Comparison Of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: pragmatic randomised Trial and economic evaluation (CONSTRUCT)

John G Williams,[1]* M Fasihul Alam,[2] Laith Alrubaiy,[1] Clare Clement,[1] David Cohen,[3] Michelle Grey,[1] Mike Hilton,[4] Hayley A Hutchings,[1] Mirella Longo,[2] Jayne M Morgan,[1] Frances L Rapport,[1] Anne C Seagrove[1] and Alan Watkins[1]

[1]Swansea University Medical School, Swansea University, Swansea, UK
[2]Swansea Centre for Health Economics, College of Human and Health Science, Swansea University, Swansea, UK
[3]Faculty of Health Sport and Science, University of South Wales, Pontypridd, UK
[4]Patient representative

*Corresponding author

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Scientific summary

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Scientific summary

Introduction

Ulcerative colitis (UC) is a chronic debilitating disease that affects about 150,000 people in the UK. Acute severe ulcerative colitis (ASC) affects 25% of patients, and requires hospital admission and treatment with intravenous steroids. About 40% of these patients do not respond to steroid therapy and until 10 years ago colectomy was the only available treatment.

The efficacy of ciclosporin and infliximab in treating steroid-resistant UC is proven, but their relative clinical effectiveness and cost-effectiveness is not known.

Objectives

Our objectives were to compare quality of life (QoL), mortality, colectomy rates, adverse events (AEs) and resource use for up to 3 years after treatment with infliximab or ciclosporin to estimate the clinical effectiveness and cost-effectiveness of these two drugs in managing ASC that had failed to respond to intravenous steroids. We also sought to explore the views of patients and professionals about the two treatments.

Methods

We conducted an open-label parallel-group, pragmatic randomised trial using mixed quantitative and qualitative methods. We recruited participants from a cohort of patients admitted with ASC to hospitals across Great Britain.

We assessed QoL through patient-completed questionnaires at baseline, 3 and 6 months after treatment and then 6-monthly for 1–3 years. Data on colectomy rates, mortality, AEs and resources were collected on case report forms (CRFs) completed by research staff at the same intervals.

We assessed the relative cost-effectiveness of the trial drugs through cost–utility analysis, which estimated differences between groups in NHS costs and quality-adjusted life-years (QALYs).

Our qualitative studies explored participants' experiences of their disease and the trial drugs, and the preferences of health-care professionals between the trial drugs and their use.

We used the Method for Aggregating The Reporting of Interventions in Complex Studies, which we had previously developed in another complex study, to integrate and compare findings from the mixed methods used in Comparison Of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: pragmatic randomised Trial and economic evaluation (CONSTRUCT). We classified our outcomes into effects on participants; effects on gastroenterological services and professionals; and effects on the rest of the NHS and society.

In due course we shall supplement our designed research data with routinely collected data. We have consent from trial participants to access their routine data and send them annual questionnaires for 10 years from recruitment.

Participants

We created a comprehensive cohort of admitted patients because we expected difficulty in identifying acutely ill patients who needed urgent treatment and in obtaining baseline data from them. We invited patients with known or suspected UC to join this cohort soon after admission and collected their baseline data as soon as possible after they gave consent.

We recruited from the cohort to the trial those patients who failed to respond to intravenous steroids, fulfilled the trial inclusion and exclusion criteria and gave informed consent. The treatment of patients who did not give consent did not change in any way.

Trial inclusion criteria

We included patients who had been admitted unscheduled with colitis judged as severe (by the criteria of Truelove and Witts, a Mayo score of at least 2 on endoscopic finding, or clinical judgement); who then failed to respond to about 2–5 days of intravenous hydrocortisone; and also had a proven histological diagnosis of UC, indeterminate colitis where clinical judgement suggested a diagnosis of UC rather than Crohn's disease, or symptoms typical of UC awaiting histology.

Trial exclusion criteria

We excluded patients aged < 18 years; from vulnerable groups or unable to consent; with an enteric infection or histological diagnosis inconsistent with UC; who were pregnant, lactating, or fertile but unwilling to use contraception for 6 months after randomisation; suffering current malignancy, except for basal cell carcinoma; with serious comorbidity, including immunodeficiency, recent myocardial infarction, heart failure, acute stroke, respiratory failure, renal failure, hepatic failure, or severe infection; with known hypersensitivity to infliximab, ciclosporin or polyethoxylated oils; using tacrolimus or rosuvastatin; whose English was poor in the absence of local translator services; needing emergency colectomy without further medical treatment; currently participating in another clinical trial; treated with either infliximab or ciclosporin within 3 months of admission; or showing any other contraindication to treatment with infliximab or ciclosporin.

Qualitative studies

We used purposive quota sampling to identify 12 representative consenting participants from each arm of the trial for two interviews. We used purposive sampling to interview 15 consultants from three strata: sites that recruited well to cohort and trial; sites that recruited well to cohort but less well to trial; and sites that recruited poorly. We also interviewed eight nurses from good recruiting sites.

Interventions

Participants randomised to infliximab received Remicade® (Merck Sharp & Dohme Ltd) in 5-mg/kg intravenous infusions over 2 hours – forthwith, and at 2 and 6 weeks after the first infusion – in accordance with local prescribing guidelines.

