How to Think About "Risk" Part 2

Introduction

In the first part of this podcast, we discussed that zero risk is impossible and that we need to think more rationally about risk. That means that we need to gather and organize data to help us make risk benefit decisions. This includes recognizing the potential severity and consequences of each risk. To highlight difficult risk/benefit decisions, I outlined several clinical trial examples and how drug developers use statistics to help predict the likelihood of a result happening.

Risk/Benefit Decisions

Without consciously thinking about it, all of us make many risk/benefit decisions a day. Let's say that you live on the North side of Indianapolis and work at a Ford plant that makes components for the F150 truck that is a 40-minute drive on the freeway from your home. You work 7-3 Monday through Friday, but today you just don't feel up to going to work and decide to stay in bed all day. You just reduced your risk of a car accident on the way to work to close to zero and it seems pretty unlikely that you will have an accident at the Ford plant since you will not be there. On the other hand, the decision you made to stay in bed, just increased your risk of a blood clot forming in the deep veins of your legs and the risk of a heart attack, stroke or pulmonary embolism because a piece of the blot in leg breaks off and lodges in a bad place. If you are outrageously dumb and smoke in bed, you also increased your risk of dying in a fire in your home.

The point is that essentially every decision you make is a risk/benefit decision. Obviously, if you asked did your decision to stay in bed increase or decrease the likelihood of encountering a harmful event, we don't know enough to provide an answer. To begin to answer that, we

would ask are you a safe driver, do you work on assembly line, with power tools or in an office? Are you obese? Do you have diabetes? Have you already had a cardiovascular event? And so on.

But whether you think about all this or not, whether you care or not, these risk/benefit calculations are taking place in real time as the laws of probability play out.

Key Point: Assessment of the risk benefit of a decision about the health of a person must be made in the context of as much information about that person as can be assembled and analyzed.

n-Lorem Is Different

In a standard clinical trial setting, as I described in Part 1, we are studying a population and making decisions to treat a population of patients, but n-Lorem is vastly different, we are treating a single patient with a severe, often rapidly progressive disease, and we know that even patients with the exact same mutation can have different phenotypes. We also know that time is critical. Thus, what we do is fundamentally different from traditional drug development, and it takes professional drug developers like me a while to get used to the differences. What this means is that everything we do and every risk/benefit decision we make is linked to an individual patient's phenotype, the severity of the syndrome, and rate of progression of the disease, and whether we think we can make a real difference in a symptom that matters to the patient and family and do that with reasonable safety and tolerability. This difference is truly critical, and it means at every step in our decision-making process, we must know as much about the patient, his or her needs and rate of progression as possible. We must also be clear about what our therapeutic goals are, how we will measure benefit, and discuss our goals with the patient and the family to be certain that if we succeed, it will make a meaningful difference in the lives of our patients.

Key Point: At n-lorem, the context in which we must make risk/benefit judgements is in the individual patient.

No Promises

As much as we would like to promise results, we cannot. Anyone who promises benefit with any therapeutic intervention in a specific patient is a charlatan, no matter how much experience there is with the intervention. Even if a patient with a specific mutation has benefited greatly, we cannot promise that the next patient treated with the same ASO will benefit. Every patient is different. So, we can be more optimistic if a previous patient has benefitted, but there are no promises.

Key Point: We can promise only that we will do our best.

Communicating About Risk

Factors that Contribute to Emotions About Risk

Perceptions Concerning Control

Multiple studies have shown that people respond with much greater fear or “dread” to risks they perceive to be beyond their control. For example, people dread the possibility of a nuclear accident to a much greater extent than more prevalent and pernicious risks that they perceive to be more in their control, like auto accidents. Nano-rare diseases strip any sense of control away. One is at the mercy of a process that cannot be controlled, so we dread the next manifestation of the mutation. We must live in fear and that makes us angry.

