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

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Abstract

Background

The efficacy of infliximab and ciclosporin in treating severe ulcerative colitis (UC) is proven, but there has been comparative evaluation of effectiveness.

Objective

To compare the clinical effectiveness and cost-effectiveness of infliximab and ciclosporin in treating steroid-res acute severe UC.

Method

Between May 2010 and February 2013 we recruited 270 participants from 52 hospitals in England, Scotland an Wales to an open-label parallel-group, pragmatic randomised trial. Consented patients admitted with severe c completed baseline quality-of-life questionnaires before receiving intravenous hydrocortisone. If they failed to respond within about 5 days, and met other inclusion criteria, we invited them to participate and used a web-b adaptive randomisation algorithm to allocate them in equal proportions between 5 mg/kg of intravenous inflix at 0, 2 and 6 weeks or 2 mg/kg/day of intravenous ciclosporin for 7 days followed by 5.5 mg/kg/day of oral ciclo until 12 weeks from randomisation. Further treatment was at the discretion of physicians responsible for clinic management. The primary outcome was quality-adjusted survival (QAS): the area under the curve (AUC) of sco derived from Crohn's and Ulcerative Colitis Questionnaires completed by participants at 3 and 6 months, and monthly over 1-3 years, more frequently after surgery. Secondary outcomes collected simultaneously includec European Quality of Life-5 Dimensions (EQ-5D) scores and NHS resource use to estimate cost-effectiveness. Bl was possible only for data analysts. We interviewed 20 trial participants and 23 participating professionals. Fur data collection finished in March 2014. Most participants consented to complete annual questionnaires and fo analyse their routinely collected health data over 10 years.

Results

The 135 participants in each group were well matched at baseline. In 121 participants analysed in each group, found no significant difference between infliximab and ciclosporin in QAS [mean difference in AUC/day 0.0297 favouring ciclosporin, 95% confidence interval (CI) -0.0088 to 0.0682; p = 0.129]; EQ-5D scores (quality-adjusted year mean difference 0.021 favouring ciclosporin, 95% CI -0.032 to 0.096; p = 0.350); Short Form questionnaire

0.788); participants with serious adverse reactions (OR 0.660 favouring ciclosporin, 95% CI 0.282 to 1.546; p = 0
numbers of serious adverse events (event ratio 1.075 favouring infliximab, 95% CI 0.603 to 1.917; p = 0.807);
participants with serious adverse events (OR 0.999 favouring infliximab, 95% CI 0.473 to 2.114; p = 0.998); deat
three who died received infliximab; p = 0.247) or concomitant use of immunosuppressants. The lower cost of
ciclosporin led to lower total NHS costs (mean difference -£5632, 95% CI -£8305 to -£2773; p < 0.001). Interview
highlighted the debilitating effect of UC; participants were more positive about infliximab than ciclosporin.
Professionals reported advantages and disadvantages with both drugs, but nurses disliked the intravenous
ciclosporin.

Conclusions

Total cost to the NHS was considerably higher for infliximab than ciclosporin. Nevertheless, there was no signi
difference between the two drugs in clinical effectiveness, colectomy rates, incidence of SAEs or reactions, or
mortality, when measured 1-3 years post treatment. To assess long-term outcome participants will be followe
10 years post randomisation, using questionnaires and routinely collected data. Further studies will be needec
evaluate the efficacy and effectiveness of new anti-tumour necrosis factor drugs and formulations of ciclospor

Trial registration

Current Controlled Trials ISRCTN22663589.

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Contents ▸

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Acknowledgements

Contributions of authors

All 13 authors contributed to design and data collection or analysis and interpretation, commented on successive drafts and approved the version to be published. More specifically:

John G Williams (Professor of Health Services Research and Consultant Gastroenterologist) was principal applicant and chief investigator of the trial. He wrote the first draft and co-ordinated the editing of the final report.

M Fasihul Alam (Health Economist and Modeller) contributed to analysing and interpreting the economic data and drafting this report, and led designing the cost-effectiveness modelling.

Laith Alrubaiy (Clinical Academic Trainee in Gastroenterology) contributed to the validation of the CUCQ and CUCQ+, screening and analysing AEs and drafting this report, in which he contributed in particular the first dra of the background and literature review.

Clare Clement (Qualitative Research Officer) collected and analysed qualitative data; she led the writing of the professional views.

Mike Hilton (service user) contributed to the design of the trial and drafting this report.

Hayley A Hutchings (Associate Professor) developed and validated the CUCQ and CUCQ+ analysis, led the MATRICS results and contributed to interpreting data and drafting this report.

Mirella Longo (Health Economist) contributed to analysing and interpreting the economic data, and drafting th report.

Jayne M Morgan (Information Scientist) was co-applicant and led the development and operational use of the data management system, GeneCIS.

Frances L Rapport (Professor of Qualitative Health Research) was coapplicant and the PI for the qualitative research.

Anne C Seagrove (Trial Manager/Research Officer) was co-applicant and trial manager; she contributed to developing and implementing the design and management of the trial. She also collected and analysed qualitative data, led the writing of the participant views and contributed to drafting and co-ordinating this repo

Alan Watkins (Senior Trials Statistician) was the trial statistician; he undertook primary statistical analysis and contributed to interpreting data and drafting this report.

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Publications and presentations

Williams JG. CONSTRUCT Breaking News. Oral presentation at British Society of Gastroenterology Annual Meeting, 17 June 2014, Manchester, UK.

Seagrove AC, Clement C, Rapport FL, Wright S, Williams JG. Infliximab or Ciclosporin: Patient Views on Treatme and the Impact of Ulcerative Colitis (UC) on Their Lives. Poster presentation at British Society of Gastroenterology Annual Meeting, 17 June 2014, Manchester, UK.

Williams JG. CONSTRUCT. Oral presentation at United European Gastroenterology Week, Vienna, October 201

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Data sharing statement

All available data can be obtained from the corresponding author via e-mail to construct@swansea.ac.uk.

Disclaimers

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