13 An Evidence-Based Practice Approach to Evaluating Biotechnologically Derived Medications

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INTRODUCTION

Recent advances in pharmaceutical biotechnology have led to the development of many different therapeutic proteins. These technologies have given credence to the legitimate promise that we, at some point, may be able to more closely match some specific patients with the most effective and safe drugs at an individualized dose—personalized/precision medicine.

BACKGROUND

Despite the clear potential for these technologies, when it comes to treating patients within an evidence-based practice framework, a number of requirements come into the clinical decision making process with the use of these agents. Clinicians will need to consider all these requirements on a patient-by-patient basis if we are to fully realise the clinical potential of these therapeutic proteins.

These requirements can be separated into evidence and individual treatment decision issues. These are outlined in Table 13.1.

At any clinical encounter where a treatment is to be recommended the obvious goal would be to "match individual patients with the most effective, and safest drugs and doses" (Sindelar 2013). Tailoring the correct medication and dose to an individual patient has been the goal and the approach of health care providers for millennia.

Over the last decade or so, much of this tailoring concept has been termed personalized medicine or precision medicine. Interestingly, these two terms have recently been co-opted by people interested in the fascinating and potentially very useful area of genomics. Despite this, it is important clinicians remember that pharmacogenomics is just one of a number of tools or approaches that can be useful as we appropriately attempt to tailor the use of medications in a more personalized way. Obviously, behavioural and environmental factors play an important role in the clinical outcomes associated with treatments and it is of value to remember these, and other similar factors, will likely never be importantly influenced by genomically-targeted medications.

Finally, the present-day personalized medicine discussion typically omits two of the most important aspects of true personalized medicine—first, patient's individual values and preferences and second, doses of medications need to be individualized based on a clear and objective review of an individual patient's response.

When it comes to these new "omic" technologies it is helpful to think through the issues outlined in Table 13.1 when trying to figure out where therapeutic proteins fit into the concept of evidence-based practice and true personalized medicine. Using six different recent examples, many of these issues will be examined. It is useful to breakdown these examples into two

(A) *Evidence requirements*
Placebo controlled RCTs of these agents
RCTs comparing these agents directly to presently established therapy
RCTs of direct head-to head comparisons of monoclonal antibodies that are in the same class/used for the same indication
Cohort data with long term follow-up to estimate any on-going long-term safety issues
(B) *Patient-centered requirements*
The promotion of the concept of shared-decision making
Defining clear, specific and measureable individual patient outcomes
When possible starting with very low doses and/or continually adjusting doses based on individual response
A discussion of how to address the potential cost issues typically seen with these agents

Table 13.1 ■ Evidence and patient-centered requirements for making therapeutic decisions

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specific therapeutic scenarios based on the overall treatment goals of the medication as this impacts the specific issues that require focus. These scenarios are prevention/risk reduction and symptom reduction.

TREATMENTS THAT REDUCE RISK

In prevention, one is taking a treatment to try to reduce the future chance of developing symptoms or of having an event such as a heart attack, stroke, hospitalization, or disease exacerbation.

Example 1: Palivizumab for Reducing the Risk of Severe RSV Infection in Children

Bronchiolitis and pneumonia in children are most commonly caused by the Respiratory Syncytial Virus (RSV). Most infants recover from this virus but serious complications can occur, especially in those with underlying medical conditions such as congenital heart disease. For those infants at higher risk of complications palivizumab (Synagis®), a monoclonal antibody produced by recombinant DNA technology, is used to reduce the risk of developing serious complications. The authors of a recent Cochrane review (Andabaka et al. 2013) state "there is evidence that palivizumab prophylaxis is effective in reducing the frequency of hospitalisations due to RSV infection" and to that end, "palivizumab prophylaxis was associated with a statistically significant reduction in RSV hospitalisations (RR 0.49, 95% CI 0.37–0.64) and a statistically non-significant reduction in all-cause mortality (RR 0.69, 95% CI 0.42–1.15) when compared to placebo". In other words palivizumab reduced the risk of RSV hospitalisations by approximately 50%.

So to properly use these numbers using an evidence-based practice framework, we need to know the baseline risk of RSV hospitalizations in these infants.

