Published in final edited form as:

Inflamm Bowel Dis. 2013 November ; 19(12): 2625–2633. doi:10.1097/01.MIB.0000437043.36338.21.

Impact of JC Virus Antibody Testing in Patients With Crohn's Disease With Loss of Response to Infliximab: A Markov Model

Frank I. Scott, MD MSCE^{*,a,b}, Mark T. Osterman, MD MSCE^a, Ryan A. McConnell, MD^c, Monica Lorusso, MD^d, Faten Abera, MD MSCE^a, Caroline Kerner, MD MSCE^a, Gary R. Lichtenstein, MD^a, and James D. Lewis, MD MSCE^{a,b}

^aDivision of Gastroenterology, Department of Medicine, University of Pennsylvania, Philadelphia, PA

^bCenter for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia PA

^cDepartment of Medicine, University of Pennsylvania, Philadelphia PA

^dDepartment of Paediatrics, Anna Meyer Children's Hospital, Division of Gastroenterology and Nutrition, University of Florence, Florence, Italy

Abstract

BACKGROUND—The optimal treatment strategy for patients with Crohn's disease (CD) who have loss of response (LOR) to the anti-tumor necrosis factor- α (anti-TNF) medication infliximab is uncertain. Natalizumab has an alternative mechanism of action, but its use has been limited by the risk of progressive multifocal leukoencephalopathy (PML). In this study, we performed a decision analysis assessing the impact of JC virus (JCV) antibody testing and natalizumab utilization for LOR to infliximab.

METHODS—We constructed a Markov model to assess the difference between unscreened natalizumab use (Option 1), JCV antibody testing with natalizumab when appropriate (Option 2), and second anti-TNF use (Option 3). The base case was a 35 year-old male with severe CD with LOR to infliximab. The time horizon was 3 years. Results are reported in quality-adjusted life years (QALYs). Deterministic and probabilistic analyses were conducted. Markov analysis using a cohort of 5000 individuals was performed. The impact of JCV antibody status on outcomes in this model was assessed.

RESULTS—Option 2 was the preferred strategy (2.0880 QALYS), followed by Option 1 (2.0875 QALYS) and Option 3 (2.0808 QALYS). Patients in Option 2 required fewer surgeries compared to Option 3. Prior JCV infection was associated with reduced QALYs with all options that allowed for natalizumab use.

CONCLUSIONS—JCV antibody testing and subsequent treatment selection yields improved outcomes over natalizumab without testing or using only a second anti-TNF in all patients.

*Corresponding Author Contact information: Frank I. Scott MD MSCE, Division of Gastroenterology, Faculty Fellow, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, 1 Convention Avenue, Penn Tower 9th Fl, Philadelphia, PA 19104, Pager: (215) 812-5006, Fax: (215) 615-1688, frankis@mail.med.upenn.edu.

Keywords

Natalizumab; JC Virus antibody; Crohn's Disease

Infliximab, a monoclonal antibody against tumor necrosis factor- α (TNF- α), has dramatically improved the effectiveness of medical therapy for Crohn's disease (CD)^{1,2}. However, many patients do not respond or eventually lose response to this medication. The optimal management for loss of response (LOR) is unknown. Options include use of a second anti-TNF or medications with a different mechanism of action³⁻⁵.

Natalizumab, a monoclonal antibody against α 4 integrin, is efficacious in CD⁶⁻⁹. Natalizumab use has been limited because of an increased risk of progressive multifocal leukoencephalopathy (PML) which results from reactivation of the JC Virus (JCV), leading to neurological deficits and often death¹⁰. Recently, it has been demonstrated that the presence of antibodies to JCV can be used to stratify risk for developing PML^{11,12}. No cases of PML have been reported among patients without JCV antibodies.

We hypothesize that the ability to stratify patients according to risk of PML should improve the benefit-to-risk balance of natalizumab, such that JCV testing and utilization of natalizumab when appropriate would be the preferred strategy for patients with LOR to infliximab, in contrast to the use of a second anti-TNF without JC virus testing. Given the absence of trials addressing this question, we tested our hypothesis using a Markov model.