Participants randomised to ciclosporin received Sandimmun® (Novartis Pharmaceuticals UK Ltd) by continuous infusion of 2 mg/kg/day, continued for up to 7 days if successful, when it was switched to twice-daily Neoral® tablets (Novartis Pharmaceuticals UK Ltd) delivering 5.5 mg/kg/day, with the dose adjusted to achieve trough ciclosporin concentration of 100–200 ng/ml. After 12 weeks, treatment was at the discretion of the participant's consultant.

For both treatments we gave centres discretion to start azathioprine or 6-mercaptopurine at therapeutic doses in week 4 and use was similar in both groups. We asked them to discontinue steroids by week 12 in participants who remained well but to reinstate them if symptoms returned. We also asked centres to give co-trimoxazole as prophylaxis against *Pneumocystis jiroveci* (formerly *carinii*) pneumonia in both groups.

Outcomes

The primary outcome was the area under the curve (AUC) of scores derived from the Crohn's and Ulcerative Colitis Questionnaire (CUCQ), a disease-specific patient-reported outcome measure which extends the validated United Kingdom Inflammatory Bowel Disease Questionnaire to cover acute illness and colectomy, and which we validated concurrently.

Secondary outcomes included change in Short Form-12 items and European Quality of Life-5 Dimensions (EQ-5D) scores; mortality; colectomies, both emergency and planned; serious adverse events (SAEs) and serious adverse reactions (SARs); and length of stay.

Economic outcomes included NHS costs and health-related quality of life (HRQoL), measured by EQ-5D.

Qualitative outcomes covered participant and professional views of the drugs and their consequences.

Sample size

Our original target analysable sample size was 360 participants, based on a primary outcome of a change in HRQoL over 2 years. However, in 2012 slower recruitment than predicted led us to revise the primary outcome and reduce the target analysable sample size to 250.

The changes required statistical imputation to exploit the resulting data set and we estimated that data from 250 participants would be sufficient to detect an effect size of 0.35 in CUCQ scores with 80% power at a 5% significance level.

Randomisation

We allocated participants at random between infliximab and ciclosporin, using a web-based password-protected adaptive algorithm to protect against subversion while ensuring that each trial arm was balanced by centre.

Blinding

As this was an open trial, there was no need for procedures to inform sites about allocated treatments. However, the chief investigator, trial methodologist, outcomes specialist, health economists and statisticians remained blind to them until the Trial Steering Committee and Data Monitoring and Ethics Committee had reviewed and approved the analysis of the primary outcome.

Statistical methods

Clinical effectiveness

Primary analysis was by treatment allocated, reflecting the pragmatic nature of the trial design. We used a general linear model to estimate differences in quality-adjusted survival (QAS) between groups, adjusting for covariates including trial site; age; gender; ethnic group; QoL at baseline; disease severity at baseline;

immunosuppressant therapy at baseline (using a binary indicator set equal to 1 for participants then taking azathioprine, 6-mercaptopurine or methotrexate); 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); QoL 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 AEs (using binary logistic regression); and mortality.

We examined residual diagnostics in analyses that assume normality, with the options of data transformation and bootstrapping when residual distributions were markedly non-normal. We excluded identified outliers and reanalysed the revised data sets. We reported analyses in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines, including estimated differences with 95% confidence intervals (CIs), representing two-tailed tests at the 5% significance level.

Imputation of missing data

We used statistical imputation of censored and missing data, to impute QoL and costs for all participants who generated data on survival, colectomy or QoL after randomisation.

Cost-effectiveness

We collected data on NHS resource use from CRFs and Participant Follow-up Questionnaires (PFQs) completed at each follow-up time point. To minimise recall bias, PFQs reported resource use over the previous 3 months, leaving gaps in the data which we imputed. We estimated all costs in 2012–13 prices inflated when necessary using the NHS Pay and Prices Index and applied a discount rate of 3.5% per annum.

Our primary economic analysis assessed cost-effectiveness over 30 months by aggregating costs and QALYs for participants for whom we had EQ-5D data. We fitted statistical models for NHS costs and QALYs using allocated drug days since randomisation and the logarithm of those days as independent variables. We used the resulting coefficients to adjust NHS costs and QALYs to a period of 730 days. Costs and QALYs were further adjusted for baseline covariates. We used non-parametric bootstrapping to generate scatterplots on the cost-effectiveness plane and produced cost-effectiveness acceptability curves (CEACs) to show the probability of treatments being cost-effective against thresholds of willingness to pay.

Results

Participant flow

We know of 2065 potentially eligible patients admitted between May 2010 and March 2013 to 62 participating hospitals in England, Scotland and Wales. Of those, 1614 were consented into the CONSTRUCT cohort. From these, 52 hospitals recruited 270 participants into the trial and followed them for 1–3 years. Each arm comprised 135 participants, of whom 121 (90%) contributed to definitive analysis of the primary outcome. Funded data collection finished in March 2014.

Baseline characteristics

At baseline, there were no statistically significant differences between arms in demographic or disease characteristics, or QoL scores.

