	36%	29%		
Time to additional or (re)start of anti-TNF treatment in weeks (median)	71 weeks [95% CI 56–n/a weeks]	32 weeks [95% CI 20–58 weeks]		0.017
Number of IBD-related surgeries[b]				
Ileocecal resection	1	5		0.157
Drainage intra-abdominal abscess	0	1		
Incision/drainage perianal abscess/fistula	1	3		
IMPACT-III scores[c]				
At baseline	60.6	57.7		0.722
At week 52	78.3	75.7		

Note: Results of clinical remission, relapses and biochemical remission were based on pooled data of the imputation sets.

Abbreviations: fcal; faecal calprotectin; FL-IFX, first-line infliximab; IRR, incidence rate ratio; OR, odds ratio; wPCDAI, weighted paediatric Crohn's disease activity index.

[a]Clinical disease activity score was completely missing and could therefore not be imputed in 4% of the visits. Physician global assessment was used for clinical disease activity score in 1% of the visits and Crohn's disease activity index in 3% of the visits.

[b]One patient in the conventional treatment group underwent surgery for both a perianal abscess as well as an ileocecal resection, another patient in the conventional treatment group underwent surgery for drainage of intra-abdominal abscess as well as ileocecal resection within 1 month.

[c]Values are presented based on output of the linear mixed-effect model.

to first-line infliximab. Additionally, various costs, such as hospital admissions, consultations by gastroenterologists and IBD-related surgery, were numerically higher in the conventional treatment group compared to first-line infliximab. This may be a reflection of a worse disease course of conventionally treated patients, which is consistent with our finding that first-line infliximab patients had higher odds of being in clinical remission for 2 years. This is in line with the results of the systematic review of Ungaro et al., which shows that early initiation with anti-TNF compared to late initiation has a beneficial effect on clinical remission, relapse rate and mucosal healing in paediatric patients with Crohn's disease.[25] Furthermore, an open-label randomised controlled trial in adults with Crohn's disease showed similar findings as our study: top-down treatment was proven to be more effective compared to accelerated step-up therapy at 1 year.[26] Although there was a higher effectiveness in terms of clinical remission, there was no significant difference in QALYs at 2 years. This may be explained by the fact that we had to rely on health utilities from one single study, which showed a relatively small difference between the health states of inactive disease (0.810) and active disease (0.694), in combination with a short time span. So, the calculation of QALYs needs to be interpreted with caution and this should be examined in further studies.

To our knowledge, only two previous studies assessed cost-effectiveness of early anti-TNF treatment compared to conventional treatment in children with Crohn's disease. The study of Singh et al. retrospectively reviewed children with Crohn's disease with early anti-TNF use (start anti-TNF <12 months of diagnosis) versus late anti-TNF use. They reported better effectiveness (lower intestinal surgery rate and trend towards decreased hospital admission) and similar healthcare costs in

