Defining management strategies for acute severe ulcerative colitis using predictive models: a simulation-modeling study

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Background/Aims: Robust management algorithms are required to reduce the residual risk of colectomy in acute severe ulcerative colitis (ASUC) refractory to standard infliximab salvage therapy. The aim of this study was to evaluate the performance and benefits of alternative ASUC management strategies using simulated prediction models of varying accuracy. Methods: This was a simulation-based modeling study using a hypothetical cohort of 5,000 steroid-refractory ASUC patients receiving standard infliximab induction. Simulated predictive models were used to risk-stratify patients and escalate treatment in patients at high risk of failing standard infliximab induction. The main outcome of interest was colectomy by 3 months. Results: The 3-month colectomy rate in the base scenario where all 5,000 patients received standard infliximab induction was 23%. The best-performing management strategy assigned high-risk patients to sequential Janus kinase inhibitor inhibition and medium-risk patients to accelerated infliximab induction. Using a 90% area under the curve (AUC) prediction model and optimistic treatment efficacy assumptions, this strategy reduced the 3-month colectomy rate to 8% (65% residual risk reduction). Using an 80% AUC prediction model with only modest treatment efficacy assumptions, the 3-month colectomy rate was reduced to 15% (35% residual risk reduction). Overall management strategy efficacy was highly dependent on predictive model accuracy and underlying treatment efficacy assumptions. Conclusions: This is the first study to simulate predictive model-based management strategies in steroid-refractory ASUC and evaluate their effect on short-term colectomy rates. Future studies on predictive model development should incorporate simulation studies to better understand their expected benefit. (Intest Res, Published online)

Key Words: Infliximab; Tumor necrosis factor-alpha; Colectomy; Inflammatory bowel diseases

INTRODUCTION

Ulcerative colitis (UC), a type of inflammatory bowel disease, is an autoimmune condition affecting the colon and affects millions of individuals worldwide.¹ Patients with UC have a 20% lifetime risk of presenting with acute severe ulcerative colitis (ASUC), a potentially life-threatening complication that may require emergency colectomy.² Although the initial management of ASUC—involving intravenous corticosteroid use and the criteria for salvage infliximab—is well established, the optimal subsequent management in the event of infliximab failure is far less clear.³ This is reflected by a 20% residual 3-month colectomy risk and 30% 12-month risk in patients who receive standard infliximab induction for ASUC.⁴ Observational studies have suggested a possible benefit in accelerated infliximab induction in steroid-refractory ASUC,⁵ while controlled studies are still ongoing (NCT02770040, NCT03937609). Although
sequential ciclosporin salvage was used occasionally in the event of infliximab failure historically, recent evidence has suggested a possible role for sequential Janus kinase inhibitor (JAK) inhibitors such as tofacitinib and upadacitinib. However, despite the recent rapid expansion of inflammatory bowel disease therapeutics, it is important to acknowledge the difficulties and impracticalities of prospective controlled trials evaluating JAK inhibitors or other agents in infliximab-refractory ASUC, yet clinicians and patients alike face this important clinical problem on a regular basis. Thus, clinicians must rely on the utilization and synthesis of the limited available evidence to formulate a practical ASUC management strategy in the absence of prospective trials for the foreseeable future.

Precision medicine aims to tailor management strategies to the individual using clinical outcome prediction and robust management strategies. An ideal strategy is to use a predictive model that risk stratifies patients based on their risk of infliximab failure to provide a criterion for alternative management options. Predictive models have historically been derived using basic statistical methods; however, advances in machine learning and artificial intelligence alongside the expansion of big data through genomics and microbiomics are likely to facilitate far more reliable and accurate models. An ideal model would be capable of predicting response to infliximab, such that patients who demonstrate a partial or incomplete response due to pharmacokinetic failure (inadequate dosing) would benefit from additional infliximab dosing, while patients who demonstrate poor response due to alternative immunologically active pathways might benefit from out-of-class therapies such as JAK inhibition. Put simply, a good predictive model should be able to identify the patients who would most likely benefit from one particular treatment over another.

