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Lost in Translation: Helping patients understand the risks of inflammatory bowel disease therapy

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Abstract

Patients with inflammatory bowel disease are commonly treated with immunomodulators and biologic therapy. These treatments can be very effective, but are associated with risks of adverse events that need to be discussed with patients. Effectively communicating risks of therapy can be challenging based on time constraints, misinformation available on the Internet and from others, and the lack of tools to efficiently share accurate data with patients and their families. Providers need to acknowledge the emotional aspect involved in the perception of risk, and be aware of mistakes that can easily be made in communicating with patients. Tools are available to make medical data easier to understand, and these techniques have been adapted for patients with inflammatory bowel disease. By more clearly communicating with patients, we can ensure that they are making informed medical decisions that fit with their personal preferences for treatment.

Introduction

Fortunately, we are learning to use the medications available for the treatment of inflammatory bowel disease (IBD) more effectively with goals to not only resolve symptoms, but to improve the natural history of the disease. For patients with moderate to severely active disease, the most commonly used classes of medications include corticosteroids, immunomodulators (6-mercaptopurine, azathioprine, methotrexate), and biologics (adalimumab, certolizumab pegol, infliximab, natalizumab). These treatments can be very effective for improving symptoms, but they are also associated with potential serious adverse events (SAEs).

When the choice is made to initiate a new therapy, it is a requirement to discuss possible side-effects with patients. In the few minutes remaining in an office visit after taking the history, performing a physical examination and discussing treatment options, it is very difficult to adequately discuss the complex and sometimes emotional topic of risk. Challenges include overcoming patients' preconceptions about risk, misinformation available from the internet and other sources, and providers' lack of accurate data and tools to efficiently share this information with patients and their families. This review aims to discuss risk and risk perception, give an update on what we currently understand about the risks of IBD therapies, and to offer guidance on how to translate complex data for more accurate communication to patients. The goal of communicating risk is not just to tell patients about the side-effects of our treatments, but to make sure that they understand how these risks balance against the benefits of therapy.

What is risk?

Risk can be defined as the probability of event occurrence multiplied by the consequence (or severity) of that event ($\text{risk} = \text{probability} \times \text{consequence}$).¹ The probability is simply the numerical chance of occurrence, which is typically objective and measurable. The consequence is more difficult to quantify, subjective, and variable dependent on the individual. For example, the probability of experiencing nausea with methotrexate is high, but the consequence is very low. In contrast, the probability of developing lymphoma as a result of immune suppressive therapy is very low, but the consequence extremely high. Furthermore, the same risk of lymphoma has a different consequence in a 7-year-old boy compared to a 75-year-old man.

Work by Slovic gives an approach on how to conceptualize risk.² There are two factors; the “dread” of the risk occurring, and the “unknown.” Dread is defined at its extreme as lack of control, catastrophic, having fatal consequences and inequitable distribution of risk and benefits. Unknown is defined at its extreme as risks that are unobservable, new, and delayed in their manifestation of harm. Slovic developed a construct by using dread as the x-axis and the unknown as the y-axis, creating four quadrants. Figure 1 gives an example of Slovic’s landmark work. Based on this model, medications that have few side-effects and are well known (e.g., mesalamine) would be in the bottom left quadrant, but anti-TNF agents and natalizumab are most likely to be in the top right quadrant. By educating patients about the known risks, making certain they have realistic estimates of the probability of occurrence, and using monitoring techniques when available (labs, imaging) to take away the lack of control, we can hopefully move patients into other quadrants where they are less fearful and more comfortable with immune suppressant therapies. Then, we need to respect their concerns, and work together towards treatments that fit with their personal preferences. As Slovic stated, “...there is wisdom as well as error in public attitudes and perceptions. Lay people sometimes lack certain information about hazards. However, their basic conceptualization of risk is much richer than that of the experts and reflects legitimate concerns that are typically omitted from expert risk assessments. As a result, risk communication and risk management efforts are destined to fail unless they are structured as a two-way process. Each side, expert and public, has something valid to contribute. Each side must respect the insights and intelligence of the other.”²

Risk perception in IBD

Patients have a broad range of their perception of risk. This has been evaluated by a survey of patients and parents of patients with IBD assessing their understanding of the risks of anti-TNF therapy.³ There were widely varying estimates of the risk of lymphoma associated with anti-TNF therapy, ranging from no increase in lymphoma risk, up to a twenty-fold increased risk compared to the general population. When the subjects were given a hypothetical scenario of a “new” medication for IBD that was associated with a risk of dying of 1 out of 250 patients (this was the rate of mortality seen in the Mayo Clinic study of infliximab use)⁴, over 60% of the respondents answered that they would not take the medication, even if it induced remission 95% of the time. Interestingly, one-third of these patients were either currently taking or had received infliximab in the past. This is concerning, since many patients may be unknowingly taking medications with risks that are higher than they would want to accept.

