Infliximab or ciclosporin for steroid-resistant acute severe ulcerative colitis? Results of a pragmatic randomised trial (CONSTRUCT)

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Lancet Gastroenterol Hepatol 2016; 1: 15–24
Published Online June 22, 2016
http://dx.doi.org/10.1016/S2468-1253(16)30003-6

Abstract

Background: Infliximab and ciclosporin are of similar efficacy in treating acute severe ulcerative colitis, but there has been no comparative evaluation of their relative clinical and cost effectiveness.

Methods: Between July 2010 and February 2013, 270 patients were recruited at 52 hospitals in England, Scotland and Wales to this mixed methods, open-label, parallel-group, pragmatic randomised trial. Consenting patients over 18 years old who had been admitted unscheduled with severe colitis and failed to respond to intravenous hydrocortisone within about five days, were randomised in equal proportions to either infliximab (Remicade® 5mg/kg intravenous infusion given over two hours at baseline, and again at two and six weeks after the first infusion) or ciclosporin (Sandimmun® 2 mg/kg/day by continuous infusion for up to seven days, followed by twice-daily Neoral® tablets delivering 5·5 mg/kg/day for 11 weeks). Randomisation used a web-based password-protected site, with a dynamic algorithm to generate allocations on request, thus protecting against investigator preference or other subversion, while ensuring that each trial arm was balanced by centre, which was the only stratification used. Local investigators and participants were aware of the treatment allocated, but the Chief Investigator and analysts were blinded. Analysis was by treatment allocated. Primary outcome was quality-adjusted survival – the area under the curve (AUC) of scores from the Crohn's and Ulcerative Colitis Questionnaire (CUCQ) completed by participants at baseline, three and six months, then six monthly over one to three years.

Findings: There was no significant difference in: quality-adjusted survival [analysable data from 121 participants (90%) in each group; mean AUC for infliximab 0.705 (sd 0.181) vs ciclosporin 0.733 (0.158); mean difference in AUC/day 0·030 favouring ciclosporin; 95% confidence interval (CI) from -0·009 to +0·068; p=0·129]; EQ-5D scores; SF-6D scores; colectomy rates (55/135 infliximab vs 65/135 ciclosporin, OR=1·350 favouring infliximab, 95% CI 0·832 to 2·188, p=0.223); time to colectomy (infliximab 810.8 days vs ciclosporin 744.1; censored data); number of serious adverse reactions (infliximab 16 reactions in 14 participants vs ciclosporin 10 in nine); serious adverse events (infliximab 21 in 16 vs ciclosporin 25 in 17); or deaths (infliximab 3 vs ciclosporin 0, p = 0·247).

Interpretation: There was no significant difference between ciclosporin and infliximab in clinical effectiveness.

Funding: NIHR Health Technology Assessment programme

ISRCTN: 22663589

(369 words)

Introduction

Ulcerative colitis (UC) is a chronic debilitating disease that affects about 150,000 people in the UK and 2 million people in Europe.[1,2] Acute severe ulcerative colitis (ASUC) affects up to 25% of patients, either on first presentation or later, and requires hospital admission for treatment with intravenous steroids.[3] About 30% of these patients are resistant to steroid therapy and until ten years ago, colectomy was the usual option.[4,5]

Previous studies have proven the efficacy of both ciclosporin and infliximab in the treatment of both moderately severe steroid-resistant ulcerative colitis;[6-8] and acute, severe, steroid-resistant disease.[9] However their relative clinical effectiveness and cost effectiveness are not known.

Objectives

To compare the clinical and cost effectiveness of infliximab and ciclosporin in the management of patients admitted unscheduled to hospital with ASUC who fail to respond to intravenous steroids.

