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The Benefit to Risk Balance of Combining Infliximab with Azathioprine Varies With Age: A Markov Model

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Abstract

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BACKGROUND & AIMS—Combination therapy with infliximab and azathioprine has demonstrated benefit over monotherapy for moderate-to-severe Crohn's Disease. Clinical trials and models have not accounted for age-specific risks associated with these therapies, including the risk of immunosuppression-related cancer and infection. After accounting for these risks, the strategy yielding the greatest benefit may vary with age.

METHODS—We assessed age-specific risks and benefits of combination therapy compared to infliximab monotherapy using Markov modeling. The base case was a 35 year-old male patient with a 1-year time horizon. We assumed the incidence of lymphoma to be 5.28-fold higher with combination therapy. Secondary analyses accounted for life expectancy, therapy beyond 1 year, and age-specific surgical and infection risks. Quality-adjusted life years (QALYs) were calculated for 25–75-years old individuals.

RESULTS—Combination therapy was found to be of greater benefit in the base case (0.7522 QALYs for combination therapy vs 0.7426 QALYs for monotherapy). Accounting for life years lost, monotherapy was the best approach if the hazard ratio for lymphoma with combination therapy was >8.1 patients 75 years old. Monotherapy provided greater net benefit to patients 55, 65, or 75 years old if therapy was extended for 9, 7, or 5 years, respectively. For 25 year-old men, monotherapy resulted in fewer deaths but only yielded greater QALYs if the annual incidence of hepatosplenic T-cell lymphoma exceeded 36/100,000 persons.

CONCLUSION—After accounting for age-specific risks of lymphoma, infection, and surgical complications, benefits of combination therapy outweighed the risks as a short-term and intermediate-term strategy for most patients with moderate-to-severe Crohn's Disease younger than 65 years. For young male patients, combination therapy yields greater QALYs, but at cost of an increased risk of death from lymphoma.

Keywords

Infliximab; Azathioprine; Lymphoma; Crohn's Disease

Combination therapy with anti-tumor necrosis factor alpha medications (anti-TNFs) and thiopurines is recommended in moderate-to-severe Crohn's disease (CD)[1–4]. Concerns remain about the safety of this combination. The two most feared complications are infection and malignancy. There are conflicting data on whether anti-TNFs, and combination therapy in particular, increase the risk of serious infections such as pneumonia[5, 6]. An increased risk of malignancy, particularly lymphoma and non-melanoma skin cancer, has been demonstrated in several observational cohorts[7–9]. The existing evidence implicates thiopurines as the principal cause of lymphoma, with a possible synergistic effect when combined with anti-TNFs[8, 10]. Thiopurines also appear to be the dominant risk factor for hepatosplenic T-cell lymphoma (HSTCL), a rare but fatal lymphoma affecting young males[11]. Therefore, discerning whether combination therapy offers an overall benefit relative to anti-TNF monotherapy is complex.

The incidence of non-Hodgkin's lymphoma (NHL) and surgical and infectious complications with combination therapy increases with age[12, 13]. Furthermore, the expected benefit of azathioprine monotherapy decreases in older populations as a consequence of increasing lymphoma risk[14]. In this study we explored the relationship between age-specific

risks and the expected net benefit of combination therapy compared to infliximab monotherapy. We hypothesized that for certain individuals, age-specific risks of lymphoma and infection with combination therapy outweigh the potential benefit, mandating personalized therapy incorporating this risk-benefit balance.

Methods

We constructed a Markov model to assess age-specific risks of combination therapy with an anti-TNF and a thiopurine compared to anti-TNF monotherapy. The base case was a 35-year old male with moderate-to-severe CD, comparable to participants in the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) trial[1], initiating either combination therapy or infliximab monotherapy. It was assumed that surgery was the least desired option. The time horizon for the primary analysis was 1 year, with a 1-month cycle length.

Combination therapy or monotherapy could initially result in remission, clinical response, or non-response (Figure 1). With response or remission, individuals could lose response, have a complication requiring cessation of the medication, experience a serious infectious complication requiring temporary withholding of medication for 1 cycle, develop lymphoma, or remain in their current state. Those without response and those that flared were transitioned to a second anti-TNF (adalimumab), with similar health states as with infliximab. All patients in the base model were continuously exposed to the age-specific probability of death of a male with CD, which was calculated using the baseline rate of death in US census data and a hazard ratio of 2.44 for those with CD on immunosuppressive therapy[15, 16].