A study was performed to explore how much risk patients with Crohn’s disease are willing to accept for certain therapeutic benefits.⁵ This survey of over 500 patients used the technique of conjoint trade-off analysis to calculate the maximum acceptable risk (i.e. risk threshold) patients would take of dying from lymphoma, serious infection or progressive

multifocal leukoencephalopathy (PML). Results showed a few important trends. First, the majority of patients in the study were willing to accept a much higher probability of these events occurring than have been reported in the literature. Second, higher risks were accepted when patients were given scenarios of being sicker and expecting a larger therapeutic benefit. Third, patients with a longer disease duration were willing to accept higher risks than those with a more recent diagnosis. The same technique was also used to survey parents of IBD patients.⁶ Parents were willing to take even higher risks for their children, but only if the disease was described as severe. They were more risk averse than patients if the child had only mild disease or a low expectation of therapeutic benefit. Taken together, patients and their parents are in general willing to accept the risks of the available biologic drugs, but they need to feel “sick enough” to believe that they deserve it. However, patients with a recent diagnosis or are only moderately ill may be less willing to accept these risks, which might be a barrier to the wide acceptance of “top-down” or early intensive therapy.

Mistakes in communicating with patients

It is easy to miscommunicate with patients. There are a number of factors that can lead to patients misinterpreting data that are presented to them. The framing effect is a term referring to the presentation of information in a certain format such that it can influence a decision. It can be purposeful or unintentional, and may lead to over- or under-exaggerated data. In one study the majority of patients preferred a hypothetical medication that would yield a 34% relative risk reduction of myocardial infarction over a drug yielding a 1.4% absolute risk reduction or number needed to treat of 71.7. Even though these numbers represent exactly the same benefit, patients clearly favored the higher numerical (albeit “relative”) number. These authors concluded that patients’ views of medical therapy are shaped by the formats (or frames) in which potential benefits (or risks) are presented. A meta-analysis on this subject also concluded that results presented as relative risk lead to a more favorable evaluation of treatment. The same applies when presenting risk, as high relative risks can lead to concern that is far out of proportion of very small absolute increases.⁸ For example, the standardized incidence ratio for the increased relative risk of developing lymphoma when taking anti-TNF agents with immunomodulators is 3.2, or a 300% increase.⁹ However, in absolute terms, this is an extra 4 patients per 10,000 treated over the course of a year.

Another area of difficulty in patient communication deals with numeracy. Numeracy is defined as “quantitative literacy” – the ability to understand numbers. Small numbers (<1.0) are the hardest to interpret. In one study, half of patients could not convert 1% to 10 per 1000, and 80% of patients were unable to convert 1 per 1000 to 0.1%.¹⁰ Furthermore, patients had a difficult time determining which was higher, 1 in 27 versus 1 in 37. Unfortunately, medical students also struggled with similar tasks.¹¹ Primers to help patients understand risk are available,¹² but may not be practical to administer to all patients before the time a medical decision is needed. To avoid misleading or confusing patients, clinicians need to be aware of framing and understand the limitations of numeracy.

A common error in risk communication is relying on verbal labels. The European Commission (EC) Pharmaceutical Committee uses verbal labels to describe the frequency of events.¹³ Their anchors are “very common” meant to represent a frequency of an adverse event of >10%, and “very rare” meant to represent a frequency of an adverse event of <0.01%. When students from the United Kingdom were presented with these same terms and asked to estimate the frequency of adverse events, the means for “very common” and “very rare” were 65% and 4%, respectively. Patients will have very different interpretations

of how often “rare” side-effects truly occur, and these terms should be used very cautiously, if at all.

Recommendations for communicating with patients

There are techniques that have been shown to be more effective for communicating risk (Table 1).^{11–14, 15} As described above, absolute risk should always be provided. Relative risk can be presented, but only if along with the absolute change. Avoid small percentages (<1.0%) and alternatively present the frequency of an event (6 per 10,000 as opposed to 0.06%). Instead of presenting lifetime risk, focus on a shorter period of time. Women had a preference for receiving risk information about breast cancer in a 10-year time frame because they perceived a decade to be the time period in which someone makes life plans.¹⁶ Although decimals imply accuracy, numbers should be rounded to allow individuals to more clearly grasp the value. Keep denominators consistent to allow for easier comparisons. As noted above, changing the denominator leads to confusion, but keeping consistent out of either 100, 1000 or 10,000 will make it easier for patients to compare risks. If possible, risks should be presented in both the “loss” and “gain” frame. For example, if 1 in 1000 patients may develop PML from natalizumab treatment, 999 in 1000 will not. Finally, people interpret different formats of data differently. When able, presenting information using different techniques (i.e., numeric, graphically, pictorially) will allow for a broader understanding of risk.

In addition to these methods, risks of therapy should be presented in the context of the risks of the disease, treatment alternatives and other life risks. A conversation regarding immunomodulator or biologic side-effects should always include the known adverse effects of corticosteroids, including the fact that corticosteroids are a key variable driving infectious complications in IBD, and are associated with higher rates of mortality.^{17, 18} The risks of requiring surgery for poorly treated disease needs to be addressed, in addition to the fact that surgery itself has inherent risks. It is easy to forget about daily life risks, but presenting the fact that in the United States the lifetime risk of dying in a car accident is 1 in 261 will keep the small absolute risks of medical therapies in perspective.¹⁹

Tools you can use

Using the above methods as a guide, figures and tables have been developed that can be shared with patients. In addition to the tables included within this article, a number of printable supplemental figures are published online. The data which fill these communication tools are the best currently available estimates, but will likely change over time.

