

# Weighing Treatment Benefits Against Treatment Risks: Crohn's Disease Patients' Willingness to Accept Risk-Benefit Tradeoffs

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## INTRODUCTION

- All medical interventions carry risks of adverse outcomes that must be evaluated against their clinical benefits.
  - Clinical trials have documented significant benefits of Tysabri for many patients with Crohn's disease (CD).<sup>1</sup>
  - Patients who take Tysabri have a potential increased risk of developing progressive multifocal leukoencephalopathy (PML), a frequently fatal central nervous system infection. Three cases of PML were observed among 3,215 patients who were treated with Tysabri in the CD and multiple sclerosis clinical trials. The estimated annualized risk of PML based on these data is 0.065%.
  - Balancing the potential benefits and potential serious adverse event (SAE) risks is a common problem in evaluating new treatments.
- The goal of this study was to quantify the willingness of CD patients to accept the risk of treatment related to SAEs in exchange for improvements in treatment efficacy.

## METHODS

### Survey Instrument Design

- Risk-benefit preferences were elicited using conjoint analysis (CA)
  - CA is the most valid and reliable technique available for quantifying patient preferences.<sup>2,3</sup>
  - CA quantifies subjects' willingness to accept tradeoffs between alternatives with multiple attributes.
- Risk-benefit tradeoff questions
  - Simulate choices among clinically relevant treatment alternatives.
  - Collect data on patients' CD status and symptoms corresponding to standard measures of CD severity.
- Treatment attributes were drawn from published literature and in consultation with medical experts.

### Survey Instrument Pretest

- Conducted cognitive interviews with 10 patients and collected pilot data from an additional 51 patients
- Assessed patients' ability to understand and accept the treatment attributes and levels
- Confirmed willingness to trade off treatment efficacy against SAE risks

### Survey Instrument Content

- Demographics
- Elements of the Crohn's Disease Activity Index (CDAI)
- Short form of Inflammatory Bowel Disease Questionnaire (IBDQ)
- Definitions of treatment attributes and levels used in the trade-off items (Table 1)
  - Comparable detail was provided in the descriptions of the serious infection, PML, and lymphoma adverse events.
  - PML definition: "Studies suggest that some medicines for CD increase your chance of getting PML. PML is a rare brain infection. The symptoms of PML are serious and may include the inability to think clearly, paralysis, blindness, and coma. PML may result in death or serious disability."

Table 1. Treatment Attributes and Levels

Treatment Attributes	Levels
Symptom severity and activity limitations	<b>Remission</b> <ul style="list-style-type: none"> <li>No pain most days</li> <li>No more than one loose stool per day</li> <li>Generally feel well</li> <li>No problems with work or leisure activities</li> </ul>
	<b>Mild Crohn's disease</b> <ul style="list-style-type: none"> <li>Mild pain most days</li> <li>About 3 diarrhea stools per day</li> <li>Generally feel below par</li> <li>Some problems with work and leisure activities</li> </ul>
	<b>Moderate Crohn's disease</b> <ul style="list-style-type: none"> <li>Moderate pain most days or severe pain on some days</li> <li>About 8 or more diarrhea stools per day</li> <li>Generally feel poorly</li> <li>Considerable problems with work and leisure activities</li> </ul>
	<b>Severe Crohn's disease</b> <ul style="list-style-type: none"> <li>Severe pain most days</li> <li>More than 12 diarrhea stools per day</li> <li>Generally feel terrible</li> <li>Unable to engage in work and leisure activities</li> </ul>
Serious complications from CD	<ul style="list-style-type: none"> <li>Treatment prevents all serious complications of CD</li> <li>Treatment reduces some of the serious complications of CD</li> <li>Treatment has no effect on the serious complications of CD</li> </ul>
Time between flare-ups	<ul style="list-style-type: none"> <li>6 months between flare-ups</li> <li>2 years between flare-ups</li> </ul>
Need to take oral steroids	<ul style="list-style-type: none"> <li>Requires taking steroids</li> <li>Does not require taking steroids</li> </ul>
Chance of death from serious infection, death or severe disability from PML, or death from lymphoma within 10 years	<ul style="list-style-type: none"> <li>None (0%)</li> <li>5 patients out of 1,000 (0.5%)</li> <li>20 patients out of 1,000 (2%)</li> <li>50 patients out of 1,000 (5%)</li> </ul>