Methods

Study design and participants

We conducted a mixed methods, open-label, parallel-group, pragmatic randomised trial in 52 district general and teaching hospitals across England, Scotland and Wales.[10] . Potential participants were identified following unscheduled admission with severe UC. Patients over 18 were recruited to the trial if they failed to respond to between two and about five days of intravenous hydrocortisone, with continuing severe disease according to Truelove & Witts' criteria[11] or clinical judgement. All patients had either a proven histological diagnosis of ulcerative colitis, or indeterminate colitis where clinical judgement suggested a diagnosis of ulcerative colitis rather than Crohn's disease, or symptoms typical of ulcerative colitis subsequently confirmed on histology of a colonic biopsy taken soon after admission.

We excluded patients under 18 years; from vulnerable groups or unable to consent; with an enteric infection or histological diagnosis inconsistent with UC; pregnant, lactating, or fertile but unwilling to use contraception for six months after randomisation; with serious co-morbidity, including current malignancy (except for basal cell carcinoma), immunodeficiency, recent myocardial infarction, heart failure, acute stroke, respiratory failure, renal failure, hepatic failure or severe infection; known to be hypersensitive to

infliximab, ciclosporin or polyethoxylated oils; taking tacrolimus or rosuvastatin; needing emergency colectomy without further medical treatment; treated with either infliximab or ciclosporin in the three months before admission; with any other contraindication to treatment with infliximab or ciclosporin; participating in another clinical trial; or with poor English without available translation.

Because we anticipated difficulty in obtaining informed consent and baseline data from acutely and severely ill patients whose health was worsening, we explained the trial to patients with known or suspected ASUC as soon as possible after admission and, with consent, asked them to complete a baseline quality of life questionnaire. This created a 'cohort' of patients with ASUC from which we recruited to the trial those who failed to respond to treatment with intravenous hydrocortisone, following further explanation and consent. The treatment of patients who did not consent to either cohort or trial was unaffected. The protocol, patient information sheets and consent forms, all questionnaires and amendments were approved by the Research Ethics Committee for Wales (08/MRE09/42) and local Research and Development Committees.

Randomisation and masking

Eligible patients were invited to participate by local investigators. Following full explanation and written consent, their details were entered onto a web-based password-protected site (hosted by Bangor University), and allocated at random to infliximab or ciclosporin. A dynamic algorithm[12] was used to generate allocations on request, thus protecting against investigator preference or other subversion while ensuring that each trial arm was balanced by centre, which was the only stratification used.

As this was an open-label trial, local investigators and participants were aware of the treatment allocated, but the Chief Investigator and all analysts remained blinded to allocation until the Trial Steering Committee and Data Monitoring and Ethics Committee had reviewed and approved the analysis of the primary outcome.

Procedures

Patients randomised to infliximab received Remicade® 5mg/kg by intravenous infusion, given over two hours at baseline, and again at two and six weeks after the first infusion, in accordance with local prescribing guidelines.

Patients randomised to ciclosporin received Sandimmun® by continuous infusion of 2 mg/kg/day, continued for up to seven days if successful; then twice-daily Neoral® tablets delivering 5·5 mg/kg/day, with the dose adjusted to achieve trough ciclosporin concentration of 100 – 200 ng/ml for 12 weeks. The drugs were dispensed by hospital pharmacies, as part of routine practice. They were not provided specifically for the trial by pharmaceutical companies, who did not support this trial in any way.

We did not mandate other therapy. Centres were encouraged to give co-trimoxazole as prophylaxis against *Pneumocystis jiroveci* (*carinii*) pneumonia, and given discretion to start azathioprine or 6-mercaptopurine at therapeutic doses in week 4. Guidance included stopping steroids by week 12 in patients who remained well, but to restart steroids in patients who became symptomatic. After 12 weeks, all treatment was at the discretion of the patient's physician.

Outcomes

Because we wished to compare the effectiveness of treatment as perceived by patients over at least a year, during which time they may experience many different health states including a post-colectomy stoma, we used quality–adjusted survival (QAS)[13] as the primary outcome measure. This was measured as the total area under the curve (Figure 1) described by scores from the Crohn's and Ulcerative Colitis Questionnaire (CUCQ),[14,15] which was completed by participants at baseline, three and six months, then six monthly over one to three years. If a participant underwent colectomy, additional questions were completed on post-operative discharge and four, eight and 12 weeks, and then six monthly. The CUCQ and its colectomy extension were developed by modifying and concurrently validating the UK Inflammatory Bowel Disease Questionnaire (UK-IBDQ)[16] to be appropriate for use by patients across a spectrum of disease states, including quiescent, mild chronic, and and acute severe colitis, and post-colectomy. Although by convention low scores indicate better health on disease-specific patient-reported outcome measures (PROMs), for the purposes of presenting the area under the curve, the CUCQ score was transformed so that a lower score indicated worse health.