Frequency displays with pictures of people have consistently been shown to be easy for patients to identify with and comprehend.¹⁶ Supplemental Figure A shows a 100 people frequency display to depict the risk of requiring surgery for Crohn’s disease over a 20 year period.²⁰ Risks of immunomodulator and anti-TNF therapy are shown as simple tables (Tables 2, 3, and 4), and the risks of non-Hodgkin’s lymphoma are shown as 10,000 people frequency displays (Supplemental Figures B–D).⁹ The decision of using immunomodulators versus anti-TNF agents versus combination therapy is a trade-off between the chance of remission and concerns over adverse events. The recent SONIC trial addressed this question, at least over the period of one year.²¹ To give the opportunity to present these data in different formats to patients, Supplemental Figures E–G show the SONIC results using three different communication techniques, including a “drug box” table format,²² a standard bar graph, and a “100 people” frequency display. The nearly equivalent rate of serious infections from this trial are also shown in Supplemental Figure H. Typically the alternative to immunomodulators and biologic therapy is prednisone, and its broad range of common

adverse events is often underappreciated. Supplemental Table 1 presents the frequency of prednisone side-effects.^{23–25} To help patients understand the importance of smoking cessation, Supplemental Figure I shows the response rate to anti-TNF agents with or without smoking.²⁶ The risk of PML associated with natalizumab can be best displayed as a 10,000 people risk template (Supplemental Figure J).²⁷

Conclusion

Communicating risk is challenging on multiple levels. The important concepts to remember are that the goal is to have patients feel that they understand the risks of treatment and how this is weighed against its benefits, and to help them feel comfortable with what they are taking. There is no consensus on the best way to communicate with all patients, but hopefully the suggestions and tools in this review can provide some help in teaching patients what we currently know. Patients should understand that data are in evolution and that these point estimates all come with statistical uncertainty, but we need to make decisions now with our patients in order to prevent their disease from controlling them. Whatever the method of communication, there is agreement that actively engaging patients in the process of informed decision making is important, and that they should feel empowered to make decisions that fit with their personal preferences. Although the ultimate decision for treatment is shared between the patient and clinician, it is the clinicians' responsibility to provide accurate information and sound recommendations. We need to continue to gather better data, and to find the best ways to communicate with individual patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Quadrants of risk. Slovic uses four quadrants to conceptualize risk perception based on the range of “dread” and “unknown” associated with a specific event. The location of the object/event on the grid represents the subjects’ perception of risk.²

TABLE 1**Tips for clear communication of risk to patients**

Use absolute as opposed to relative numbers
Avoid small percentages (0.06%), use 6 per 10,000 instead
Present comparisons with a common denominator
Describe both gains and losses to diminish framing
Do not use vague descriptive words (e.g., rare, common)
Discuss the risk of untreated disease, and give perspective of daily life risks

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TABLE 2

Important side-effects associated with 6-mercaptopurine and azathioprine

Event	Estimated Frequency (annual)
Stop therapy due to adverse event	11% (11/100) *
Allergic reactions	2% (2/100) *
Nausea	2% (2/100) *
Hepatitis/abnormal liver tests	2% (2/100) *
Pancreatitis	3% (3/100) 29
Serious Infections	5% (5/100) *
Non-Hodgkin's lymphoma	0.04% (4/10,000) 9

* Weighed average from Siegel and Sands.28; Pancreatitis rate reported in Present et al. 29

TABLE 3

Important side-effects associated with anti-TNF agents

Event	Estimated Frequency (annual)
Stop therapy due to adverse event	10% (10/100) [*]
Infusion or injection site reactions	3%–21% ³⁰
Drug related lupus-like reaction	1% (1/100) [‡]
Serious infections	3% (3/100) [*]
Non-Hodgkin's lymphoma [^]	0.06% (6/10,000) ⁹
Multiple sclerosis, heart failure, serious liver injury	Case reports only

TNF = tumor necrosis factor;

^{*} Weighted average from Siegel et al³⁰;[‡] Rate of lupus-like reaction derived from Vermeire et al³¹;[^] Risk associated with combination anti-TNF and immunomodulator therapy

TABLE 4

Risk of Non-Hodgkin's Lymphoma associated with IBD therapy*

Treatment	Estimated Frequency (annual)	Relative Risk [^]
Baseline risk without treatment	2 per 10,000 (0.02%)	-
6-mercaptopurine or azathioprine	4 per 10,000 (0.04%)	-
		3.2 (compared to no treatment)
Anti-TNF + immunomodulator	6 per 10,000 (0.06%)	
		1.7 (compared to immunomodulator alone)

* Results from Siegel et al.9;

[^] Relative risk is equivalent to standardized incidence ratio;

IBD=inflammatory bowel disease; TNF=tumor necrosis factor