And Now For Something...

The promise and financial impact of gene therapy is the topic of episode 17 as we welcome expert Dr. Luca Pani as our special guest.

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Completely Indifferent

What’s Inside

Gene Therapies as the Next Game Changer: A Cautionary Tale

Page 2

What’s Up...

Opioids update

Mandatory cannabis education for Ontario pharmacists

Study suggests vaccine immunity wears off

Page 8
The industry certainly won’t forget anytime soon the huge impact of biologics and other high-cost drugs—especially hepatitis C therapies and their eye-opening price tag. But will we learn from the recent hepatitis C experience in terms of… let’s call it emergency preparedness? This is a critical question as new gene therapies—with massive costs in the range of hundreds of thousands of dollars—are positioned to be a game changer, even eclipsing the impact of hepatitis C drugs. Not only do gene therapies represent the next leap forward in potentially curative medicine, but they also pose the next coverage and affordability dilemma.

This time around, let’s let our lack of preparedness be our cautionary tale. Let’s listen to the moral of the hepatitis C story now, before these new innovations hit the market big time. As one of the world’s great inventors, Alexander Graham Bell, once said, “Before anything else, preparation is the key to success.” So no time like the present to get into the gene therapy head space…

**Definitely groundbreaking, but what actually is gene therapy?**

The media coverage around Health Canada’s recent approval of a gene therapy called Kymriah—for pediatric and young adult leukemia and adult lymphoma—sounds eerily familiar. The last time we heard buzzwords like “game changing,” “revolutionary,” and “cutting edge,” it was about new curative medications like those for hepatitis C. Now it’s all about gene therapies.

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**WHAT’S GOING ON WHERE?**

The Canadian Agency for Drugs and Technologies in Health (CADTH) reports that as of January 28, 2018, ten gene therapy products had been approved for marketing in at least one country in the world. For all of the clinical trials in the works, check out these databases:

Simply put, in its broadest sense, instead of using drugs or surgery, gene therapy aims to treat and ideally cure a disease by changing the patient’s genetic makeup. This could involve:

→ Replacing genes that are causing disease,
→ Disabling genes that aren’t functioning properly, or
→ Introducing new genes.4

The process is done either outside or inside the body. For example, Kymriah uses an outside-the-body approach where cells are taken out of a patient, modified in a lab, and then infused back into the patient. Whereas, with the gene therapy called Luxturna for improving vision in patients with an inherited type of blindness, the doctor uses a genetically engineered injection (known as a vector) to carry the genetic material into the patient’s eye. And both these therapies, like other gene therapies under development, are one-time treatments.

Certainly sounds like groundbreaking medical technology, but how good are gene therapies? Are they effective? Does just a one-time therapy actually do the trick?

Make diseases curable (hopefully)

Gene therapies have the potential to deliver lifelong benefits—and one-and-done cures are the goal. Now that certainly sounds like groundbreaking efficacy. However, as is typically the case with new therapies under development, their “newness” doesn’t yet have the kind of longevity or rigour around them to warrant the label “curative.” But the scientific evidence so far is proving that many gene therapies are “durable” in that they are showing results like stabilization and/or improvement in health.

HOW DOES KYMRIAH WORK?

Kymriah uses a combination of gene therapy and cell therapy. Although both gene and cell therapy treat disease by changing a patient’s genetic makeup, they go about it in different ways. Gene therapy introduces, removes, or changes the genetic material in a patient’s cells. Whereas, cell therapy infuses or transplants whole cells into a patient. As a combined therapy, Kymriah uses what’s called chimeric antigen receptor T-cell therapy—or CAR T-cell therapy—to modify the patient’s own immune cells (called T-cells) so that the cells have the ability to attack cancerous cells. How?

→ First, the doctor draws a sample of the patient’s blood,
→ Next, a specialized lab genetically modifies the T-cells to be able to identify cancerous cells,
→ Then, the doctor infuses the cells back into the patient,
→ Now the genetically modified cells not only kill off cancerous cells, but also are on the lookout for the development of additional cancerous cells, essentially acting like a drug that is continually working within the patient.5

For more about gene therapy, cell therapy, and newer areas of research called cell editing—which aims to remove or correct faulty genetic material—watch this refreshingly understandable explanation: https://youtu.be/aO4-KFEz8NE.
In many ways, gene therapies have been used as a last resort for what could be considered “what do you have to lose?” scenarios. But patients still have had to weigh the trade-off between potentially life altering—if not life-saving treatment—and possible safety risks, some of which could be severe.

