Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: A cost-effectiveness analysis

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KEYWORDS
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Abstract

Background: Combination therapy with infliximab (IFX) and azathioprine (AZA) is significantly more effective for treatment of active Crohn's disease (CD) than IFX monotherapy. However, AZA is associated with an increased risk of lymphoma in patients with inflammatory bowel disease.

Aim: To evaluate the cost-effectiveness of combination therapy with IFX plus AZA for drug-refractory CD.

Methods: A decision analysis model is constructed to compare, over a time horizon of 1 year, the cost-effectiveness of combination therapy with IFX plus AZA and that of IFX monotherapy for CD patients refractory to conventional non-anti-TNF-α therapy. The treatment efficacy, adverse effects, quality-of-life scores, and treatment costs are derived from published data. One-way and probabilistic sensitivity analyses are performed to estimate the uncertainty in the results.

Results: The incremental cost-effectiveness ratio (ICER) of combination therapy with IFX plus AZA is 24,917 GBP/QALY when compared with IFX monotherapy. The sensitivity analyses reveal that the utility score of nonresponding active disease has the strongest influence on the cost-effectiveness, with ICERs ranging from 17,147 to 45,564 GBP/QALY. Assuming that policy makers are willing to pay 30,000 GBP/QALY, the probability that combination therapy with IFX plus AZA is cost-effective is 0.750.

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1. Introduction

Crohn’s disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract of unknown etiology. CD is characterized by relapsing and remitting episodes that progress to stricture, fistula, and/or abscess, and disease onset is typically between 15 and 30 years of age. There is no established curative therapy for CD as yet, and therefore not only achieving but also maintaining symptom-free remission is an important goal in CD treatment.

Over the last decade, the advent of biologic therapy has significantly improved the clinical management of CD. Infliximab (IFX) has been shown to induce and maintain clinical remission in patients unresponsive to conventional drug therapies such as corticosteroids or immunomodulators. The ACCENT 1 trial revealed that regular maintenance therapy with IFX was significantly more effective than placebo in maintaining clinical remission in patients responsive to an initial infusion. Recently, combination therapy with IFX plus azathioprine (AZA) was shown to be more effective than IFX alone in the treatment of immunomodulator-naïve patients with moderate to severely active CD who were refractory to conventional drug therapy. A randomized clinical trial conducted by Colombel et al. involving 508 adult patients with moderate to severe CD who had not previously undergone immunosuppressive or biologic therapy demonstrated that the combination of IFX and AZA was superior to either IFX or AZA alone. At week 26 (the primary end point), 56.8% of patients receiving IFX plus AZA were in steroid-free remission, compared with 44.4% of patients receiving IFX monotherapy.

However, immunomodulators such as AZA and 6-mercaptopurine (6-MP) have been implicated in the development of lymphoma among patients with inflammatory bowel disease (IBD). A recent prospective nationwide study in France by the Cesame Study Group that involved almost 20,000 IBD patients found a significant increase in the risk of lymphoma development in patients receiving immunomodulators. Moreover, in a meta-analysis reported by Kandel et al., an approximate 4-fold increase in the risk of lymphoma was suggested in IBD patients treated with AZA or 6-MP.

Several studies have attempted to estimate the cost-effectiveness of IFX in CD; however, the cost-effectiveness of IFX in combination with AZA is not currently known. This study aimed, therefore, to assess the cost-effectiveness, from the perspective of the UK National Health Service (NHS), of combination therapy with IFX plus AZA for refractory CD among nonresponders to conventional drug therapy.

2. Methods

2.1. Model

A decision tree was constructed to assess the cost-effectiveness of combination therapy with IFX plus AZA in the treatment of CD compared with that of IFX monotherapy (Fig. 1).

The root of the decision tree consisted of a hypothetical cohort of 25-year-old men, weighing 60 kg, who were biologic-naïve CD patients refractory to conventional non-anti-TNF-α therapy and who had a score of 220 to 450 points on the Crohn’s Disease Activity Index (CDAI). An age of 25 years was chosen as the entry age since CD onset typically occurs in the late teens to age 30. The time horizon for the model was 1 year. Both therapies are given in only the year of study.