Individuals entering a lymphoma state remained there, and were exposed to both age-specific and sex-specific all-cause and lymphoma-specific mortality. Lymphoma-specific mortality was derived from Surveillance, Epidemiology, and End Results (SEER) age- and sex-specific data[22, 23]. It was assumed that all patients received standard of care chemotherapy for lymphoma.

Patients undergoing surgery were exposed to an increased risk of peri-operative mortality for one cycle. They then entered a post-surgical remission state for the remainder of the study period, without exposure to medications and their risks.

Transition probabilities and outcome estimates

Transition probabilities were derived from relevant clinical trials (Table1, Supplemental Methods). The transition probabilities related to infliximab induction, maintenance, and complications were derived from the SONIC trial[1]. The Gauging Adalimumab Efficacy in Infliximab Non-responders (GAIN) study was used to inform initial remission and response rates for adalimumab[17]. Relapse, infection, and adverse event rates for adalimumab were derived from the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) study. As there was no clear difference between combination therapy and monotherapy with adalimumab for relapse in CHARM, which has been confirmed in two recent meta-analysis of adalimumab combination and monotherapy, these

transition probabilities were considered equivalent and were derived from those previously exposed to infliximab in CHARM[18–20].

It was assumed that the hazard ratios (HR) for azathioprine and infliximab were independent of each other. The baseline HR for azathioprine was determined to be 5.28 from the Cancers Et Surrisque Associé aux Maladies Inflammatoires Intestinales En France (CESAME) cohort, and was treated as a continuous risk[8]. The baseline HR for infliximab was 1.0, based on the non-significant standardized incidence ratios (SIR) in CESAME and the TREAT registry[21]. These hazards were applied to the age-specific rate of lymphoma as determined by SEER[22].

Quality adjusted life year (QALY) estimates were derived from previously published estimates and expert opinion (Supplemental Methods)[14, 23, 24]. QALY estimates were assumed to be constant over all age ranges (Table 1).

Statistical Analysis

Analyses were conducted from age 25 to 75 using TreeAge Pro 2013 (TreeAge Software, Inc., Williamstown, MA). Means and standard deviations (SD) for QALY estimates were derived from first-order Monte Carlo simulations (FOMCS) using 50,000 subjects. Probabilistic analyses were performed using distributions derived from clinical trials for all transition probabilities and QALY estimates (Supplemental Methods)[25]. To simulate outcomes at the end of 1 year, Markov cohort analysis was performed using a cohort of 1,000,000 patients for all age ranges.

Sensitivity Analyses

One-way sensitivity analyses were performed for all transition probabilities, hazard ratios, and rewards. Alternative model designs were also examined assessing the impact of 1) using a second anti-TNF by conducting an analysis allowing only infliximab; 2) life-years lost due to death during the first year of therapy by modifying the final reward; 3) increased risk of perioperative mortality in those over 65 years of age; 4) increasing age-specific risks of serious infection and infection-related mortality for those over 65 years of age; 5) lymphoma-specific life years lost for duration of therapy up to 9 years; 6) a gradual increase rather than instantaneous risk of lymphoma with azathioprine; and 7) including an additional risk of HSTCL for 25-year-olds treated with combination therapy (Supplemental Methods).

Results

Combination therapy with infliximab and azathioprine was the preferred option in the base model (Expected QALYs: 0.7522 versus 0.7426, Incremental effectiveness (IE) 0.0096). This benefit was also appreciated in first order Monte Carlo analysis (IE 0.0097) and probabilistic analyses (mean Expected QALYs 0.7521 versus 0.7426, IE0.0095 (95% Cl −0.0076–0.0268)). Over 50,000 iterations of the probabilistic model, combination therapy was the preferred strategy 86.1% of the time. In Markov Cohort analysis, combination therapy resulted in a greater number of patients in remission (22.9% versus 20.7%) and with response (26.8% versus 22.5%), fewer in post-operative remission (25.5% versus 30.1%), and fewer with active disease (24.4% versus 26.3%) at one year (Supplemental Figure 1).