The patients studied were infants with serious medical conditions such as chronic lung disease, congenital heart disease, or those born preterm. In the placebo group, roughly 10% of the infants ended up being hospitalized for RSV over a 5-month period. Giving palivizumab reduces that risk by roughly 50%. Putting this into absolute numbers, the risk went from roughly 10% (in the placebo group) down to 5% (in the palivizumab group). This absolute 5% benefit means for every 20 children who got this agent (typically for 5 months) one benefited, or in other words 95% got no benefit from this treatment. To be fair, even if this treatment prevented all RSV hospitalizations, reducing a 10% risk down to 0% would still only mean 1 in 10 would benefit from treatment. In this example, unfortunately there is no way to predict which of these higher risk infants will benefit and there is also no way to titrate the dose to an effect. So when it comes to evidence-based practice we have evidence that this new medication has an effect in the population studied but this benefit needs to be balanced with the fact that 5-monthly injections will cost a total of roughly $10,000US for a 1 in 20 chance of benefiting. In addition, cohort studies would be required to determine the long-term effects of immunoprophylaxis on asthma, mortality and other important clinical outcomes. And finally, at present there are no studies comparing this agent to other potential treatments.

Example 2: Evolucumab for Hyperlipidemia and Reducing the Risk of Heart Disease

Another example of a risk reduction treatment is evolocumab (Repatha®) a monoclonal antibody (PCSK9 inhibitor) designed for the treatment of hyperlipidemia and recently approved to reduce the risks of heart attacks strokes and coronary revascularization. The study that evaluated the benefit of evolocumab was called the FOURIER study (Sabatine et al. 2017). The authors of this study investigated people with established heart disease, average age 63, and gave this agent for 2.2 years. Their primary outcome was the risk of a combined CVD endpoint - cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The result was a reduction in the risk of combined CVD - hazard ratio of 0.85 (0.79–0.92) - or in other words a 15% relative benefit. Comparatively, these relative benefits (15%) are numerically less than that seen with statins and/or medications used for blood pressure (25–30%) but there are no head-to-head comparisons between these different treatments so comparisons are at best speculative.

Looking at the absolute numbers, 11.3% in the placebo group ended up with this CVD endpoint and this occurred in 9.8% of the group on evolocumab. This is a 1.6% absolute benefit or 63 people need to be treated to benefit one. As with palivizumab there can be no dosage titration because only a single dose has been studied and there is no endpoint to which to titrate. The cost of this agent is roughly $15,000 US a year for a 1 in 63 benefit and at present there is no information on the long-term benefits and harms of this agent. This is clearly an example where patient values and preferences will need to be taken into account via a shared-decision making process.

Example 3: Romosozumab or Alendronate for Fracture Prevention

Fractures increase morbidity and possibly mortality and there are some new biologic treatments that appear to reduce the risk of these fractures. An example of a very useful head to head study in this area is the ARCH study (Saag et al. 2017) where roughly 4100 subjects were randomized to receive either romosozumab (Evenity®) or alendronate in a blinded fashion for

12 months followed by both groups receiving alendronate alone for 12 more months. Over the 24 months, clinical fractures occurred in 9.7% of the romosozumab and 13% in the alendronate group—RR 0.73 (0.61, 0.88). This 27% relative benefit or 3.3% absolute benefit means that 30 people would need to take romosozumab over alendronate for 1 year for one additional person to benefit. Unfortunately, in this trial there was an increase in cardiovascular events in the subjects receiving romosozumab. In the romosozumab group, 2.5% had a serious cardiovascular event compared to 1.9% in the alendronate group. So for every 167 people taking romosozumab over alendronate, one would have a serious cardiovascular event. Because of this the FDA has at present decided not to approve this medication and is requiring the company to look at cardiovascular event data from all the clinical trials of this agent. There was also a 1.8% absolute increase in injection site reactions in the romosozumab group.

So in this scenario we have a new agent that is more effective at reducing fractures than the gold standard but it may also increase the risk of serious cardiovascular disease. If this agent is eventually approved, this is where shared decision-making becomes an essential part of the discussion. Does a 3.3% absolute reduction in fractures justify a 0.6% increase in serious cardiovascular events? Only an informed patient can participate in that sort of decision. On top of the benefits and harms discussion other considerations such as the requirement for injections, the lack of long-term follow-up data and the very likely fact that romosozumab will be considerably more expensive than generic alendronate need to be incorporated into the shared-decision.

