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Treatment persistence during therapeutic sequences with adalimumab and infliximab in the treatment of Crohn’s disease

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Conflicts of interest
Taxonera C has received fees for lectures and/or consultancy from MSD, AbbVie, Ferring, Falk Pharma, Shire Pharmaceuticals and Gebro Pharma. Robledo P has received fees for lectures and/or consultancy from MSD, AbbVie, Faes and Falk Pharma. Rodriguez A has received fees for lectures and/or consultancy from MSD and AbbVie.

Author contributions: Taxonera C, Robledo P and Rodríguez A designed the study, developed the model and validated the model inputs and assumptions. Taxonera C drafted the manuscript. Robledo P and Rodríguez A contributed to a critical revision of the manuscript. All authors read and approved the final manuscript.

ABSTRACT
Background and aim: Tumor necrosis factor (TNF) inhibitors have demonstrated efficacy and safety in the treatment of Crohn’s disease (CD). However, the loss of response over time means that they are usually used sequentially. The aim of this study was to compare treatment persistence with different sequences of TNF inhibitors in patients with active luminal CD.

Methods: A Markov model (3-month cycles) was developed to simulate the therapeutic sequences of beginning biological treatment with infliximab or adalimumab, with a time horizon of three years. Each state of the model represented treatment (induction, standard dose or escalated dose) with each TNF inhibitor or the state without biological treatment. The transition probabilities between states were determined by the clinical response to TNF inhibitors obtained from the literature. The likelihood of discontinuation due to adverse effects was also considered.

Results: After three years, the percentage of CD patients receiving infliximab and adalimumab as a first TNF inhibitor that remained in treatment was 52.8% and 59.3% (p = 0.1) respectively. Median time to discontinuation of the standard dose was 26.26 months in patients who started with adalimumab and 24.39 months in patients who started with infliximab.

Conclusion: In the model, there were no significant differences in persistence after three years with the initial drug among patients with active luminal CD starting treatment with infliximab or adalimumab.

Key words: Crohn’s disease. Adalimumab. Infliximab. Persistence. Adverse events.

INTRODUCTION
There is currently no cure for Crohn’s disease (CD). However, the development of biological therapies such as infliximab (IFX) and adalimumab (ADA) have been an important advance in the treatment of the disease due to their proven efficacy in the induction and maintenance of the remission of clinical symptoms (1-3). Both IFX and ADA have demonstrated efficacy and safety in the treatment of CD in several clinical trials (4-10), although some aspects such as the loss of response over time and the ideal time for the initiation, maintenance and discontinuation of these anti-TNF agents
remain unclear (11). As there is a loss of response over time for both IFX and ADA, it is common for the two drugs to be used sequentially (3,11).

Therefore, the objective of this study was to compare simulations of treatment persistence for two treatment sequences with anti-TNF (beginning with IFX and switching to ADA after loss of response and vice versa) in patients with moderate to severe active luminal CD with an inadequate response to conventional therapy.

METHODS

A model of therapeutic sequences was developed as a Markov model with three monthly cycles in which each state represented treatment with each of the two anti-TNF agents approved in Spain (IFX and ADA) or the state without anti-TNF therapy ("no-biologic-treatment") (Fig. 1). The model simulated the therapeutic sequence of a hypothetical cohort of patients with moderate to severe active luminal CD who did not respond to conventional therapy and who initiated treatment with IFX or ADA with a three-year time horizon. The model structure, assumptions and transition probabilities were validated by a panel of experts in CD.

The cohorts enter the model receiving induction treatment with the first anti-TNF (IFX in one arm and ADA in the other), and the response to induction was determined after the first three-month cycle. If there was no clinical response to induction, the patient transitioned to the "no-anti-TNF-treatment state" (90%) or switched to the second anti-TNF (10%). Patients that responded to induction treatment continued to receive a standard dose as long as the response was maintained. If there was a secondary loss of response during the treatment cycles, the patient transitioned to the "escalated-dose state" and if there was no immediate response to escalation, the anti-TNF was switched. The patient remained in the "escalated-dose state" as long as the response was maintained (it was assumed that there was no return to "standard-dose state"). If there was a complete loss of response, the patient switched to the other anti-TNF. The flow of the cohort was identical to the second anti-TNF, except that there was no further switch of anti-TNF and, therefore, the patient passed to the "no-anti-TNF-treatment state". Patients could discontinue treatment in any state due to adverse events (AEs), resulting in a transition (first anti-TNF to second anti-TNF and second
anti-TNF to “no-anti-TNF-treatment state”).