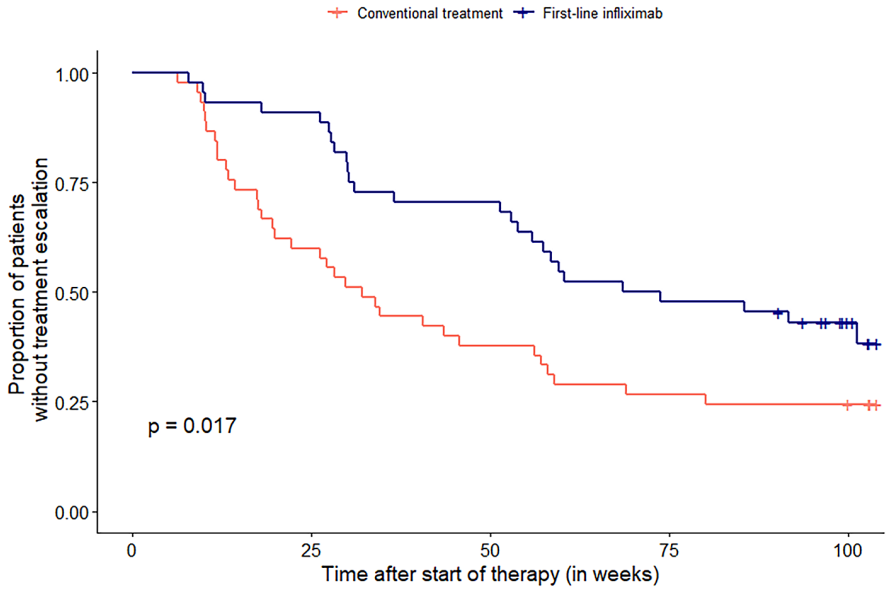

FIGURE 4 Kaplan–Meier estimates of the time to additional anti-tumour necrosis factor treatment after start of therapy.

patients with early anti-TNF use compared to late anti-TNF use, which is in line with the results of our study.[7] However, our cost-effectiveness results contradict the findings from Bashir et al. although a better effectiveness of early anti-TNF (<3 months after diagnosis) was reported compared to standard treatment, early anti-TNF was more expensive than step-up treatment (Canadian $127,628 vs. Canadian $96,516) over a period of 3 years.[6] Due to the different study designs, it is challenging to compare these results with those from our study. The TISKids study was a randomised controlled trial, while the study of Bashir et al. used a probabilistic microsimulation model, where clinical and outcome data were derived from the prospective cohort RISK-PROKIIDS study. However, one reason for the difference between studies may be that, as defined in our study protocol, infliximab was stopped after five infusions in first-line infliximab-treated patients, while this was not the case in the study of Bashir et al.

This study has several limitations. First of all, consultation with healthcare providers outside of the treating hospital and indirect costs were not evaluated. However, these costs may be similar between the two treatment groups. For example, work productivity losses by parents and travel costs to the hospital may be strongly related to the number of infliximab infusions. These were similar between the groups and would therefore minimally affect the difference in costs. Second, healthcare costs were calculated based on input provided by the hospitals and medication costs based on registrations in Castor database, which were not specifically designed for collecting data for this cost-effectiveness analysis. Healthcare consumption or medication changes may not have been adequately reported (in case doctors forgot to administer healthcare consumption or additional medication), leading to a possible underestimation of mean costs. As groups were randomised, we assume that this possible underestimation is equal for both groups. Additionally, clinical remission is not the strongest outcome measure to evaluate disease activity in Crohn's disease. Treatment targets as defined in the STRIDE-II guideline, such as endoscopic healing, were not available at 2 years.[27] Furthermore, some data were missing and had therefore to be imputed. However, these are the best data available in this study to assess the effectiveness, and clinical remission is one of the treatment targets in children with Crohn's disease.[27] Additionaly, the more objective faecal calprotectin results are in line with the results from clinical remission. Another limitation of this study is that it was 'piggybacked' onto a clinical trial, which was not powered for the cost-effectiveness analysis.

Furthermore, this study may have limited external validity for several reasons. First, although the study protocol mainly reflects clinical practice, three endoscopies within a year are not regular. The total real-world costs for both groups may therefore be slightly lower. Second, this study was performed in a high-income country with a public healthcare system. However, the cost-effectiveness of healthcare treatments might vary from place to place, for example, due to differences in clinical practice patterns and relative prices of healthcare. Third, first-line infliximab is currently advised in children with high risk of poor disease outcomes, and not yet in children with moderate-to-severe Crohn's disease, as was the case in our study. Nonetheless, previous results of the TISKids study indicated that treatment with first-line infliximab is beneficial for patients with moderate-to-severe Crohn's disease.[4] Fourth, generally, patients do not cease infliximab therapy after five infusions, as was the protocol in our study for patients treated with first-line infliximab. An analysis of subgroup of patients who continued first-line infliximab after five infusions in comparison with conventional treatment would not be feasible as this subgroup would experience the worst disease outcome, and may not be representative of the regular patient receiving infliximab. Additionally, no data on ethnicity were available within this study, which limits the generalisability of our findings with respect to other continents. Further economic evaluations and modelling would help increase the validity and knowledge of cost-effectiveness of first-line infliximab compared to conventional treatment. These studies should also incorporate indirect costs, and evaluate the use of subcutaneous infliximab, as this may decrease indirect costs.[28] Furthermore, other studies should evaluate adalimumab as well, as this is also an important anti-TNF treatment in children with Crohn's disease.[3]