Secondary outcome measures included: change in CUCQ scores, and those from two generic quality of life measures (SF-12, from which the SF-6D was derived, and EQ-5D), completed by participants at the time intervals described above. Case report forms were completed by local research professionals, and from these were derived mortality; incidence of colectomy, both emergency and planned; length of stay; and incidence of malignancies, serious infections and renal disorders. Adverse events were monitored via reports from Principal Investigators,

and used to triangulate the incidence of malignancies, serious infections and renal disorders. All incident malignancies were classified as 'possibly related' to the treatment received. Because of differing pharmacokinetics, we classified infections as 'possibly related' if the diagnosis was within one month of the last dose of ciclosporin, or six months after infliximab. Thereafter they were classified as 'unlikely to be related'. New symptoms arising after treatment were documented in adverse event reports, and analysed and analysed by clinical system affected when associated with readmission.

Statistical analysis

Our hypothesis was that there is no difference in the clinical effectiveness of these two treatments, as measured by quality of life. Our original target sample size was 360 participants with analysable data, based on an equivalence design, an effect size of 0·30, and a primary outcome of change in CUCQ scores at two years. In 2012, slower recruitment than predicted led us to reduce the analysable sample size to 250, still sufficient to detect an effect size of 0·35 with 80% power at 5% significance level. To mitigate the effect of attrition we introduced a length of follow-up of one to three years, and redefined our primary outcome as QAS, measured as the area under the curve described by CUCQ scores (including after colectomy).

Primary analysis was by treatment allocated, reflecting the pragmatic nature of the trial design. The primary outcome measure used a general linear model to estimate differences in QAS between groups, adjusting for covariates including: trial site; age; gender; ethnic group; social deprivation (derived from truncated post-codes); baseline quality of life; disease severity; and time in follow-up.

Secondary analyses adjusted for the same covariates as primary analysis and compared between groups: QAS per day (again using general linear models); CUCQ scores (using methods for repeated measures); proportion of participants undergoing colectomy (using binary logistic regression); time to colectomy (censored at the end of follow up, and analysed by Cox regression); proportion of participants suffering one or more adverse events (using binary logistic regression); and mortality.

Residual diagnostics were examined in analyses that assume Normality, with the options of data transformation and boot-strapping when residual distributions were markedly non-Normal. Identified outliers were excluded and the revised datasets reanalysed. Analyses are summarised by descriptive comparisons between groups in accordance with CONSORT

guidelines[17], notably estimates with 95% confidence intervals representing two-tailed tests at the 5% significance level.

This was a mixed methods trial which also evaluated cost effectiveness, through a cost utility study conducted alongside the clinical trial. The methods and results are available in detail elsewhere.[15] In summary, costs were assessed by prospectively monitoring total health service resource use by patients in both arms of the trial, collected in case report forms at each follow up. These data were multiplied by relevant unit costs and expressed in 2012-13 prices. Effectiveness was assessed in terms of Quality Adjusted Life Year (QALY) generated from EQ-5D data.
We also sought the views of patients and professionals during this mixed methods study. The method and findings are report in full elsewhere[15] and summarised in the on-line appendix to this paper.

The study is registered as an International Standard Randomised Controlled Trial, number ISRCTN 22663589.