2.2. Assumptions

We assumed that patients in the IFX monotherapy branch of the tree received intravenous infusion of IFX 5 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter. In contrast, patients in the combination therapy with IFX plus AZA branch were assumed to have received oral AZA capsules at a dose of 2.5 mg/kg daily in addition to equivalent IFX therapy.

Clinical response was defined as a reduction from the baseline CDAI score of at least 70 points or 25% (whichever was the greater), and clinical remission was defined as a CDAI score of less than 150 points. Furthermore, we made the following assumptions: if any serious adverse effects related to IFX occurred, then this occurrence was at initial infusion (i.e., at week 0); patients who did not achieve clinical response at 12 weeks would not be offered retreatment with IFX; and nonresponders would have the same prognosis as those receiving nonbiologic therapy. Nonbiologic therapy included treatment with 5-aminosalicylic acid, antibiotics, immunomodulators, corticosteroids, or surgery. In the combination therapy, we assumed that AZA discontinuation could occur for patients who received IFX maintenance therapy.

2.3. Model parameters

The probability of clinical efficacy, the probability of therapy discontinuation owing to adverse events or lymphoma risk, the quality of life scores, and the treatment costs were derived from published data (Tables 1 and 2).

The response rate at 12 weeks for each therapy was based on a Hungarian nationwide multicenter report by Mihellet al., and the maintenance remission rate at 1 year for each therapy was calculated from the weighted means of randomized controlled trials. However, since response rates were not reported by Lemann et al. and Colombel et al., the response rate at 1 year for each therapy was assumed to be 1.35-fold of the remission rate reported by the ACCENT 1 trial.

The probability of developing each adverse effect of IFX or AZA was determined according to meta-analyses and the most recent single-center safety profile data. Likewise, the value used for the annual risk of lymphoma in the

Conclusions: Combination therapy with IFX plus AZA appears to be a cost-effective treatment for drug-refractory CD when compared with IFX monotherapy. Furthermore, the additional lymphoma risk of combination therapy has little significance on its cost-effectiveness.
general population was based on the most recently available surveillance epidemiology and end results data. In accordance with a recent meta-analysis conducted by Kandiel et al., we assumed no increase in the baseline risk of lymphoma for a patient with CD and a 4.18-fold increase in lymphoma risk when a patient was treated with AZA.

Treatment response estimates in the nonbiologic therapy branch of the decision tree were derived from a previous analysis using a cohort Markov model of European CD patients who did not receive biological therapy. Age-specific death rates for the general population were estimated from data for England and Wales between 2001 and 2007. The drug costs of IFX and AZA were also extracted from UK sources. Annual care costs were obtained from Sprakes et al., who assessed the care costs of CD patients for the 12 months before and after IFX therapy by looking at NHS reference costs. These annual costs included inpatient admissions, day case admissions for IFX infusions, outpatient visits, surgical procedures, endoscopic procedures, radiological investigations, blood tests, and the cost of all prescribed medications. However, no evidence was found for the cost associated with lymphoma complicated by CD. Therefore, an annual cost of 4,908.43 GBP was assumed in this work based on a study of illness costs in Germany. All costs were converted into GBP using 2008 exchange rates reported by the Organization for Economic Co-operation and Development. Owing to the perspective chosen for this study, productivity costs were omitted accordingly.

The primary measure of effectiveness in the present analysis was quality-adjusted life years (QALYs). Values for health-related quality of life, which vary from 0 (death) to 1 (perfect health), were taken from Gregor et al., who used a standard gamble approach to define utility scores with CDAI. However, since utility scores were not given by Gregor et al. for nonresponding active disease or lymphoma complicated by CD, we assigned a utility of 0.4 to the nonresponding active state based on a consultation with a panel of UK gastroenterologists reported by Lindsay et al., and assumed that the lymphoma state decreased utility scores by 0.15 following Lewis et al.