In these three risk reduction examples, the only way clinicians and patients can make decisions about the use of these medications is to have a rough idea of the magnitude of the effect on clinically important endpoints and how these agents compare to either placebo or established therapies. This information, mixed with the cost and the potential long-term benefits and harms must be discussed with patients in the realm of a shared-decision.

TREATMENTS THAT REDUCE SYMPTOMS

In contrast to treatments that reduce risk, treatments for symptoms are used with the goal of reducing or eliminating disease-specific symptoms.

Example 4: Guselkumab Used in the Treatment of Plaque Psoriasis

Patients with moderate to severe psoriasis can experience not only physical discomfort but chronic psoriasis can lead to psychological distress secondary to the appearance of lesions over large portions of a person's body. In addition psoriasis is associated with the development of arthritis, worsened cardiovascular risk factors and other conditions like inflammatory bowel disease.

The VOYAGE 1 study is an example of a well-designed and informative trial of guselkumab (Tremfya®) for patients with moderate to severe psoriasis (Blauvelt et al. 2017). The VOYAGE 1 study had three arms—guselkumab (weeks 0–48), adalimumab (weeks 0–48), and a placebo arm (weeks 0–16) after which patients taking placebo crossed over to receive guselkumab from weeks 17–48. This very useful design answers two important questions: Is guselkumab better than placebo and is guselkumab better than an established therapy (adalimumab) from a similar class?

The main endpoint in this trial was a 90% or greater improvement in the Psoriasis Area Severity Index (PASI 90). This score is used to express the overall severity of psoriasis by combining erythema, induration and desquamation with the percentage of the affected area.

At week 16, roughly 3% of the placebo subjects had a PASI 90 score, whereas this occurred in 50% in the adalimumab arm and 73% in the guselkumab arm. The roughly absolute 25% advantage of guselkumab over adalimumab was maintained at week 24 and week 48. In other words, the 50% benefit in the adalimumab group means that for every two people given adalimumab one person will achieve a PASI 90 score. The 25% additional benefit for guselkumab over adalimumab means for every four people who get guselkumab instead of adalimumab one extra person will get a PASI 90 score. When one lowers the benefit threshold to a PASI 75, approximately 90% ended up with improvement in the guselkumab group.

In addition, overall quality of life was improved. A Dermatology Life Quality Index is a score from 0 to 30 with a higher score indicating more severe disease. These subjects started at ~13–14 on this scale. On placebo, this score remained essentially unchanged over the duration of the study. However, the score on this scale for subjects on these agents went down by between 9 and 11. For this scale a minimally important change is considered ~2–3. So not only do these agents clear up psoriatic lesions, this change is also associated with an impressive improvement in a subject's quality of life.

Over this 48-week trial, adverse effect data were collected and there were no greater numbers of people with regard to outcomes such as upper respiratory infections. Adverse events such as malignancies and major adverse coronary events occurred in less than 1% in all groups. While promising, this was only a 48-week study and any impact positively or negatively these agents might have on malignancies or cardiovascular disease may not be seen for years.

So in contrast to the first three examples, in this case we have a treatment that clearly provides clinically important benefits for the vast majority of people for an endpoint that is clear, specific and measureable (PASI score and quality of life). This allows clinicians and patients the opportunity to figure out if an individual patient gets a clinically important response from a therapeutic trial.

In addition, having an endpoint that is measurable in an individual patient allows clinicians and patients to evaluate different treatments and also to determine the lowest effective dose for an individual patient.

So how could clinicians and patients use this information? From this trial adalimumab is effective in roughly 50% of subjects so a reasonable approach could be to try adalimumab first as it is less expensive and there is likely more long term data as adalimiumab has been around longer than guselkumab. If an acceptable response is not seen, then one could switch to guselkumab. Regardless of which agent is chosen, once a response has been seen, the next step would be to find the lowest effective dose by either lowering the dose or increasing the interval of the injections and seeing what happens to patient response. This approach would hopefully reduce the cost and potentially reduce the risk of adverse events given the majority of adverse effects for medications are dose-related.

Example 5: Dupilumab for Uncontrolled Persistent Asthma

Roughly one-quarter of asthmatics have moderate to severe disease with an increased risk for exacerbations, hospitalizations and an impairment of quality of life. Dupilumab (Dupixent®) is an agent used for eczema but it has also recently been studied in subjects with moderate to severe asthma. Dupilumab was evaluated in 769 subjects with uncontrolled persistent asthma despite being on inhaled corticosteroids and a long acting beta-agonist (Wenzel et al. 2016). Subjects received either placebo or one of four different doses of dupilumab, for a total of 24 weeks.

