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Out-of-Pocket Cost Is a Barrier to Therapeutic Drug Monitoring in Inflammatory Bowel Disease

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Abstract

Background—Therapeutic drug monitoring (TDM) is increasingly performed to optimize biologic therapy in inflammatory bowel disease (IBD). However, patients and physicians may be reluctant to perform TDM due to concerns related to potential out-of-pocket costs.

Aims—The aim of this study was to evaluate patient understanding and attitudes toward TDM in different clinical scenarios with and without potential out-of-pocket costs.

Methods—Adult IBD patients at a tertiary gastroenterology clinic were anonymously surveyed from March to September 2016 to assess their understanding of and willingness to undergo TDM in a variety of clinical scenarios, both with and without a potential out-of-pocket cost. Responses were analyzed for associations with changes in attitudes if out-of-pocket costs were involved.

Results—Of 118 completed surveys, 68.2% of patients were aware of or had previously undergone TDM. Patient willingness to undergo TDM was high both with and without potential out-of-pocket costs (70 and 98%, respectively); however, patients were significantly less willing with out-of-pocket cost ($p < 0.01$). Higher disease-related quality of life scores, as measured by the short inflammatory bowel disease questionnaire (SIBDQ), was significantly associated with an increased willingness to assume a potential out-of-pocket cost ($p = 0.007$).

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Conflict of interest BPV has served as a speaker, a consultant and an advisory board member for Janssen and Abbvie, and has received research funding from Roche and Takeda. The remaining authors declare that they have no conflict of interest.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conclusions—Overall, patients understand and are willing to undergo TDM in certain potentially beneficial clinical scenarios, however, are significantly less willing if paying out-of-pocket. A higher SIBDQ score was associated with an increase in willingness to undergo TDM when out-of-pocket cost was involved. Physicians should discuss TDM with their patients in order to make an informed and personalized treatment decision.

Keywords

Inflammatory bowel disease; Therapeutic drug monitoring; Patient preferences; Health expenditures

Introduction

Anti-tumor necrosis factor-alpha (anti-TNF) agents have revolutionized the treatment for inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC); however, their use is limited by the development of loss of response, frequently in the setting of antibody formation [1]. Therapeutic drug monitoring (TDM) is the measurement of serum drug concentrations with the intent to optimize or change therapy. TDM is an increasingly utilized strategy in IBD for managing biologics in the setting of treatment failure (i.e., reactive TDM) and to prevent loss of response (i.e., proactive TDM) [2, 3]. Higher serum biologic concentrations are consistently associated with improved rates of clinical response in multiple post hoc and retrospective studies [4–15]. Reactive TDM impacts patient care positively and is a cost-effective strategy versus empirically escalating the dose of anti-TNF in the setting of treatment failure [16–18]. Recently, evidence suggests that proactive TDM can increase remission rates and other clinical outcomes and prevent loss of response to anti-TNFs [19–21]. The American Gastroenterological Association (AGA) newly released clinical guideline recommends TDM in the reactive setting, however, makes no recommendation regarding proactive TDM [22].

A key limitation to the clinical implementation of routine TDM is the cost of drug concentration and anti-drug antibody testing. While some studies have demonstrated that routine TDM is cost-equivalent or cost-effective, many insurance providers do not cover the cost of testing, exposing patients to potential out-of-pocket expenses [20, 23]. The cost for TDM testing to the patient can vary depending on the test manufacturer, and frequently specialty laboratories will offer patient assistance programs to decrease the out-of-pocket cost burden [24, 25]. However, given this potential cost burden, many physicians are reluctant to perform TDM on a routine basis. The aim of this survey was to determine patient attitudes toward treatment and assess their understanding of TDM, as well as their willingness to undergo blood tests in certain potentially beneficial scenarios associated with TDM, both with and without potential out-of-pocket costs.

Materials and Methods

Study Population

Participants included in this study were adult (18 years and older) patients with IBD seen at a tertiary gastroenterology clinic practice (University of Minnesota in Minneapolis, MN).