However, whether the use of a predictive model to guide decision-making actually reduces the risk of colectomy and improves outcomes remains unclear. Due to the same aforementioned impracticalities, prospective trials evaluating the use of predictive models in ASUC management are unlikely to occur in the near future. In light of this, simulation and modeling can be used to synthesize and summarize the limited available evidence to help guide real-world decision making.

The aim of this study was to evaluate the performance and benefits of emerging ASUC management strategies based on currently available evidence using a hypothetical cohort of steroid-refractory ASUC patients receiving infliximab salvage therapy.

**METHODS**

1. Study Design

This was a simulation-based modeling study using a hypothetical cohort of 5,000 patients with steroid-refractory ASUC receiving salvage infliximab. The 2 key components of management that were simulated included: (1) derivation of a predictive model to risk-stratify patients based on their probability of failing infliximab and (2) response to different clinical management strategies based on 3-month colectomy risk. The simulated predictive model was used to inform subsequent management decisions. Management strategies included accelerated infliximab induction and/or sequential JAK inhibition with tofacitinib and/or upadacitinib. Assumptions of efficacy of management strategies were based on published literature (Tables 1, 2). Management strategies were assessed by the estimated reduction in the residual 3-month colectomy risk. The 3-month time point was chosen due to its depen-

### Table 1. Studies Comparing SD Infliximab Induction and AD Infliximab Induction, Including Propensity Score Matched Patients

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>SD infliximab</th>
<th>AD infliximab</th>
<th>Propensity score matching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Colectomy-free rate</td>
<td>No.</td>
</tr>
<tr>
<td>Syal et al. (2021)</td>
<td>29</td>
<td>86% (3 mo); 79% (12 mo)</td>
<td>34</td>
</tr>
<tr>
<td>Gibson et al. (2019)</td>
<td>87</td>
<td>62% (6 mo)</td>
<td>58</td>
</tr>
<tr>
<td>Sebastian et al. (2019)</td>
<td>102</td>
<td>80% (3 mo); 72% (12 mo)</td>
<td>29</td>
</tr>
<tr>
<td>Chao et al. (2019)</td>
<td>37</td>
<td>95% (3 mo)</td>
<td>35</td>
</tr>
<tr>
<td>Nalagatla et al. (2019)</td>
<td>132</td>
<td>86% (3 mo); 73% (12 mo)</td>
<td>81</td>
</tr>
<tr>
<td>Shah et al. (2018)</td>
<td>120</td>
<td>72% (12 mo)</td>
<td>26</td>
</tr>
<tr>
<td>Gibson et al. (2015)</td>
<td>35</td>
<td>63% (1 mo)</td>
<td>15</td>
</tr>
</tbody>
</table>

SD, standard dose; AD, accelerated dose.
dence on the efficacy of induction strategies, as opposed to later points such as 12 months which can be affected by subsequent maintenance regimens. Ethics approval was waived as no new data were generated from this study.

2. Study Cohort

We generated a hypothetical cohort of 5,000 patients with steroid-refractory ASUC who receive standard induction of infliximab at 5 mg/kg at weeks 0, 2, and 6. All patients were then followed-up for up to 3 months. Each patient’s “true propensity” to fail infliximab was generated by applying a logistic transformation of a uniform random variable. The true propensity represents the unobserved or hidden probability that a patient will fail infliximab induction and require colectomy, with range between 0 and 1. The true propensity was calibrated to achieve a 3-month colectomy rate of 23% and a 12-month colectomy rate of 30% based on prior studies.

We used a Weibull distribution to generate the failure times, with a shape parameter of 0.7 (chosen heuristically) and a scale parameter proportional to the inverse of the true propensity.

3. Predictive Model

A predictive model for infliximab failure might include patient and disease factors such as C-reactive protein (CRP), albumin, lymphocyte count and endoscopy. Predictive models can be useful if they can identify patients at high risk of failing standard dose infliximab, who might benefit from alternative salvage therapies. We simulated the derivation of a predictive model shortly after the first 5 mg/kg infliximab dose (between day 1 and day 7 post infliximab), which then guided subsequent management.