Methods

Model Design

We constructed a Markov model to assess the effect of JCV testing and appropriate natalizumab use compared to a second anti-TNF alone. In our model, the base case was a 35-year-old male with severe CD with LOR to combination therapy with infliximab and azathioprine. It was assumed that all attempts had been made to achieve remission with the initial combination therapy of a thiopurine and infliximab, including dose escalation and dose interval shortening. We did not assume that drug level and antibody to infliximab level testing has been performed, but later addressed the potential impact of such testing on our results in a sensitivity analysis. It was also assumed that surgical options were discussed with the patient and determined to be the least desired option. As such, surgery was not included in the model as a primary treatment option. Rather, the model focuses on medical therapy options for patients wishing to avoid surgery. The cycle length was 3 months, consistent with clinical trial data regarding the length of time assessed for remission to either NAT or a second anti-TNF. A time horizon of 3 years was chosen to allow for potential exposure to each medication and for the occurrence of PML. A 3% annual discount rate was applied to all transition rewards, starting after the first year, to increase the value of current and immediate health states compared to those in the future.

We modeled three treatment options (Figure 1). Option 1 was initiation of natalizumab without screening for JCV. Option 2 was JCV testing, with use of natalizumab in those with a negative test for JCV antibody and use of a second anti-TNF (adalimumab) in those testing

positive for JCV antibody. Option 3 was initiation of a second anti-TNF, and was designed to simulate those who did not wish to undergo therapy with NAT regardless of JCV antibody status.

In Options 1 and 2, patients who achieved remission remained on natalizumab, while those who were not in remission were transitioned to a second anti-TNF after 1 cycle of severe CD. This additional cycle was incorporated to simulate allowing for natalizumab washout before initiating adalimumab. Patients on natalizumab were exposed to risk of serious infections other than PML, resulting in cessation of medication and surgery if the patient survived. While on natalizumab, PML risk was varied based on duration of therapy and previously reported underlying JCV antibody prevalence. If a patient developed PML, they could experience a mild or severe course, though both resulted in significant disability and no further therapy (see Supplemental Materials).

In Option 3, infection, lymphoma, surgical events, and risk of death were modeled in the same manner as in Options 1 and 2. If lymphoma occurred in patients while receiving a second anti-TNF, those who survived underwent surgery. Patients that relapsed or did not respond to a second anti-TNF underwent surgery. Allowing patients to re-consider and undergo antibody testing was assessed in an additional sensitivity analysis (see below).

In all three options, patients who underwent surgery were exposed to increased perioperative mortality, and then entered a 1-cycle post-operative period with reduced quality of life. After this cycle, patients remained in post-operative remission until the 3-year horizon was reached.

All patients were continuously exposed to the probability of death of a 35 year-old 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 severe CD on immunosuppressive therapy as described previously^{13,14}.

Transition Probabilities

Transition probabilities for all events were derived from clinical trials when available (Table 1). For those initiating natalizumab, the probability of entering remission (0.33) was based on the ENACT-1 trial⁸. The probability of subsequent relapse (0.1525 / 3 months) was derived from ENACT-2⁸, where 39% of those initially in remission at week 12 remained in remission 48 weeks later.

The prevalence of JCV infection (0.536) was derived from a study in a large population with multiple sclerosis¹¹. Rates of PML with natalizumab were derived from Bloomgren et al¹². For patients who were JCV antibody positive, the baseline probability of PML at the initiation of natalizumab was 0.002 and increased linearly to 0.011 over 8 cycles; This was done to simulate the observed increased risk of PML with greater than 2 years of exposure to natalizumab as well as a history of immunosuppression prior to this medication, as is the case with our base case. The probability of PML in those who were JCV antibody negative was defined as 0.00001, as there are currently no reported cases of PML in those without JCV.

The probability of remission after initiation of a second anti-TNF (0.21) was derived from the GAIN trial, a large randomized controlled trial of adalimumab in patients who had lost response to infliximab⁵. As no serious infections were reported during GAIN, serious infection rates for the initial adalimumab cycle were derived from a pooled rate of three other studies^{3,5,15}. Probabilities of relapse and subsequent serious infection were derived from pooled data from the CHARM trial, incorporating both dosing levels in that study¹⁵.

Quality adjusted life year (QALY) estimates are shown in Table 2. Details of how other transition probabilities and QALYs were estimated for each health state are included in the Supplemental Materials.

Statistical and sensitivity analyses

Outcomes were calculated in overall QALYs for each arm of the tree using TreeAge Pro 2012 (TreeAge Software, Inc, Williamstown, MA). First-order Monte Carlo simulation (FOMCS) using 50,000 cases was conducted to determine means and standard deviations (SDs) for QALY estimates. Incremental effectiveness was reported using both expected values and means with standard deviations from the FOMCS. Probabilistic analyses using second order Monte Carlo simulation (SOMCS) were performed to assess standard error and calculate 95% confidence intervals for point estimates (see Supplemental Materials). To simulate outcomes at the end of 3 years, Markov cohort analysis was performed using a cohort of 5,000 patients.

