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Guide to Discussing the Risks of Immunomodulator and Anti-TNF Therapy with Inflammatory Bowel Disease Patients

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The risks of treatment associated with immunomodulators and biologic therapy for inflammatory bowel disease (IBD) are of concern to both patients and physicians. It is a complicated matter as the actual risks are uncertain, and how these risks apply to individual patients unknown. Patients appear to have misperceptions regarding the risks and benefits of IBD therapy, but when asked how much risk they are willing to take, patients will accept more risk than has been reported in the literature for these medications. When communicating risk information to patients, it is important to acknowledge the uncertainty of the data, present the data as an absolute risk, and discuss risk in the context of the risk of their disease and everyday life. For patients to make an informed and preference based decision, physicians must develop accurate and clear methods of describing the balance of risks versus benefits of treatment.

The treatment of inflammatory bowel disease (IBD) has changed over the past decade to include new agents (specifically the anti-TNF class) and trends towards more aggressive therapy (e.g., combination therapy, earlier treatment with immunomodulators and top-down therapy). Early data shows that these more aggressive treatment plans have the potential to alter the natural history of disease and avoid excessive corticosteroid use, but they are not without costs. When deciding upon a treatment approach, both the expected benefits and risks of therapy need to be addressed. This review aims to discuss what is known about the risks of immunomodulators and anti-TNF agents, and how we should communicate this information to our patients.

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WERE DO RISK DATA COME FROM?

To appreciate the complexity of determining the risks of adverse events from medications, it is important to understand where safety data comes from. Clinical trials are helpful to elucidate common events, however, in individual IBD trials the total enrollment is at most a few hundred patients with study duration generally just one year. This is suboptimal for identifying rare events and those that might occur after a longer duration of therapy. Furthermore, in many of the anti-TNF trials, all patients received some open-label treatment before the responders were randomized, making interpretation of adverse events difficult. Most data on the safety of pharmaceuticals comes from post-marketing surveillance, which is gathered after a drug has been on the market for a while. For IBD drugs, sources include the Food and Drug Administration (through their MedWatch program), case series, population based studies, administrative databases and pharmaceutical registries. These all have some value, but each has limitations that may bias the results.

THE DATA WE KNOW

Immunomodulators

6-mercaptopurine (6MP) and azathioprine (AZA) have been used for the treatment of inflammatory bowel disease since the 1970s (1) and safety data was reported as early as 1979 (2).

Serious adverse events are fortunately rare, but well-reported. Most side-effects of 6MP/AZA fit into the categories of either direct or indirect toxicity. Direct toxicities include pancreatitis, bone marrow suppression, allergic reactions and drug-induced hepatitis (3). Indirect toxicity refers to processes that result as sequelae from direct toxicity, and includes infections, lymphomas and other cancers (specifically skin and cervical) (4–6). Many of the non-Hodgkin's lymphomas reported are Epstein-Barr Virus related (7), and a recent meta-analysis summarized the lymphoma risk associated with 6MP/AZA as 4-fold higher than the general population (8). Assuming a general population risk of approximately 2/10,000 (9), this translates to a lymphoma risk of about eight patients per 10,000 (yielding a number need to harm of approximately 2,000). A

recently described, almost universally fatal form of lymphoma (hepatosplenic T-cell lymphoma or HSTCL) associated with IBD therapy has generated significant concern. Most reported cases were with combination immunomodulator plus anti-TNF therapy; however, there have been three cases in the literature in patients treated with azathioprine alone (10–12). Table 1 summarizes estimated risks of the most significant direct and indirect toxicities associated with 6MP/AZA. We are unable at this time to comment on the rate of HSTCL with monotherapy or combination therapy using immunodulators plus anti-TNF agents.

Methotrexate (MTX) is used less frequently than 6MP/AZA, in part due to its perceived toxicity. In practice when used for the treatment of Crohn's disease it is generally well tolerated. The most hesitation comes from concerns over lung disease (hypersensitivity pneumonitis) and liver toxicity. Hypersensitivity pneumonitis is reported in up to 1% of patients with rheumatoid arthritis (13), but only rare cases have been reported in IBD (14,15). Liver toxicity also appears to vary based on the underlying disease in which MTX is being used to treat. In patients with psoriasis nearly a quarter of patients have evidence of liver disease (16); however, in IBD patients (more similar to rheumatoid arthritis

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Table 1
Serious side-effects of 6-mercaptopurine and azathioprine

Event	Frequency (annual)
Allergic reactions	3% (3/100) (6)
Pancreatitis	3% (3/100) (6)
Severe infection	5% (5/100)*
Death (sepsis)	0.15% (15/10,000) (25)
Lymphoma	0.08% (8/10,000)^
Death from lymphoma	0.02% (2/10,000) (25,30)

Adapted from Siegel CA. Comprehensive approach to patient risk. Risk versus benefit of biologics and immune suppressants. In: Targan S, Shanahan F, Karp L, eds. *Inflammatory Bowel Disease: Translating basic science into clinical practice.* In press, 2007.

