Benefit of Additional Screening for Progressive Multifocal Leukoencephalopathy in Patients With Multiple Sclerosis Taking Natalizumab: A Decision Analysis

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Objective: Patients with multiple sclerosis (MS) taking natalizumab are at risk for progressive multifocal leukoencephalopathy (PML). We sought to describe the outcomes of discontinuing natalizumab on the basis of PML risk and those of obtaining additional screening across a range of scenarios using decision tree models.

Methods: Health state probabilities and values, measured as the proportion of quality–adjusted life years (PQALY) relative to baseline health, were based on literature review. Probabilities of worsening MS while continuing and discontinuing natalizumab were set to 0.23 and 0.44. For discontinuing therapy, PML risk, worsening MS value, and PML value were varied. For additional screening, the probability of discontinuing natalizumab without screening, PML risk, worsening MS value, and PML value were set to 33%, 1.1%, 0.88, and 0.09, respectively, with test sensitivity and specificity varying from 0.50 to 1.

Results: Discontinuing natalizumab provided no benefit until PML risk reached 2.9%, assuming an MS relapse value of 0.88 and a PML value of 0.09. Additional screening changed the PQALY by −0.3% to 1.5%, largely influenced by specificity. Assuming a sensitivity of 80% and a specificity of 99%, screening increases the PQALY by 1.2%.

Conclusions: The highest PML risk identified by stratification is below 2.9%, suggesting that continuing natalizumab outweighs PML risk for most patients on the basis of theoretical calculations. However, decisions based on additional screening with high-specificity tests, including polymerase chain reaction cerebrospinal fluid tests for John Cunningham virus, may provide benefit and should be clinically tested. Increased precision of probabilities and quality-of-life values are also needed to improve decision making.

Key Words: multiple sclerosis, progressive multifocal leukoencephalopathy, natalizumab

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Natalizumab was approved for the treatment of relapsing multiple sclerosis (MS) in 2004 based in part on the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) trial, which showed that natalizumab significantly decreased MS relapses, decreased disease progression, and increased quality of life compared with placebo.[1,2] A year later, natalizumab was withdrawn after several patients developed progressive multifocal leukoencephalopathy (PML), a rare and severe neurological condition caused by infection or reactivation of the John Cunningham (JC) virus.[3–5]

Because of its efficacy compared with alternative therapies, natalizumab was then brought back to the market in 2006, accompanied by the Tysabri outreach: unified commitment to health program, which restricted access to registered health care providers.[6] The program also required evaluating patients 3 and 6 months after starting natalizumab and every 6 months thereafter. The program relied on clinical evaluation and did not specify a role for risk factor screening.

Under this model, more than 350 patients developed PML.[7] Review of these cases identified several risk factors for developing PML including duration of natalizumab therapy, prior immunosuppression therapy, and serum JC virus antibodies.[8] Although these factors discriminate patients by relative PML risk, their absolute discrimination is poor, with a difference of only 1.1% separating the highest- and lowest-risk patient groups. These factors also fail to identify all at-risk patients.[9,10]

Currently, more than 100,000 patients take natalizumab with most having one or more risk factors.[8] More than half have JC virus antibodies in their serum, more than half have taken natalizumab for 2 or more years, and nearly half have received prior immunosuppressive therapy.[8,11,12] If these patients remain on natalizumab, some are expected to develop PML. Recommendations for clinical practice now include stratifying patients by risk factors and discontinuing therapy in patients positive for all 3 risk factors or even fewer.[13–17]

For some patients, natalizumab is the last-line therapy and the only mechanism by which to control their disease.[18] For these patients, the discontinuation of natalizumab and the likely onset of worsening MS must be compared with their risk for developing PML. For these patients, it is unclear what absolute risk for developing PML justifies discontinuing natalizumab. Patient-centered data suggest that many are willing to tolerate PML risk to avoid worsening MS.[19,20] Although PML can be a devastating complication in patients with MS, recent evidence suggests that natalizumab-induced PML may be less severe than that more commonly seen in patients with HIV.[21,22]

Additional screening may identify patients where the decision to continue or discontinue natalizumab is better justified. We sought to determine the risks and benefits of continuing natalizumab across increasing levels of PML risk and those of obtaining additional screening through decision analysis.