One-way sensitivity analyses were performed for all transition probabilities and QALY estimates. In addition, we varied the time horizon of the study, assessing the effect on preferred outcome at 1, 2, and 3 years.

Alternative model designs were also examined. In the base model, patients receiving natalizumab could transition to adalimumab if they did not respond or lost response to natalizumab. It was assumed that patients entering the second anti-TNF would not want natalizumab, even if adalimumab were not effective. In one alternative model design, patients receiving a second anti-TNF initially could reconsider and undergo JCV testing if adalimumab was ineffective or they lost response. If negative, they could then receive natalizumab (Supplemental Figure 1). Therefore, in this alternative model, crossover was allowed in all three options. In another alternative model, crossover between treatment strategies was not allowed for any option.

We also created several variants of the crossover model to assess other clinical scenarios. We created a model that allowed the relapse rate to decrease over time to simulate the stability often appreciated in clinical trials of patients who are able to maintain remission. Previous research has suggested a JCV Ab seroconversion rate of 2–3% per year. To assess this effect, which would result in discontinuation of natalizumab, we increased the natalizumab relapse rate by 1% per cycle, or 4% per year. In another model, we assessed the efficacy of natalizumab and adalimumab in primary non-responders to infliximab (PNRs), which were not included in GAIN. To perform this analysis, we used transition probabilities based on an open label trial (CARE), which demonstrated a remission rate of 37% with adalimumab in PNRs³. We also performed an analysis using response rates instead of

remission rates to define effective therapy and another model using reduced post-operative QALYs to account for early relapse (see Supplemental Materials).

We assessed the effect of JCV testing on overall outcomes and in Markov analyses. To perform these analyses, we set the prevalence of a positive JCV antibody for the entire cohort to 0%, simulating a population without prior JCV infection, followed by an iteration in which prevalence of JCV antibody was set to 100%. We then assessed the differences in QALY estimates between models for each strategy. Parametric tests of significance were performed (t-test) to compare QALY estimates at JCV antibody = 0% and JCV antibody = 100% over 1000 iterations of the model. We also assessed changes in the magnitude of difference between treatment strategies when JCV antibody is positive versus negative. We also estimated the percentage of individuals that would be spared surgical intervention at 1 year and 3 years.

We performed an additional sensitivity analysis of the effects of dose adjustment for adalimumab to assess the degree of added benefit this would need to add in both the base model and in a population who were JCV antibody negative to become the preferred strategy over JCV testing. To do this, we performed one-way sensitivity analyses of adalimumab relapse rates in both the base model and in the model of patients with JCV antibody prevalence set to 0%. We then compared the decrease in relapse rate per 3-month cycle that would be required to become the preferred strategy.

Results

In the deterministic analysis, JCV testing (Option 2) was the preferred strategy (yielded the most QALYs), with an expected value (EV) of 2.0880 QALYs, compared to natalizumab without screening (Option 1, EV 2.0875 QALYs) or treatment with a second anti-TNF (Option 3, EV 2.0808 QALYs). Option 2 was also the preferred strategy in FOMCS (mean EV 2.0870 QALYs vs. 2.0794 QALYs for Option 3, incremental effectiveness 0.0076 (SD 0.1531)). Results of FOMCS comparing Option 1 to Option 2 yielded equivalent results (2.0871 QALYs vs. 2.0870 QALYs, respectively). Although JCV testing yielded greater QALYs than a strategy of using a second anti-TNF in the deterministic and FOMCS models, the difference was not statistically significant in probabilistic analyses (incremental effectiveness 0.0088 (95% CI -0.0118, 0.0241)).

In all strategies, the majority of patients were in post-operative remission, with the second anti-TNF arm having the greatest number of patients in post-operative remission (Table 3). Mortality was greatest in Option 1 and all cases of PML (34 total) occurred in Option 1.