Traditionally, predictive models or scores can be created using standard statistical models such as Cox proportional hazards regression (for survival outcomes) or logistic regression (for binary outcomes). In both cases, candidate predictors (such as age, sex, disease severity markers, etc.) are entered into the statistical model, which generates beta coefficients (or weights) based on the importance of each predictor in explaining the outcome. The weighted linear combination of the predictors is then used as a predictive score. When applied to an individual patient, the predictive score generates a number. Usually, the higher the number is relative to other patients, the higher the risk of the predicted outcome. This predictive number can then be used to risk stratify patients, by assigning cutoff values and grouping patients based on the number. In this way, the predictive number should be highly
correlated with the patient’s true risk of the outcome.

In order to simulate the derivation of a predictive model, first recall that each simulated patient was assigned a “true propensity” or true risk of failing infliximab and requiring colectomy. If the true propensity (which is simply a number) is used to create the predictive model, the model would nearly perfectly predict the outcome (with area under the curve [AUC] close to 100%) as the model and the true risk are perfectly correlated. In order to generate realistic predictive models, we needed to reduce the correlation between a theoretical model and the true propensity. Thus, the predictive model was simulated by introducing random noise into each patient’s true propensity to fail infliximab. Specifically, we added a normally distributed random number with mean 0 to the logit of each patient's true propensity, where the standard deviation of the random number was calibrated to produce predictive scores of varying accuracies. The resulting number was treated as the predictive score. As more noise is introduced, the correlation between the predictive model and the true propensity decreases, thus decreasing the predictive utility and the AUC. We calibrated the predictive models to have AUCs of 70% (low), 80% (medium), and 90% (high). Current predictive models have modest AUCs between 70% and 80%, while a hypothetically strong model with 90% AUC might be achievable with the discovery of additional, novel biomarkers.

4. Management Strategies
The simulated management strategies were based on the use of the generated predictive model to risk stratify patients into 2 or 3 groups, where subsequent treatment depended on the risk category (Fig. 1). If the predictive model predicted a patient to have a high probability of failing standard infliximab induction, the patient’s therapy was escalated or changed according to the intervention strategy (Fig. 1). We tested a combination of accelerated infliximab induction and sequential JAK inhibition as subsequent therapies for the management strategy.

1) Strategy 1: Accelerated Infliximab Induction
Non-controlled studies have suggested a possible benefit in accelerated induction of infliximab in steroid-refractory ASUC (Table 1), while controlled studies are ongoing (NCT02770040, NCT03937609). The clinical rationale for a higher infliximab dose is based on high infliximab losses that occur in patients with a high inflammatory burden, such that a proportion of infliximab-failures are due to underdosing. If the latter theory holds, then a proportion of infliximab non-responders could achieve response and avoid colectomy if they receive accelerated (shortened dose interval or increased dose) induction. In practice, clinicians tend to select high-risk patients (reflected by high CRP and/or low albumin) for accelerated induction. Hence observational studies cannot directly compare colectomy rates in patients receiving standard vs. accelerated induction, so the proposed benefits of accelerated dosing remain to be proven.

Strategy 1 relied on dividing the cohort into halves according to the predictive model after the first 5 mg/kg infliximab dose: the top 50% constituted the high-risk group, while the bottom 50% constituted the low-risk group. High-risk patients proceeded to receive accelerated infliximab induction, while low-risk patients continued standard induction. We assumed that the probability of responding to accelerated induction depended on the true propensity. That is, we assumed a high correlation between response to standard and accelerated infliximab. We based our efficacy assumptions on previously reported colectomy rates (Table 1). Sebastian et al. suggested that accelerated induction led to a 45% residual risk reduction of colectomy by 12 months in a propensity score matched cohort (not to be confused with the “true propensity” for infliximab failure), while Shah et al. suggested a 34% residual risk reduction after propensity score matching. In our simulations, we tested different efficacy assumptions corresponding to residual colectomy risk reductions of 57%, 35%, or 13%. That is, based on our cohort’s 77% 3-month colectomy-free rate of standard induction, we tested an optimistic 90% 3-month colectomy-free rate for accelerated induction (57% residual risk reduction), an intermediate 85% colectomy-free rate (35% residual risk reduction) and a pessimistic 75% colectomy-free rate (13% residual risk reduction) at 3 months.