METHODS

Decision tree models were created to compare possible choices of patients with MS taking natalizumab with models depicting paths from choices to the health states that could result. The outcome of each choice was defined as the sum of the probabilities of the resulting health states after that choice multiplied by the values of the health states. Choices were compared by both probabilities of the resulting health states,

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expressed per 1000 patients, and outcomes that incorporated the values of these states. Decisions were examined across a range of health state probabilities and values so that choices could be compared across this spectrum of scenarios. These probabilities and health state values were selected on the basis of literature review.

The first model was for patients taking natalizumab deciding to continue therapy on the basis of concerns over PML risk versus discontinuing therapy (Fig. 1A). It was assumed that these patients showed no clinical signs of PML and that their MS was well controlled on therapy. For patients choosing to continue therapy, 1 of 3 potential health states could result: develop PML, have worsening MS, or remain at baseline health. Worsening MS was considered to be a hybrid health state and represented deterioration from baseline greater than expected as compared with a more indolent disease course. For patients choosing to discontinue therapy, 1 of 2 potential states could result: have worsening MS or remain at baseline health.

The second model was for patients taking natalizumab deciding whether to pursue additional screening on which to base their decision to continue therapy versus basing this decision on risk factor stratification alone (Fig. 2A). It was assumed that these patients show no clinical signs of PML and that their MS is well controlled on therapy. Further, it was assumed that these patients have all 3 risk factors currently proposed for stratifying patients: have been on natalizumab for 2 years, received immunosuppressive therapy, and have serum JC virus antibodies. For patients choosing to receive additional screening, 1 of 3 screening test results could result: false negative, true negative, or positive, either false or true. For patients with a