Mortality rates were similar between groups, with 19 fewer deaths per million individuals at one year in combination therapy (Table 2).

Combination therapy remained the preferred therapy throughout the lifespan (Figure 2). The increase in rates of lymphoma with age, particularly in the combination therapy arm (Supplemental Figure 5), resulted in increased mortality in the combination therapy arm compared to monotherapy for those older than 55. Per 1,000,000 patients treated, there were 29 more deaths with combination therapy at age 55, 147 at age 65, and 455 at age 75 (Table 2).

Alternative model structures

Combination therapy yielded greater QALYs in alternative models that: 1) did not allow for crossover to a second anti-TNF (Expected Value (EV) 0.7341 versus 0.7232, IE 0.0109); 2) utilized final rewards to account for remaining life-years in the base case (EV 43.0403 versus 43.00299, IE 0.0104) and throughout the lifespan (data not shown); and 3) increased the risk for perioperative mortality in those over 65 by 2-fold (65 year old: 0.7375 versus 0.7285, IE 0.0090, 75 year old: 0.7160 versus 0.7075, IE 0.0085) or 5-fold (data not shown).

Assessing the impact of HSTCL in younger males, combination therapy remained the preferred strategy (EV 0.7524 versus 0.7428, IE 0.0096). However, in our Markov cohort analysis, there were 37 excess deaths with combination therapy due to 67 additional HSTCL-related deaths. When accounting for life-years lost due to HSTCL, the margin of benefit was reduced compared to the base model (IE 0.0075). Monotherapy became the preferred strategy if the incidence of HSTCL was greater than 36.0 per 100,000, or 3.2-fold greater than the baseline estimate.

In one-way sensitivity analysis of the HR for azathioprine-related lymphoma accounting for life years lost due to death, monotherapy became the preferred strategy in 65 year olds if the HR for combination therapy was >13.6, and in 75 year olds if the HR was >8.1 (Figure 3AB).

When extending the time horizon, combination therapy remained the preferred strategy for all ages for up to 3 years of therapy (Figure 4, Supplemental Table 1). Monotherapy was preferred in patients age 75 with more than 5 years of therapy and in those age 55 or older with over 9 years of therapy.

Sensitivity analyses

The model was not sensitive to changes in transition probabilities across a range from 50% lower than to 50% greater than the base value for adverse event, response, relapse, mortality, or infection rates for combination or monotherapy. However, if the probability of remission with combination therapy with infliximab and azathioprine decreased to 20.8%, or 8.8% below the monotherapy remission probability, monotherapy became the preferred therapeutic option. If the remission rate with infliximab monotherapy exceeded 42.1%, monotherapy became the preferred strategy. The model was not sensitive to increases in the risk of lymphoma with infliximab over a range of HRs from 1 to 10 (Supplemental Methods, Supplemental Figure 4). The model was not sensitive to QALY estimates ranging 15%

above or below baseline value, and was not sensitive to QALYs assigned to lymphoma over a wide range of values (0.20–0.80).

The model was robust to estimates of infection risk. The model was not sensitive to infection rates related to anti-TNFs or combination therapy when increased to up to 5 times of the base estimate, regardless of age (Supplemental Methods, Supplement Figure 3). In a 2-way sensitivity analysis, monotherapy became the preferred strategy when the odds of infection with combination therapy were >10x monotherapy and the infection-specific mortality exceeded 10% (Supplemental Figure 2).

Discussion

Concerns about age-related risks with immunomodulators and biologic therapies in IBD have markedly impacted willingness to use our most effective therapies in the youngest and oldest patients. In this study, we modeled the age-specific risks and benefits associated with combination therapy for moderate-to-severe CD, demonstrating that combination therapy may yield the greatest clinical benefit for short-term therapy in patients aged 35 to 65. However, the risks associated with combination therapy may outweigh the benefits for those over 65, particularly with longer treatment periods. This appears to be driven by lymphoma-related complications as opposed to increased risks of surgical complications or infection, even though infectious complications are far more common than lymphoma. Our sensitivity analyses highlight this finding, demonstrating no change in the optimal therapy with increasing age-specific risks of infection or surgery.