We used independent Bernoulli trials to determine whether each patient required colectomy by 3 months, with probability of colectomy being proportional to the patient’s true propensity (after calibration to achieve the target efficacy assumption).

2) Strategy 2: Sequential JAK Inhibition
Recent non-controlled studies have suggested efficacy in sequential use of JAK inhibitors such as tofacitinib and upadacitinib after infliximab failure in ASUC (Table 2). Due to the differing mechanisms of actions between JAK inhibitors and anti-tumor necrosis factor (TNF) therapies such as infliximab, some patients who do not respond to infliximab salvage are theorized to have over-active alternate immunological path-
ways that continue to drive inflammation despite suppression of TNF. In support of this possibility, JAK inhibitors have shown good efficacy in both UC and Crohn’s disease patients even with prior biologic experience.

Strategy 2 again relied on halving the cohort based on the predictive model, where high-risk (top 50% risk) patients were switched to a JAK inhibitor after the first 5 mg/kg infliximab dose and low-risk patients (bottom 50% risk) continued on standard infliximab induction. Contrary to the correlation between response to accelerated and standard dose infliximab, we assumed the response to JAK inhibition to be independent of response to infliximab in our models. Therefore, response to JAK inhibition only depended on population-level estimates of response rates (and not related to the underlying true propensity to fail infliximab). A review of the evidence showed a wide range of 3-month colectomy rates often in small cohorts or case series (Table 2). Our review identified 168 patients with an overall crude 3-month colectomy rate of approximately 20%, representing a colectomy-free rate of 80%. Due to possible publication bias, we treated the 80% efficacy rate as an optimistic assumption. Additionally, we tested a more modest colectomy-free rate of 70% and a pessimistic rate of 60%.

We used independent Bernoulli trials to determine whether each patient required colectomy by 3 months, with probability of colectomy being equal to 20%, 30%, or 40% depending on the assumed efficacy of JAK inhibition.

3) Strategy 3: Accelerated Infliximab and JAK Inhibition
The final strategy utilized both accelerated infliximab induc-
tion as well as JAK inhibition. We hypothesized that patients who are underdosed on infliximab, but otherwise do not have a high true propensity of failing infliximab, would benefit from accelerated induction, while patients who have a high true propensity of failing infliximab would benefit from a switch to JAK inhibition. This algorithm relied on dividing the cohort into 3 groups: (1) a low-risk group who continued standard infliximab induction; (2) a medium-risk group who escalated to receive accelerated infliximab induction; and (3) a high-risk group who were switched to JAK inhibition.

We tested 2 risk-stratification methods. The first was to divide the cohort into risk quartiles, then use the top quartile (25%) to define the high-risk group who received sequential JAK inhibition and the second quartile (25%) to define the medium-risk group who received accelerated infliximab induction, leaving the bottom 2 quartiles (50%) to define the low-risk group who received standard infliximab induction. This resulted in half the cohort requiring treatment change.

The second method was to divide the cohort into equal risk tertiles (33% in each risk group), where the top 33% were considered to be high-risk and received sequential JAK inhibition, while the middle 33% were considered to be medium-risk and received accelerated infliximab induction, resulting in two-thirds of the cohort requiring treatment change. We used independent Bernoulli trials using the same rules as strategies 1 and 2 to determine whether each patient required colectomy by 3 months.

5. Statistical Analysis

The Kaplan-Meier method was used to estimate survival curves. Receiver operator characteristic (ROC) analysis was used to assess discriminative performance of the theoretical predictive models, summarized by the AUC. All predictive models were simulated with differing AUCs of 90%, 80%, and 70%. We ran 1,000 simulations for each combination of predictive model accuracy, management strategy and efficacy assumption, where each simulation involved predictive model derivation, risk group allocation and colectomy status assignment based on the management strategy. The simulations were used to generate Monte Carlo confidence intervals (the 2.5th to 97.5th percentiles of the simulated colectomy rates) for the overall 3-month colectomy rate in each management strategy. All model building, simulation and analysis was performed using the R statistical programming language version 4.3.0 (RStudio 2023.06.1, Boston, MA, USA).

