

Patients' Willingness to Accept Risk-Benefit Tradeoffs in Treating Crohn's Disease

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ABSTRACT

Background: All medical interventions carry risks that must be evaluated against clinical benefits.

Objectives: To evaluate the willingness of Crohn's disease (CD) patients to accept treatment-related serious adverse event (SAE) risks in exchange for clinical improvements.

Methods: An online panel of CD patients >18 years old in the US completed a carefully designed and tested questionnaire containing stated preference (SP) benefit-risk trade-off items. The SP method is used by health economists to quantify the relative importance of treatment processes and outcomes. The questionnaire asked patients to select between treatment alternatives with different levels of benefit and risk attributes. Attributes included severity of daily symptoms, rate of serious CD complications (fistulas, abscesses, bowel obstructions), time between flare-ups, oral steroid use, and varying levels of SAE risks (disability and death from Progressive Multifocal Leukoencephalopathy [PML], serious infection, or lymphoma). Information was collected on demographics, disease history, and functional status. The maximum acceptable 1-year risk (MAR) for SAE development was calculated for various levels of clinical benefit using logistic models.

Results: Mean age of the 342 respondents was 45; 73% were female. Higher MAR, indicating greater risk acceptance, was observed for trade-off tasks involving higher levels of clinical benefit, among patients with lower current functional status, and among patients reporting a low level of worry about the potential adverse events. For PML, the mean (95% CI) MARs for an improvement from severe daily symptoms to remission and moderate daily symptoms to mild daily symptoms were 0.70% (0.60–0.80%) and 0.22% (0.14–0.30%), respectively. For serious infection and lymphoma, respectively, the mean (95% CI) MARs for an improvement from severe symptoms to remission were 0.73% (0.66–0.81%) and 0.82% (0.72–0.92%), and from moderate symptoms to mild symptoms were 0.37% (0.17–0.57%) and 0.42% (0.33–0.52%). The lowest observed MAR for any of the three studied SAEs is higher than observed rates of SAE occurrence with natalizumab and commonly used CD medications.

Conclusions: CD patients indicated they are willing to accept a defined risk of death or disability in exchange for defined levels of clinical effectiveness. This type of trade-off information can inform treatment and regulatory decisions.

CONFLICT OF INTEREST

The design and analysis of this study were conducted by the employees of RTI Health Solutions, a nonprofit research organization. Data collection was conducted by MRxHealth, an international market research and consulting firm. This study was funded in part by Elan Pharmaceuticals.

BACKGROUND

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).¹

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.

OBJECTIVES

The aim of this study is to evaluate the willingness of CD patients to accept treatment-related SAE risks in exchange for improvements in treatment efficacy.

METHODS

Survey Instrument Design

Risk-benefit preferences were elicited using a stated preference (SP) method.

SP is the most valid and reliable technique available for quantifying patient preferences.^{2,3}

SP 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)

Table 1. Treatment Attributes and Levels

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

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."

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

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

Tysabri Patient Panel (N=98): patients recruited from clinical practice sites who had participated in a Tysabri clinical trial

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 Table 2.

Table 2. Example of Conjoint Tradeoff Task Comparing CD Treatment Options

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

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 $p < 0.05$.

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 3)

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 3. 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%
	Male	27%	34%	47%
Age*	Mean	45	39	43
	Standard deviation	11	11	11
Years of education*	Mean	16	16	15
	Standard deviation	2	2	2
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 4)

Abdominal pain, general well-being, and the impact of CD on activities were 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 Patient Panel had the worst total IBDQ score, and the Tysabri-Naïve Clinical Panel had the best total IBDQ score ($p < 0.05$).