## Subjects

- Adult (≥18 years) patients who were US residents and who provided online informed consent
- Samples drawn from 3 patient panels
  - "Tysabri-Naïve Internet Panel" (N=342): drawn from a list of subscribers to the HealthTalk Web site, a Web service that provides chronically ill patients with access to information on advanced treatments and disease management

Figure 1. Example of Conjoint Tradeoff Task Comparing CD Treatment Options

Treatment Features	Treatment A	Treatment B
<b>Severity of daily Crohn's symptoms</b>	<b>Moderate</b> <ul style="list-style-type: none"> <li>Moderate pain on most days or severe pain on some days</li> <li>About 8 or more diarrhea stools per day</li> <li>Generally feel poorly</li> <li>Considerable problems with work and leisure activities</li> </ul>	<b>Mild</b> <ul style="list-style-type: none"> <li>Mild pain most days</li> <li>About 3 diarrhea stools per day</li> <li>Generally feel below par</li> <li>Some problems with work and leisure activities</li> </ul>
<b>Effect on serious complications (fistulas, abscesses, bowel or obstructions)</b>	<b>Prevents all</b> serious complications	<b>Reduces some</b> of the serious complications
<b>Time between flare-ups</b>	2 years	6 months
<b>Treatment requires taking oral steroids</b>	Yes	Yes
<b>Chance of dying from a serious infection within 10 years</b>	<b>None</b> would die	<b>None</b> would die
<b>Chance of dying or severe disability from PML within 10 years</b>	<b>5 patients out of 1,000 (0.5%)</b> would die or have severe disability	<b>None</b> would die or have severe disability
<b>Chance of dying from lymphoma within 10 years</b>	<b>None</b> would die	<b>None</b> would die
<b>Which treatment would you choose?</b>	<input type="checkbox"/> Treatment A	<input type="checkbox"/> Treatment B

- "Tysabri-Naïve Clinical Panel" (N=140): patients who had no record of participation in any CD clinical trial recruited from clinical practice sites
- "Tysabri Patient Panel" (N=98): patients who had participated in a Tysabri clinical trial recruited from clinical practice sites

## Study Design and Analytic Techniques

- All data were collected via a Web-enabled survey instrument.
- Each patient completed 10 conjoint tradeoff tasks in one of six versions of the survey. An example of one of the tradeoff tasks is provided in Figure 1.
- The survey included several internal validity tests to ensure data quality.
- Between-panel comparisons of continuous variables were made using one-way analysis of variance (ANOVA) with post-hoc tests conducted using the Tukey procedure.
- Chi-square tests were conducted for tests of categorical variables. All tests were conducted using  $p \leq 0.05$ .
- A random utility modeling (RUM) approach was used to estimate CD patient preferences from the observed pattern of choices in the tradeoff tasks.

## Primary Endpoints

- The relative contribution of the treatment efficacy and risk attributes to patient preferences
- The mean maximum acceptable annual risk (MAR) of the SAEs for combinations of the treatment efficacy attributes. The 10-year risk levels were converted to annual risk for the purpose of comparison.
- The percentage of patients accepting various levels of PML risk for a combination of treatment efficacy attributes

## RESULTS

### Demographic Characteristics (Table 2)

- The panels were significantly different with regard to gender, age, education, and duration of CD experience but were similar in race, employment status, and annual household income.

Table 2. Demographic Characteristics of the Study Panels

Variable	Response Category	Tysabri-Naïve Internet Panel (N=342)	Tysabri-Naïve Clinical Panel (N=140)	Tysabri Patient Panel (N=98)
Gender*	Female	73%	66%	53%
Age*	Mean	45	39	43
Years of Education*	Mean	16	16	15
Years Since CD Symptoms Developed*	< 2	11%	16%	3%
	3-5	25%	22%	18%
	6-10	19%	23%	19%
	11+	46%	40%	61%

\* $p < 0.05$

### Disease and Quality-of-Life Experience (Table 3)

- Abdominal pain, general well-being, and the impact of CD on activities was much greater ( $p < 0.001$ ) in the Tysabri Patient Panel.
- The Tysabri Patient Panel also reported a significantly higher number of diarrhea stools in the last 7 days.
- The Tysabri-Naïve Internet Panel had the worst total IBDQ score, and the Tysabri-Naïve Clinical Panel had the best total IBDQ score ( $p < 0.05$ ).