Role of the funding source

The trial was funded by the NIHR Health Technology Assessment Programme (project number 06/78/03). The funder had no role in the design of the study apart from the detailed scrutiny and feedback from their independent peer reviewers before funding was awarded. The views and opinions expressed are those of the authors and do not necessarily reflect those of the Department of Health. The trial was sponsored by Swansea University, whose clinical trials unit contributed to the design of the study, analysis and reporting of the data through AW and HH. AW, HH, DC, FA, ML, JMM and JGW had access to the raw data, but remained blind to allocations until the analysis of the primary outcome had been approved at a joint meeting of the Trial Steering Committee and Data Monitoring Committee.

Results

Patient flow

Between May 2010 and February 2013, 2065 potentially eligible patients were admitted to 62 hospitals in England, Scotland and Wales, and 1614 of those were consented into the cohort. From July 2010 until March 2013, 270 of these patients were recruited into the trial at 52 hospitals, and were followed for one to three years until follow-up ceased in February 2014. There were 135 patients in each arm (Figure 2a), of whom 242 (90%) contributed to definitive

analysis of the primary outcome (Figures 2b). Median follow-up (IQR) was 765 days (398 days) overall [766 days (404 days) for infliximab, and 764 days (385 days) for ciclosporin]. At baseline, there were no statistically significant differences between the groups in demographic, disease characteristics, haemoglobin, inflammatory markers, albumin, or quality of life scores (Table 1). The mean duration of treatment with intravenous steroids was similar in both groups (5.32 days, sd 2.66 before infliximab; 5.43 days, sd 2.89 before ciclosporin). Failure to respond was assessed by clinical judgement rather than Truelove and Witts scores in 36 patients in both groups.

Primary outcome

There was no significant difference in QAS between infliximab and ciclosporin: the observed means (standard deviations) for total area under the CUCQ curve were 564.0 (241.9) and 587.0 (226.2), respectively, and the mean adjusted difference was 7.9 favouring ciclosporin [95% confidence interval (CI) from -22·0 to 37·8; p = 0·603]. The observed means (standard deviations) in AUC/day were 0.705 (0.181) and 0.733 (0.158) for infliximab and ciclosporin, respectively, and mean adjusted difference in AUC/day was 0.030, favouring ciclosporin (95% CI from -0·009 to 0·068; p = 0·129] (Table 2).

Secondary outcomes

At no time after randomisation was there any significant difference between allocated groups for: CUCQ scores (mean adjusted difference in AUC/day of survivors = 0·020 favouring ciclosporin; 95% CI from -0·019 to 0·0581; p=0·319) (Figure 3), SF-6D scores (mean adjusted difference = 0·005 favouring ciclosporin; 95% CI from -0·025 to 0·035; p=0·737) (Figure 4); or EQ-5D scores (QALY mean adjusted difference = 0·021 favouring ciclosporin; 95% CI from -0·032 to 0·096; p=0·350) (Figure 5). There was also no significant difference between allocated groups in colectomy rates [in-hospital: 29/135 (21.5%) on infliximab versus 34/135 on ciclosporin (25.2%); at 3 months: 39/135 (28.9%) versus 41/135 (30.4%); 12 months: 47/135 (34.8%) versus 61/135 (45.2%); overall: 55/135 (40.7%) versus 65/135 (48.1%); odds ratio (OR) =1·350 favouring infliximab; 95% CI from 0·832 to 2·188; p = 0·223]; or time to colectomy (mean 811 days on infliximab versus 744 days; hazard ratio = 1·234 favouring infliximab; 95% CI from 0·862 to 1·768; p = 0.251) [Figure 6]. Although length of stay after randomisation ostensibly did not differ between allocated groups (mean adjusted difference = 1·542 days more for ciclosporin; 95% CI from -1·297 to 4·381 assuming Normal distribution of residuals in general linear model; p = 0·286), the distribution was so skewed as to invalidate the assumption of Normality. Stays were therefore transformed by taking logarithms and stay after first dose of ciclosporin was a factor of 1·523

times longer than that after first dose of infliximab (95% CI from factor of 1·278 to factor of 1·817; p < 0·0001) (Table 2). Treatment with infliximab was continued for longer than ciclosporin after the designated intervention period (Figure 7); no-one received ciclosporin after six months, but many participants continued to receive infliximab for two years or more, resulting in mean treatment durations of 126 days for infliximab versus 56 days for ciclosporin. Median treatment duration was 43 days for infliximab versus 60 days for ciclosporin. Nine participants randomised to ciclosporin were subsequently given infliximab (four at three months; two at six; and three at 12 months after randomisation). One participant randomised to infliximab received oral ciclosporin at three months. There were no significant differences between the two arms of the study in use of azathioprine, 6-mercaptopurine, or methotrexate at any time point (Table 3), either when given alone or in combination.

