MC: Welcome to The Med Thread, your monthly dose of all things drugs.

CB: I'm Cathy

MC: and I'm Mike and today we talk biological drugs, how we got here and where it's going in the future. We'll touch on why it costs a fortune to make, a fortune to buy, and how we're trying to make it cheaper. The whole process from before the prescription, to the pharmacy and to our patients!

The history of biologics: Life-saving therapies

CB: When I think of biologics I think of Humira and Remicade which I've dispensed a fair bit for arthritis and Crohn's, and then also Lantus for diabetes, and these are just a few examples. This class of drugs has definitely expanded since I graduated in 2011 and I'm glad to have an expert here to help me wrap my head around these drugs!

MC: We speak of biologics as new things, but we have been using biologics since the beginning of medicine. Health Canada describes a biologic drug as a drug that comes from living organisms or their cells.

CB: Essentially, almost all drugs prior to modern chemistry were isolated or made from plants and animals. With the advent of pharmaceutical chemistry, we had an explosion of using small chemical compounds made in the lab to treat disease. Now I imagine we're revisiting biology in a more wholesome way.

MC: A bit of background: Within Schedule D of the Food and Drugs Act are the biological drugs. They include a number of items. For example, blood derived factors or stuff you find in blood.

And if you recall our second episode when we chatted about anemia, blood transfusions were perhaps the earliest example of what we consider biological drugs. Giving blood from one animal or person to another could be life-saving.

CB: Next on the list are vaccines. Ingrafting, or scratching little bits of crusted pustules of smallpox-infected individuals into healthy people was seen to be effective in protecting them from the virus in the future. Taken from earlier practices in eastern medicine, western medicine started this in the early 1700s. They called it variolation from the Latin name for small pox 'variola'.

MC: It wasn't until the end of the 1700s, 1796 to be exact, when Edward Jenner took bits of cowpox lesions from a milkmaid and inoculated an 8-year old boy. The milkmaids knew that if they had cowpox, they would not get smallpox. Jenner then inoculated the boy with cow pox and behold, no problems! He named what he did vaccine, from 'vacca' meaning 'cow'. He called the smallpox material 'virus' directly from Latin 'virus' meaning 'poison'.
(Strathern, 2005)

CB: We've been giving vaccines ever since!

MC: Not many from cows anymore!

CB: Fast forward a hundred years later, to the roaring 20s, we see the discovery of insulin, and diabetics now had a life-saving drug. This was isolated from cows and pigs for a long time.

We had to wait until the 1970s and 80s before recombinant human insulin, brand name Humulin, could be produced in bacteria. We consider this the first protein-based biologic drug. In simple terms, the recombinant DNA technology allowed scientists to produce the human gene for insulin and insert that into E. coli bacteria DNA. As the bacteria grow and reproduce, they also make insulin, which is then purified and extracted. How they get this done on an industrial scale is fascinating!

MC: A few years after Humulin, a drug called Digibind was produced. It was first antibody approved by the FDA. Digibind was, and the current version, called DigiFab is STILL made by sheep!

CB: Sheep are immunized with an analogue of digoxin and produce these antibodies, which are then extracted from their blood. As an antibody that binds specifically to the drug digoxin, it was able to eliminate digoxin from the body in the case of an overdose. Now we could begin to take full advantage of the specificity of antibodies to their targets and many, many lives were saved and continue to be saved.
(Pezzuto, 1993, Paladin Labs, 2014)

MC: There are clear regulations and a clear history of these older biological drugs. But today, we move away from farm animals and talk about new classes of biologics such as the monoclonal antibodies.

[The Fray – How to Save a Life]

How are they made: Chemistry and biology

CB: One major difference between biologic drugs and your ibuprofen, is the molecular size of the drug. Where ibuprofen has 33 atoms in it, a monoclonal antibody has well over 10,000 or even 20,000 atoms.

MC: So you really can't make them through a chemical reaction. And unlike insulin, which we could take from animal sources, what we need to do with these new drugs, is grow them.