Table 3. CD Symptom and Quality-of-Life Experience of the Study Panels

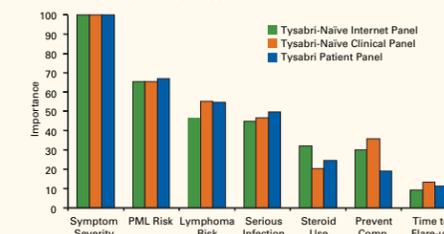
Variable	Response Category	Tysabri-Naïve Internet Panel (N=342)	Tysabri-Naïve Clinical Panel (N=140)	Tysabri Patient Panel (N=98)
Abdominal Pain in Past 7 Days*	None-Mild	73%	73%	58%
	Moderate-Severe	27%	27%	42%
Well-Being in Past 7 Days*	Well	47%	52%	28%
	Below Par-Poor	47%	44%	63%
	Very Poor-Terrible	6%	4%	9%
Impact on Activities in Past 7 Days*	No-Some Problems	85%	89%	71%
	Considerable-Unable	15%	11%	29%
# Diarrhea Stools*	Mean	15	13	26
IBDQ Score*	Mean	144	154	132

\* $p < 0.05$

### Treatment Preference Estimates (Figure 2)

- Across panels there was strong agreement in estimates of the relative importance of the treatment attributes.
- Improvement in daily symptom severity is the most important treatment attribute. PML risk was the next most important attribute, followed by the risk of death from lymphoma and serious infection.
- Data quality checks confirm the patients' ability to interpret the choices and validate the reported estimates.

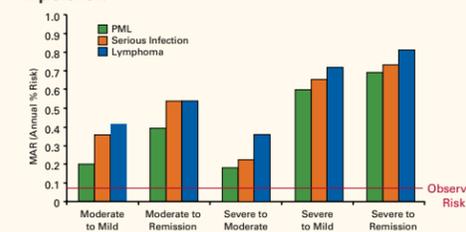
Figure 2. The Relative Contribution of the Treatment Efficacy and Risk Attributes to Patient Preferences



### Maxium Acceptable Annual Risk of Serious Adverse Events (Figure 3)

- Greater symptom improvements are associated with greater risk tolerance.
- A weighted-mean MAR was calculated using the observed proportion of patients who experienced each level of benefit in the Tysabri clinical trials. The mean MAR of PML death or disability is 0.44% for a benefit equal to that seen in the Tysabri clinical trials.
- The MARs for the five benefit levels are substantially above the currently estimated risk of the SAEs.

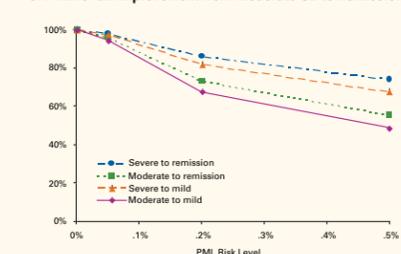
Figure 3. MAR of Serious Adverse Events by Amount of Clinical Improvement



### Percentage of Patients Accepting Various Levels of PML Risks by Benefit Level (Figure 4)

- Predicted percentage of patients accepting different benefit-risk tradeoffs for the three patient panels.
- The larger the risk, the lower the percentage of patients who would accept risk in order to receive this level of benefit.
- About 95% of patients would accept the estimated PML risk to achieve an improvement from moderate CD symptoms to remission.

Figure 4. Percentage of Patients Accepting Various Annual Risks of PML for an Improvement from Moderate CD to Remission



## CONCLUSIONS

- Stated MAR for PML for a clinically relevant benefit level is well above an extrapolation of the currently estimated PML risk.
- About 95% of patients would accept the currently estimated annual risk of PML death or disability to obtain the typical clinical efficacy observed in the Tysabri clinical trials.

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