**Transition probabilities**

The transition of the cohort through the states of the model was based on the clinical response to anti-TNF and discontinuations due to adverse events (AEs). Table 1 shows the estimated transition probabilities.

The response to induction with both anti-TNF agents (P1 and P5) determined at 12 weeks was obtained from observational studies (12,13). Clinical trials of ADA and IFX where the response to treatment was determined by Crohn’s Disease Activity at week 2 and 4 respectively showed lower response rates to induction therapy than those observed in observational studies where therapy often continues for at least 8-12 weeks (11). Therefore, effectiveness data from these observational studies was used rather than the efficacy data reported in controlled clinical trials.

Patients on maintenance treatment in the “standard-dose state” are likely to suffer a secondary loss of response requiring dose escalation (P2 and P6). To estimate the probability of loss of response per cycle, a random effects meta-analysis based on the studies identified in systematic reviews of IFX and ADA (14,15) was performed. The probability of regaining response to anti-TNF immediately after escalation (P3 and P7) was obtained from a systematic review of ADA (15) and from a pool of studies for IFX (16-18). Patients who regained a response remained in the “escalated-dose state” and had a further probability of tertiary loss of response (P4 and P8) equal to that estimated for the “standard-dose state”. It was assumed that the probability of losing response with the second anti-TNF was equal to the probability of losing response with the first anti-TNF (P5 to P8 are equal to P1 to P4). The probability per cycle of an AE leading to discontinuation of anti-TNF treatment was obtained from clinical trials (5,6,10).

**RESULTS**

After three years, 52.8% (95% CI 47.5-58.2) of patients who started treatment with IFX as the first anti-TNF continued on the initial treatment (39.0% and 13.7% with the standard and escalated doses respectively) and 59.3% (95% CI 53.7-65.2; p = 0.1) of
patients who started treatment with ADA continued on the initial treatment (41.6% and 17.8% with the standard and escalated doses, respectively). Intermediate results one year after initiation of biological therapy showed that 75.8% of patients who started treatment with IFX remained on IFX (65.0% and 10.7% with standard and escalated doses, respectively), and 78.6% of patients who started treatment with ADA remained on ADA (65.5% and 13.2% with standard and escalated doses, respectively). The median time to discontinuation of the standard dose, whether due to complete loss of response or due to AEs, was 26.26 months in patients who started with ADA compared with 24.39 months in patients who started with IFX.

DISCUSSION
The objective of this analysis was to simulate clinical practice in the treatment of moderate to severe active luminal CD where both IFX and ADA are used sequentially, and to estimate treatment persistence with both sequences. The results of this study, which is the first to analyze treatment persistence throughout therapeutic sequences for CD, showed that there was a trend towards a higher proportion of patients remaining on ADA when ADA was the initial drug compared with the proportion remaining on IFX when this was the initial drug. The probability of loss of response to ADA estimated in the meta-analysis of randomized effects was offset by the increased probability of discontinuation due to AEs observed with IFX.