*weighted average from Siegel, et al (6)
^ calculation based on four times increased risk of lymphoma (8) over general population risk of 0.02% (9)

Table 2
Serious side-effects of anti-TNF agents

Event	Frequency (annual)†	Range*
Lymphoma (NHL)	0.2% (2/1000)	0%–1.6%
Death from lymphoma	0.067% (7/10,000)	0%–0.53%
HSTCL	unknown	unknown
Stop treatment due to AE	9.6% (1/10)	3.6%–16%
Death from sepsis	0.4% (4/1000)	0%–1.0%
Tuberculosis	0.05% (5/10,000)[26]	0.01%^–1.0%[27]

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† Frequency of event from systematic analysis (25)
* Range of risk of event from systematic analysis (25)
^ Data on file, Centocor, Inc.
NHL = non-Hodgkin's lymphoma
HSTCL = hepatosplenic T-cell lymphoma
AE = adverse event

patients) the majority have either normal biopsies or only mild steatosis/inflammation (17). Leukopenia is much less common as compared to 6MP/AZA, but has been reported an can be life-threatening (18). Lymphoma associated with methotrexate is well-reported in the rheumatoid arthritis literature (19,20), but probably rare in IBD (21). There have been no cases reported of HSTCL associated with the use of MTX.

Anti-TNF Agents

Currently available anti-TNF agents for the treatment of IBD include infliximab and adalimumab, with the expectation that certolizumab pegol will be available in the near future. The majority of information on risks of this class of drugs comes from infliximab due to the fact that it has been around the longest (FDA approved in 1998). The range of reported serious events with infliximab is broad and the actual rate is controversial. Focusing on two of the most concerning associated risks, lymphoma and sepsis leading to death, the TREAT registry (22), which at the time of a recent update included over 3,000 IBD patients, reported that after multivariate analysis there was no increased rate

of lymphoma or infection attributable to infliximab. On the other end of the spectrum, a population based study from Sweden showed a nearly 2/100 rate of lymphoma (23) and the Mayo clinic reported a 1/100 rate of death thought attributable to infliximab (24). With an attempt to develop a summary estimate, a systematic analysis was performed that concluded that the annual rate of lymphoma can be estimated at 2/1,000 and risk of death of 4/1,000 infliximab treated patients (25). Table 2 summarizes these data.

Other adverse events that should be reviewed with patients when initiating anti-TNF therapy include: Tuberculosis; multiple sclerosis; heart failure; hepatic toxicity; autoimmunity (clinically significant) and pancytopenia. Other than tuberculosis (approximate annual risk 0.05% [26,27]), the others are so rare it is difficult to determine a possible range. In an effort to not overwhelm patients with too much information, a fair way to address these risks with patients is to state that these events can occur, but are even more infrequent than the risks noted for lymphoma and sepsis.

THE DATA WE DON'T KNOW

Although we have a range of estimates of the rate of these adverse events, there is still significant uncertainty. Furthermore, we do not understand which patients are at most risk, how concomitant medications influence efficacy and side-effects and how duration of treatment plays a role. The currently available risk estimates are predominantly annual risks. How long-term (or lifetime) therapy influences the risk is unknown. For instance, most of the lymphomas as reported above were within the first year or two of therapy. Are these risks all up front (if you don't get lymphoma in the first two years you will not get it at all), or is it cumulative? These are critical questions that need to be answered in the future.

PUTTING RISK IN PERSPECTIVE

When discussing risk of treatment with patients, it is easy to lose perspective on how risk plays into our everyday lives. For instance, the annual risk of developing lymphoma in the general population is two in 10,000, and the lifetime risk of lymphoma is one in 50(9). The lifetime risk of dying in a car accident is one in 80, and the chance of anyone dying from cancer is one in eight (28). Taking these risks are for the most part an obligatory component of life, and therefore are acceptable. However, when knowingly taking what is perceived as optional risk (i.e., starting a new medication) even a very small chance of an adverse effect may become intolerable.

It is important for patients to understand the risks of their disease so that they can appreciate that suboptimal treatment may be the riskiest choice. Approximately 18% of patients with Crohn's disease require surgery within the first year of their diagnosis, and up to 80% have surgery by 20 years (29). Operative mortality is low, but measurable (approximately 8/10,000) and although it is very uncommon to die from a complication of Crohn's disease, it has been estimated to occur about 15/10,000 (25,30).

HOW PHYSICIANS MIGHT BALANCE RISKS AND BENEFITS

To help guide physicians on how to balance the risks and benefits of treatment, decision analytic models have been developed for both immunomodulators (specifically azathioprine) and biologics (infliximab). The azathioprine decision analysis modeled the natural history of alternate management strategies to maintain a steroid-induced remission of Crohn's disease (30). Although azathioprine increased the incidence of lymphoma, the death rate decreased due to improved disease control. Therefore, patients taking azathioprine had an overall improvement in quality-adjusted life expectancy.

The decision analysis for infliximab modeled 200,000 hypothetical patients with moderately-active Crohn's disease (25). In this simulated clinical trial, half of the patients received infliximab and the other half were maintained on standard therapy (corticosteroids, immunomodulators, surgery). The patients who received infliximab had an increase in lymphoma, and death due to sepsis, however, due to the significant amount of patients who improve clinically from infliximab, overall quality of life was higher in the infliximab group. The message from both of these models is that in properly selected patients, the benefits of these medications outweigh the risks.