Adverse Events

There was no statistically significant difference between the two drugs in serious adverse reactions (SARs), or serious adverse events (SAEs): 16 reactions in 14 participants given infliximab and 10 in nine given ciclosporin were classified as SARs (event ratio = 0·938 favouring ciclosporin; 95% CI from 0·590 to 1·493; p = 0·788) [Table 4]. 21 events in 16 participants given infliximab and 25 in 17 given ciclosporin were classified as SAEs not related to disease progression or colectomy (event ratio = 1.075 favouring infliximab; 95% CI 0·603 to 1.917; p = 0·807). Table 4 shows the clinical systems affected for SARs. There were two malignancies on infliximab (basal cell carcinoma and colorectal cancer), and one on ciclosporin (endometrial cancer). Eleven participants were noted to have impaired renal function on ciclosporin but only one was reported as a serious adverse reaction, and all resolved with dose reduction. More infections were attributed to infliximab (8/135; 5.9%) than ciclosporin (1/135; 0.7%), but more SAEs due to an infection unrelated to the intervention occurred after ciclosporin (16/135;11.9%) than infliximab (8/135; 5.9%). Three patients died, all after taking infliximab (p = 0·247): two of perioperative pneumonia with sepsis (at 20 and 65 days following start of treatment; both had multiple co-morbidities including diabetes); and one of disseminated colorectal cancer (at 278 days, 20 years after UC was first diagnosed).

The cost-utility analysis found that total health service cost over 30 months were £5632 higher for infliximab patients, due mainly to the higher acquisition costs for infliximab (95% CI £2,773 to £8,305, p<0.001). Effectiveness over this period was similar in both groups, and

a mean adjusted difference of 0.21 QALYs in favour of ciclosporin was not statistically significant (95% CI from -0.032 to 0.096; p=0.350.

Discussion

CONSTRUCT has shown that both infliximab and ciclosporin improve quality of life in patients suffering from acute severe colitis that has not responded to intravenous steroids. Nevertheless, 40% of patients (108/270) still undergo colectomy within one year. There was no significant difference between allocated treatment in terms of quality of life, colectomy rates, adverse events, or mortality, even though three patients died of complications that were possibly related to infliximab (two sepsis and one cancer). Although more infections were thought to be possibly related to infliximab (8) than ciclosporin (1) participants were treated with infliximab for longer, and differing pharmacokinetics were also taken into account when assessing the length of time over which relatedness was possible.

The trial was pragmatic, conducted in 52 hospitals, and designed to reflect current clinical practice across the UK. Local investigators were aware of treatment allocations, but the Chief Investigator and analysts remained blind to allocations until the Trial Steering and Data Monitoring Committees had approved the analysis of the primary outcome. The protocol mandated either three infusions of infliximab over six weeks, or intravenous ciclosporin for up to seven days, followed by oral administration for 12 weeks. After this, principal investigators were given discretion to continue or stop treatment. In keeping with current practice, infliximab tended to be used for longer than ciclosporin (with similar medians, but a mean difference of 70 days). Although this may have improved the effectiveness of infliximab, it certainly increased costs. Treatment with immunosuppressants during and after infliximab or ciclosporin was similar in both groups. Neither the rate nor timing of colectomy differed between allocated groups. Importantly post-colectomy quality of life scores and interviews with participants who had undergone surgery both suggest that colectomy is not a bad outcome. There is evidence from observational studies that the cumulative rate of colectomy rises over time, not only with ciclosporin, but also with infliximab.[18-24] Hence we plan to follow the trial and cohort participants for ten years following recruitment, using routine NHS data to monitor readmissions and colectomies, with annual questionnaires to monitor trial patients' quality of life.