Whether just durable or also (hopefully) curable, all told, gene therapies are showing life-altering results for several difficult-to-treat conditions. Now add to this the tremendous expansion in the works into not-so-rare diseases, and gene therapy’s game-changer status shoots way up.

Packed pipeline (… in fact, jam-packed)

Here’s the thing—the exciting and mind-boggling thing: almost any gene in the human genome can be targeted meaning the potential for new gene therapies is significant. The U.S. biopharmaceutical industry reports that “with nearly 300 cell and gene therapies in development, targeting more than 100 diseases, 2019 could be set to be a big year for cell and gene therapies.”

Cancer continues to be a main focus for gene therapy, however, more common conditions are also now under the microscope, such as heart disease. According to the most recent statistics, 2.4 million Canadians were living with heart disease in 2012/13, and an additional 669,600 Canadians were living with diagnosed heart failure. Clearly, expanding into more common diseases is exciting with a huge potential to help as many people as possible.

For example, back to Kymriah, in its main clinical trial, just over 80% of the children and adolescents with acute lymphoblastic leukemia—who hadn’t responded to other treatments or had relapsed—went into remission within three months after treatment. And two years later, 62% were still in remission. Is it a cure for these patients? Only time will tell; hopefully years down the road, they will still be in remission, and Kymriah will earn the curative label. One thing is for sure, it’s definitely a game changer for these patients so far.

A main focus for gene therapies has been on helping patients with diseases where no treatment options exist. They have also aimed to help patients who have tried all available treatments and where, without intervention, the prognosis is disability or death. In addition, gene therapies are focusing on patients with conditions that require intensive and ongoing maintenance therapies. For example, gene therapies have targeted:

- **Rare or inherited disorders** like hemophilia (unexpected and excessive bleeding), sickle cell disease (wide range of symptoms—lung problems, stroke, and damage to most organs), spinal muscular atrophy (deteriorating physical abilities, making it impossible to walk, eat, or breathe), and a variety of eye diseases that can lead to vision loss and even blindness.
- **Advanced-stage cancers** that don’t typically respond well to other treatments like pancreatic cancer, skin cancer that has spread, liver cancer, blood cancers like leukemia, and certain brain tumours.

WEIGHING THE POTENTIAL SIDE-EFFECTS

Therapies like Kymriah and Yescarta (another CAR T therapy that Health Canada has approved) have warnings like “may cause side-effects that are life-threatening and can lead to death.” For example, the risk of cytokine release syndrome which can cause high fever, nausea, headache, rash, rapid heartbeat, low blood pressure, difficulty breathing, neurological issues, and in its severest form, death.

Fortunately, as research and development into gene therapies continues, it looks like there will be a greater number of promising therapies with fewer risks on the horizon. For example, just hot off the internet, an April 2019 study done by the University of Southern California is reporting an advancement in CAR T therapy that appears to eliminate its severe side-effects. Although early days, this could represent a breakthrough in making it safer, or even one day potentially available to outpatients.

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However, the gene therapy pipeline isn’t just a jam-packed one, it’s also a very high-cost one (as in very, very, very high cost). So just how much does Kymriah cost? Although it has been approved for sale in Canada, the manufacturer hasn’t actually brought it on the market. This means no one outside clinical trials has received it here yet. In the United States, the cost for a one-time treatment for acute lymphoblastic leukemia is US$475,000 and for lymphoma patients it’s US$373,000. That converts to approximately $640,000 and $507,000 in Canadian dollars.9 Yes, you read that correctly (…we’ll give you a moment to let that sink in).

CADTH recently released its recommendation that Kymriah be covered publicly as long as the drug manufacturer agrees to reduce its price. Cancer Care Ontario is leading pricing negotiations on behalf of the provinces. But what about when what has been described as a “tsunami of gene therapies innovations” hits the market?10 New gene therapies for more common conditions—and therefore, much bigger patient pools—have the potential to positively impact plan member health. So, in theory, gene therapies could be considered for coverage under private plans. But in practice, how would this work?

Work it out sooner rather than later

Today, gene therapy research and development is going well beyond the realm of rare diseases. For example, researchers are investigating the potential for new gene therapies in Parkinson’s disease, Huntington’s disease, and cystic fibrosis, as well as cancers that are more common like various gynecologic and prostate cancers and multiple myeloma (cancer of the white blood cells in bone marrow). Exciting but incredibly costly in wider populations.

