Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262): clinical effectiveness systematic review and economic model

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Scientific summary

Treating active ulcerative colitis after the failure of conventional therapy

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Scientific summary

Background

Ulcerative colitis (UC) is recognised as the most common form of inflammatory bowel disease in the UK. Peak incidence is between 15 and 25 years of age, with a potential second peak between 55 and 65 years. Inflammation in UC typically occurs in the colon and rectum. Symptoms include the development of bloody diarrhoea with or without mucus, abdominal pain, weight loss, fatigue and an urgent need to defecate. UC can have a substantial impact on the health-related quality of life (HRQoL) of patients owing to the young age of disease onset for some patients, the severity of symptoms and the likelihood of relapse. The burden of UC for the NHS is substantial.

Objectives

The aim of this assessment is to assess the clinical effectiveness and cost-effectiveness of infliximab (IFX) [Remicade®, Merck Sharp & Dohme Ltd (MSD)], adalimumab (ADA) (Humira®, AbbVie) and golimumab (GOL) (Simponi®, MSD) for the treatment of patients with moderately to severely active UC after the failure of conventional therapy.

The objectives of the assessment are:

- to evaluate the clinical effectiveness of each intervention
- to examine the effect of disease duration on the clinical effectiveness of each intervention (subject to the availability of evidence)
- to evaluate the adverse effect profile of each intervention
- to evaluate the incremental cost-effectiveness of each intervention compared (1) against each other and (2) against all comparators (including medical and surgical options)
- to estimate the expected net budget impact associated with implementing each intervention
- to identify key areas in which future research may be valuable.

Data sources

The following databases were searched from inception to December 2013 for clinical effectiveness searches and from inception to January 2014 for cost-effectiveness searches for published and unpublished research evidence: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effects, the Health Technology Assessment (HTA) database and NHS Economic Evaluation Database; ISI Web of Science, including Science Citation Index, and the Conference Proceedings Citation Index-Science and Bioscience Information Service Previews. The US Food and Drug Administration website and the European Medicines Agency (EMA) website were also searched as were research registers, conference proceedings and key journals.

Methods

A systematic review of the literature including network meta-analyses (NMAs) was conducted in order to evaluate the clinical effectiveness and safety of IFX, ADA and GOL in the treatment of moderately to severely active UC after the failure of conventional therapy. The protocol for this review is registered with PROSPERO (CRD42013006883). A review of the existing cost-effectiveness literature was also undertaken. A de novo health economic model was constructed by the Assessment Group in order to evaluate the cost-effectiveness of the interventions under assessment.

Results

Number and quality of studies

A total of 10 randomised controlled trials (RCTs) were identified in the clinical effectiveness systematic review. Five, three and two RCTs evaluated the use of IFX, ADA and GOL, respectively, in the treatment of moderately to severely active UC. Nine trials related to adults and one trial was conducted in a paediatric population. All of the adult RCTs (with the exception of one trial, UC-SUCCESS) were performed against placebo (PBO). No head-to-head RCTs were identified in which the interventions of interest were assessed against each other.

The risks of bias associated with included RCTs were assessed using the Cochrane risk-of-bias instrument. Only three RCTs could be considered as being at overall low risk of bias (as allocation concealment, blinded outcome assessment and completeness of outcome data were all judged as low risk). It should be noted that one of the maintenance trials [Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment (PURSUIT)-Maintenance] rerandomised patients who had previously responded to GOL induction therapy in two previous trials; the extent of this potential bias on patient outcomes is unclear.

Summary of benefits and risks

The outcome measures specified in the final National Institute for Health and Care Excellence (NICE) scope were all addressed by the included trial evidence, with the exception of rates of relapse. Clinical response and remission data based on complete Mayo scores were well reported across trials. Evidence was identified to demonstrate that patients receiving IFX, ADA or GOL were more likely to achieve clinical response and remission at induction and maintenance time points than patients receiving PBO. Patients in the UC-SUCCESS trial who received combination treatment with IFX and azathioprine (AZA) experienced the most favourable rates of steroid-free remission when compared with IFX and AZA treatment groups. Seven RCTs performed on adult populations contributed data on clinical response and remission at induction or maintenance time points to NMAs.