Cost-effectiveness analysis

Cost-effectiveness was evaluated by using the incremental cost-effectiveness ratio (ICER): the ratio between cost increments and QALY increments. Here, ICER represents the additional cost necessary to achieve one extra QALY when comparing combination therapy with IFA plus AZA and IFX monotherapy. In accordance with the National Institute for Health and Clinical Excellence guidelines, an ICER of less than 30,000 GBP/QALY was defined as being cost-effective.

First, we performed a base-case analysis that incorporated the baseline parameters shown in Tables 1 and 2. Second, to assess the variability of the results, multiple one-way sensitivity analyses were conducted by adjusting parameters such as treatment efficacy, adverse effect rate, lymphoma risk, annual care cost, and quality of life utility scores. Lastly, probabilistic sensitivity analyses (PSA) using Monte Carlo simulations involving 10,000 samples were performed to consider the uncertainty in the base-case results of the
estimated costs and QALYs. For each run of the simulation, input values for parameters were drawn at random from appropriate distributions. In PSA, the transition probabilities and quality of life utility scores were explored by assuming a beta distribution, whereas annual care costs were varied according to a normal distribution. Here, means and standard deviations derived from values given in the data sources were used to estimate the distribution parameters. Triangular distributions were introduced for the percentage of maintenance responders at 1 year and for the lymphoma risk by using the lower and upper ranges of these two variables. Additionally, a two-way sensitivity analysis was performed to examine the influence of parameters on the relative risk of lymphoma and on the maintenance remission rate of the combination therapy.

All analyses were performed using the TreeAge Pro 2009 software program (TreeAge Software, Williamstown, MA).

3. Results

3.1. Base-case analysis

In the base-case, combination therapy with IFX plus AZA yielded an additional 0.064 QALYs at an additional cost of 1593.35 GBP compared with IFX monotherapy. Thus, the resulting ICER of combination therapy with IFX plus AZA was estimated at 24,917 GBP/QALY. Since this value is lower than the 30,000 GBP/QALY limit, the combination therapy can be considered to be cost-effective in comparison with IFX monotherapy (Table 3).

3.2. Sensitivity analysis

The one-way sensitivity analysis demonstrated that ICERs remain in the 17,147–45,564 GBP/QALY range (Table 4), and
that quality of life utilities for nonresponding active disease had the highest impact on ICER (45,564 GBP/QALY over IFX monotherapy). The impact of changes in lymphoma risk was less significant, with ICERs for the lower and upper risk rates being 24,849 and 25,026 GBP/QALY, respectively. The cost-effectiveness plane and acceptability curve resulting from PSA for combination therapy with IFX plus AZA are shown in Figs. 2 and 3, respectively. If a cost of 30,000 GBP/QALY is deemed acceptable, then the probability of combination therapy with IFX plus AZA being less than or equal to this value is 0.750 (Fig. 3). By simultaneously considering the lymphoma risk and maintenance remission rate, Fig. 4 shows the boundary at which the combination therapy has an ICER below 30,000 GBP/QALY, and thus when it becomes the dominant strategy.

4. Discussion

The choice between anti-TNF-α monotherapy and combination anti-TNF-α therapy with an immunomodulator is a difficult one for both the provider and patient. Although randomized controlled trial data shows improved treatment from combination therapy, concern still exists that this benefit is not worth the increased risk of using two immunosuppressant medications. The current analysis shows that over a period of 1 year, combination therapy with IFX plus AZA was cost-effective for drug-refractory CD in comparison with IFX monotherapy.

We chose a 1-year time horizon for this analysis because reliable follow-up data are not available beyond this time frame. Long-term clinical efficacy of combination therapy after 1 year is not yet known, and the risks of lymphoma are possibly increased when using AZA and IFX in combination; however, we are unable to make such predictions from the existing data.

