Adverse Events Do Not Outweigh Benefits of Combination Therapy for Crohn's Disease in a Decision Analytic Model

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BACKGROUND & AIMS: The Study of Biologic and Immunomodulator-Naïve Patients With Crohn's Disease (SONIC) showed that combination therapy with infliximab and azathioprine (IFX/AZA) is more effective than treatment with IFX alone. Numbers and types of adverse events were roughly equivalent among groups, although enrollment was limited, so it was not clear how rare adverse events might affect overall outcomes in practice. We sought to define the frequency at which a rare adverse event would have to occur for the risks of combination therapy to outweigh the benefits of treatment. **METHODS:** We constructed a decision model to compare the risks and benefits of IFX/AZA with IFX monotherapy. Model parameters were taken from SONIC and other published literature. The base-case analysis was patients with active Crohn's disease who are naïve to both medications (similar to those in SONIC) who were treated for 1 year. We used sensitivity analyses to determine the thresholds at which the risks of side effects from IFX/AZA outweigh its benefits. **RESULTS:** During 1 year, the benefits of IFX/AZA would outweigh the risks, unless serious infections occurred in 20% or more of the population or lymphoma in 3.9% or more. These thresholds are 5-fold and 65-fold higher than base-case estimates, respectively. **CONCLUSIONS: On the basis of data from 1 year of SONIC, the combination of IFX/AZA was more effective than IFX alone in patients with Crohn's disease who are naïve to either drug. For the risks of combination therapy to outweigh the benefits in this time frame, the incidence of serious adverse events would have to be higher than seems clinically realistic.**

Keywords: Inflammation; Anti-Tumor Necrosis Factor (TNF) Agent; Side Effect; Intestine; IBD; Complication.

Crohn's disease is a chronic inflammatory bowel disease affecting more than half a million people in the United States.[1] If not treated appropriately, Crohn's disease can lead to substantial morbidity because of persistent symptoms and multiple surgeries. The goal of medical therapy is to induce and maintain a clinical remission without the need for long-term steroid use. The 2 classes of medications used most effectively to achieve this goal include immunomodulators (6-mercaptopurine, azathioprine [AZA]) and anti–tumor necrosis factor (TNF) agents (infliximab [IFX], adalimumab, and certolizumab pegol). Anti-TNF agents were approved for use in the treatment of Crohn's disease in 1998 and have proved to be effective when immunomodulators have failed.[2] During the past decade since anti-TNF agents have been available, gastroenterologists have been working to optimize use of these agents. Similar to a treatment approach in rheumatology,[3] one important question has been whether anti-TNF agents are most effective if used alone or together with immunomodulators.

To answer the question of whether combination therapy is more effective in Crohn's disease, a recent randomized controlled trial studied the efficacy of AZA versus IFX versus combination therapy (AZA/IFX).[4] This study (Study of Biologic and Immunomodulator-Naïve Patients With Crohn's Disease [SONIC]) showed a clear benefit for combination therapy versus either drug alone. However, concerns that 2 immunosuppressant drugs taken together will lead to a higher rate of adverse events has dampened enthusiasm for these findings. Specifically, the rate of non-Hodgkin lymphoma (NHL) and serious infections might be higher in patients treated with combination therapy.[5,6] Despite the superiority of combination therapy for the treatment of Crohn's disease, physicians might be reluctant to use this approach unless they are comfortable with the tradeoff of benefits and risks.

Because severe adverse events (SAEs) are rare, it is unlikely that a clinical trial will ever be adequately powered to compare the safety of anti-TNF monotherapy versus combination therapy. The purpose of this study was to use decision analytic techniques to evaluate the benefits and risks of IFX monotherapy versus combination AZA/IFX therapy and to determine how high the risk of combination therapy would have to be for this regimen to no longer be the favored approach.

Methods

Patient Population

The population of interest was 35-year-old patients with moderately to severely active Crohn's disease who are naïve to both immunomodulators and anti-TNF agents. This population represents both patients who would receive these treat-

Abbreviations used in this paper: AZA, azathioprine; IFX, infliximab; NHL, non-Hodgkin's lymphoma; QALY, quality-adjusted life-years; SAE, serious adverse event; SEER, Surveillance, Epidemiology and End Results; SONIC, Study of Biologic and Immunomodulator-Naïve Patients With Crohn's Disease; TNF, tumor necrosis factor.