RESULTS

1. Study Cohort

Of 5,000 hypothetical steroid-refractory ASUC patients receiving standard dose salvage infliximab (5 mg/kg at weeks 0, 2, and 6), 759 patients required colectomy by 1 month, 1,156 patients required colectomy by 3 months and 1,514 patients required colectomy by 12 months, corresponding to 1-, 3- and 12-month colectomy rates of 16%, 23% and 30% (Fig. 2).

Fig. 2. Results of simulation modeling. (A) Kaplan-Meier survival curve for hypothetical study cohort receiving standard infliximab induction (n = 5,000). (B) Receiver operator characteristic curves of first 50 simulations of predictive score generation with target area under the curve (AUC) thresholds of 90%, 80% and 70%, highlighting example curves (randomly selected).
2. Predictive Models

Fig. 2 demonstrates the ROC curves of the simulated models predicting infliximab failure, calibrated to have average AUCs of 90%, 80%, and 70%. Table 3 demonstrates the 3-month colectomy rates after using the simulated predictive models to divide the baseline cohort into different risk groups. After risk stratification into 2 groups using a highly accurate prediction model with 90% AUC, low-risk patients had 3-month colectomy rate of 2% compared to 44% for the high-risk group. Using a modest prediction model with 80% AUC instead, the 3-month colectomy rates for low and high-risk patients were 7% and 40%, while the respective rates for a less accurate 70% AUC model were 12% and 34% (Fig. 3).

Using the same models to stratify patients into 3 groups instead of 2, where the upper 50% risk patients are further divided into high risk (top quartile) and medium risk (second quartile), the 3-month colectomy rates for medium and high-risk groups using the 90% AUC model were 19% and 69%. The colectomy rates for the 80% AUC model were 26% and 53% for the medium and high-risk groups, while the respective rates for the 70% AUC model were 26% and 42%.

Instead using the models to divide patients into equally sized risk tertiles, the 3-month colectomy rates for low, medium and high-risk patients using the 90% AUC model were 1%, 8% and 60% respectively. Using an 80% AUC model, the respective colectomy rates were 4%, 17%, and 48%, while the respective rates for a 70% AUC model were 9%, 21%, and 39%.

3. Management Strategies

1) Strategy 1: Accelerated Infliximab Induction

Table 4 demonstrates colectomy rates by treatment algorithm after 1,000 simulations. Assuming a 90% AUC for the prediction model and optimistic efficacy of accelerated induction (overall response rate of 90%), the 3-month colectomy rate was reduced to 11%, representing an overall residual risk reduction of 52%. Correspondingly, only 20% of the high-risk group required colectomy (55% residual risk reduction). Assuming a more modest 80% AUC for the prediction model and moderate efficacy of accelerated induction (overall response rate of 85%), the overall 3-month colectomy rate was reduced to 17% (29% residual risk reduction), while the colectomy rate in the high-risk group was 26% (35% residual risk reduction). Assuming a less accurate 70% AUC prediction model and a lower efficacy of accelerated induction (overall response rate of 80%), the overall 3-month colectomy rate was 21% (9% residual risk reduction), with a colectomy rate of 30% in the high-risk group (12% residual risk reduction).

2) Strategy 2: Sequential JAK Inhibition

Assuming a 90% AUC prediction model and an optimistic efficacy of 80% for sequential JAK inhibitors, the overall 3-month colectomy rate was reduced to 11% (52% residual risk reduction), with a colectomy rate of 20% in the high-risk group (55% residual risk reduction). With a modest 80% AUC prediction model and 70% treatment efficacy, the overall 3-month colectomy rate was 18% (22% residual risk reduction) and the colec-
Fig. 3. Kaplan–Meier survival curves of study cohort, risk-stratified by prediction scores. (A) Score with 90% area under the curve (AUC), upper 25% as high risk, middle 25% as medium risk. (B) Score with 90% AUC, upper 33% as high risk, middle 33% as medium risk. (C) Score with 80% AUC, upper 25% as high risk, middle 25% as medium risk. (D) Score with 80% AUC, upper 33% as high risk, middle 33% as medium risk. (E) Score with 70% AUC, upper 25% as high risk, middle 25% as medium risk. (F) Score with 70% AUC, upper 33% as high risk, middle 33% as medium risk.
Table 4. Results of Simulation Study Using Hypothetical Cohort of 5,000 Steroid-Refractory ASUC Patients Requiring Standard Dose IFX Salvage, with 23% Requiring Colectomy by 3 Months