We did not explore whether these results can be generalized to other anti-TNF-α agents used for the treatment of CD. Generalization is dependent upon whether adalimumab (ADA) and certilizumab pegol also show increased effectiveness when used in combination with immunomodulators, and whether the profiles of these medications are different from IFX.

To determine how the key parameters in the mono and combined therapies affected cost-effectiveness, these parameters were varied by one-way sensitivity analyses. The analyses showed that the quality of life utility associated with nonresponding active disease was the most influential parameter on the cost-effectiveness of the therapies. At the highest utility score for nonresponding active disease, the analyses suggested that the cost of combination therapy was too high for CD treatment.

Model uncertainty was estimated by bootstrapping techniques and graphically represented on a cost-effectiveness plane. PSA demonstrated that the model results were consistent
across multiple stochastic runs. Furthermore, a cost-effectiveness acceptability curve was presented to indicate the probability of combination therapy with IFX plus AZA being cost-effective for a given ICER investment ceiling that policymakers are willing to invest. At an investment of 30,000 GBP/QALY, 75.0% of the simulations showed that combination therapy was cost-effective. The results also illustrated that any uncertainty around the input parameters does not significantly influence the above conclusions.

In our study, the base-case consisted of a hypothetical cohort of CD patients refractory to conventional non-anti-TNF-α therapy because biologic therapy with IFX must be applied to moderate or severe cases of CD or when a patient is refractory to other treatment. However, there are limited data available regarding the use of combination therapy. The SONIC trial did not address the question of whether combination therapy is superior to IFX monotherapy after failure of AZA. The benefits of combination therapy found in that trial may not extend to patients who are already known to be nonresponders to AZA.

Exceptions may also exist regarding the benefits of combination therapy, since certain patient groups may be at a higher risk for adverse events. For example, young patients appear to be at high risk for hepatosplenic T-cell lymphoma, and older patients taking concomitant corticosteroids are more likely to develop serious infections. Moreover, risk data for combination therapy with IFX plus AZA are limited, and whether the risk of lymphoma is increased in patients receiving this combination therapy is not yet known. Although the rate of lymphoma in the 1st year is likely to be low,

### Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base-case estimate</th>
<th>Sensitivity estimate</th>
<th>ICER a (GBP/QALY)</th>
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<tr>
<td>IFX monotherapy</td>
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<tr>
<td>Initial response rate</td>
<td>0.735</td>
<td>0.609</td>
<td>24,326</td>
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<tr>
<td>Maintenance remission rate</td>
<td>0.309</td>
<td>0.234</td>
<td>24,203</td>
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<tr>
<td>Combination therapy with IFX plus AZA</td>
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<td></td>
<td></td>
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<tr>
<td>Initial response rate</td>
<td>0.882</td>
<td>0.846</td>
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<tr>
<td>Maintenance remission rate</td>
<td>0.446</td>
<td>0.358</td>
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<td>Percentage of responders (%)</td>
<td>135</td>
<td>120</td>
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<td>IFX serious adverse effect rate</td>
<td>0.111</td>
<td>0.075</td>
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<td>Mortality associated with IFX</td>
<td>0.004</td>
<td>0.000</td>
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<tr>
<td>AZA adverse effect rate</td>
<td>0.089</td>
<td>0.060</td>
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<td>Annual incidence of lymphoma</td>
<td>27.1</td>
<td>10.0</td>
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<td>Lymphoma risk RR=4.18</td>
<td>2.07</td>
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<tr>
<td>CD-related cost post-IFX (GBP)</td>
<td>2214.37</td>
<td>1,304.27</td>
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<tr>
<td>Percentage of costs in remission</td>
<td>75</td>
<td>100</td>
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<tr>
<td>Lymphoma-related cost (GBP)</td>
<td>4908.43</td>
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<tr>
<td>Utility of remission</td>
<td>0.89</td>
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<td>Utility of post-surgery remission</td>
<td>0.86</td>
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<td>Utility of mild disease</td>
<td>0.77</td>
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<td>Utility of nonresponding active disease</td>
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<tr>
<td>Decrement utility of lymphoma</td>
<td>0.15</td>
<td>0.00</td>
<td>24,893</td>
</tr>
</tbody>
</table>

IFX: infliximab; AZA: azathioprine; RR: relative risk; CD: Crohn’s disease.
ICER: incremental cost-effectiveness ratio.