Table 4. 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–Unusable	15%	11%	29%
No. diarrhea stools*	Mean	15	13	26
IBDQ score*	Mean	144	154	132
	Standard deviation	22	22	22

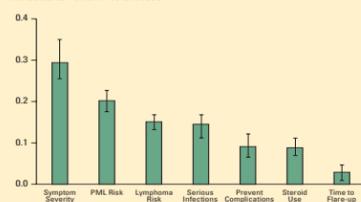
* $p < 0.05$

Treatment Preference Estimates (Figure 1)

Using a log likelihood ratio test, the three panels were found to be similar in their preferences for treatment attributes, and their data were pooled for further analysis.

Improvements 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.

Figure 1. The Relative Contribution of the Treatment Efficacy and Risk Attributes to Patient Preferences



Maximum Acceptable 1-Year Risk of PML Death or Disability (Table 5)

Greater symptom improvements are associated with greater risk tolerance.

MAR estimates ranged from 0.19% to 0.82% annual risk.

The MARs for the five benefit levels are substantially above the 1-year observed risk of PML.

For each treatment benefit, MARs are highest for lymphoma risk and lowest for the PML risk, implying that individuals are more willing to accept the risk of lymphoma than the risk of PML.

Table 5. Maximum Acceptable Annual Serious Adverse Event Risk for Selected Treatment Benefits

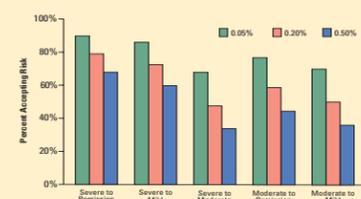
Initial Health State	Final Health State	PML			Serious Infection			Lymphoma		
		Mean (Lower Bound, Upper Bound)								
Severe	Remission	0.70% (0.60, 0.80)	0.73% (0.66, 0.81)	0.82% (0.72, 0.92)	0.19% (0.11, 0.28)	0.28% (0.02, 0.54)	0.39% (0.27, 0.52)	0.39% (0.17, 0.57)	0.42% (0.33, 0.52)	0.42% (0.33, 0.52)
	Mild	0.61% (0.53, 0.70)	0.67% (0.61, 0.73)	0.73% (0.64, 0.81)	0.19% (0.11, 0.28)	0.28% (0.02, 0.54)	0.39% (0.27, 0.52)	0.39% (0.17, 0.57)	0.42% (0.33, 0.52)	0.42% (0.33, 0.52)
Moderate	Remission	0.19% (0.11, 0.28)	0.28% (0.02, 0.54)	0.39% (0.27, 0.52)	0.19% (0.11, 0.28)	0.28% (0.02, 0.54)	0.39% (0.27, 0.52)	0.19% (0.11, 0.28)	0.28% (0.02, 0.54)	0.39% (0.27, 0.52)
	Mild	0.22% (0.14, 0.30)	0.37% (0.17, 0.57)	0.42% (0.33, 0.52)	0.22% (0.14, 0.30)	0.37% (0.17, 0.57)	0.42% (0.33, 0.52)	0.22% (0.14, 0.30)	0.37% (0.17, 0.57)	0.42% (0.33, 0.52)

Percentage of Patients Accepting 0.05%, 0.2%, and 0.5% Annual PML Risks by Benefit Level (Figure 2)

The larger the risk, the lower the percentage of patients who would accept risk in order to receive this level of benefit.

More than half of the patients would accept the currently estimated risk of PML death or disability, approximately 0.07%, to obtain a clinically relevant benefit.

Figure 2. Percentage of Patients Accepting 0.05%, 0.2%, and 0.5% Annual PML Risks by Benefit Level



CONCLUSION

Instrument pretest demonstrated patients' ability to understand and accept the treatment attributes and levels, and confirmed their willingness to trade off treatment efficacy against SAE risks.

Despite baseline differences among groups, the groups showed similar preferences regarding clinical benefits and risks.

Greater symptom improvements are associated with greater risk tolerance.

For each treatment benefit, MARs are highest for lymphoma risk and lowest for the PML risk, implying that individuals are more willing to accept the risk of lymphoma than the risk of PML.

Stated MAR for PML for a clinically relevant benefit level is well above an extrapolation of the currently estimated PML risk.

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