The risk of a severe exacerbation over the 24-week study period was reduced from ~25% in the placebo group down to ~15% in those receiving a dupilumab every 4 weeks and to ~10% of subjects on the twice weekly doses of dupilumab. In other words 1 in 10 benefitted from monthly injections and 1 in 6 benefitted from every 2-week injections.

As with the plaque psoriasis study, these investigators also looked at the impact of this agent on quality of life using an Asthma Quality of Life Questionnaire. The score on this questionnaire ranges from 1 to 7 with higher scores indicating a better quality of life. Subjects started at a score of roughly 4 and the scores increased by 0.9 in the placebo group and by approximately 1.1–1.2 in the dupilumab group. A minimally important change on this scale is considered to be a change of 0.5. Interestingly, in contrast to the previously mentioned psoriasis study, the placebo group in this asthma study experienced a quality of life change (0.9) that would be considered clinically important. However, the difference between the treatment and placebo groups of ~0.2–0.3 (1.1 to 1.2 minus 0.9) on this 1–7 scale would not, on average, be considered clinically important. This makes evaluation of this agent on an individual basis much trickier because of the "benefit" seen in the placebo group and the minimal difference between placebo and dupilumab.

Overall, when given this medication, patients will on average experience what they perceive to be a benefit in their quality of life (as an improvement was seen in both the placebo and the active drug group). However, almost all of this improvement is secondary not to the impact of the medication, but likely a combination of regression to the mean, the natural history of the condition and possibly the placebo effect. For this reason, dose titration to symptom control in this example is not a reasonable approach. Dupilumab did however reduce the risk for severe exacerbations in roughly 1 in 5–10 people. Finally cost and the lack of long-term data would need to be given due consideration in the decision-making process.

Example 6: Enzyme Replacement for Fabry Disease

People with the genetic disorder Fabry disease lack the enzyme alpha-galactosidase A. This enzyme is responsible for the breakdown of certain lipid compounds (globotriaosylceramide) and without this enzyme these compounds build-up in blood vessels and affect the function of the eyes, skin, kidney, heart, gastrointestinal system, brain and nervous system. This build-up can lead to symptoms of pain in the hands and feet, cloudiness in the eye, a decreased ability to sweat, hearing loss, and dark red spots on the skin. In addition, life expectancy is also reduced. Two recombinant enzyme replacement therapies are available, agalsidase alfa (Replagal®) and agalsidase beta (Fabrazyme®).

One of the first studies of enzyme replacement randomized 58 patients to either agalsidase beta 1 mg/kg IV or placebo every 2 weeks for 20 weeks followed by open-label agalsidase beta for 6 months (Eng et al. 2001). The primary end point was the percentage of patients in each group who were free of microvascular endothelial deposits of globotriaosylceramide in renal-biopsy specimens. After 20 weeks, in the enzyme replacement arm, 31% patients had deposits but 100% had deposits in the placebo arm. Patients in the enzyme replacement arm also had lower scores on deposits in the heart and skin. Interestingly however, in this study, overall pain scores and quality of life

scores were not different between the two groups. Infusion related adverse effects were higher in the enzyme group ~50% rigors, ~20% fevers, ~10% headache, ~15% chills than in the placebo group. A roughly 3-year follow-up study suggested that enzyme replacement therapy resulted in continuously decreased plasma globotriaosylceramide levels however this follow-up study was not designed to evaluate the impact of enzyme replacement on clinical relevant outcomes (Wilcox et al. 2004).

A recent Cochrane review (nine trials of either agalsidase alfa or beta in 351 subjects) concluded "Trials comparing enzyme replacement therapy to placebo show significant improvement with enzyme replacement therapy in regard to microvascular endothelial deposits of globotriaosylceramide and in pain-related quality of life" (ElDIb et al. 2016). Pain scores were reduced by ~2 points (a clinically relevant change) on a 10 point scale in studies of agalsidase alfa over a period of 6 months. However, the authors also stated "The long-term influence of enzyme replacement therapy on risk of morbidity and mortality related to Anderson-Fabry disease remains to be established."