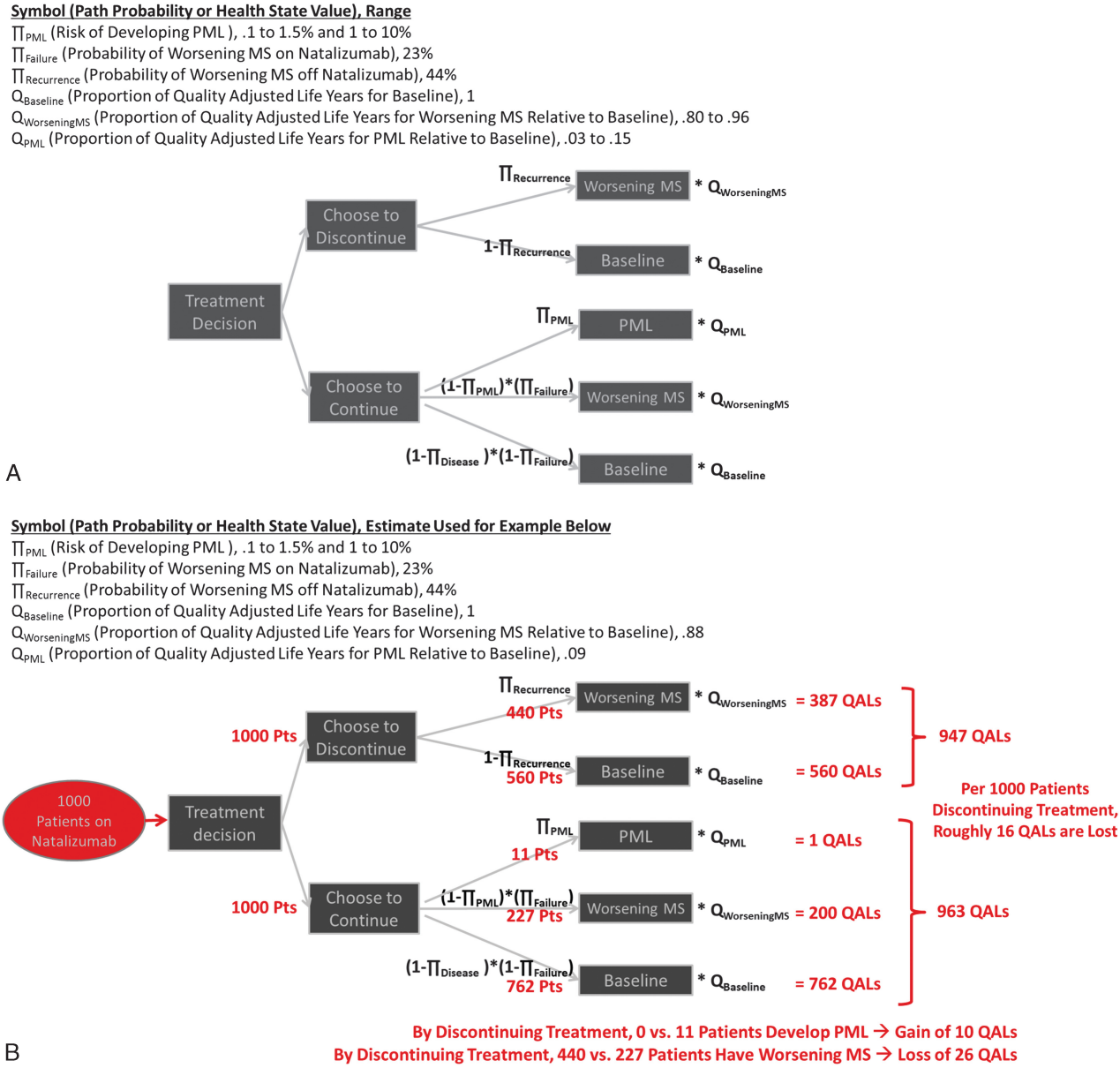

FIGURE 1. Decision tree model of the decision to continue natalizumab (A) with analysis of a specific scenario provided (B). Pts indicates patients; QAL, quality-adjusted lives.