Surveys were collected between 3/22/16 and 9/15/16. All patients seen at gastroenterology and IBD clinics of the University of Minnesota (four physicians seeing IBD patients) were eligible to receive the survey. Surveys were administered at the start of the clinic visit and collected anonymously by clinic staff or in a designated bin.

Survey Development

This study utilized a cross-sectional, qualitative questionnaire for data collection. Once the research question and hypothesis were determined, objectives of the survey were developed and used to identify the following dimensions or factors to be measured: (1) quality of life; (2) level of awareness of TDM; (3) level of treatment engagement; (4) attitudes toward treatment; and (5) willingness to undergo TDM with and without potential out-of-pocket cost.

The short inflammatory bowel disease questionnaire (SIBDQ) was used to assess health-related quality of life (HRQOL) [26, 27]. The SIBDQ was used with permission, approval number IBDQ16–038. The SIBDQ consists of an average of ten questions resulting in a total score of 10–70. Higher scores are associated with a better HRQOL [26].

The other survey items were written through a round-robin technique by the research team, which included a survey methodologist, and aligned to each dimension. Answers to awareness, engagement, and attitudes questions were separated into “higher” and “lower” categories (higher level of awareness/engagement, more aggressive attitude toward therapy) based on patient responses. Additional questions were specifically developed to assess willingness to pay out-of-pocket for TDM (with a potential cost of up to \$250) in certain potentially beneficial scenarios based on prior studies (i.e., if TDM could potentially improve symptoms, prevent infusion reactions, prevent flares of disease, or allow the treatment to be effective for a longer period of time). Patients were able to respond on a 1–7 scale to these questions with the following category designations: 1–3 = unlikely; 4 = not sure; 5–7 = likely.

After numerous revisions, a pilot survey was pretested for content and wording by 10 patients presenting to a gastroenterology outpatient clinic for the treatment of IBD. Potential problems with wording and interpretation of questions were sought by a member of the research team. The survey was modified with this feedback. The survey required < 5 min to complete by all 10 patients. The final survey instrument, dimension mapping, and higher/lower designations are available in Supplementary Table 1.

Data and Statistical Analyses

The primary outcome of this analysis was the change in willingness to undergo TDM after the introduction of an out-of-pocket cost, which was analyzed as a continuous variable. Additional covariates collected included demographic data (age range, self-reported IBD diagnosis, gender, highest level of education), current use of biologic medications, and SIBDQ composite score. Paired *t* tests were used to compare mean differences in responses of willingness to pay with and without out-of-pocket costs. Change in response scores between willingness to pay with and without out-of-pocket costs were analyzed as a continuous variable for associations with other question responses, such as SIBDQ, level of

awareness of TDM, level of treatment engagement, attitudes toward treatment, and demographic information. The changes in scores were skewed, because it was assumed that they had to be negative (i.e., individuals would not become more likely to undergo TDM if they had to pay out-of-pocket). Therefore, for primary analyses, nonparametric tests were used, and these were supplemented with regression models. For SIBDQ, Spearman's correlation was used to test for association with the change in score, and supplemented with a linear regression model. For questions involving level of awareness of TDM, level of treatment engagement, and attitudes toward treatment, these were first simplified to two levels (higher and lower) as described in Supplementary Table 1. To test for association with the change in the score, the Wilcoxon test was used. Medians and quantiles were calculated, along with the median of differences, with CI calculated using a bootstrap method, and were tested for significance using the Wilcoxon test. These were supplemented by adding these variables to a regression model. For demographic information, the Wilcoxon test, the Kruskal–Wallis test, and Spearman's correlation were used, as appropriate, and supplemented by adding as a covariate to the regression model. All variables were included into the final multivariate regression model. To determine the measure of association of significant covariates, the outcome of decrease in willingness to pay after an out-of-pocket cost was dichotomized and odds ratios calculated. Missing answers were not included in data analysis. Statistical analyses were completed using SPSS software, and JMP Pro 13; $p < 0.05$ was considered significant.

Ethical considerations

This study was approved by the University of Minnesota Institutional Review Board on 7/16/2015.