LET THIS SINK IN...

$640,000

Acute lymphoblastic leukemia

$507,000

Lymphoma

LESSONS LEARNED INTERNATIONALLY...

→ Glybera to treat lipoprotein lipase (a very rare disease with symptoms like stomach pain, pancreatitis, and fatty growths underneath the skin) was approved in Europe in 2012 at an estimated cost of €1 million. However, in 2017—due to lack of demand—the company decided to no longer market it. In addition to lessons learned, like sustainability from the manufacturer’s standpoint, it’s also interesting that the manufacturer thought that requirements like additional studies and surveillance of patients were too burdensome and costly to continue.14

→ Strimvelis to treat ADA-SCID (known as “boy in the bubble disease” where patients are highly susceptible to infections) was approved in Europe in 2016 at a cost of about €594,000. Like Glybera, its viability is questionable because of its high cost and small target population. However, in terms of lessons learned, interestingly, the payment agreement includes a risk-sharing strategy where, in cases of treatment failure, there is a partial refund. Also, there was a short time between approval and development of its reimbursement agreement. This appears to be the case because of high-quality research and strong health-outcome data paving the way for a smooth process.15

→ Kymriah has led to ongoing discussions about using an outcomes-based pricing model in the United States, which apparently, is one of the options open for discussion in the Canadian negotiations. Although our health care system differs from the U.S. system, there may be lessons to learn in terms of alternative payment models.
When grappling with the affordability issue, one of the number-crunching scenarios is that one-time gene therapies save larger amounts in the long run. This comparison takes into account that, with traditional treatments, patients may have to rely on them for years, if not for the rest of their lives, often with difficult to handle side-effects. These cost/benefit scenarios are similar to how the cost of a kidney transplant costs hundreds of thousands less than years of dialysis.

In these scenarios, the researcher compares the current standard of care with the new therapy using what is known as the “quality adjusted life years” (QALYs) gained. The QALYs gained quantifies how long each therapy benefits the patient’s quality of life—so the higher the QALYs gained, the better. For example, one cost-effectiveness evaluation found that over a 10-year timeframe, hemophilia gene therapy that costs US$1 million resulted in 8.33 QALY gained. By contrast, the standard of care for preventing bleeding episodes is prophylaxis, which typically involves injecting products, called clotting factor concentrates, two to three times a week, costs $1.7M and resulted in 6.62 QALY gained.¹³

Although the long-term cost/benefit may be positive, this doesn’t solve the immediate issue of how to pay for the gene therapy in the first place. Today, our reimbursement model is based on largely predictable drug costs and health outcomes closely tied to each other over time. The challenge of affording gene therapies turns this model on its head. How can we reimburse for potentially curative, one-time treatments that have huge front-loaded costs with, at this point in the research, no hard guarantee of long-term positive outcomes? This is just one of many questions that need to get on our radar screen sooner rather than later. Here are some others:

- With long-term uncertain efficacy, would plans even cover the new gene therapies?
- If covered, would plans pay for the huge cost upfront or make payments over the rest of the plan member’s life?
- What happens as patients move from plan to plan?
- Would the government or drug manufacturers offer cost-sharing programs?

This leads to the bigger-picture question for society: How do we pay for a cure?

There is little precedent for tackling this problem. In many ways, it’s an absolutely great problem to try to solve given that technological advances are starting to produce actual cures. But the challenge remains that the rate of innovation is outpacing our ability to pay. So our planning efforts need to focus on having our reimbursement models evolve along with the evolving gene therapies.
For example, deferred payment models that structure payments to fall over many years are certainly worth investigating. And then there are also pay-for-performance agreements where payments stop if the gene therapy stops working. And what about even more customized approaches to reimbursement? Just like each gene therapy is unique, maybe reimbursement models need to be uniquely tailored to each new therapy—not a one-size-fits-all approach to reimbursement.

**Keep calm and plan on**

Let’s get our act together by putting our heads together: plan sponsors, private payors, governments, regulators, academics, health care professionals and of course, industry stakeholders like the Canadian Life and Health Insurance Association. It will be a critical dialogue in health care.