In fact, diseases rob us of a sense of control and the most logical path to gaining control of the disease is to seek medical and scientific help. But that means that, at some point, one must cede control to the medical system, typically led by a physician. The granting of control of your health to another human being is an act of extraordinary trust that must be taken despite the fact that most health professionals seem to speak a foreign language and never provide certainty, but rather the uncertainty of probability-based comments. Nano-rare mutations exacerbate the sense of lost control because it is usually difficult to find anyone who knows anything about the syndrome or is interested in research about the mutation and often, almost impossible to find a research physician and institution willing and able to care for a nano-rare patient.

So, what does this set of comments teach?

First, it is natural to be angry-after all, none of us like being treated unfairly and having a nano-rare disease is grossly unfair. It is also natural to try to find someone to blame. But, if you are to make the best of the situation, you must control your anger by focusing it on finding solutions.

Second, Inequities abound. Wealthy families simply can spend more money to get help for their loved ones. Once again, that is terribly unfair, but the most effective way to deal with the anger that is natural, but not helpful, is to support organizations that demonstrate that they are committed to equitable delivery of care.

Third, though most people are well meaning, understanding how knowledgeable, experienced, and capable the individuals and organizations available to help are is vital. It is also vital to understand that each individual encountered will have limits to the areas of expertise. For example, it makes little sense to think that because a

person is an excellent pediatric neurologist, that person has the knowledge and experience to create a therapeutic agent.

Key Point: A nano-rare disease is unfair, it robs our sense of control first, then leads to a sense of hopelessness and helplessness. Though natural, if you hope to make the best decisions, you must control and channel those emotions.

Key Point: Before you entrust anyone with your future or the future of your loved ones, invest in diligence.

Exposure

We react very differently to risks with which we are familiar, or said another way, we react with less emotion to risks to which we have been exposed, than we do to novel risks. All of the risk vignettes I discussed are examples of known risks with which we have a lot of experience and to which we have been exposed for decades, and we are comfortable with them. But to see how a relative lack of exposure to risk affects risk perceptions and responses, consider our response to Covid. For centuries we lived with the risk of infectious disease, and we were comfortable with it though it killed 2 out of 5 children for centuries, but the eradication of most infectious diseases with enhanced public health, effective treatments and vaccine, was partially accountable for our radically different approach to coping with Covid.

Another great example is Coumadin, the first anticoagulant. As you may recall, coumadin has a therapeutic index of less than one meaning you are more likely to have a side effect than benefit when treated with coumadin, and the side effects include potentially fatal bleeding. Nevertheless, when new more effective and far safer anticoagulants were introduced, it took years of effort to convince physicians to convert to the newer and better agents; they failed to understand that

just because they were familiar with a risk didn't justify exposing patients to what had become an unnecessary risk.

Key Point: The presence of a nano-rare mutation means that the patient and family will need to contend with many novel risks. to manage the risk/benefit decision making thoughtfully, the patient and family must benchmark the novel risks to risks with which they are familiar and recognize that a novel risk may seem scarier than a risk to which they are used to being exposed, but they need to think logically about the nature of the risk, the probability of the risk and potential consequences.

Compression

Compression is a term used to describe the fact that often humans exaggerate the risk of more novel or sensational risks. A good example is the risk of an intruder causing harm in a household. Of course, that happens, but when it does, it is almost always sensationalized, and the response greatly exaggerated relative to the extremely low probability of such an event.

A nano-rare mutation comes out of the blue. It is a shock and terrifying. Compression means you likely will exaggerate the risks and nano-mutations can range in severity from immediately fatal to serious, but treatable. Try your best to hold your emotions in check when making risk/benefit decisions.

Omission

Risks can occur as a result of acts committed, or as a result of actions not taken. Humans tend to exaggerate the risks encountered by acts of commission, yet the failure to act often has a greater level of risk.

Key Point: Risks can be encountered because of actions taken and failure to act. in the case of progressive diseases, the failure to attempt to treat a patient is associated with significant risk. consequently, the most fundamental risk/benefit calculation must compare the risks of treatment to the risks associated with no treatment.

