Are Adults More Averse to Treatment Risks for Their Children Than They Are for Themselves?

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CONFLICT OF INTEREST

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BACKGROUND

- Anecdotal evidence suggests that adverse-event incidence rates regarded as too risky by safety regulators may be acceptable to patients.
- Patient preferences regarding the risks and benefits of drug therapy have not been subject to rigorous examination.
- Adult patients may have different perceptions of adverse event risks than do parents of child patients.[1]

OBJECTIVE

To estimate the willingness of adult Crohn's disease (CD) patients and parents of child CD patients to accept serious adverse event (SAE) risks in exchange for therapeutic benefits. In this study, we are particularly interested in how preferences differ for adult patients compared to parents of child patients.

METHODS

Survey Instrument Design

- Risk-benefit preferences were elicited using a choice-format stated-preference (SP) method:
  - SP quantifies subjects' willingness to accept trade-offs among alternatives with multiple attributes.
  - SP is the most valid and reliable technique available for quantifying patient preferences.[2,3]
- Risk-benefit trade-off 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 (Table 1).

Subjects

- Adult patient inclusion criteria
  - Adult (≥18 years) US residents diagnosed with CD
  - Online informed consent
- Adult patient recruiting sources
  - Subscribers to the HealthTalk Web site, a Web service that provides chronically ill patients with access to information on advanced treatments and disease management (N=342)
  - Clinical practice sites (N=238)
- Parent inclusion criteria
  - US parent or guardian of a child (≤18 years) diagnosed with CD
  - Online informed consent

Table 1. Treatment Attributes and Levels

Treatment Attribute	Levels
Symptom severity and activity limitations	• Remission • Mild Crohn's disease • Moderate Crohn's disease • Severe Crohn's disease
Serious complications from CD	• 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
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	• None (0%) • 5 patients out of 1,000 (0.5%) • 20 patients out of 1,000 (2%) • 50 patients out of 1,000 (5%)

- Parent recruiting source
  - Subscribers to HealthTalk Web site (N=105)

Study Design and Analytic Techniques

- Data were collected via a Web-enabled survey instrument.
- Each respondent completed 10 conjoint trade-off tasks. Table 2 shows an example of one of the trade-off tasks.
- The survey included internal validity tests.
- A random utility model was used to estimate preference parameters.

Table 2. Example of Conjoint Trade-off 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	
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	
Which treatment would you choose?	❑ **Treatment A**	❑ **Treatment B**

RESULTS

Demographic Characteristics (Table 3)

- The adult patient and child patient samples were significantly different with regard to age, annual household income, and duration of CD experience ($p < 0.05$).

Table 3. Demographic Characteristics

Variable	Response Category	Adult Patients (N=580)	Child Patients (N=105)
Age	Mean	44	14
Annual household income	Mean	$75,000	$104,000
Years since CD symptoms developed	<1 year	4%	21%
	1–2 years	7%	17%
	3–5 years	23%	52%
	6–10 years	19%	9%
	>10 years	47%	1%

Disease and Quality of Life Experience (Table 4)

- Adult patients had significantly more severe symptoms than child patients ($p < 0.05$).
- 66% of the adult patients had been diagnosed with CD for 6 or more years; 90% of the child patients had been diagnosed with CD for less than 6 years.
- About 45% of the adult patients and 65% of the child patients had current general well-being at the "well" level.
- The Inflammatory Bowel Disease Questionnaire (IBDQ) score was at the remission level (>170) for 27% of the adult patients and 59% of the child patients.

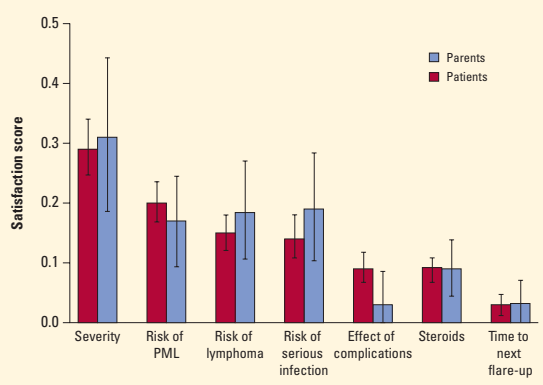
Table 4. CD Symptom and Quality of Life Experience of the Study Panels

Variable	Response Category	Adult Patients (N=580)	Child Patients (N=105)
Abdominal pain in past 7 days	None–Mild	70%	85%
	Moderate–Severe	30%	15%
Well-being in past 7 days	Well	45%	65%
	Below Par–Poor	49%	33%
	Very Poor–Terrible	6%	2%
Impact on activities in past 7 days	No–Some Problems	84%	90%
	Considerable–Unable	16%	10%
No. diarrhea stools in past 7 days	Mean	16	5
IBDQ score	Mean	144	172

Relative Satisfaction Scores for Treatment Attributes (Figure 1)

- Improvement in daily symptom severity is the most important treatment attribute (satisfaction score of 0.29 for patients and 0.31 for parents).
- For adult patients, the three SAE risks were in the second tier of importance behind treatment efficacy, with PML risk the next most important attribute, followed by the risk of death from lymphoma and serious infection.
- Parents also judged SAE risks to be second in importance to efficacy, but the relative importance of the risks of serious infection (0.19), lymphoma (0.18), and PML (0.17) were very similar.