We employed several novel techniques in estimating the age-specific benefits and risks of combination therapy. We utilized age-dependent rates of NHL, infection, and surgery to better capture these risks for all individuals, and assessed the impact of these rates on long-term therapy. Using these approaches, we demonstrated that monotherapy yielded greater clinical benefit in patients older than 75 when therapy exceeded 5 years, and was preferred in those over 55 years of age if therapy exceeded 9 years. This highlights the complicated risk benefit analyses required to ascertain the preferred strategy for a given individual.

We determined thresholds for lymphoma risk that would indicate change in preferred strategy. For only 1 year of therapy, the HR of lymphoma with combination therapy would need to be greater than 8.1 for monotherapy to become the preferred strategy in those over 75; this threshold is well within the 95% CI reported in CESAME (HR 5.28, 95% CI 2.01 – 13.9)[8].

This model is the first to assess the impact of HSTCL in younger males. We demonstrated that there was a trade-off between the small increased risk of death from HSTCL and increased therapeutic efficacy with combination therapy. We estimated that the risk of HSTCL must exceed a threshold of 36 per 100,000 person-years of exposure to thiopurines for monotherapy to yield greater QALYs. It seems unlikely that the true incidence is this high. The annual incidence of NHL among 25-year old American males is approximately 4 per 100,000. Therefore, the estimated annual incidence in thiopurine-exposed is only 21 per

100,000 based on the relative risk estimates from CESAME, well below the threshold of 36 per 100,000.

We can also utilize this sensitivity analysis to consider the impact of other thiopurine-related complications in young males. Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal complication associated with primary EBV infection when taking azathioprine. CESAME reported two fatalities from complications related to primary EBV infection in young males using thiopurines, for an estimated incidence rate of 10 per 100,000 person-years[8]. When considering only young males who are EBV seronegative, the incidence of this event may be as high as 290 per 100,000 person-years[26]. Combining the more conservative estimate of 10 per 100,000 with our estimated rate of HSTCL, the overall incidence rate of these two fatal complications of thiopurine therapy is 21.2 per 100,000 person-years, which is much closer to the threshold we estimated. If the true incidence of fatal primary EBV infection among EBV seronegative patients is closer to 290 per 100,000 person-years, our model would strongly favor monotherapy in this sub-population.

There are several important caveats to interpreting our results. The overall incremental effectiveness is small. However, in Markov analysis, there were clear differences in favor of combination therapy, with 64,102 more individuals with clinical improvement and 62,072 fewer individuals requiring surgery, suffering with active disease, or dying.

The key transition probabilities were derived from large clinical trials. Notably, in a recent meta-analysis comparing combination therapy and monotherapy, the pooled odds of remission at 24 weeks was 1.64, favoring combination therapy, similar to the OR of 1.62 in SONIC [27]. Pooled estimates of infection and adverse events were also comparable to those in SONIC[27]. Recent meta-analyses also support our assumption of equivalent relapse rates for adalimumab combination and monotherapy [19, 20]

We did not model dose escalation or antibody measurement with loss of response. There are limited and conflicting data regarding the efficacy of this treatment strategy[28, 29]. As our model was insensitive to relapse transition probabilities, utilization of these tests would not markedly impact our results.

We assumed that the risk of lymphoma begins immediately with azathioprine initiation. This risk may increase over time with therapy[30]. We therefore assessed models with extended time horizons and performed a sensitivity analysis increasing azathioprine-related risk of lymphoma over time. These models yielded similar results, demonstrating that for those over 65, the risks of combination therapy beyond 6 years may outweigh the potential benefits.

Our estimated rate of HSTCL was based on limited data; if true rates are much lower, combination therapy would be the preferred strategy in younger males. Some reports suggest that HSTCL rarely occurs prior to several years of therapy with thiopurines, and we therefore may have over-estimated the impact of HSTCL. We did not model the impact of discontinuing azathioprine after the first few years of therapy in models with longer time horizons. As more data become available, future models should evaluate this potential strategy. We did not model the impact of combination therapy with methotrexate in young

males, though a recent trial failed to demonstrate a therapeutic advantage with this regimen compared to anti-TNF monotherapy[31].

Lastly, we focused on the risk of lymphoma as opposed to other neoplasms. Our model does not take into account increased rates of certain skin cancers with these medications or the possible increased risk of other tumors recently appreciated with combination therapy [9, 32, 33]. We did, however, account for increasing age-related risks of infection and surgery and demonstrated that they did not impact the optimal strategy.