Impact of JCV test results on preferred strategy

For each option, the expected QALY estimates were significantly lower among patients who were JCV antibody positive who had the opportunity to use natalizumab ($P < 0.001$ for Options 1 and 2) (Figure 2A). When prevalence of prior JCV infection is set to 0%, natalizumab is preferred over second anti-TNF (EV 2.0962 vs. 2.0808, incremental effectiveness 0.0154, 95% CI -0.0125, 0.0158). Though this margin of benefit is greater than seen in the base-case model, where the JCV prevalence is 0.536, it is not statistically

significant in probabilistic analysis. When prevalence of JCV antibody is set to 100%, second anti-TNF and JCV antibody testing are equivalent (second anti-TNF EV 2.0808 vs. natalizumab EV 2.0808). This model estimates that incorporating natalizumab into the treatment algorithm (Option 2) would prevent 1328 surgeries in the first year among a cohort of 5000 patients who were JCV antibody negative (Table 4). In a cohort of 5000 patients where the prevalence of prior JCV infection is 54%, Option 2 would prevent 614 surgeries within the first year of follow-up. By three years, the difference in surgery rates is attenuated (428 per 5000 with JCV prevalence=0%; 200 per 5000 with JCV prevalence = 54%).

When assessing these estimates in an alternative model allowing for natalizumab use in the second anti-TNF arm (Option 3 with crossover), natalizumab was again the preferred strategy in a population of patients who were JCV antibody negative (natalizumab EV 2.0962 vs. second anti-TNF EV 2.0908) (Figure 2B). The margin of benefit in those who were JCV antibody negative was significantly smaller in this model than the margin of benefit appreciated in those who were JCV antibody negative in the base model ($p<0.0001$).

Sensitivity analyses

One-way sensitivity analyses were conducted for all transition probabilities and QALY estimates in the model (Supplemental Figure 2A–L). Using a second anti-TNF drug only became the preferred strategy for 3 transition probabilities: 1) if the natalizumab remission rate was less than 24.6%, 2) if relapse rates for an anti-TNF decreased to below 3.2% per cycle, or 3) if natalizumab relapse rates increased to above 21.2% per cycle (See Supplemental Material). The model was also sensitive to two QALY estimates. If the QALY estimate for severe CD decreased to less than 0.54 per year, a second anti-TNF was the preferred strategy. The model was also sensitive to QALY estimates for medical remission; if the QALY estimate for medical remission was reduced to 0.84, second Anti-TNF became the preferred strategy.

We also assessed the impact of adalimumab dose adjustment on decreasing rates of relapse in the base model and in a population without JCV Ab (Figure 3AB). In both of these iterations, adalimumab only became the preferred strategy if the relapse rate could be decreased below 3.2% per cycle, or 72% lower than the 17% rate appreciated in the GAIN trial and used in this model.

Alternative Model structures

Results for all other model iterations were comparable to those in the base model, with Option 2 remaining the preferred strategy over Option 3 (see Supplemental Materials). These iterations include limiting crossover in any treatment strategy, allowing crossover in all strategies including a second anti-TNF, increasing the loss of response rate in natalizumab by 1% per cycle or 4% per year to simulate JCV seroconversion, reducing QALY estimates for post-op remission to simulate a percentage of patients who will flare, estimating the effect of response rates instead of remission rates for transition probabilities, and assessing effects in PNRs to infliximab.

Discussion

We modeled the treatment options for patients with CD who have lost response to an initial anti-TNF medication. We compared three strategies: (1) using a second anti-TNF medication, (2) testing for JCV antibody and treating with natalizumab if this test is negative, or (3) treating all patients with natalizumab regardless of JCV antibody status. We observed that testing for prior JCV infection and selecting the next therapy using these data yielded the greatest expected QALYs, fewest numbers of surgeries, fewest cases of PML, and lowest rates of death as compared to only using a second anti-TNF or natalizumab without screening, although the magnitude of difference in outcomes was small. Specifically, in the absence of prior JCV infection, natalizumab was the preferred treatment strategy, while this strategy was equivalent to a second anti-TNF medication in a cohort of patients who were seropositive. We also demonstrated that among patients who otherwise would not use natalizumab, knowledge of negative JCV antibody status with selection of natalizumab could prevent more than 1300 surgeries per 5000 patients in the first year and more than 400 surgeries over three years.

In an alternative model allowing those patients receiving a 2nd anti-TNF to crossover to natalizumab after adalimumab failure, natalizumab again provided greater benefit for patients without prior JCV infection. In this iteration of the model, the availability of natalizumab as a therapeutic option for those without prior JCV infection had a greater impact on outcomes than the sequence of medications used (i.e. natalizumab prior to second anti-TNF or vice versa).