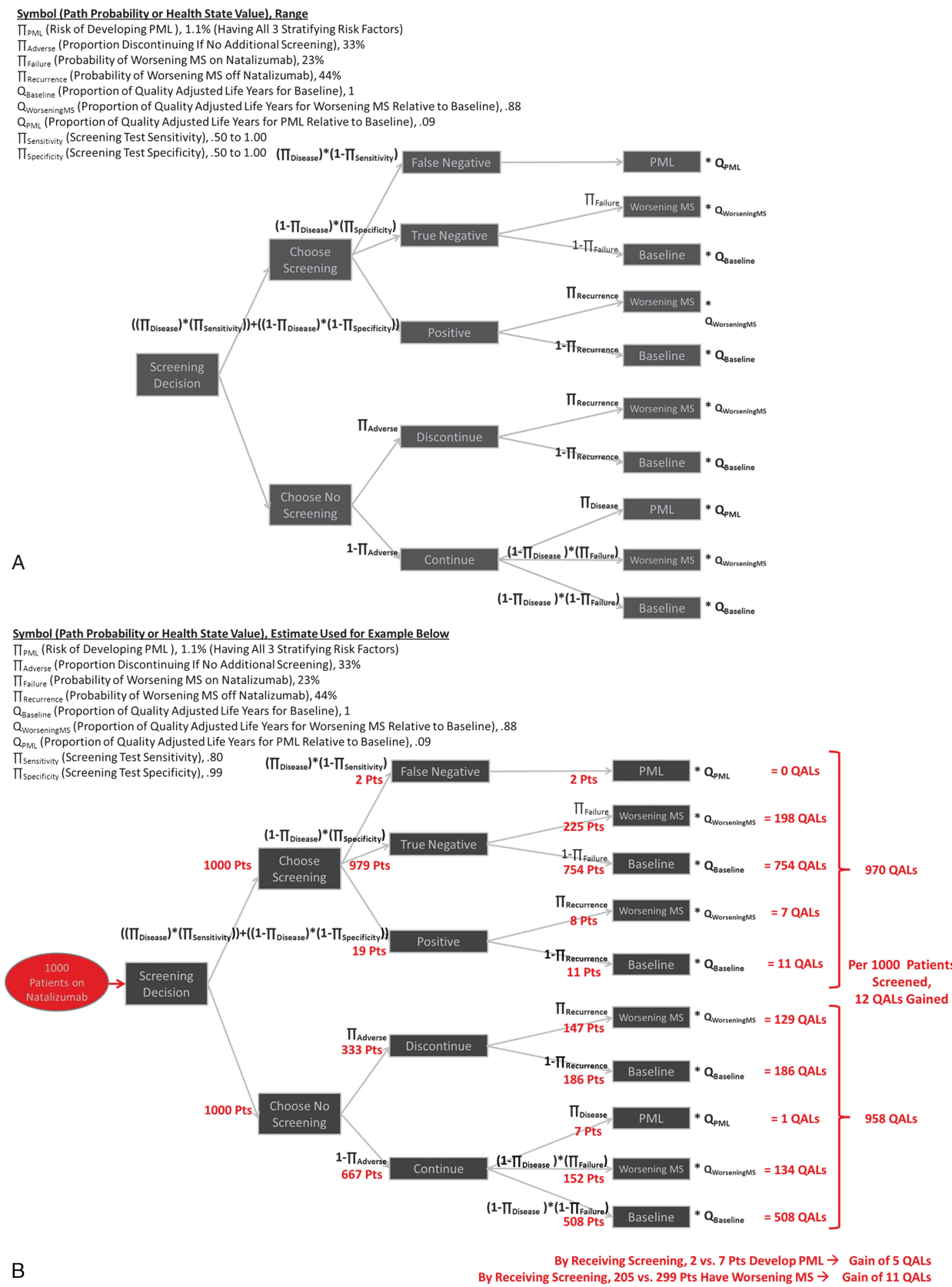

FIGURE 2. Decision tree model of the decision to receive additional screening for PML upon which to base the decision to continue natalizumab (A) with analysis of a specific scenario provided (B). Pts indicates patients; QAL, quality-adjusted lives.

false-negative result, it was assumed that all developed PML. For patients with a true-negative result, it was assumed that they continued therapy and either had worsening MS or remained at baseline health. For patients with a positive test, it is assumed that they discontinued therapy and either had worsening MS or remained at baseline health.

In the first model, the risk for PML while taking natalizumab was first allowed to vary from 0% to 1.5% to represent the range of PML risks predicted by the currently proposed method of risk stratification. Second, the risk for PML varied from 1% to 10% to assess a wider range of PML risks that might be predicted by incorporating additional screening results. The risk for worsening MS while taking natalizumab and not taking natalizumab were estimated on the basis of the MS relapse rates for the therapy and placebo groups from AFFIRM trial at 23 and 44%, respectively. The probability of baseline health was then defined as 1 minus both the probability of PML and worsening MS.

In the second model, the risk for PML while taking natalizumab was set equal to 1.1% because this model was for patients positive for all 3 risk factors. For patients deciding on the basis of risk factor stratification alone, the probability of choosing to discontinue therapy was set at 33% on the basis of recent recommendations by some that these patients discontinue therapy. For patients pursuing additional screening, the probability of a false-positive test result was set equal to the risk for PML multiplied by 1 minus screening test sensitivity. The probability of a true-negative result was set equal to 1 minus PML risk multiplied by screening test specificity. The probability of a positive-test result was set equal to PML risk multiplied by screening test sensitivity plus 1 minus PML risk multiplied by 1 minus screening test specificity. Both specificity and sensitivity were evaluated across the range from 0.50 to 1 to capture the range of values that could be associated with additional screening tests. The PML value was set to 0.09; the worsening MS value, to 0.88.