Based on the NMA, in the induction phase all treatments were associated with statistically significant beneficial effects relative to PBO, with the greatest effect being associated with IFX. For patients classified as responders at the end of the induction phase, treatment effects were not statistically significant, although the greatest effect at 8–32 weeks was associated with 100 mg of GOL. At 32–52 weeks, only IFX and 50 mg of GOL were associated with beneficial effects on clinical response. For patients classified as being in remission at the end of the induction phase, all treatments except for ADA were associated with beneficial treatment effects relative to PBO, with the greatest effect being associated with 50 mg and 100 mg of GOL, although the effects were not statistically significant at 8–32 weeks. At 32–52 weeks, all treatments except 50 mg of GOL were associated with beneficial treatment effects relative to PBO, with the greatest effect being associated with ADA (the only treatment with statistically significant effect). ADA was associated with the highest probability of staying in remission and the smallest probability of moving from remission to response and from remission to no response.

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Sensitivity analyses were conducted to assess the impact of including different studies and subgroups in the NMA. The sensitivity analyses conducted included replacing Ulcerative colitis Long-Term Remission and maintenance with ADA treatment of moderate to severe ulcerative colitis (ULTRA2) anti-tumour necrosis factor alpha (TNF-α)-naive data with ULTRA2 intention-to-treat (ITT) data (sensitivity analysis 1), including Suzuki *et al.* (Suzuki Y, Motoya S, Hanai H, Matsumoto T, Hibi T, Robinson A, *et al.* Efficacy and safety of ADA in Japanese patients with moderately to severely active ulcerative colitis. *Journal of Gastroenterology* 2014;**49**:283–94) (sensitivity analysis 2), and replacing ULTRA2 anti-TNF-α-naive data with ULTRA2 ITT data plus including Suzuki *et al.* (sensitivity analysis 3).

Available data on hospitalisation outcomes were very limited but suggested that outcomes may be more favourable for ADA-treated and IFX-treated patients compared with PBO (with no data available from GOL trials). Data on the use of surgical intervention were also very sparse, with a potential inconclusive benefit for intervention-treated patients compared with PBO. No trials reported whether or not surgical outcomes were elective or emergency in nature. However, more data are required to demonstrate the impact of interventions on hospitalisation and surgical intervention more conclusively. Data were available from a single trial to support the use of IFX in induction and maintenance treatment in a paediatric population.

The main safety issues highlighted in the RCT evidence appeared to be generally consistent with those previously discussed in the respective Summary of Product Characteristics (including serious infections, malignancies and administration site reactions). Deaths occurring during and after the study period were described in some trials evaluating GOL (PURSUIT-Maintenance) and IFX [Active Ulcerative Colitis Trials (ACTs)] of which infection or malignancy were most commonly implicated. This underlines the importance of monitoring and treating serious infections and malignancies in patients receiving immunosuppressive treatment.

Two biosimilars (Remsima®, Celltrion Healthcare, and Inflectra®, Hospira) to Remicade were considered as part of the evidence base for IFX within this assessment. The sponsor submission received from the manufacturers of Remsima and the European Public Assessment Reports for Remsima and Inflectra indicated that both biosimilars were approved by the EMA on the basis of reported similar pharmacokinetic and efficacy profiles to Remicade (demonstrated in ankylosing spondylitis and rheumatoid arthritis patients). No further trials of Remsima or Inflectra were identified over the course of this assessment.

Summary of cost-effectiveness evidence

The manufacturers of ADA, IFX and GOL submitted economic models to assess the cost-effectiveness of biological therapies versus conventional treatment. The MSD IFX submission model indicates that the estimated incremental cost-effectiveness ratio (ICER) for IFX versus standard non-biological treatment (colectomy) is £37,682 per quality-adjusted life-year (QALY) gained. The MSD GOL submission reports an estimated ICER of £27,322 per QALY gained. The AbbVie submission reports a base-case ICER of £34,590 per QALY gained. The Assessment Group identified several problems with these models. In particular, none of the models included all relevant treatment options specified in the final NICE scope and each model adopted a short time horizon (10 years). The Assessment Group does not consider that the cost-effectiveness evidence submitted by either manufacturer represents a sufficient basis for informing decision-making.

In order to address the problems identified within the manufacturers' submitted economic models, the Assessment Group developed a de novo cost-effectiveness model to assess IFX, ADA, GOL, conventional non-biological treatments and elective surgery within the moderate to severe UC population over a lifetime horizon. Underpinning the Assessment Group model is a series of NMAs that synthesise all relevant evidence relating to IFX, ADA, GOL and conventional non-biological therapies [5-aminosalicylates (5-ASAs), corticosteroids, immunosuppressants and surgery] in the induction and maintenance settings.