**Sources**


OPIOIDS UPDATE

The Public Health Agency of Canada reports that between January 2016 and September 2018, more than 10,300 Canadians died due to apparent opioid-related overdose. Fentanyl and other fentanyl-related substances continue to be a “major driver” of Canada’s opioid crisis. Health officials feel that the latest numbers emphasize the importance of finding innovative ways to stop the opioid epidemic. For details about the Public Health Agency of Canada statistics, visit https://www.canada.ca/en/public-health/news/2019/04/updated-numbers-on-opioid-related-overdose-deaths-in-canada.html.

Fortunately, there are some positive developments:

First-of-its-kind implant to treat opioid addiction

Doctors with special training can now implant a time-released version of Probuphine as an alternative to taking daily doses of Suboxone pills—the recommended treatment for opioid addiction. The implant helps control cravings and has a low risk of withdrawal by providing an ongoing low dose of Probuphine for six months. There is also the potential for another six months with a new implant in the other arm. The implant allows more flexibility, so patients can work toward living a normal life. They no longer have to remember to take a daily medication, get to the pharmacy, or worry about withdrawal symptoms. It’s important to have a number of treatment options available because medical experts feel there’s no one-size-fits-all solution for curbing the opioid crisis. The implant was approved in April 2018, and the drug manufacturer is now training doctors in Canada’s major cities on how to insert it. If a doctor has not received training but identifies a patient they feel would benefit from the implant, the idea is that the patient would have access to a trained doctor located as close as possible. For more information visit https://nationalpost.com/news/world/six-month-implant-newest-option-to-treat-addiction-amid-opioid-crisis.

Important warning hopes to help prevent addiction

The recent study called *Chronic use of tramadol after acute pain episode: cohort study* finds that tramadol—an opioid thought to be less addictive than other opioids and increasingly prescribed after surgery—is in fact as addictive as other opioids. It has a similar risk of long-term dependence or long-term opioid use compared to other opioids. Overall, the researchers conclude that there is no such thing as a safe opioid. Although the researchers feel that the focus on prescribing opioids should have started years ago, what can be done now is to rethink what makes a successful surgery. The risk of opioid addiction starts to increase after five to seven days of taking opioids, so if a patient stays on opioids long term after surgery, it should not be considered a successful surgery. As an alternative to manage pain, the researchers recommend NSAIDs (non-steroidal anti-inflammatories) like ibuprofen. For more information, visit https://www.bmj.com/content/365/bmj.l1849.
MANDATORY CANNABIS EDUCATION FOR ONTARIO PHARMACISTS

The Ontario College of Pharmacists (OCP) is making it mandatory for Ontario pharmacists to complete a course on cannabis education by March 27, 2020. The legalization of recreational cannabis may increase its more open use, and although pharmacists don’t dispense cannabis, the OCP wants to make sure that pharmacists are well prepared to manage patient questions and concerns.

Just like pharmacists provide education regarding the interaction of medications and alcohol use, patients may require this kind of advice regarding interactions with cannabis. Accordingly, the course covers the benefits and risks of cannabis, dosage forms, and common side-effects, as well as pharmacists’ ethical, legal, and professional responsibilities.

It’s up to each province’s pharmacist regulatory body to determine what requirements are necessary for the province’s pharmacists. So far, Ontario is the only province to require completion of a cannabis course.

For more information, visit http://www.ocpinfo.com/practice-education/practice-tools/support-materials/cannabis-training-requirements-courses/.

STUDY SUGGESTS VACCINE IMMUNITY WEARS OFF

A recent study suggests that the vaccine for pertussis—commonly known as whooping cough—works well for a decade after vaccination, but then immunity may fail. Therefore, ensuring protection from whooping cough may require a booster shot. The study is called Pertussis vaccine effectiveness in a frequency matched population-based case-control Canadian Immunization Research Network study in Ontario, Canada 2009–2015.

The findings point to the issue of under-vaccination that has come increasingly under the microscope as cases of measles continue to crop up in North America. Some doctors are raising awareness that many adults may be inadvertently under-vaccinated. Canadians born before 1970 are generally considered immune since measles infections were so common then. However, those born after 1970 and before 1996 may no longer be fully protected. The recommendation is that anyone born between that time period—especially if planning to travel outside of North America or where measles is circulating—should have a blood test to check their immunity. Alternatively, there is no downside to just getting the measles shot again even if previously vaccinated.


June / July Haiku

Gene therapy is
The newest amazing thing
Can we afford it?
Congratulations to E. RIZOV, of TORONTO, ON, the winner of our monthly draw for a Fitbit. Through this contest, one name will be drawn each month from plan members who have registered for Plan Member Online Services for that month.