Results

Demographics

A total of 118 surveys were collected during the study timeframe. Baseline demographic and disease information are listed in Table 1. CD was the most prominent disease subtype, accounting for 51.4% of patients. Notably, 11% of patients were unsure if they had CD or UC. Otherwise, sex, age, and education level were relatively equally distributed among the patient population. Mean SIBDQ score was 48.1 [standard deviation (SD) 12.3] out of 70. Fifty-six percent of patients were currently on or had previously been on a biologic (anti-TNF) medication, and 39.4% reported they had undergone TDM at some point.

Awareness, Engagement, and Attitudes Toward Treatment and TDM

Data on survey responses regarding past experience with biologics, knowledge of TDM, and attitudes toward therapy are presented in Supplementary Table 2. Most patients (68.2%) were aware of TDM (either had a biologic concentration checked in the past or indicated they knew such testing existed). Notably, 29% of patients reported knowing that they could obtain a drug concentration but had not had one tested. It is unknown if these patients assumed that these tests existed or had discussed this with a physician previously and decided not to pursue testing.

Self-reported knowledge of medication dosing and compliance were considered surrogates for engagement in therapy. Patients who are more engaged in their therapy may be more likely to want to undergo TDM. Approximately half of patients reported knowing their current medication doses. However, 20% of patients reported missing doses at least “a little of the time.”

A patient’s attitude toward therapy was measured by their willingness to change medications or doses in specific clinical situations regarding increasing symptoms or experiencing side effects to medications. Overall, the majority of patients preferred a more aggressive approach to therapy, defined as wanting to change medication doses or add a second medication if they experienced worsening IBD symptoms (59.7%), or change medication doses or stop their medication and try a new medication if they experienced side effects (88.8%).

Willingness to Undergo TDM

Complete data on willingness to undergo TDM were available for 98 of the 118 subjects. Four subjects were excluded from the analysis as they consistently became more willing to undergo TDM when they had to pay out-of-pocket, calling into question their understanding of the question. Another sixteen subjects did not fully answer the questions. Demographic data for excluded patients are presented in Supplementary Table 3. Notably, excluded patients were more likely to be older in comparison with included patients ($p = 0.02$).

The vast majority of subjects (98%) were willing to undergo TDM when no cost was involved; however, only 70% of individuals were likely to undergo TDM with the potential for an out-of-pocket cost (Fig. 1). When no cost was involved, subjects were extremely likely (Likert scale 6.7/7, SD 0.53) to want to undergo TDM. With the potential for out-of-pocket costs, this decreased to only somewhat likely (Likert scale 5.3/7, SD 1.75). Potential out-of-pocket costs significantly decreased the willingness to undergo TDM in all clinical scenarios [mean difference 1.40 (SD 1.64); $p < 0.01$; Fig. 2]. Interestingly, willingness to pay was similar between TDM in reactive settings (moderately/substantially improve symptoms) and proactive settings (prevent drug reactions/disease flares, treatment effective for longer) for each set of clinical scenarios, both with no cost and potential out-of-pocket cost.

Variables Associated with Change in Willingness to Undergo TDM with Out-of-Pocket Cost

Predictors of willingness to undergo TDM when potential out-of-pocket cost was present are presented in Table 2. On univariate analysis, education level and SIBDQ were associated with willingness to undergo TDM with potential out-of-pocket costs. Education seemed to be driven by those with a doctoral degree who experienced a minimal change in the willingness to undergo TDM when a cost was involved. However, on multivariate analysis, education was not predictive of willingness to undergo TDM when potential out-of-pocket cost was present. SIBDQ score was significantly associated with change in the overall willingness to undergo TDM when patients had to pay out-of-pocket on univariate analysis (Spearman’s $\rho = 0.28$, $p = 0.007$), with a higher SIBDQ score associated with a greater willingness to undergo TDM when potential out-of-pocket costs were involved. SIBDQ was