In summary, this study is the first to assess the impact of age-specific risks on the decision to use combination therapy versus monotherapy for patients with moderate-to-severe CD. In our model, increased lymphoma, infection, and surgery risks do not outweigh the greater efficacy of combination therapy for those aged 35 to 65 when considering therapy for up to 3 years. However, the risk of lymphoma may outweigh the benefits of combination therapy for those older than 65, particularly with long-term therapy. These data highlight the need to further examine de-escalation strategies with long-term remission. Our model also suggests that combination therapy in young adult males may be the preferred strategy, providing greater QALYs, albeit at the cost of an increased risk of HSTCL-related deaths. Our data also support a potential strategy of screening for EBV in those younger than 25 before embarking on combination therapy to prevent primary EBV infection-related complications. This may represent a greater risk than HSTCL in this population[26]. These data help to better inform conversations with individual patients of all ages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

CD	Crohn’s Disease
CESAME	Cancers Et Surrisque Associé aux Maladies Inflammatoires Intestinales En France
CHARM	Crohn’s Trial of the Fully Human Antibody Adalimumab for Remission Maintenance
EBV	Epstein Barr Virus
FOMCS	First Order Monte Carlo Simulation
GAIN	Gauging Adalimumab Efficacy in Infliximab Non-responders
HLH	Hemophagocytic Lymphohistiocytosis

HSTCL	Hepatosplenic T Cell Lymphoma
IE	Incremental effectiveness
NHL	Non-Hodgkin's Lymphoma
QALY	Quality Adjusted Life Year
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results
SIR	Standardized Incidence Ratio
SOMCS	Second Order Monte Carlo Simulation
SONIC	Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease
TNF	Tumor Necrosis Factor