We have also demonstrated that JCV antibody status has an impact on overall outcomes in those with LOR or PNR to infliximab due to selection or elimination of therapeutic options, with the largest negative impact of JCV status occurring in those in Option 1 due to increasing rates of PML. These results remained consistent through multiple iterations of the model, though in three specific circumstances use of natalizumab without screening became marginally preferable (no crossover in all arms, reduced QALYs for post-operative recurrence, and study lengths less than 30 months). However given the increased risks of mortality and PML, this option is not likely to be clinically viable, despite the increase in overall QALYs in these selected scenarios.

This study has several important strengths. To our knowledge, this is the first model to formally test the impact of JCV antibody test results on outcomes. JCV antibody testing has become the standard of care before utilization of natalizumab, and this model demonstrates that screening with this test is appropriate before initiating therapy with this drug. This is highlighted by comparison to a model that did not include testing before initiating natalizumab, which results in the development of 34 cases of PML over the course of 3 years. Therefore, based on these results, Options 2 and 3 are the most clinically relevant scenarios. One could consider an additional model evaluating an agent that may have a similar mechanism of action as natalizumab without the risk for PML; however, there is currently a paucity of published data to inform such a model at this time. Assuming that the effectiveness and durability of response of the new drug and natalizumab are the same, one

can extrapolate from our model to the new drug by examining our results where the prevalence of a positive JCV antibody is 0.

An additional strength of this model is the use of variable PML rates. Previous models have utilized constant PML rates over time; to our knowledge, this model is the first to assign an increasing risk over time^{12,16}. Using data derived from Bloomgren et al, we assigned an increasing rate of PML risk for those with JCV antibody positive. However, it is possible that even these rates are underestimated. Therefore, we performed a sensitivity analysis increasing the PML rate to as high as 25% per cycle for those who were JCV antibody positive and received natalizumab; This only impacted the blind natalizumab model, with a reduction in QALYs as the rate of PML increased (See Supplemental Figure 2L).

In addition, we tested several important assumptions, including comparing the results when patients treated with a second anti-TNF therapy would or would not use natalizumab if needed to avoid surgery. By doing this, we have modeled the two main clinically relevant scenarios. Finally, we used both deterministic and probabilistic methods to account for uncertainty in the probability estimates incorporated into our model.

There are a number of potential caveats when interpreting the results of this study. In the primary model, the magnitude of difference in QALYs for Options 2 and 3 were small. The overall QALY differences are smaller than those seen in some prior models comparing infliximab to immunomodulators (QALY difference of 0.02) and maintenance with azathioprine to less immunosuppressive therapies (QALY difference 0.05)^{17,19}. However, as in most decision models, there are some patients who reap large benefits and others who receive no benefit from JCV testing. In Monte Carlo simulation of 5000 individuals within each arm, it was shown that JCV antibody testing resulted in 10 fewer deaths and 34 fewer cases of PML when comparing the two options that allowed for testing (Options 2 and 3) to Option 1, which did not. In addition, when considering the implications for an individual patient, it is more relevant to focus on those who are JCV antibody negative, for whom natalizumab or a second anti-TNF would be a viable option. In this setting, the magnitude of difference increased, particularly in the primary model that did not allow transition from a second anti-TNF to natalizumab (incremental effectiveness of 0.0154 QALYs). This implies that using JCV testing increases the treatment options for patients without prior infection and may improve quality of life, with QALY estimates approaching those seen in other studies. Furthermore, this demonstrates that JCV testing and subsequently considering natalizumab use even after a second anti-TNF has failed results in reduced rates of surgery and improved quality of life.

The small difference in QALYS was calculated using deterministic methods, and persisted over all permutations of the model. The low incidence of PML and similar relapse and death rates likely contributed to this small marginal benefit. That probabilistic analyses using distributions derived from the original literature demonstrated that this incremental effectiveness was small enough to have occurred by chance further highlights the need for a randomized controlled trial comparing these strategies.