An important strength of this study is that it is the first to assess the cost-effectiveness of first-line infliximab compared to conventional treatment based on real-world data from a randomised controlled trial in therapy-naïve patients. Since healthcare costs are rising, it is necessary to evaluate costs when considering the role of different treatments for Crohn's disease. There are only few studies reporting prospective long-term data on effectiveness and costs in children with IBD. This study provides novel and unique data on the cost-effectiveness of first-line infliximab and conventional treatment and thereby contributes to minimising the knowledge gap of Crohn's disease treatment costs. The effectiveness of the two treatment strategies could be thoroughly assessed with minimal risk of confounders (such as higher disease activity at baseline in one of the groups) improving the reliability of the results due to randomised design of this study. Another strength of the study is that none of the included patients were lost to follow-up at 104 weeks and that data were prospectively collected.

In conclusion, treatment with first-line infliximab is more effective, yet not more expensive than conventional treatment after 104 weeks. Based on results of this study, it would be beneficial to start treatment with five infliximab infusions of first-line infliximab in children with moderate-to-severe Crohn's disease. In order to further optimise the efficacy of first-line infliximab and minimise healthcare costs, additional research is necessary to more precisely identify patients who would benefit most from treatment with first-line infliximab and which patients are eligible to cease infliximab after five infusions.

AUTHOR CONTRIBUTIONS

Stephanie A. Vuijk: Writing – original draft; writing – review and editing; formal analysis; project administration; data curation; investigation; validation; visualization. **Maria M. E. Jongsma:** Data curation; formal analysis; investigation; project administration; visualization; writing – review and editing; writing – original draft. **Britt M. Hoeven:** Data curation; formal analysis; project administration; visualization; writing – review and editing; writing – original draft; investigation. **Maarten A. Cozijnsen:** Conceptualization; investigation; methodology; project administration; writing – review and editing. **Merel van Pieterson:** Data curation; project administration; writing – review and editing. **Tim G. J. de Meij:** Investigation; writing – review and editing. **Obbe F. Norbruis:** Investigation; writing – review and editing. **Michael Groeneweg:** Investigation; writing – review and editing. **Victorien M. Wolters:** Investigation; writing – review and editing. **Herbert van Wering:** Investigation; writing – review and editing. **Thalia Hummel:** Investigation; writing – review and editing. **Janneke Stapelbroek:** Investigation; writing – review and editing. **Cathelijne van der Feen:** Investigation; writing – review and editing. **Patrick F. van Rheenen:** Investigation; writing – review and editing. **Michiel P. van Wijk:** Investigation; writing – review and editing. **Sarah Teklenburg:** Investigation; writing – review and editing. **Dimitris Rizopoulos:** Formal analysis; writing – review and editing. **Marten J. Poley:** Writing – review and editing; writing – original draft; formal analysis. **Johanna C. Escher:** Investigation; writing – review and editing. **Lissy de Ridder:** Investigation; writing – review and editing; funding acquisition; conceptualization; formal analysis; methodology; project administration; writing – original draft; supervision.

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AUTHORSHIP

Guarantor of the article: Lissy de Ridder.

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

CLINICAL TRIAL REGISTRATION

Top-down Infliximab Study in Kids With Crohn's Disease (TISKids) has been registered under trial registration number: NCT02517684.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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