So in this example we have patients with a specific enzyme deficiency that will clearly negatively impact their health over the long-term. We have evidence that enzyme replacement therapy reduces the surrogate marker of endothelial deposits and possibly leads to a reduction in pain but long-term impacts on clinical important outcomes may never truly be known because of the ethics of doing long-term placebo trials in these subjects. These unknowns make funding and medical decisions tricky because these enzyme replacements can cost in excess of $200,000US a year.

CONCLUSION

Using these examples, it is clear there is no single way to approach clinical decisions around the use of these "omic" technologies. However, even though these novel agents may have unique mechanisms, and in some cases clinically important benefits, they are yet just another treatment option. Given that, they should be incorporated into clinical practice just like any other treatment option, which is by using the best available evidence and balancing benefits and harms.

All of the requirements in Table 13.1 come into play as they would with any new medication entering the marketplace and clinical use. The individual decisions revolve very much around what the best available evidence shows and what condition is being treated. A personalized approach in each of these cases is crucial because each patient and response will be very unique. The benefits may be as small as one in 50–100 people benefitting, or in some cases 50–75% of people will derive a clinical benefit. These numbers are very much determined by the baseline risk of a patient and the overall effectiveness of the medication.

Regardless of condition, every decision needs to be informed by the best available evidence, which hopefully includes how these agents compare to not only placebo, but also how they compare to the gold standard treatments and other agents within in the same class.

To effectively use these agents, as with all medications, one needs to know what happens clinically in the placebo group, the magnitude of the change in the treatment group. Each of these examples bring to light the many different and unique aspects that need to be considered.

For medications like palivizumab, evolucumab and romosozumab clinicians need to be able to communicate the magnitude of the risk reduction to patients and to also discuss the adverse effects, the cost, the inconvenience and the fact that knowledge of the long-term effects is often fairly limited.

For agents like dupilumab and in particular guselkumab where one may be able to evaluate the individual response to a particular medication and dose, individualization and titration to the lowest effective dose becomes a key step in the overall use of these medications.

Finally, for medications like the enzyme replacement therapies for Fabry disease we may never know if life-long use of these treatments will actually lead to a clinically important improvement in quality of life or a reduction in negative clinical outcomes.

With these new "omic" technologies, there is certainly a possibility these new agents may be more effective or may in fact be the only effective treatment for a number of difficult to treat or uncommon conditions. However, every one of these new medications must be evaluated using the exact same principles of evidence-based practice presently used for all new and old treatments alike.

SELF-ASSESSMENT QUESTIONS

Questions

1. Is there anything unique about therapeutic proteins and how clinicians need to assess them?
2. If a medication produces a 25% relative reduction in the chance of developing heart disease does that mean 25% of people who take the medication benefit?
3. For any new medication that has an effect on symptoms, how does one go about figuring out the best dose for an individual patient?
4. When a new medication comes on the market there is often limited long-term safety data so how should a clinician deal with this problem?
5. Is cost an important issue when it comes to the new "omic" technologies?

Answers

1. Not really. As with all new therapeutic options they need to be evaluated with appropriately designed RCTs, and then the decision about their value should be based on a combination of evidence and patient-centered requirements.
2. No, any relative benefit needs to be applied to the baseline event rate in the placebo group. For instance if the baseline risk of a heart attack in the placebo group is 20% then applying a relative 25% benefit to the 20% baseline risk means that 15% of the treatment group end up getting a heart attack. The absolute risk difference is 20% minus 15% or an absolute benefit of 5% which translates to having to treat 20 people to benefit one.
3. One can (a) start with the dose used in the studies and then if a benefit is seen a dose titration down can be done to identify the lowest effective dose or, (b) start with a dose 1/4 to an 1/8th of that used in the initial clinical studies and then titrate the dose up to the dose that best controls the patients symptoms with a minimum of side effects.
4. In general, unless the new medication provides an important clinical benefit over other existing therapies it may be best to wait until longer-term adverse effect data is available before incorporating it into practice.
5. Cost is always an important issue when it comes to the selection of any therapeutic treatment. If a new agent doesn't provide a clinically important improvement over older treatments, then cost should be a determining factor in the selection process. If a new agent does provide a clinically relevant improvement in prevention or symptomatic treatment then the increased cost should be proportional to that increased benefit.

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