For the analysis of both models, health state values were measured as the proportion of quality–adjusted life years (PQALY) associated with having that health state for 2 years relative to remaining at baseline health for those 2 years, defined as the expected life of a patient with controlled MS. The quality-adjusted life years associated with remaining at baseline health for those 2 years were set equal to 1. The PQALY associated with other health states could be reduced because of either a decreased duration of life or a decreased quality of life. Decreased quality of life associated with a health state was considered to be both the quality during the 2-year period and any deferred impact on quality. For worsening MS and PML, evidence suggests that decreased duration and quality of life likely both impair the PQALY.

For PML, short-term mortality rates vary significantly with studies of PML in HIV-positive patients reporting mortality at 50% and higher.[23] However, for PML associated with natalizumab, mortality seems to be lower.[21] For surviving patients with natalizumab-associated PML, quality of life is significantly impaired, but most patients stabilize several months after diagnosis.[21] To reflect this heterogeneity and uncertainty, the PQALY associated with PML varied from 0.03 to 0.15. The lower bound of this range also reflects the long-term effect of developing this health state relative to remaining at baseline health.

For worsening MS, long-term survival is impaired and highly correlated with accumulating disability.[24] In addition, although the long-term effects of worsening MS over a period such as 2 years are not possible to predict, it is this perception of risk that patients are forced to grapple with when weighing the risks of benefits of continuing therapy. These patients may have a decreased life-span relative to patients with MS remaining at baseline health.[25] Patients with worsening MS also have a reduced quality of life as measured in cohort studies and the AFFIRM trial.[26–28] To reflect this heterogeneity and uncertainty, the PQALY associated with worsening MS during a 2-year span varied from 0.80 to 0.96. The upper bound of this range also reflects the potentially modest deficit of having worsening MS during a limited 2-year period.

Although the health state probabilities and values varied and the outcomes of each choice measured across these