the strongest predictor of willingness to incur a potential out-of-pocket cost, although did not achieve statistical significance when included in the full multivariate regression model ($p = 0.06$). However, a predictive model including only SIBDQ was not notably different compared to the full model ($p = 0.88$), suggesting that SIBDQ predominantly explained the change in willingness to pay for TDM when out-of-pocket costs were involved. The odds of a subject being less willing to undergo TDM with an associated cost were 1.7 times lower for every 10 unit decrease in the SIBDQ (95% CI 1.2, 2.4). An ROC analysis identified an SIBDQ cutoff of 44 as a predictor of willingness to undergo TDM with an out-of-pocket cost (Supplementary Figure 1). When assessing patient knowledge, engagement, and attitudes toward treatment, no patient group (higher or lower awareness or engagement, or a more or less aggressive approach toward therapy) was significantly associated with a change in the overall willingness to undergo TDM when an out-of-pocket cost was present.

Discussion

TDM is an important tool that is increasingly utilized in IBD patients; however, the insurance coverage of this practice is limited and as such patients may experience an out-of-pocket cost. Our study addresses a practical, clinical question that providers treating IBD patients frequently face. Anecdotal experience suggests that physicians are reluctant to adopt a TDM-based strategy due to the potential financial burden to the patient. We found that patients are overall willing to undergo blood testing for TDM both without and with potential out-of-pocket costs, indicating that a possible out-of-pocket cost should not be a barrier to discussing TDM with patients. While patients were significantly less likely to want to pursue TDM with a potential out-of-pocket cost, 70% were still likely to want to undergo TDM despite a potential cost. Notably, this was not limited to situations where patients were experiencing symptoms or side effects (i.e., reactive testing), but also when testing could help prevent loss of response (i.e., proactive testing).

Surprisingly, patients with lower SIBDQ scores (indicating worse HRQOL) predominantly accounted for the significant drop in willingness to pay from no cost to out-of-pocket cost. One reason for this finding is that patients experiencing better HRQOL may be more willing to pay for an additional test to maintain their quality of life. Similarly, those with higher SIBDQ scores may have a more optimistic view of pursuing and paying for further therapies, given the success they have had with their current treatment. In a prior study assessing willingness to pay for gastroesophageal reflux disease relief, patients with moderate disease were willing to pay significantly more for possible relief than those with severe disease, similar to the results of our study [28]. This phenomenon may be related to “response shift,” where a patient’s disease perception and internal standard of measurement may be recalibrated by previous experiences [29]. In addition, our results parallel a study of CD patients evaluating willingness to exchange adverse events and symptom relief when evaluating therapies; in this study, patients with mild disease were more willing to risk adverse events to prevent worsening symptoms than patients with more severe disease [30]. The authors hypothesized that patients with milder symptoms may have a larger potential loss in quality of life from worsening symptoms, and thus are willing to incur more therapies and risk. However, it should be noted that other confounding variables that are not disease related, such as income, may be associated with better overall quality of life and

subsequently willingness to pay. Nonetheless, this finding is significant as patients with lower SIBDQ scores may have the most potential benefit from TDM and yet appear to be less willing to pay out-of-pocket for TDM if required.

Various factors such as patient awareness, engagement, or attitudes toward treatment did not predict willingness to pay for TDM. The majority of patients surveyed were considered engaged in their care (80% never or hardly missed medication doses) and preferred an aggressive approach (59.7% when symptoms worsened and 88.8% when side effects occurred), thus the size of the comparison group may not have been large enough to detect a difference. While not predictive of willingness to pay for TDM, it is notable that 20% of subjects reported missing doses of their medications at least some of the time, with 10% missing medication doses a “good bit of the time,” “most of the time,” or “all of the time.” As biologic serum concentrations are closely related to adherence to a dosing schedule, this represents a potential care gap that can be improved upon.

When analyzing demographic variables, the only significant correlation with change in willingness to undergo TDM with out-of-pocket cost was in education. Doctoral degree holders had a smaller change in willingness scores when going from no cost to out-of-pocket cost in univariate analysis. A potential explanation for this is that more highly educated individuals have higher incomes. Prior studies have found those with higher levels of education more willing to pay for treatments with high copayments in oncology, and for implantable cardioverter-defibrillators (ICD) in cardiology [31, 32].