CB: We knew about antibodies from immunology, and we developed a way to hijack mice biology to make them for us.

I promise that's the last animal sound effect. By exposing them the mice to a particular antigen or protein we wanted to target, their immune system would produce a response and create these antibodies.

MC: You may be thinking; each mouse is different, and so wouldn't each antibody be different too? And there aren't enough mice in the world to make enough! And you would be absolutely right! We need something else to continue making them.

This is where it gets complicated. When making monoclonal antibodies, we call them monoclonal because they come from the same cell. But what cell?

CB: What cell lives really long and is essentially the same all the time? What about cancer cells! We can take those antibodies produced by mice and induce cancer cells to continuously make lots and lots of these antibodies for us.

Now if you just used the mouse antibodies, humans would mount immune responses to those similar to an allergic reaction. We also need to make sure that our bodies don't label the drug as 'foreign' compounds and attack it. Part of the process is to 'humanize' the antibody, so it is more than 95% human.

MC: Overall the process varies wildly and quite oversimplified in our explanation, especially when it comes to producing these industrially, but the concept of using natural biology to produce drugs remains similar. An article last year in The Conversation describes in easily understood language, how biologics are different than conventional pharmaceuticals. I'll post the link on our webpage. *(Haydon, 2017)*

CB: There is a lot of basic scientific research that goes into creating a drug, but sometimes, they're just found to work through screening thousands of different chemicals. The trial and error process of pharmaceutical chemistry made many of the drugs we know now; some of which we still don't know how exactly they work in the body. But for the biologics, it becomes more difficult because you sort of need to know exactly what you are targeting.

MC: With complex biotechnology, it became clear that understanding the disease process, molecular biology and essentially what's going on in the condition is quite necessary to develop these drugs.

For example, we know that the activity of certain receptors are upregulated, meaning more are produced and active. Particularly in cancers, one drug that comes to my mind right away is Herceptin or trastuzumab. It blocks the HER-2 receptor involved in breast cancer, but not everyone with breast cancer has an increased amount of that.

What are they used for: Specificity but also broadness

CB: This brings us to, what exactly are these biologics used for? Are we on the cusp of really personal medicine?

To find some answers, we're lucky to have to Sheldon Baines in studio with us. He is a pharmacist working at BioScript Pharmacy, which specializes in delivering patient care in relation to these biologic drugs, among other things. We are going to pick his brain for all the therapeutic and practical knowledge he has.
(Bioscript Pharmacy: https://bioscript.ca/bioscript-pharmacy/)

Hi Sheldon, thanks for joining us!

SB: Thanks for having me.

CB: So, let's start off just talking a little bit about BioScript. How is BioScript different from your traditional Community Pharmacy

SB: When I usually introduce BioScript, I usually start with the name itself. We call ourselves Bio Script to emphasize the fact that we focus on biologic prescriptions. 'Bio' 'script', biologic prescription, smashed together to make the name. So, the biologics, a lot of the high-end injection medications, infusion medications, unlike a regular community pharmacy, we're not filling hundreds of high blood pressure medications or antibiotics, anything like that during a run of the day. All day, every day, we focus on these specialty products, which allows us to become a little bit more familiar, not just with the medications and the conditions they're used to treat, but with any number of the other wrinkles that could potentially go along with these therapies as well.

CB: And it's really cool, because these drugs have certainly taken off over the past couple years. And you think a pharmacy like Bio Script, wouldn't have really existed years ago. So, it's cool that there's now a specific pharmacy or specialist area in this 'biologic prescriptions'.

SB: The needs became apparent, basically once a lot of the medications were being infused in the hospital setting were moving out into the community and unfortunately a lot of the clients were falling through the cracks. Medication not being available at their pharmacies, not being stored or handled appropriately, suboptimal therapeutic results were the end result of that sort of thing. So, a pharmacy focused on these sorts of medications, the need for something like that became apparent.