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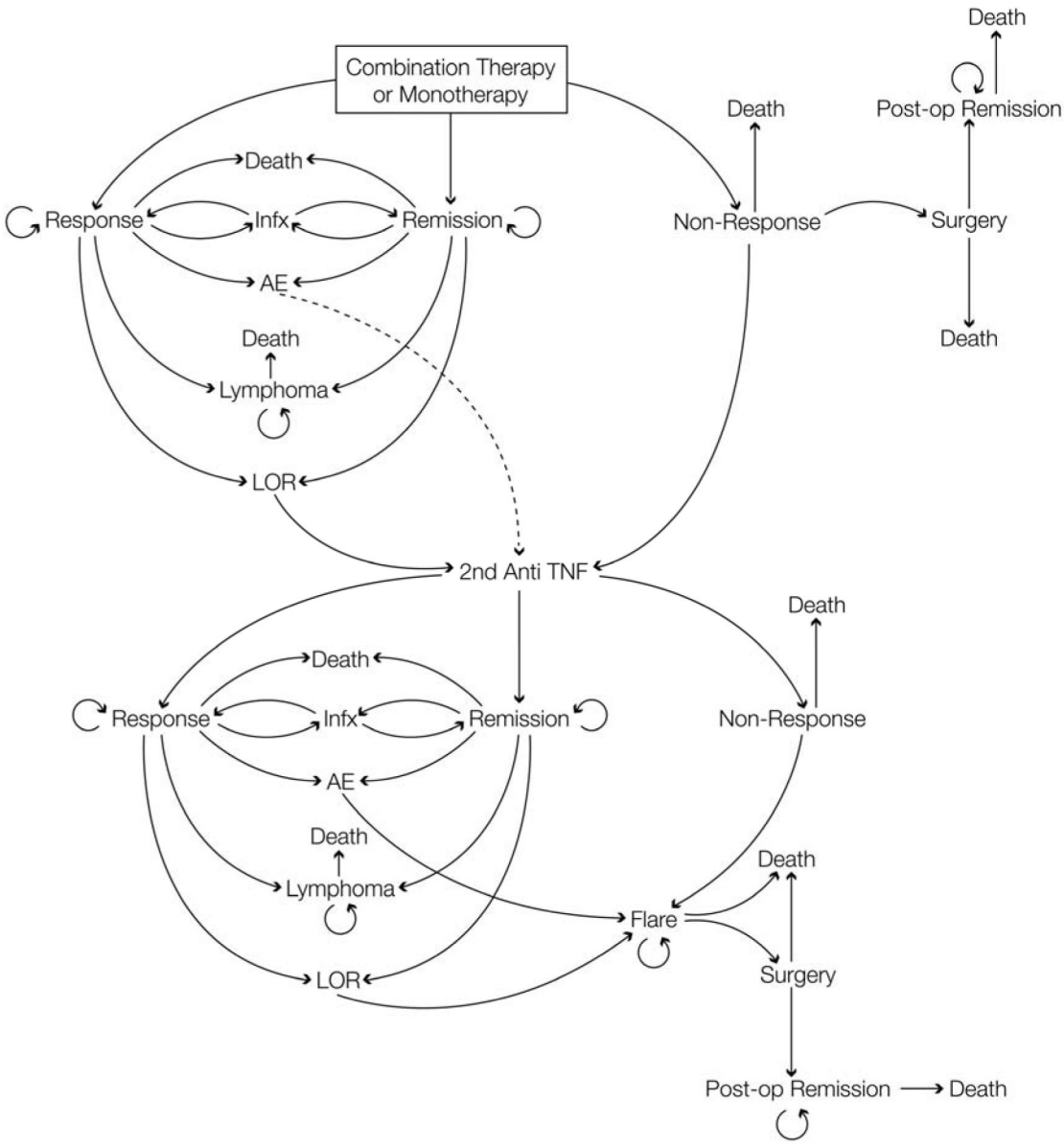
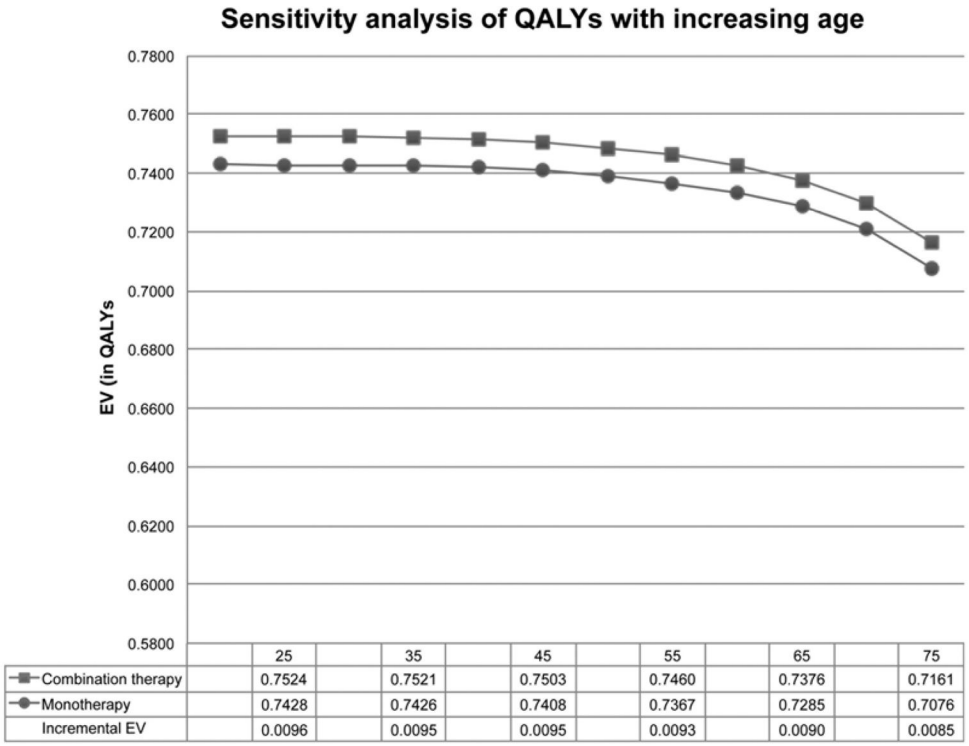


Figure 1. Model structure for combination therapy and monotherapy

This is the structure of the model for the combination therapy arm. The monotherapy arm is identical, without inclusion of azathioprine.