In addition, Markov models are limited by the quality of the data available for model inputs. However, our model was generally robust to a wide range of estimates across all of the variables except for natalizumab remission rate and extremes of relapse rates for both drugs. The estimates used for natalizumab remission rate (33%) are based on patients previously treated with anti-TNF, but do not account for continued use of thiopurines, which was allowed in ENACT-1. Patients that used concomitant immunosuppressants demonstrated higher response rates, but these estimates were not stratified by anti-TNF use. Therefore we chose the more conservative and relevant estimate⁸. In addition, we derived our adalimumab remission rate from the GAIN trial, one of the only available randomized controlled trials in this patient population⁵. It may be possible that efficacy was underestimated; an open label trial (CARE) has demonstrated higher remission rates³. This again highlights the need for comparative effectiveness trials of natalizumab vs. a second anti-TNF drug. We also assessed improved rates of relapse for adalimumab that could occur via dose adjustment, and determined that a 72% improvement would be required to overcome the benefit of natalizumab. Similarly, while the QALY estimates that were used in this study are the same as those used repeatedly in decision analyses and Markov modeling in IBD, it is important to remember that they are also potentially subjective in nature^{17–19}. However, as with the transition probabilities, we attempted to assess the impact of this error via the use of probabilistic analyses.

We assumed that patients would remain on therapy only if they achieved remission. This approach was selected as estimates of remission rates in clinical trials in CD typically use the same rigorous definition and are less subjective than clinical response. However, some patients may elect to remain on a treatment that induces response rather than remission. As such, our estimated surgical rates are higher than would be observed if we allowed patients to remain on drug with less than a complete remission. However, in sensitivity analyses using response rates, our results did not change. Further, these approaches allow one to consider the proportion of patients who could benefit from new therapeutic agents and to determine the strategy that is most likely to reduce surgical rates and maintain remission in a 3-year window.

An additional assumption was that patients had exhausted dose adjustment strategies in making the decision to switch medications. However, our model did not take into account the results of additional testing to determine drug levels or antibodies against the anti-TNF drug, only noting that patients had active disease requiring a change. It is possible to use drug levels to inform this decision, and this may impact the balance between these strategies. We addressed these possibilities via a sensitivity analysis of adalimumab response. In order to model the effect of drug levels, one could hypothesize that if the adalimumab drug level was high and infliximab antibody testing was negative, the expected response to the second anti-TNF would likely be lower than the transition probability used for our model, thereby favoring Options 1 and 2. Alternatively, if there were positive antibodies to infliximab, the response to a second anti-TNF (ADA) therapy may be higher than the estimate used in our model, favoring Option 3 (See Supplemental Materials for results of this sensitivity analysis). However, even when increasing the response rate to >55% for a second anti-TNF, in this sensitivity analysis, we did not observe a response rate where the second anti-TNF becomes the preferred strategy.

The estimate for JCV antibody seroprevalence was calculated in a population of patients with multiple sclerosis¹¹; it is possible that the prevalence of JCV infection is higher in CD²⁰. Importantly, in our analysis comparing treatment strategies exclusively among patients who have a negative (or positive) JCV antibody, the prevalence of a positive JCV antibody in the population should not influence the results. Rather, a higher prevalence of JCV antibody would only influence the proportion of patients for whom natalizumab therapy is not an option.

In summary, this study demonstrates the potential benefit and improved overall QALYs in those with CD and LOR to infliximab who have a negative JCV antibody status via the availability of an effective medication with a different mechanism of action. Furthermore, this simulation demonstrates that a strategy of JCV antibody testing is preferable to a strategy of treating with natalizumab or a second anti-TNF without JCV antibody testing. Notably, for treatment strategies that use both a second anti-TNF and natalizumab in patients without evidence of prior JCV infection prior to surgery, the order of medication selection appears less important. Prior to the availability of JCV antibody testing, natalizumab use was extremely limited by concern for PML. Our results imply that this may have been a missed opportunity for many patients who lost response to initial anti-TNF therapy and were not JCV antibody positive. Comparative effectiveness trials of these two strategies are needed to confirm our model results in this population with otherwise limited therapeutic options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant Support via NIH: T32- DK007066-36, K08-DK095951-01, K24-DK078228

Abbreviations not featured in the Style Guide

EV	Expected Value
FOMCS	First Order Monte Carlo Simulation
JCV	JC Virus
LOR	Loss of response
NAT	Natalizumab
PNR	Primary Non-Responder to infliximab
QALY	Quality Adjusted Life Year
PML	Progressive Multifocal Leukoencephalopathy
SEER	Surveillance, Epidemiology, and End Results Database
SOMCS	Second Order Monte Carlo Simulation