Figure 1. Relative Satisfaction Scores for Treatment Attributes



Maximum Acceptable 1-Year Risk of PML, Serious Infection, and Lymphoma (Table 5)

- Greater symptom improvements are associated with greater risk tolerance.
- Maximum acceptable risk (MAR) estimates ranged from 0.18% to 0.81% annual risk for adult patients and from 0.06% to 1.05% for parents.
- The MARs of PML for the five benefit levels are substantially above the 1-year estimated risk of PML.[4]
- For each treatment benefit, MARs are highest for lymphoma risk and lowest for the PML risk for adult patients, whereas there is no clear distinction among the SAEs for parents.
- Parents usually have higher MARs for improvements from severe CD than adult patients, whereas adult patients usually have higher MARs for improvements from moderate CD than do parents.

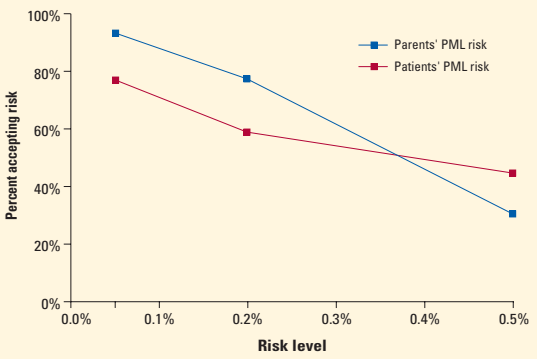
Table 5. Maximum Acceptable Annual PML, Serious Infection, and Lymphoma Risks for Selected Treatment Benefits

	Risk of PML (Mean, 95% CI)		Risk of Serious Infection (Mean, 95% CI)		Risk of Lymphoma (Mean, 95% CI)	
Improvement	**Patients**	**Parents**	**Patients**	**Parents**	**Patients**	**Parents**
Severe to Remission	0.69% (0.55 – 0.83)	0.87% (0.59 – 2.18)	0.73% (0.64 – 0.87)	0.74% (0.52 – 1.66)	0.81% (0.68 – 1.05)	1.05% (0.58 – 2.68)
Severe to Mild	0.60% (0.48 – 0.72)	0.65% (0.26 – 1.45)	0.66% (0.58 – 0.79)	0.57% (0.20 – 1.17)	0.72% (0.61 – 0.93)	0.68% (0.26 – 1.72)
Severe to Moderate	0.18% (0.09 – 0.28)	0.52% (0.10 – 1.14)	0.22% (0.05 – 0.53)	0.46% (0.08 – 0.91)	0.36% (0.19 – 0.52)	0.47% (0.15 – 1.20)
Moderate to Remission	0.39% (0.25 – 0.52)	0.38% (0.15 – 0.65)	0.55% (0.43 – 0.63)	0.32% (0.13 – 0.54)	0.55% (0.46 – 0.67)	0.29% (0.16 – 0.53)
Moderate to Mild	0.20% (0.11 – 0.30)	0.11% (0.01 – 0.30)	0.36% (0.12 – 0.55)	0.06% (0.01 – 0.26)	0.42% (0.28 – 0.54)	0.13% (0.04 – 0.20)

Percent of Subjects Accepting PML Risk (Figure 2)

- For each benefit level, the predicted percentage of subjects accepting risk decreases with higher risk levels.
- Parents are more willing to accept risk than adult patients at lower risk levels.
- Parents are less willing to accept risk than adult patients at higher risk levels.

Figure 2. Percent of Subjects Accepting 0.05%, 0.2%, and 0.5% PML Risk



CONCLUSIONS

- Adult patients and parents of children with CD indicated they are willing to accept defined mortality risks in exchange for clinical efficacy.
- Parents were usually more willing to accept higher SAE risks for improvement of severe CD symptoms, whereas adult patients were usually willing to accept higher risks for improvement of moderate CD symptoms.
- Parents are more willing than adult patients to accept risk at lower risk levels, but less willing to accept risk at higher levels.
- Adult patients are least tolerant of PML and most tolerant of serious infection, whereas parents do not distinguish among SAE types.

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