	25	35	45	55	65	75
Combination therapy	0.7524	0.7521	0.7503	0.7460	0.7376	0.7161
Monotherapy	0.7428	0.7426	0.7408	0.7367	0.7285	0.7076
Incremental EV	0.0096	0.0095	0.0095	0.0093	0.0090	0.0085

Figure 2. Impact of age on overall QALY estimates

The margin of benefit of short-term combination therapy declined with increasing age.

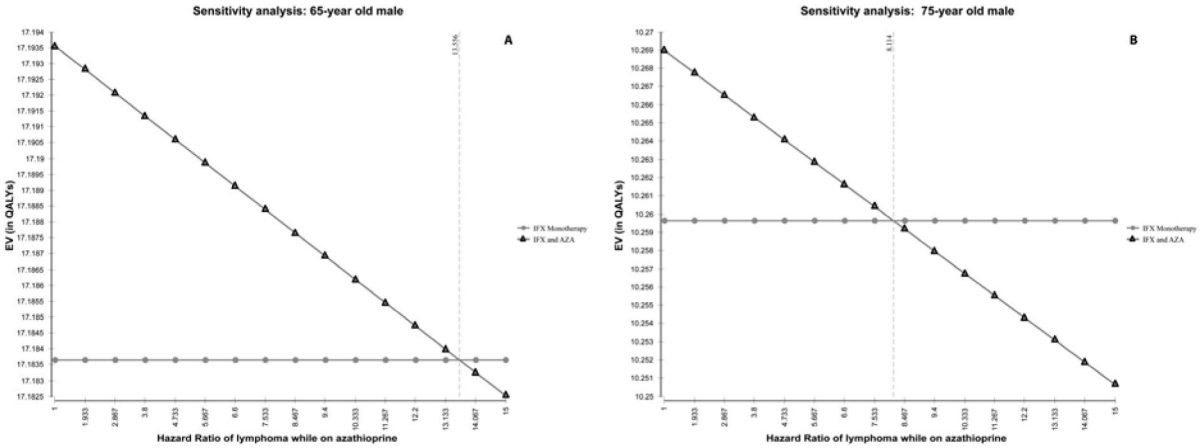


Figure 3. One-way sensitivity analysis of the hazard ratio of lymphoma with azathioprine

In models accounting for life-years lost due to death, monotherapy is preferred if the HR of lymphoma exceeded 13.6 in those 65 years of age (A), and if it exceeded 8.1 in those 75 or older (B).

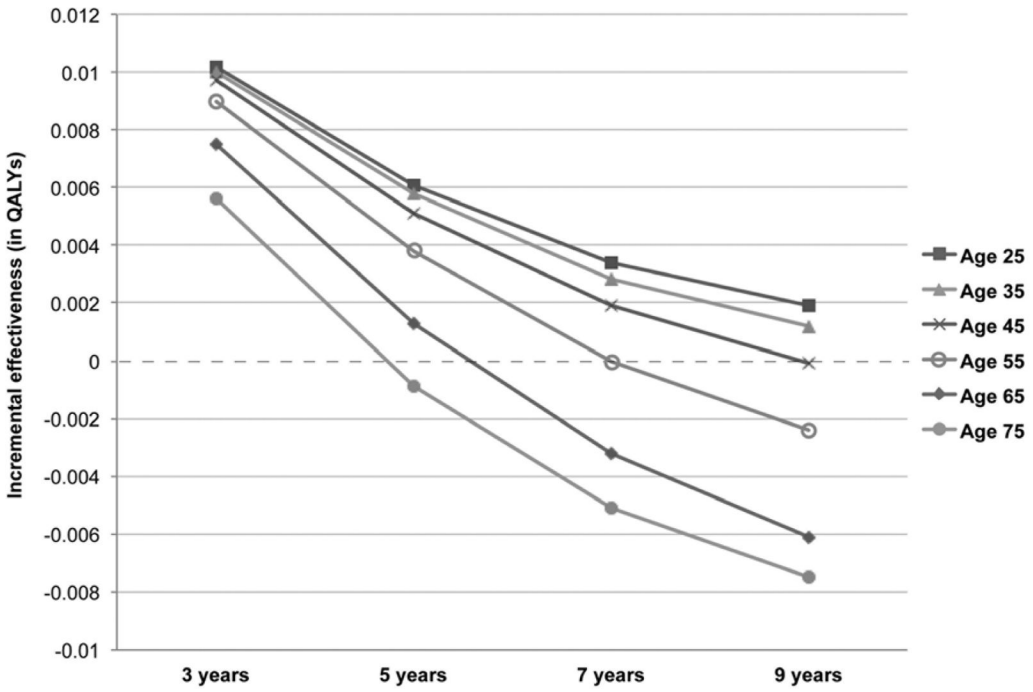


Figure 4. Impact of age with increasing time horizon

Impact of age on preferred strategy in models that account for 3, 5, 7, and 9 years of exposure, from 25 years old to 75 years old.