<table>
<thead>
<tr>
<th>Treatment strategy &amp; risk stratification</th>
<th>Risk score</th>
<th>Treatment efficacy</th>
<th>3-mo colectomy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>Low-risk group</td>
<td>Medium-risk group</td>
</tr>
<tr>
<td></td>
<td>n (95% CI)</td>
<td>%</td>
<td>n (95% CI)</td>
</tr>
<tr>
<td>Accelerated IFX in high-risk patients, standard IFX in low-risk patients; Low risk 50%, high risk 50%</td>
<td>90%</td>
<td>IFX 90%</td>
<td>46 (39–53)</td>
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<tr>
<td></td>
<td>85%</td>
<td>IFX 85%</td>
<td>46 (39–53)</td>
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<tr>
<td></td>
<td>80%</td>
<td>IFX 80%</td>
<td>46 (39–53)</td>
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<tr>
<td></td>
<td>80%</td>
<td>IFX 90%</td>
<td>166 (149–182)</td>
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<tr>
<td></td>
<td>85%</td>
<td>IFX 85%</td>
<td>164 (148–182)</td>
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<tr>
<td></td>
<td>80%</td>
<td>IFX 80%</td>
<td>165 (149–182)</td>
</tr>
<tr>
<td></td>
<td>70%</td>
<td>IFX 90%</td>
<td>304 (282–325)</td>
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<tr>
<td></td>
<td>85%</td>
<td>IFX 85%</td>
<td>304 (283–325)</td>
</tr>
<tr>
<td></td>
<td>80%</td>
<td>IFX 80%</td>
<td>304 (282–326)</td>
</tr>
<tr>
<td>Switch to JAK inhibitor in high-risk patients, standard IFX in low-risk patients; Low risk 50%, high risk 50%</td>
<td>90%</td>
<td>JAK 80%</td>
<td>46 (39–53)</td>
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<tr>
<td></td>
<td>70%</td>
<td>JAK 70%</td>
<td>46 (39–53)</td>
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<td></td>
<td>60%</td>
<td>JAK 60%</td>
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<td>80%</td>
<td>JAK 80%</td>
<td>165 (150–182)</td>
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<td>70%</td>
<td>JAK 70%</td>
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<td>60%</td>
<td>JAK 60%</td>
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<td></td>
<td>70%</td>
<td>JAK 80%</td>
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<td></td>
<td>80%</td>
<td>JAK 80%</td>
<td>303 (281–325)</td>
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<tr>
<td></td>
<td>60%</td>
<td>JAK 60%</td>
<td>304 (281–326)</td>
</tr>
<tr>
<td>JAK inhibitor in upper high-risk, accelerated IFX in medium-risk, standard IFX in low-risk patients; Low risk 50%, medium risk 25%, high risk 25%</td>
<td>90%</td>
<td>IFX 90%/JAK 80%</td>
<td>46 (39–53)</td>
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<tr>
<td></td>
<td>85%</td>
<td>IFX 85%/JAK 70%</td>
<td>46 (39–53)</td>
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<td>80%</td>
<td>IFX 80%/JAK 60%</td>
<td>45 (39–53)</td>
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<td>IFX 90%/JAK 80%</td>
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<td>85%</td>
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<td>165 (150–183)</td>
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<tr>
<td></td>
<td>80%</td>
<td>IFX 80%/JAK 60%</td>
<td>304 (283–326)</td>
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(Continued to the next page)
tomy rate in the high-risk group was 30% (25% residual risk reduction). With a 70% AUC prediction model and a pessimistic 60% JAK inhibitor treatment efficacy, the overall 3-month colectomy rate increased to 26%, which was 13% higher than the baseline 3-month colectomy rate, while the colectomy rate in the high-risk group was 40% (18% higher than the base case).