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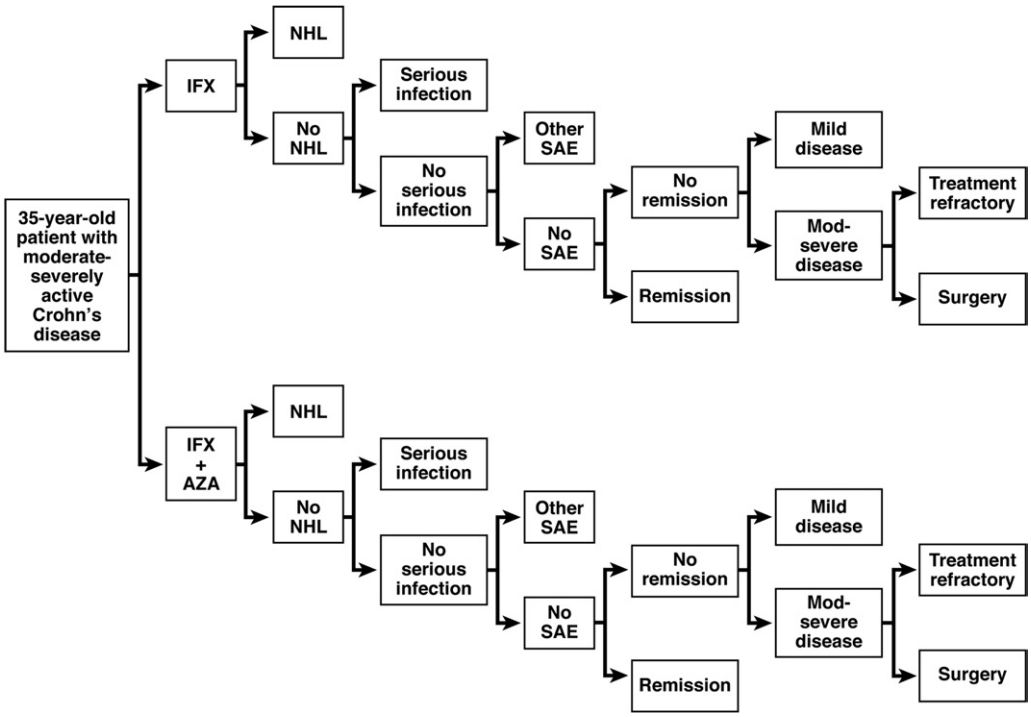

Figure 1. Simplified model schematic showing the 2 treatment arms of IFX monotherapy and IFX + AZA combination therapy. When treatment is withdrawn because of a serious infection, other SAE, or because a patient is treatment refractory, then they remain in the moderate-severe disease activity state.

ments in clinical practice and the study population of the SONIC trial.[4]

Model Structure

A decision tree model was constructed to compare IFX monotherapy with combination treatment with AZA and IFX over a 1-year time horizon (Figure 1). The model assesses the expected health utility measured by quality-adjusted life-years (QALYs).

In each treatment arm, patients can develop lymphoma, a serious life-threatening infection, another SAE, or have no adverse events and either respond or not respond to treatment (Figure 1). If patients do respond, they either go into clinical remission or improve to mildly active disease. When treatment is withdrawn because of a serious infection or other SAE, patients remain in the moderate-severe disease activity state. If they do not respond to treatment, they either remain in moderate-severe active disease or undergo surgery for Crohn's disease. In both groups, death could result from lymphoma, a severe infection, a Crohn's disease flare, a surgical complication, or some other age-specific cause of mortality. The model was constructed by using a decision analysis software program (TreeAge Pro Suite 2009, Williamstown, MA).

Assumptions

The model includes several important assumptions. First, other than lymphoma and serious infections, there are other SAEs that are non–life-threatening but lead to cessation of therapy and continued disease in the moderate-severely active state ("other SAE"). Second, combination therapy is associated with a higher risk of NHL than monotherapy with IFX, and IFX monotherapy has the same risk of NHL as AZA monotherapy. Although there are meta-analysis data to estimate the risk of NHL with combination therapy[5] and immunomodulator monotherapy,[7] this assumption is required because there are not enough patients treated with anti-TNF monotherapy without prior exposure to immunomodulators to provide a baseline estimate.

Model Inputs

Benefits and risks of therapy. The base-case estimates for the chance of remission after treatment with AZA/IFX combination therapy or IFX monotherapy come from the SONIC trial.[4] To use the most conservative estimate of efficacy, week 50 data are used for all randomized patients, assuming that patients who did not enter the trial extension did not achieve the end point through week 50. The percentage of serious infections for each treatment arm comes from SONIC week 54 data, and SAEs other than serious infections were calculated by subtracting the rate of serious infections from the overall SAE rate (which included serious infections) to yield the "other SAE" rate. Death related to serious infection was calculated on the basis of the proportion of patients who died of serious infection as identified in a previous systematic review.[8] The lymphoma rates were based on 2 recent meta-analyses, one on the rate of NHL associated with immunomodulator exposure and the other with the use of combination anti-TNF and immunomodulator treatment.[5,7] The base-case estimates for these and other variables are shown in Table 1. These point estimates all have associated uncertainty based on the sample size and design of the study from which they were derived, and this uncertainty is addressed in the sensitivity analyses.

Quality of life estimates. Quality of life health utility weights for patients with Crohn's disease were derived from previous work including Gregor et al[9] and Lewis et al.[10] Utilities for patients with lymphoma were taken from work by Uyl de-Groot et al.[11] Table 2 shows these estimates. Patients with treatment refractory disease who do not have surgery or die continue to have the health utility of moderate-severe active disease.