Table 1
Transition probabilities and QALY estimates

Transition probabilities and QALY estimates for both combination therapy and monotherapy. All transition probabilities were assessed via one-way sensitivity analysis over a range of +/− 25%. For QALY inputs used for the model, sensitivity analyses were conducted varying the value by +/− 15%.

Transition probability for:	Value	Source
Remission with combination therapy with infliximab	0.3254	1
Clinical response with combination therapy with infliximab*	0.3077	1
Remission with combination therapy with adalimumab	0.2192	17
Flaring when in remission with combination therapy with infliximab, per year	0.5385	1
Flaring with clinical response with combination therapy with infliximab per year	0.213	1
Clinical response with combination therapy with adalimumab	0.3836	17
Adverse event requiring drug cessation with combination therapy with infliximab	0.207	1
Adverse event requiring drug cessation with combination therapy with adalimumab, per year	0.058	18
Infectious complication with combination therapy with infliximab per year	0.0391	1
Infectious complication with combination therapy with adalimumab per year	0.0271	18
Remission with monotherapy with infliximab	0.2959	1
Clinical response with monotherapy with infliximab*	0.2485	1
Remission with monotherapy with adalimumab	0.2093	17
Clinical response with monotherapy with adalimumab	0.3736	17
Flaring when in remission with monotherapy with infliximab, per year	0.6509	1
Flaring with clinical response with monotherapy with infliximab per year	0.2784	1
Adverse event requiring drug cessation with monotherapy with infliximab per year	0.1779	1
Adverse event requiring drug cessation with monotherapy with adalimumab per year	0.058	18
Flaring with clinical response with adalimumab per year	0.5562	18
Flaring in remission with adalimumab per year	0.6795	18
Infectious complication with monotherapy with infliximab per year	0.0491	1
Infectious complication with monotherapy with adalimumab per year	0.0271	18
Surgery during acute flare	0.1	14
Mortality rate with an infectious complication	0.001	14
QALY Estimates		
Medical Remission	0.89	14, 23
Clinical Response	0.76	**
Severe CD	0.62	14, 23
Surgical Remission	0.8	14, 23
Surgery	0.25	14, 23
Infectious Complication	0.62	14, 23
Adverse Event	0.62	14, 23
Lymphoma	0.47	14, 23

* Clinical response rates for combination therapy and monotherapy with infliximab were derived from residual response rates (CDAI decrease >100pts) after subtracting % with remission at 6 weeks in SONIC.

** For clinical response, the average between medical remission and severe CD was used, per expert opinion.

Table 2

Markov Cohort Analysis: Age-specific results

Age-specific outcomes for a cohort of 1,000,000 individuals demonstrating those in remission, clinical response, post-operative remission, death, active CD, and lymphoma states at 1 year

	Combination therapy						Monotherapy					
Age	Medically induced remission	Clinical Response	Post-Operative Remissions	Death (All causes)	Moderate-to-severely active disease	Lymphoma	Medically induced remission	Clinical Response	Post-Operative Remissions	Death (All causes)	Moderate-to-severely active disease	Lymphoma
25	224056	261653	248714	3607	237847	132	202108	219355	292800	3637	255823	24
35	223855	261421	248557	4245	237665	293	201967	219207	292623	4264	255652	51
45	222640	260018	247405	9056	236433	623	200954	218122	291283	9058	254366	106
55	219846	256792	244720	20288	233577	1262	198594	215597	288148	20259	251367	216
65	214381	250484	239482	42234	228004	2601	193995	210673	282037	42087	245526	446
75	201129	235178	226224	98134	214139	4196	182402	198259	266465	97679	230731	722