References

1. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* Apr 15; 2010 362(15):1383–1395. [PubMed: 20393175]
2. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med.* May 6; 1999 340(18):1398–1405. [PubMed: 10228190]
3. Lofberg R, Louis EV, Reinisch W, et al. Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: results from CARE. *Inflamm Bowel Dis.* Jan; 2012 18(1):1–9. [PubMed: 21351211]
4. Ho GT, Mowat A, Potts L, et al. Efficacy and complications of adalimumab treatment for medically-refractory Crohn's disease: analysis of nationwide experience in Scotland (2004–2008). *Alimentary pharmacology & therapeutics.* Mar 1; 2009 29(5):527–534. [PubMed: 19183339]
5. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med.* Jun 19; 2007 146(12):829–838. [PubMed: 17470824]
6. Targan SR, Feagan BG, Fedorak RN, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. *Gastroenterology.* May; 2007 132(5):1672–1683. [PubMed: 17484865]
7. Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. *N Engl J Med.* Jan 2; 2003 348(1):24–32. [PubMed: 12510039]
8. Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med.* Nov 3; 2005 353(18):1912–1925. [PubMed: 16267322]
9. MacDonald JK, McDonald JW. Natalizumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev.* 2007; (1):CD006097. [PubMed: 17253580]
10. Hellwig K, Gold R. Progressive multifocal leukoencephalopathy and natalizumab. *J Neurol.* Nov; 2011 258(11):1920–1928. [PubMed: 21647730]
11. Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol.* Sep; 2010 68(3):295–303. [PubMed: 20737510]
12. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med.* May 17; 2012 366(20):1870–1880. [PubMed: 22591293]
13. Lewis JD, Gelfand JM, Troxel AB, et al. Immunosuppressant Medications and Mortality in Inflammatory Bowel Disease. *Am J Gastroenterol.* Jul; 2008 103(6):1428–1435. [PubMed: 18494836]
14. Statistics NCfH. National Vital Statistics Reports. Sep 20; 2011 59(9):1–61.
15. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology.* Jan; 2007 132(1):52–65. [PubMed: 17241859]
16. Ananthakrishnan AN, Hur C, Korzenik JR. Certolizumab pegol compared to natalizumab in patients with moderate to severe Crohn's disease: results of a decision analysis. *Dig Dis Sci.* Feb; 2012 57(2):472–480. [PubMed: 21909990]
17. Siegel CA, Hur C, Korzenik JR, Gazelle GS, Sands BE. Risks and benefits of infliximab for the treatment of Crohn's disease. *Clin Gastroenterol Hepatol.* Aug; 2006 4(8):1017–1024. [PubMed: 16843733]
18. Siegel CA, Finlayson SR, Sands BE, Tosteson AN. Adverse events do not outweigh benefits of combination therapy for Crohn's disease in a decision analytic model. *Clin Gastroenterol Hepatol.* Jan; 2012 10(1):46–51. [PubMed: 21963958]
19. Lewis J. Azathioprine for Maintenance of Remission in Crohn's Disease: Benefits Outweigh the Risk of Lymphoma. *Gastroenterology.* Feb 01.2000 :1–7.
20. Verbeek J, Van Assche G, Ryding J, et al. JC viral loads in patients with Crohn's disease treated with immunosuppression: can we screen for elevated risk of progressive multifocal leukoencephalopathy? *Gut.* Oct; 2008 57(10):1393–1397. [PubMed: 18436577]

21. Clifford DB, DeLuca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *The Lancet Neurology*. May 01; 2010 9(4):438–446.
22. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol*. Aug; 2009 7(8):874–881. [PubMed: 19558997]
23. SEER. Surveillance, Epidemiology, and End Results Database. Nov 6. 2007 Available at: <http://seer.cancer.gov/>
24. Waterman M, Xu W, Dinani A, et al. Preoperative biological therapy and short-term outcomes of abdominal surgery in patients with inflammatory bowel disease. *Gut*. Mar; 2012 62(3):387–394. [PubMed: 22619367]
25. Lichtenstein GR, Rutgeerts P, Sandborn WJ, et al. A Pooled Analysis of Infections, Malignancy, and Mortality in Infliximab- and Immunomodulator-Treated Adult Patients With Inflammatory Bowel Disease. *Am J Gastroenterol*. Jun 22; 2012 107(7):1051–1063. [PubMed: 22613901]
26. Gregor J, McDonald J, Klar N, et al. An Evaluation of Utility Measurement in Crohn's Disease. *Inflammatory Bowel Diseases*. 1997; 3(4):265–276. [PubMed: 23282873]

Figure 1. Markov model structure

FIGURE 2. 1-Way Sensitivity Analysis for JCV Ab status

1- Way sensitivity analysis of JCV Ab status and impact on QALYs at year 3 for the base model (A) and a model allowing natalizumab use in Option 3 (B).