**a Base-case = 24,917 GBP/QALY.**

Fig. 2 Cost-effectiveness plane resulting from probabilistic sensitivity analysis.

Fig. 3 Cost-effectiveness acceptability curve of combination therapy with IFX plus AZA.
Cost-effectiveness of combination therapy

Fig. 4 Two-way sensitivity analysis evaluating thresholds for simultaneous change in lymphoma risk and maintenance remission rate.

patients can perceive this risk as being higher. Therefore, as shown in Fig. 4, we conducted a two-way sensitivity analysis that compared the risk of lymphoma and the maintenance remission rate. At a relative risk of lymphoma of greater than 129.0, the combination therapy dominated the IFX monotherapy when the maintenance remission rate at 1 year was 44.6%. The lymphoma risk reported in the literature is 1/30 of the relative risk threshold found here. Hence, larger clinical trials with longer follow-up times are needed to further assess the efficacy and safety profile of this combination therapy.

In our study, we did not include a number of IFX-related adverse effects that are only rarely reported, such as immune phenomena, hematologic abnormalities, liver failure, tuberculosis, demyelinating disease, and vasculitis. Because the rates of these events are especially low, we believed it unlikely that their inclusion would have an impact on model outcomes. Rates of AZA-related adverse effects such as specially pancreatitis and nausea in the combination therapy were of a similar level to other adverse effects. However, we did not include a number of AZA-related effects since they did not significantly influence the switch in treatment strategy.

Several studies have attempted to estimate the cost-effectiveness of IFX for patients with CD. Lindsay et al. performed a cost-effectiveness analysis by using a Markov model of a group of hypothetical adult CD patients weighing 60-kg and treated with IFX (5 mg/kg every 8 weeks), based on the regimen in the ACCENT 1 trial. They found that IFX maintenance therapy was cost-effective for both active luminal and fistulizing CD in comparison with standard care if a threshold of 30,000 GBP/QALY was used. Bodger et al. estimated a more favorable cost-effectiveness for both IFX and ADA. Specifically, the authors estimated that the cost per QALY of ADA and IFX were 21,300 GBP and 10,301 GBP, respectively, when compared with standard care. In contrast, a French lifetime cost-utility analysis of IFX using costs estimated by expert opinion reported that IFX therapy is cost-effective only in cases of episodic treatment. However, the ICER calculated in that study exceeded the threshold value predetermined according to their criteria for maintenance therapy. In addition, a model has been recently presented that uses IFX and ADA for CD. We therefore conclude from this systematic review of four previous economic evaluations that, in all cases, the studies found higher ICERs for IFX compared to standard care. As regards combination therapy, recently Siegel et al. suggested that combination therapy yielded higher expected QALYs than IFX monotherapy over a period of 1 year. However, they did not evaluate the cost-effectiveness of combination therapy in their study.

In Japan, IFX is one of the anti-TNF-α agents available for clinical application. IFX has been approved for remission induction therapy in patients with active CD since 2002 and for maintenance therapy after induction of remission since 2007, in accordance with guidelines issued by the Ministry of Health, Labour and Welfare. In 13 university hospitals in 2010, 21.3% of Japanese CD patients were treated with IFX.

In conclusion, for patients with drug-refractory CD, combination therapy with IFX plus AZA is cost-effective in comparison with IFX monotherapy. The results of our study can help guide the informed consent process, aid both decision makers and physicians in determining therapy alternatives for CD, and hopefully stimulate further research addressing cost-effectiveness and risk/benefit tradeoffs for medical therapy of IBD. Future economic evaluations of CD are needed to focus further on the lymphoma risk identified and on other adverse events associated with biologics and immunomodulators.

Conflict of interest

None.

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References