There are a few important limitations to this study that should be noted. The answers to demographic and disease questions were patient-reported, and thus could not be verified due to the anonymous nature of the survey. As such, disease severity could not be directly assessed and HRQOL was used as a surrogate, which may be affected by non-IBD-related factors such as irritable bowel syndrome or other comorbid illnesses. Additionally, our patient population was a single academic center and may not be generalizable. However, our subject mix was diverse in terms of age and education level. Next, in completing analyses of willingness to undergo TDM with and without out-of-pocket costs, we excluded surveys with incomplete data on these questions. Those excluded surveys did have a higher proportion of older patients (> 55 years), introducing a potential source of bias. Lastly, we did not collect data on income levels of patients, which may influence willingness to pay, as well as quality of life as discussed above. Income was intentionally excluded as we fundamentally believe the availability and discussion of TDM should be equitable regardless of income. However, as such, it is not clear if SIBDQ truly predicts willingness to pay, or if it is confounded by income.

In summary, patients are aware of and interested in TDM regardless of cost across a variety of potentially beneficial clinical scenarios. However, out-of-pocket cost is associated with a significant decrease in the willingness of patients to undergo TDM. Those with a higher HRQOL may be more willing to undergo TDM to maintain their quality of life. While providers will have to determine for themselves, based on the evidence, if TDM is clinically beneficial for an individual patient, our results suggest that a potential out-of-pocket cost should not be a deterrent to discussing TDM with patients in either the reactive or the

proactive setting. Further efforts should be made to increase both low-cost and no-cost availability of drug level and anti-drug antibody testing in TDM, either through insurance coverage or through pharmaceutical patient assistance programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Overall willingness to undergo TDM with and without potential out-of-pocket cost. Patients were able to respond on a 1–7 scale (1 = extremely unlikely, 7 = extremely likely) with the following category designations: 1–3 = unlikely; 4 = not sure; 5–7 = likely. All comparisons between cost and no cost were significant ($p < 0.01$)

Fig. 2.

Mean patient responses for likelihood to be willing to undergo blood testing for TDM in various scenarios with no out-of-pocket costs (black bars) versus potential out-of-pocket costs of up to \$250 (gray bars) (* $p < 0.01$)

Table 1

Baseline demographic characteristics

Variable	Frequency	Percent ^a
<i>Sex</i>		
Male	49	44.1
Female	60	54.1
Not listed	2	1.8
<i>Age</i>		
18–24	17	15.3
25–34	23	20.7
35–44	22	19.8
45–54	21	18.9
55–64	18	16.2
65 +	10	9.0
<i>IBD type</i>		
Crohn's disease	56	51.4
Ulcerative colitis	33	30.3
Indeterminate colitis	8	7.3
Not sure	12	11.0
<i>Education</i>		
High school or GED	30	27.0
Post-high school training	19	17.1
Undergraduate college degree	34	30.6
Master's degree or equivalent	20	18.0
Doctoral degree or equivalent	8	7.2
<i>Currently on biologic</i>		
Yes	45	38.8
No, never been on biologic	51	44.0
No, but on biologic in past	20	17.2
<i>Awareness of TDM and prior TDM</i>		
Aware, but no prior TDM	30	28.8
Aware and prior TDM	41	39.4
Neither aware or prior TDM	33	31.7
SIBDQ, mean (SD)	48.1 (12.3)	

^aValid percent excluding missing responses

Association of variables with change in mean willingness to undergo TDM between no cost and out-of-pocket cost in nonparametric and multivariate analyses

Table 2

Variable	<i>p</i> value	
	Nonparametric	Multivariate
<i>Demographics</i>		
Age	0.76	0.95
Gender	0.49	0.67
Education	0.02	0.47
<i>IBD type</i>	0.14	0.53
<i>Awareness</i>		
Aware of testing	0.19	0.42
Currently on biologic	0.31	0.32
<i>Engagement</i>		
Knowledge of current dose	0.57	0.82
Frequency of missed doses	0.16	0.29
<i>Attitudes toward therapy</i>		
Treatment preference if worsening symptoms	0.36	0.29
Treatment preference if side effects	0.41	0.73
<i>SIBDQ</i>	0.007	0.06