3) Strategy 3: Accelerated Infliximab and JAK Inhibition
A similar overall residual risk reduction was achieved using both risk stratification methods (equal tertiles and upper 25% as high risk). Assuming a 90% AUC prediction model and the most optimistic treatment efficacy (90% response rate for accelerated infliximab, 80% response rate for sequential JAK inhibition), the overall 3-month colectomy rate was reduced to 8% (65% residual risk reduction); the high-risk colectomy rate was reduced to 20% (67% to 71% residual risk reduction). Assuming an 80% AUC prediction model with modest treatment efficacy, the overall 3-month colectomy rate was reduced to 15% (35% residual risk reduction). By instead assuming a 70% AUC prediction model with pessimistic treatment efficacy, the overall 3-month colectomy rate was reduced to 22% (4% residual risk reduction).

**DISCUSSION**

Predictive tools and novel management algorithms are required to reduce the residual risk of morbidity in ASUC. In addition to prediction model development and further controlled studies in ASUC, a deeper understanding of the expected benefit of different management options is crucial for good decision-making. In this study, we have demonstrated the expected reduction in the residual risk of colectomy using different combinations of predictive models and management algorithms. Furthermore, we also demonstrated that in pessimistic circumstances, a poor predictive model with low sequential salvage efficacy can actually lead to an increase in the 3-month colectomy rate. Thus, the expected benefit of various management strategies can be weighed against healthcare costs and resource allocation in cost-benefit analyses to identify the strategy with the greatest overall utility. The best-performing management strategy divided steroid-refractory ASUC patients into 3 groups, where patients deemed to be at medium risk of infliximab failure were escalated to accelerated induction, while patients deemed to be at high risk of failure were switched to a JAK inhibitor instead. However, overall performance was highly dependent on the accuracy of the

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**Table 4. Continued**

The numbers of observed colectomies per group are presented as median (95% CI), and the colectomy rates are calculated as a percentage using the median value. Risk stratification models and treatment strategies are each analyzed with 1,000 simulations. Response defined as proportion of patients avoiding colectomy by 3 months. Standard IFX induction with assumed overall 3-month colectomy-free rate of 77%; accelerated IFX response rate tested at 80%, 85%, and 90%, using the same propensity of response as standard IFX; JAK inhibitor response rate tested at 70% and 80%, using the same propensity of response as standard IFX; IFX, infliximab; JAK, Janus kinase inhibitor.
predictive model and the efficacy of salvage therapies, especially JAK inhibitors.

We have shown that the development of highly effective management strategies is expected to drastically reduce the residual risk of adverse outcomes in ASUC given appropriate conditions. When considering only modest predictive model accuracy assumptions (AUC 80%), in line with currently available predictive models, as well as modest treatment efficacy, the residual risk of colectomy was reduced by more than one-third from 23% to 15% using both accelerated infliximab induction and sequential JAK inhibition, as opposed to 17%–18% when using either strategy in isolation. Assuming a more accurate predictive model with 90% AUC can be developed in future, and with optimistic treatment efficacy assumptions, the combined accelerated infliximab and JAK inhibitor approach could reduce the 3-month colectomy rate by almost two-thirds to 8%, compared to 11% with either treatment alone. Our modeling also demonstrates that good outcomes can be achieved by both better predictive models as well as efficacious treatments. Despite the most pessimistic treatment efficacy, using a highly accurate model with 90% AUC could achieve an overall 3-month colectomy rate of 15% to 16% (30% to 35% residual risk reduction) using the combined accelerated infliximab/JAK inhibition strategy. Similarly, despite using a low accuracy model with 70% AUC but assuming the most optimistic treatment efficacy, the combined algorithm achieved a similar 3-month colectomy rate of 13% to 14% (39% to 43% residual risk reduction).

The concept of a hidden propensity for infliximab failure is useful to understand the evolving ASUC treatment paradigm. Patients with ASUC suffer a high inflammatory burden and consequently may suffer high infliximab losses. Patients who lack response due to pharmacokinetic failure, where standard infliximab induction is unable to achieve adequate serum levels, would theoretically benefit from additional dosing. However, these patients must have a low propensity of failing infliximab, explained biologically by an inflammatory process that can be switched off by achieving an adequate level of TNF inhibition. Patients who have accessory pathways of inflammation that are inadequately moderated by TNF inhibition, thereby having a high propensity for infliximab failure, are unlikely to benefit even from optimized infliximab dosing. These patients would benefit most from alternative, non-TNF-based therapies.