The base-case analysis of the Assessment Group model suggests that colectomy is expected to produce 14.71 QALYs at a cost of approximately £56,300 over the patient's remaining lifetime. All medical options are expected to produce substantially fewer QALYs at a greater cost than colectomy; hence, colectomy is expected to dominate IFX, ADA, GOL and conventional non-biological treatments. For some patients, elective colectomy may not be considered an acceptable or preferable option. In circumstances whereby only drug options are considered acceptable, the Assessment Group model suggests that IFX and GOL are expected to be ruled out because of dominance, while the incremental cost-effectiveness of ADA versus conventional non-biological treatment is expected to be approximately £50,300 per QALY gained.

A separate economic analysis of IFX, conventional non-biological treatments and colectomy was undertaken within a paediatric population (mean age of 15 years). When colectomy is an acceptable treatment option, the economic analysis suggests that this option is expected to dominate IFX and conventional non-biological treatments. When colectomy is not an acceptable option, the economic analysis suggests that the incremental cost-effectiveness of IFX versus conventional treatments is approximately £68,000 per QALY gained. However, this analysis is based on adult efficacy evidence and, thus, it should be interpreted with some degree of caution.

A number of sensitivity analyses were undertaken using the Assessment Group model. These suggested that the results of the economic analysis are largely insensitive to changes in the model assumptions, except for scenarios in which the post-surgery utility value is altered. When utility scores from Swinburn *et al.* are used in the model (Swinburn P, Elwick H, Bean K, Curry A, Patel S, Bodger K, *et al.* The Impact of Surgery on Health Related Quality of Life in Ulcerative Colitis. Gut Conference: Digestive Disorders Federation Meeting, Liverpool; 2012) [rather than those reported by Woehl A, Hawthorne A, McEwan P. The relation between disease activity, quality of life and health utility in patients with ulcerative colitis. *Gut* 2008;**57**(Suppl. 1):A153], colectomy produces the lowest QALY gain and conventional management and GOL are ruled out as a consequence of extended dominance. Within this scenario, the incremental cost-effectiveness of ADA versus elective colectomy is estimated to be £79,714 per QALY gained, while the incremental cost-effectiveness of IFX versus ADA is estimated to be £178,982 per QALY gained. Although these results are very different from the Assessment Group's preferred base-case analysis, the economic conclusions that should be drawn from this sensitivity analysis are not.

Discussion

Strengths, limitations of the analyses and uncertainties

The systematic review was based on rigorous methods, with comprehensive searches for evidence, a good level of consistency between reviewers in study selection and double-checking of data extraction. Clinical response and remission data were well reported across included trials and study authors were consistent in their use of the complete Mayo score, which aided the comparison of trials. NMAs were performed to permit a comparison of the efficacy of interventions in terms of clinical response and remission.

The Assessment Group's economic analysis has a number of strengths:

- The treatment pathway represented within the model was based on considerable expert opinion from several leading UC experts.
- The Assessment Group model is underpinned by a complex NMA across all drug options, thereby synthesising relevant efficacy outcomes data within a single network of evidence.
- The model generally adheres to the NICE reference case and fully addresses the decision problem set out in the final NICE scope.
- When appropriate and possible, systematic search methods have been used to identify, select and use evidence to inform the model's parameters (efficacy, HRQoL and colectomy rates).
- The Assessment Group has undertaken extensive sensitivity analyses to examine the impact of alternative assumptions and sources of evidence on the robustness of the results of the model.

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The Assessment Group model is also subject to a number of limitations:

- There is considerable uncertainty associated with Assessment Group's extrapolation of short-term trial data (maximum 54 weeks) to a lifetime horizon.
- The model does not consider an explicit sequential pathway of non-biological treatments. Instead, during any cycle, a proportion of patients are assumed to receive 5-ASAs, immunomodulators and steroids.
- Evidence relating to complications of colectomy was identified through consideration of approaches used within previous models rather than through a full systematic review; however, these assumptions were tested within the sensitivity analyses.

Key uncertainties in this assessment include:

- the optimal duration of intervention treatment in responding patients
- the maintenance of efficacy outcomes and safety of interventions beyond the limited study lengths available
- the maintenance of outcomes in responding patients following cessation of anti-TNF-α treatment.

Generalisability of the findings

The trials included in the clinical effectiveness systematic review typically excluded patients with ulcerative proctitis, patients with fulminant/acute severe disease, those with a history of or at imminent risk of bowel surgery, pregnant or lactating women, and patients with diseases of the central nervous system (e.g. demyelinating disease). Furthermore, patients with history of serious infection and/or immunodeficiency were also typically excluded, as were individuals with a history of malignancy or signs of dysplasia. Therefore, the effects of ADA, GOL or IFX in these UC populations have not specifically been investigated.

Study registration

This study is registered as PROSPERO CRD42013006883.

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