Figure 3. 1-way sensitivity analysis of adalimumab relapse rates

1-Way sensitivity analysis of adalimumab relapse rates in (A) the base model and (B) a model comprised of patients with negative JCV antibody. In both models, a relapse rate decrease to 3.2% would be required for a second Anti-TNF to become the preferred strategy.

Table 1

Transition probabilities used in primary model

Transition probability	Deterministic value	Range for sensitivity analysis	Source of estimate
Positive JCV Ab	0.535	0–1	11
NAT-related probabilities			
Probability of remission	0.33	0–0.55	8
Probability of relapse	0.1525	0–0.3	8
Probability of serious infection (NAT)	0.01	0–0.10	8
Probability of PML (JCV Ab–)	0.00001	0–0.00001	12
Probability of PML (JCV Ab+, <2y)	0.002	0–0.25	12
Probability of PML (JCV Ab+, >2y)	0.011	0–0.25	12
Probability of severe disability from PML	0.66	0–0.7	21
Probability of death from PML	0.29	0–0.29	21
Second TNF- α related probabilities			
Probability of remission	0.21	0–0.55	5
Probability of relapse	0.17	0–0.3	4, 15
Probability of serious infection	0.0255	0–0.05	3, 5, 15
Probability of lymphoma	0.00015	0–0.003	22
Probability of dying from lymphoma	0.055	0–0.11	22, 23
Surgery related probabilities			
Probability of perioperative death	0.0008	0–0.25	24
Probability of Surgical complication	0.423	0–0.8	24
Probability of death from serious infection	0.001	0–0.1	13, 25
Probability of death in 35 year-old man with CD	0.0018	0–0.01	14

Table 2

QALY estimates used in model

QALY estimates	QALY value	Range used for sensitivity analysis**	Source
Death	0	0	*
Severe CD	0.62	0.2–1	19,26
Severe infection	0.62	0.4–0.8	*
Remission	0.89	0.7–1	19,26
Surgery complication	0.15	0–0.62	*
Post-operative period, no complication	0.25	0.1–0.65	*
Post-operative Remission	0.80	0–1	19,26
Lymphoma	0.47	0–0.47	17,19,26
Surviving lymphoma	0.67	0–0.67	17,19,26
Severe PML	0	0–0.3	*
Mild PML	0.32	0.1–0.6	*

* Estimate based on researcher consensus

** Range given in QALYs, sensitivity analysis conducted in QALQs (QALY/4)

Table 3

Markov Cohort Analysis of 5000 patients

Markov cohort analysis at the end of 1 year (Y1), 2 years (Y2), and 3 years (Y3), for total number of infections, total number of surgeries, total number of surgical complications, total number of individuals in surgical remission, total cases of PML, and overall mortality. Patients undergoing surgery could subsequently enter the surgical remission state, either via a complicated or uncomplicated course.

	Option1			Option 2			Option 3		
	Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3
Total Infections	248	346	398	220	289	324	238	301	331
Total Surgeries	2986	3935	4422	3699	4352	4667	3720	4369	4680
Total Surgical Complications	1093	1588	1833	1448	1770	1949	1456	1796	1952
Total in Surgical Remission	99	3514	4167	2152	4051	4474	3929	4511	4729
Total PML	14	26	34	0	0	0	0	0	0
Total Dead	31	67	104	25	60	94	25	60	94

Table 4
Markov Cohort Analysis of 5000 patients without JCV antibody

Markov cohort analysis at the end of 1 year (Y1), 2 years (Y2), and 3 years (Y3) in a cohort who were JCV Ab negative, for the total number of infections, total number of surgeries, number of surgical complications, total number of individuals in surgical remission, total cases of PML, and overall mortality. Patients undergoing surgery could subsequently enter the surgical remission state, either via a complicated or uncomplicated course.

	0% JCV antibody prevalence					
	JCV testing (Option 2)			Second Anti-TNF (Option 3)		
	Y1	Y2	Y3	Y1	Y2	Y3
Total Infections	251	353	406	197	240	258
Total Surgeries	2992	3945	4440	4314	4706	4868
Total Surgical Complications	1094	1590	1837	1755	1962	2048
Total in Surgical Remission	100	3519	4179	3930	4511	4729
Total PML	0	26	0	0	0	0
Total Dead	27	60	94	24	59	94