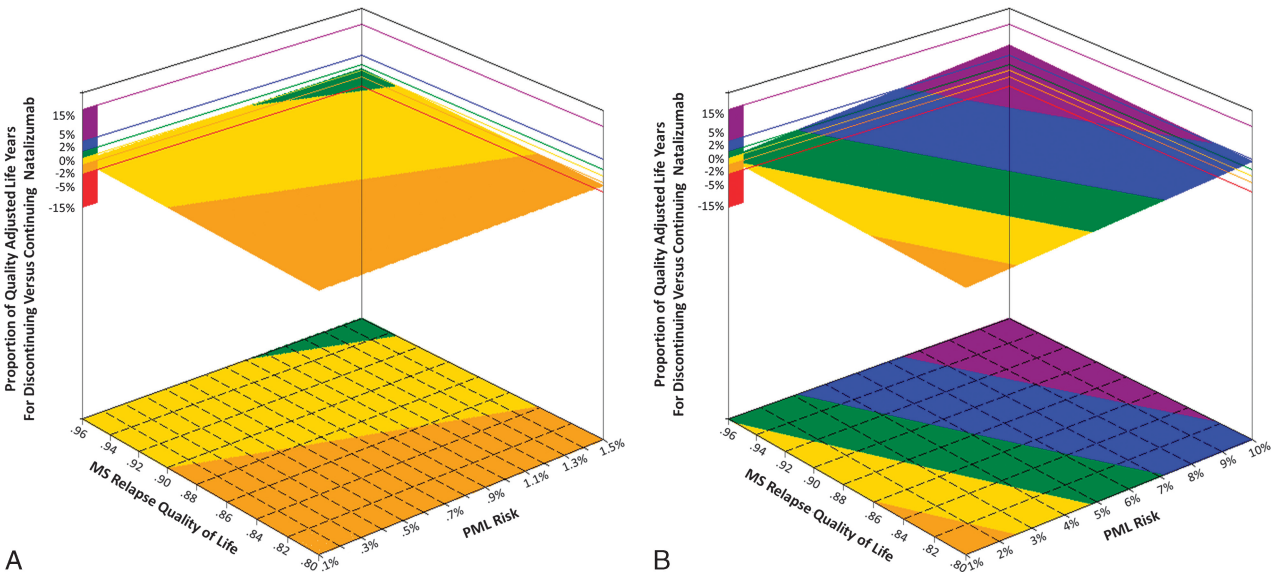

FIGURE 3. Change in the PQALY associated with discontinuing compared with continuing natalizumab by PML risk and worsening MS value with PML value set at 0.09 across PML risks consistent with risk factor stratification levels from 0% to 1.5% (A) and a broader range from 1% to 10% (B).

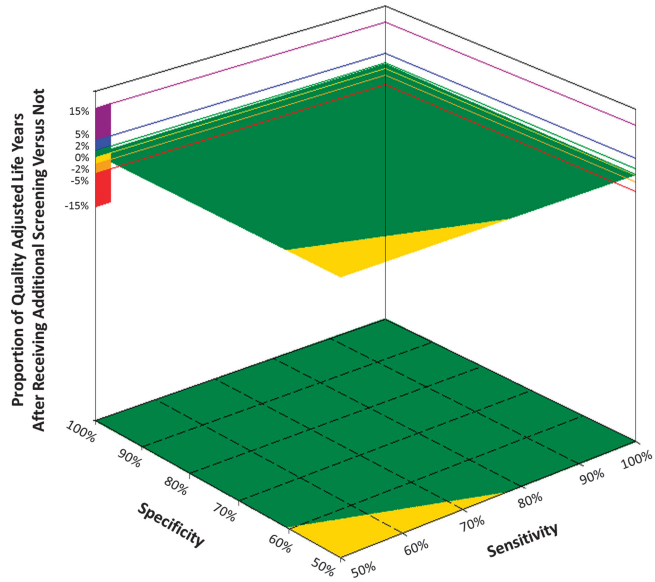

FIGURE 4. Change in the PQALY associated with receiving additional screening for PML upon which to base the decision to continue natalizumab compared with basing the decision on risk factor stratification alone. The proportion discontinuing natalizumab without additional screening, PML risk, PML value, and worsening MS value were set at 33%, 1.1%, 0.09, and 0.88, respectively.

different scenarios, examples analyzing specific scenarios are also provided (Figs. 1B, 2B).

RESULTS

For every 1000 patients discontinuing natalizumab in scenarios with PML risk levels consistent with risk factor stratification, there were 1 to 15 fewer PML cases but 207 to 210 more worsening MS cases. Those discontinuing therapy had a change in their PQALY from a loss of 4.1% to a gain of 0.6% across these scenarios. When the PML value was held at 0.09, the change in PQALY after discontinuing therapy varied from a loss of 4.1% to a gain of 0.5%, depending on MS worsening value (Fig. 3A).

For every 1000 patients discontinuing natalizumab in scenarios with PML risk levels from 1% to 10%, there were 10 to 100 fewer PML cases but 189 to 207 more worsening MS cases. Compared with patients continuing natalizumab, those discontinuing therapy had a change in their PQALY from a loss of 3.4% to a gain of 8.8% across these scenarios. When the PML value was held at 0.09, the change in PQALY after discontinuing therapy varied from a loss of 3.3% to a gain of 8.3%, depending on worsening MS value (Fig. 3B). When the values of PML and worsening MS were held at 0.9 and 0.88, respectively, the PML risk at which patients discontinuing versus continuing therapy had greater PQALY was 2.9%.

For every 1000 patients with all 3 stratifying risk factors receiving additional screening versus basing their decision on stratification alone in the scenarios examined, there were between 7 and 2 fewer cases of PML and from 67 fewer to 38 more cases of worsening MS. Compared with patients basing their decision on stratification alone, those receiving additional screening had a change in their PQALY from a loss of 0.3% to a gain of 1.5% across these scenarios, and this varied on the basis of the sensitivity and specificity of the additional screening test with specificity appearing to have a larger influence (Fig. 4).