Although not explored in this study, the timing of predictive model development is a key factor that is often overlooked in model derivation. Ultimately, a predictive model is only clinically useful if it can be used to inform decision-making. In the currently accepted ASUC management algorithm, the True-love and Witt’s criteria is used to define ASUC (the first decision point), while the Oxford and Lichtiger indices are commonly used to define steroid-refractoriness (the second decision point), necessitating commencement of salvage infliximab. Assuming the optimal starting dose of infliximab is known, the third key decision point is at some point after the initial infliximab dose, in order to predict or determine infliximab failure, necessitating treatment modification. Previously, sequential ciclosporin was the only alternative to emergency colectomy in the event of infliximab failure, which was associated with poor outcomes and a reported 12-month colectomy-free rate of only 42%. With the advent of accelerated infliximab and JAK inhibition, this third decision point has become critically important, which has formed the basis of the management strategies that we have investigated in this study. Previous studies have identified that a higher CRP, lower albumin and lower lymphocyte count after infliximab salvage have predicted infliximab failure. However, a robust predictive model has yet to be validated.

As precision medicine continues to advance, the likely eventuality is that a patient’s optimal therapy can be determined at the second decision point instead (at the time of steroid failure, prior to commencing infliximab). This could be achieved by advances in pharmacokinetic profiling (determining the patients who will have high infliximab losses), immunological profiling (determining patients with accessory pathways who will not respond to infliximab), genetic profiling using genomics, as well as machine learning approaches (black box prediction approach using big data). With the advent of newer biologic agents and small molecule therapies, truly robust management algorithms tailored to the individual will become possible, which will likely further reduce the residual risk of colectomy.

This study’s strengths include a robust simulation-modeling approach to answer the study’s aim. Through simulation, a realistic cohort of steroid-refractory ASUC patients could be generated, and predictive models of various accuracies in combination with different management algorithms could be tested. The study is limited by its reliance on the efficacy assumptions made of different treatments. Due to the lack of high-quality evidence, the assumptions on the efficacy of accelerated infliximab induction and JAK inhibition might be inaccurate. In particular, due to the low quantity of retrospective
data available, especially with regards to JAK inhibition (Table 2), the true efficacy of these treatments may be overestimated due to publication bias. In order to mitigate this risk, we explored multiple levels of assumed efficacy, including pessimistic assumptions, to produce a robust modeling study. Furthermore, in terms of external validity of the findings from our study, the colectomy rates used to generate the hypothetical cohort are based only on published studies (Table 1), thus our results may only be applicable to ASUC cohorts of similar baseline characteristics as those reported from external studies from Table 1. Further, our models assume an independence between propensity to respond to infliximab and propensity to respond to JAK inhibition, whereas in reality, they may be correlated (albeit with a low correlation). If so, our results for JAK inhibition may be optimistic. Future modeling-simulation studies should be performed when there is more clarity regarding treatment efficacy and response behaviors. Finally, our simulated predictive models had fairly symmetric ROC curves (favoring neither false positives nor false negatives). In practice, derived predictive models may have skewed ROC curves, which may require choosing risk thresholds at different locations to better risk stratify patients (for example, at the 60% percentile as opposed to the 50% percentile).

In conclusion, this is the first study to model novel management algorithms in steroid-refractory ASUC and simulate their effect on long-term colectomy rates. A management algorithm incorporating both accelerated infliximab induction as well as sequential JAK inhibition appears to be the most robust and achieves the greatest residual colectomy risk reduction by 3 months. However, management strategies incorporating a predictive model for risk stratification should ideally be evaluated within controlled trials before their use can be routinely recommended in clinical practice. Optimizing outcomes in ASUC relies on both accurate predictive models as well as efficacious treatment alternatives. Future studies on predictive model development should consider incorporating simulation studies to better understand their expected benefit.

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