Primary outcomes

There was no significant difference in QAS between infliximab and ciclosporin; the mean adjusted difference in total area under the CUCQ curve was 7.9 favouring ciclosporin (95% CI –22.0 to 37.8; $p = 0.603$); and mean adjusted difference in AUC per day was 0.0297 favouring ciclosporin (95% CI –0.0088 to 0.0682; $p = 0.129$).

Secondary outcomes

At no time point after randomisation was there any significant difference between groups in CUCQ scores (mean adjusted difference in AUC/day of survivors 0.0195 favouring ciclosporin, 95% CI –0.0191 to 0.0581; $p = 0.319$), Short Form questionnaire-6 Dimensions scores (mean adjusted difference 0.0051 favouring ciclosporin, 95% CI –0.0250 to 0.0353; $p = 0.737$); EQ-5D scores (QALY mean adjusted difference 0.021 favouring ciclosporin, 95% CI –0.032 to 0.096; $p = 0.350$). There was also no significant difference between groups in: mortality (all three who died had taken infliximab; $p = 0.25$); colectomy rates [odds ratio (OR) 1.350 favouring infliximab, 95% CI 0.832 to 2.188; $p = 0.223$]; or time to colectomy (hazard ratio 1.234 favouring infliximab, 95% CI 0.862 to 1.768; $p = 0.251$). Although length of hospital stay after randomisation ostensibly did not differ between groups (mean adjusted difference 1.542 days more for ciclosporin, 95% CI –1.297 to 4.381 days assuming normal distribution of residuals in general linear model; $p = 0.286$), that distribution was so skewed as to invalidate the assumption of normality; hence, we transformed these stays by taking logarithms and estimated that the geometrical mean of adjusted stays after ciclosporin was a factor of 1.527 times longer than that after infliximab (95% CI 1.278 to 1.817; $p < 0.001$).

Adverse events

There was no statistically significant difference between the two drugs in SARs or SAEs. Fourteen infliximab participants reported 16 SARs and nine ciclosporin participants reported 10 SARs (event ratio 0.938 favouring ciclosporin, 95% CI 0.590 to 1.493; $p = 0.788$; OR 0.660 favouring ciclosporin, 95% CI 0.282 to 1.546; $p = 0.338$). Sixteen infliximab participants reported 21 SAEs and 17 ciclosporin participants reported 25 SAEs not related to disease progression or colectomy (event ratio 1.075 favouring infliximab, 95% CI 0.603 to 1.917; $p = 0.807$; OR 0.999 favouring infliximab, 95% CI 0.473 to 2.114; $p = 0.998$). There were two malignancies on infliximab (basal cell carcinoma and colorectal cancer) and one on ciclosporin (endometrial cancer). Three participants died, all following infliximab ($p = 0.247$). The cause of death was disseminated malignancy from colorectal cancer in one and perioperative pneumonia with sepsis, in the presence of multiple comorbidities, in two.

Cost-effectiveness

In the primary analysis at 30 months, total health service costs for ciclosporin (£14,609) were significantly lower than for infliximab (£20,241) (mean adjusted difference –£5632, 95% CI –£8305 to –£2773; $p < 0.001$): despite the average difference of nearly 2 days in length of hospital stay after recruitment needed to complete ciclosporin treatment, the difference in cost was because of the much higher cost of acquiring infliximab. QALY gains were similar in both groups: the mean adjusted difference of 0.021 QALYs favours ciclosporin, but is not statistically significant (95% CI –0.032 to 0.096 QALYs; $p = 0.350$). The CEAC shows ciclosporin to have 85% probability of being cost-effective over a wide range of thresholds of willingness to pay. Sensitivity analysis showed similar results at 12 and 24 months. Technically, therefore, ciclosporin dominates infliximab.

Qualitative results

Interviews with participants revealed the substantial impact of UC on their QoL, and the potential benefits from these medical treatments and from surgery. Participants treated with infliximab generally spoke more positively about the treatment than those treated with ciclosporin. Interviews with nurses showed preference for infliximab, largely because of the resource-intensive infusion protocol for ciclosporin. Although some consultants favoured infliximab, most were indifferent, perceiving both drugs as effective, with a more predictable speed of benefit with ciclosporin balancing a perceived higher rate of side effects.

Discussion

We have shown that ciclosporin costs the NHS much less than infliximab but is clinically no less effective. Even so, 120 participants (45%) needed a colectomy. Our findings are consistent with those of the study Comparing Cyclosporine with Infliximab in steroid-refractory severe attacks of ulcerative colitis (CySIF), the

only other randomised trial of these two drugs for acute severe UC. However, CySIF was much smaller and did not collect data on costs, QoL or the views of participants or professionals.

Our interviews highlighted the debilitating effect of UC; participants liked infliximab better than ciclosporin, but doctors were more equivocal, whereas nurses disliked the more resource-intensive infusion requirements of ciclosporin. By following participants over the next 10 years, through both questionnaires and routine data, we plan to extend our quantitative findings, especially on colectomies and other readmissions.

Trial registration

This trial is registered as ISRCTN22663589.

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