ARE PATIENTS WILLING TO TAKE THE RISKS OF IBD THERAPIES?

Individual patients have different thresholds of the amount of risk they are willing to accept. A recent study showed that patients are willing to take higher risks of lymphoma and/or dying than have been reported in the literature (31). However, it was dependent on (1) the severity of their illness and (2) how much benefit they expected to receive from treatment. As anticipated, the sicker patients who were promised more treatment benefit had a higher threshold for risk (as high as a 0.82% risk of dying from lymphoma). Parents of children with IBD were also asked the same questions. Interestingly, parents took higher risks for their children than adults took for themselves (over a 1% annual risk of lymphoma), but only if their children were severely ill (32). In addition, physicians were surveyed using the same instrument, and were yet more risk taking than patients and parents, tolerating up to a 2.5% risk of lymphoma (33). As seen with the other groups, their threshold of risk was highly dependent on the severity of their patients' disease.

Although in the above studies patients appear risk taking, when asked how much risk they believe their medications carry, they underestimate the risks, while overestimating the benefits (34). This creates a problem, as patients may not be getting what they think for a risk/benefit tradeoff. For instance, when patients were given a hypothetical "new" drug for the treatment of IBD that carried a specified risk of lymphoma and death (unbeknownst to them reflecting what has been estimated for infliximab) nearly two-thirds of patients stated that they would not take the medication. Amazingly, one-third of these patients were either currently taking or had already taken infliximab. These data set the stage for the fact that we are collectively doing a bad job communicating risk and benefit data to our

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Table 3
Practical Considerations in Presenting Risk to Patients

1. Acknowledge uncertainty of the data
2. Present data as absolute risk (X out of 100,1000,10000)
3. Attempt to keep denominators consistent
4. Avoid framing
5. Present risk in the context of other life (and disease related) risks
6. Don't overwhelm patients with too much data, focus on the most important information

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patients, and we need to think of new approaches to ensure that this occurs more effectively.

HOW SHOULD WE TELL OUR PATIENTS ABOUT RISK?

Knowing the correct data is only half of the equation in communicating risk information to patients. Finding the most effective way of presenting these data can be even more complex. Dealing with risks of therapy often demands the accurate interpretation of small numbers (<1%), which requires a high level of numeracy (skill with numbers). Previous work has shown that in general patients have a difficult time with this (35,36). For instance, in one study 80% of patients were unable to make conversions such as one per 1,000 to 0.1% (35). Unfortunately, medical students were not much better at these tasks with 25% unable to perform basic mathematical calculations and only 60% correctly interpreted quantitative data (37).

There are multiple methods of presenting data, including levels of statistical significance, absolute risk, relative risk, odds ratio and number needed to treat (NNT). Absolute risk and relative risk appear to be the easiest concepts for patients to comprehend (38), and odds ratios can be very misleading (especially when the effect size is large, as odds ratios tend to exaggerate the relative difference). A recent study showed that results presented as the NNT led to more patients consenting to therapy (39). This is due to the effects of framing. Framing refers to the unintentional (or perhaps intentional) presentation of data in such a way as to influence a choice of therapy. This was shown clearly by Malenka, et al when they asked patients to consent to a therapy for heart disease that decreased their risk of myocardial infarction from a risk of 4.1% to 2.7% (40). In this format (a 1.4% absolute risk reduction), only 42% of patients accepted treatment When the same results were presented as a relative risk reduction of 34%, 88% of patients consented to therapy. This can work in both directions, and care needs to be taken to avoid framing and presenting data as accurately as possible. Absolute numbers, presented over a common denominator may be the most comprehensible format to deliver risk data to patients (X out of 100, 1000, or 10,000) (41). For example, the annual risk of lymphoma in the general population is 2/10,000, as compared to the risk of lymphoma associated with immunomodulators up to 8/10,000 and the risk of lymphoma attributable to anti-TNF drugs as high as 20/10,000 patients.

From a practical standpoint, there should be some documentation that issues of treatment risk were discussed with patients. Although some physicians in the country require informed signed consent before beginning immunomodulators or biologic therapy, this may send the wrong message to patients (having them accept the risk themselves). Another approach is to review the data carefully with patients, and then to document that the conversation took place, what data were reviewed, and that an informed choice was made together with the patient.

CONCLUSION

As current treatment algorithms evolve and new agents are developed it will be critically important to have methods to clearly communicate risk and benefit data with our patients. A move towards "shared decision making" (the process of interaction with patients who wish to be involved with their health care providers in making medical decisions) will likely influence all medical practice. Shared decision making hinges upon the accurate and clear delivery of information. In IBD, we need to work on both of these components. First, we need to understand how much risk the treatments really carry, and then we can develop effective methods of communicating this information to our patients. For

now, we should review the best available information, avoid framing, and allow patients to be involved in preference based decisions regarding their treatment. ■

Acknowledgment

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