In general, rates of serious adverse events such as serious infections, malignancy or others were similar for ADA and IFX (5,6,10). However, the rates of serious infusion reactions and serum sickness-like reactions (myalgia and/or arthralgia with fever and/or rash) leading to discontinuation that was reported in the IFX 5 mg/kg scheduled arm of the ACCENT 1 trial (6) were significantly greater than the rates of injection site reactions leading to discontinuation reported in the ADA 40 mg every other week arm of the CHARM trial (10). Differences between drugs may be explained by the different immunogenicity of IFX and ADA. The presence of antibodies to infliximab is associated with a significantly higher risk of acute infusion reactions but not delayed hypersensitivity reactions in patients with CD (19). A meta-analysis reported that all TNF inhibitors were associated with anti-drug antibodies (ADABs). Of the patients
using infliximab, 25.3% (95% CI 19.5-32.3) developed ADABs compared with 14.1% (95% CI 8.6-22.3) using adalimumab (20). ADABs are associated with an increased incidence of infusion reactions and injection site reactions. An issue that deserves consideration in the management of patients with inflammatory bowel disease is economic burden, mostly regarding biologic therapy. Biologics are highly effective in the treatment of CD but they are expensive and were responsible for most of the direct costs related to patients with CD (21). Recently, a study in our setting reported that pharmacy costs associated with biologics represent a major concern in the management of inflammatory bowel disease (22). This study did not evaluate the theoretical costs associated with persistence with either therapeutic sequence for CD. These data may be relevant for planning the best cost-effective strategy in CD patients with an inadequate response to conventional therapy. The study has some limitations. Firstly, as in all theoretical models, long-term extrapolations are made using data from shorter-term studies. Secondly, due to the lack of studies in which IFX is the second anti-TNF after ADA, there is no clear evidence whether the probability of loss of response of IFX as second anti-TNF is greater than that seen in naïve patients. In ulcerative colitis patients, “real life” outcomes with ADA after failing IFX were smaller than the efficacy observed in naïve patients (23,24). Conversely, in a large observational cohort of CD patients, prior IFX therapy did not influence clinical response to adalimumab treatment (25). Thirdly, the possibility of IFX or ADA de-escalation was not considered, since this therapeutic strategy has not been well evaluated (26). We decided not to include therapeutic drug monitoring in the model as proactive trough-level based dose escalation was not superior to dose escalation based on symptoms alone in the prospective randomized Tailorix trial in patients with active CD (27). With respect to the inclusion of AEs in the model, a meta-analysis found significant differences between IFX and ADA only in those AEs leading to a discontinuation (28). Therefore, as the objective was to compare therapeutic sequences where discontinuation is a key factor, only these AEs were considered in the model. In conclusion, the results of this analysis of therapeutic sequences showed that in patients with moderate to severe active luminal CD, there were no significant
differences in the proportion of patients remaining on ADA when ADA was the initial drug compared with the proportion remaining on IFX when this was the initial drug.

REFERENCES


Table 1. Transition probabilities for infliximab and adalimumab

<table>
<thead>
<tr>
<th>Cod.</th>
<th>Description of probability</th>
<th>Infliximab</th>
<th>Adalimumab</th>
</tr>
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<tr>
<td>$P_1$</td>
<td>First anti-TNF Response to induction</td>
<td>0.891</td>
<td>0.903</td>
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<tr>
<td>$P_2$</td>
<td>Dose escalation due to loss of response*</td>
<td>0.086/0.030</td>
<td>0.106/0.037</td>
</tr>
<tr>
<td>$P_3$</td>
<td>Response to escalation</td>
<td>0.722</td>
<td>0.714</td>
</tr>
<tr>
<td>$P_4$</td>
<td>Loss of response to escalated doses*</td>
<td>0.086/0.030</td>
<td>0.106/0.037</td>
</tr>
<tr>
<td>$P_5$</td>
<td>Second anti-TNF Response to induction</td>
<td>=$P_1$</td>
<td>=$P_1$</td>
</tr>
<tr>
<td>$P_6$</td>
<td>Dose escalation due to loss of response*</td>
<td>=$P_2$</td>
<td>=$P_2$</td>
</tr>
<tr>
<td>$P_7$</td>
<td>Response to escalation</td>
<td>=$P_3$</td>
<td>=$P_3$</td>
</tr>
<tr>
<td>$P_8$</td>
<td>Loss of response to escalated doses*</td>
<td>=$P_4$</td>
<td>=$P_4$</td>
</tr>
<tr>
<td>$P_9$</td>
<td>Discontinuation due to AEs</td>
<td>0.031</td>
<td>0.018</td>
</tr>
</tbody>
</table>
Fig. 1. Diagram of the Markov model of therapeutic sequences. P1-P8: Transition probabilities for first and second anti-TNF.