Timing

The temporal relationship of a risk to an action is a critical determinant of how we react to risk. We react to immediate risk far more vigorously than risks that may manifest in the future. Compare the reaction to someone who suggests we join him climbing El Capitan vs someone who offers us a cigarette. If you have never climbed a rock, the idea of climbing El Capitan is immediately terrifying. Yet, we know that if we smoke it is likely that we will die due to a smoking related disease and we know those diseases are terrible with deeply painful and debilitating ends of life.

Key Point: Do not be fooled by the clock.

Official Positions

If you wonder how official positions affect our perceptions and responses to risks, consider how we responded to infectious disease risks throughout modern history vs how we reacted and are reacting to Covid. Despite the toll of winter pulmonary infections, for many decades, we went to work and school, we wore no masks, and we never quarantined the healthy. That certainly was not how we responded to Covid.

The point is to consider official positions but do your own thinking as well.

Inferring Individual Risk from Averages

We can say that if a person is exposed to a particular infectious disease, let's say the flu, 50% with come down with the flu and 10% of those may require hospitalization. Knowing those average risks tells us nothing about an individual's risk of being infected or the severity of the consequences of the infection.

This means that even if an ASO to a particular mutation has caused benefit in all 3 patients treated, that does not guarantee that the next patient will benefit. Similarly, knowing that two-thirds of smokers will die due to a smoking related disease does not mean that we can tell the next smoker that he will, in fact, die from a smoking related disease.

Key Point: Averages of rates of benefit and side effects of a medicine provide valuable information that may encourage or discourage the treatment of a specific patient, but the average response does not provide a guarantee that the next patient treated will respond like the average response.

Anchoring and Communicating Risk

As I have said, it is important to place a novel risk in the context of better understood risks. That is called anchoring, that is, we use known risks to help us proportionalism our response to a novel risk. However, when we contextualize a novel risk by comparing it to a better-known risk, there are effective ways to communicate and many that mislead.

For example, I like Milk Duds, and Rosanne reminds me daily that they are bad for me. Fortunately, I am pretty good at ignoring advice I don't want. On the Milk Dud box, in big red letters, it says 30% less fat, and in fine print it says, "than the leading chocolate candy brand." Obviously, the company that makes Milk Duds is doing its best to communicate

accurately about risk. Of course, I am joking. The labeling is a perfect example of misleading communication about risk, but it demonstrates several ways to miscommunicate about risk.

Suppose I were to tell you that the results of the 10 mg dose study with our new antihypertensive drug showed that patients were three times as likely to experience nausea than the 5 mg dose. That is accurate but communicates about risk poorly. If I said the 10 mg dose resulted in a net decrease of 15 mmHg in blood pressure and three of 50 people treated had one episode of mild nausea while the 5 mg dose reduced blood pressure by 5 mmHg and only one patient experience mild nausea, that too is accurate, but now provides a more useful statement about risk/benefit. You may think that this example is obvious, but every day, risk/benefit is communicated this badly, and far too often the communication is like my Duds communication - deliberately misleading. Many times, there are protagonists and antagonists for drugs and each side takes deliberately biased positions. Don't fall for deliberate or accidental miscommunication about risk/benefit. If you are sick or a loved one is sick and you must make decisions about care, you cannot afford to make mistakes about risk/benefit.

The term to describe the process I just went through with our new antihypertensive and my Milk Duds is called anchoring. Anchoring is a key step in understanding risk that must accompany a statement about relative risk. Because it gives insight into the absolute frequency of risks. Yes, at 10mg daily our new antihypertensive caused nausea in three times as many patients as the 5 mg daily dose, but that means that only 3 out of 50 patients experienced nausea.

Key Point: To understand risk, you must understand the absolute incidence of the risk and compare the relative rates of encountering

that risk in the context of absoluter rates and you must demand that providers speak clearly and simply about risk vs opportunity.

Conclusions

I know that this has been somewhat lengthy and complex, but of all the “lectures” in this series, I think understanding the basis of risk/benefit decision making is likely the single most important skill that will help you make as informed and effective decisions as possible in the context of a nano-rare mutation. I hope that I have helped and that if you have questions or are confused, you post them or write me. I think those questions and comments might help me follow these “lectures” up by answering key questions that should help resolve confusions.