DISCUSSION

For patients without other therapeutic options and PML risk at levels consistent with risk factor stratification, 0% to 1.5%, the benefits of continuing natalizumab likely outweigh the possible effects of PML. For patients assigning values relative to baseline of 0.09 for PML and 0.88 for worsening MS during a 2-year period, their risk for PML would need to be at least 2.9% for the effect of PML to outweigh the benefit of continuing natalizumab and having a reduced probability of worsening MS. As PML risk exceeds 5%, few patients would likely benefit from continuing therapy, although this level is roughly 5 times greater than the highest level predicted by risk factor stratification. Identifying patients with such a high predicted risk will require additional screening, which our results suggest should be highly specific to provide the greatest benefit.

The manner in which patients actually weigh the risks for PML and worsening MS is not well understood. Some patients may be willing to tolerate more PML risk, especially if the disease course is less severe than that reported in other populations such as HIV patients.[18–20] Given the complexity of the scenarios and the lack of data on the precise probabilities involved, decision making of the patient is challenging and inexact. Even the quality of life associated with these health states is difficult to estimate and varies across individual patients, further complicating patient counseling.

In a review of more than 2000 patients with MS enrolled in clinical trials of natalizumab, patients experiencing a relapse had significantly worse physical functioning.[2] The progressive nature of these relapses and disease progression over increased follow-up are not known. In a review of 35 patients with natalizumab-induced PML and a median follow-up of 5 months, 25 survived, although nearly half of these patients were severely disabled.[21] A physician-guided, patient-centered approach will hopefully maximize decision quality. Additional data on health state probabilities and quality-of-life measures as well as decision support tools are also likely to help the decision-making process.

For patients at the highest PML risk level identified by stratification, our data suggest that additional screening might provide additional benefit. Of note, the model in this study evaluated 1-time screening and assessed the outcomes of different choices on the basis of the effects of having a health state for just 2 years. In actual practice, sequential screening would

likely be used and resulting health states would be of longer duration. Although ideal screening frequency is beyond the scope of the current analysis, more screening would likely result in the prevention of PML cases while increasing the number of patients unnecessarily discontinuing natalizumab.

Several tests have been proposed for additional screening including magnetic resonance imaging[29,30] and cerebrospinal fluid (CSF) testing.[7,31–33] The test with the most promise may be CSF testing for JC viral DNA by quantitative PCR, which is highly specific and has even been used diagnostically in several studies.[7] Cerebrospinal fluid testing also seems to have a high sensitivity especially with the advent of low-threshold tests, which can detect viral DNA at levels as low as 10 to 50 copies per milliliter.[31,34] Of note, the simplified models analyzed in this study did not include screening complications other than those associated with false tests. Although complications with lumbar puncture are minimal when conducted in appropriate settings, they should be measured in future studies. Physicians may wish to consider offering additional screening such as quantitative PCR with CSF fluid.

A limitation of this study is the simplicity of the models. The possible health states, baseline health and worsening MS, are composites of more specific health states. Although these distinctions would increase the exactness of the models, it is not clear whether patients incorporate this level of specific information into their decision-making process. The probabilities of these health states were taken from the AFFIRM trial relapse rates. The natalizumab to placebo ratio seems stable across outcomes and trials likely minimizing the possibility of significant bias.[35] In addition to the probability values, the quality-of-life values are only estimates. However, models were analyzed across broad ranges of health state value probabilities and values.

In conclusion, for patients whose only therapeutic option is natalizumab, continuing the drug outweighs PML risk at the highest level identified by stratification, on the basis of theoretical calculations. However, decisions based on additional screening with high-specificity tests, such as the low-threshold CSF test for JC virus, may benefit the decision-making process. Clinical studies are needed to confirm these findings and further elucidate best management practices for these patients. Of course, all of these decisions should be physician-guided and patient-centered and will be improved when more precise estimates of probability and quality-of-life values for specific health states become available.

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