To measure effectiveness from a patient perspective we used the CUCQ, a 32 item questionnaire with an additional ten questions for patients with a stoma. This PROM was

derived from the UKIBDQ[16], and validated concurrently during the trial.[15] We used it to assess quality of life of participants over one to three years as they passed through different health states, including colectomy and stoma. The concept of quality adjusted survival (QAS) is not new[13], but it is the first time it has been applied to inflammatory bowel disease.

Our findings of equivalent effectiveness reinforce the efficacy findings of CySIF[9], a European trial which assessed treatment failure at three months as the primary outcome. Three year follow-up data from CySIF reported in oral presentation in 2015 do not show differences in colectomy rate, even though a majority of patients continued infliximab and many allocated to ciclosporin subsequently switched to infliximab[25]

The cost utility analysis found that UK NHS costs over 30 months were £5632 higher for infliximab patients, due mainly to the higher acquisition costs for infliximab. On this basis, ciclosporin is the more cost effective treatment in the UK, although differences in the cost of ciclosporin and infliximab are apparent world-wide. With the advent of anti-TNF biosimilars, the cost of infliximab is falling.[26] Nevertheless, while the cost remains higher than ciclosporin our findings question the justification of treating patients with infliximab as it does not produce any additional health benefits. While we accept that economic grounds are not the only grounds for decision making, the opportunity cost to other patients has to be borne in mind when choosing a treatment option that is not cost effective.

We note that the US Food and Drug Administration has expressed its dissatisfaction with current use of disease activity scores as primary endpoints in IBD trials, and is moving towards Patient Reported Outcome measures.[27] CONSTRUCT is the first major pragmatic drug trial in inflammatory bowel disease to employ a disease specific PROM to assess primary outcome, and used an instrument that enabled measurement of change in quality of life through different disease states, including after surgery. This will provide a benchmark for the evaluation of re-costed infliximab, and a model for evaluating newer biologic treatments or colonic release preparations of ciclosporin.[28] We hope our innovative approach will be also be a model for IBD trials in the future.

Conclusions

There are no significant differences in clinical effectiveness, colectomy rates, incidence of serious adverse reactions or mortality following treatment with ciclosporin or infliximab for patients with ASUC who do not respond to treatment with intravenous steroids.

Contributions of authors

All authors made substantial contributions to the conception or design of the study and/or the acquisition, analysis or interpretation of the data; commented on drafts of this paper; and approved the final version. All authors agree to to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved Additionally, individual authors contributed as follows:

JGW was the chief investigator who conceived and designed the study, interpreted data, and drafted and critically revised the report. He has had full access to all the data in the study and took final responsibility for the decision to submit for publication. IA, JG, BH, AJ, JM, SS, IS and ST were local investigators. JM and ST were also members of the Trial Steering Committee. AS managed the trial. JMM led the development and operational use of the data management system. HH and LA developed and validated the CUCQ. LA also assisted the screening and analysis of adverse events. AW analysed the clinical effectiveness data. DC designed the cost effectiveness method, and oversaw the health economic analyses and interpretation. FA and ML both contributed to the analysis and interpretation of the economic data. FR oversaw the qualitative studies, analysed and interpreted the data. CC and AS collected and analysed qualitative data. MH contributed to the design of the trial and data collection from a service user perspective.

All authors declare that they have no conflict of interest.

Acknowledgements

Many people have contributed to this study and a full list of acknowledgements can be found in the full report to the NIHR Health Technology Assessment Programme.[15]

We have listed in the on-line appendix all the local Principal Investigators and Research Professionals who supported the study, with our thanks for the invaluable role they played in helping to identify, recruit, and randomise participants, and collect data. We would also like to thank their clinical colleagues for referrals to the study; pharmacy personnel who helped dispense trial treatment; and the research support teams who provided helpful assistance throughout the study.

(3,810 words)

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