CB: And that's great! What do you see biologics used for most here in Newfoundland? How does that compare to the rest of the country? Where do we stack up?

SB: Well they're used in a lot of areas, for sure. Certainly, here in Newfoundland in particular, but all across the country we see a lot of autoimmune conditions. Things like:

- Multiple sclerosis
- Inflammatory bowel disease including Crohn's, ulcerative colitis
- Rheumatological conditions like rheumatoid arthritis, ankylosing spondylitis
- Dermatological conditions like psoriasis, hidradenitis suppurativa
- Various combinations of those like psoriatic arthritis or enteropathic arthritis, etc.

Many of these conditions seem to have a genetic component and in Newfoundland, we seem to have a more prominent predisposition compared to many other jurisdictions across the country or around the world. They are certainly used in many other areas like oncology as you've mentioned but they are also expanding into new treatment areas such as migraine.

CB: So certainly not just for one condition, a whole long list of conditions.

Efficacy and Safety: Stories

MC: So sometimes, small changes in chemical structure can have differences in pharmacological effect. Take for example, within the penicillin group of antibiotics, tweaking a molecular group here and there can help the drug overcome bacteria resistance. But sometimes, drugs that are similar and target the same biological pathway are essentially equal in effectiveness, for example, the commonly used ACE-inhibitors for lowering blood pressure.

When it comes to biologics and particularly, monoclonal antibodies, different drugs can target the same protein and they attach very specifically to it. There are currently 4 monoclonal antibody TNF-alpha inhibitors available in Canada. TNF is tumour necrosis factor, which is associated with many inflammatory and autoimmune conditions including psoriasis, inflammatory bowel disease and rheumatoid arthritis, some of the conditions Sheldon has been talking about.

So how effective are these medications over the other options and compared to each other?

SB: First of all, I have to say that I hear many of the medications that we deal on a daily basis are referred to as 'Miracle Drugs'. So many clients essentially report that they feel like they have been given their lives back or that they have a new lease on life and it is very rewarding to be at least some small part of that. Many of these patients, unfortunately have languished for years potentially taking less effective treatments, either due to delays in getting to see a specialist for proper assessment and treatment or in the marathon of hurdles they sometimes have to jump over to meet the criteria to qualify for coverage of some of these more expensive therapies.

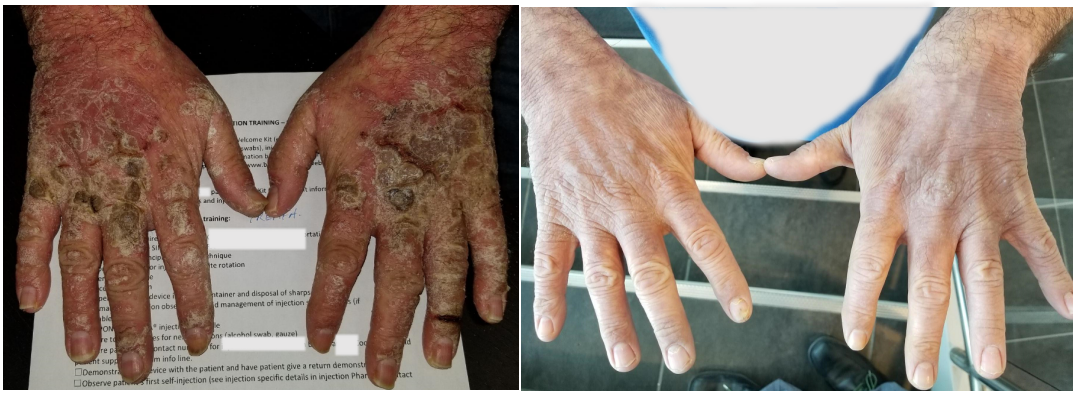
Many of them are at the end of their ropes or forgot what it was like to lead a "normal" life, or gave up hope that getting back there was ever possible again. But then when they finally get on one of these life-altering treatments it can be a very emotional experience to say the least.

I had a gentleman that I did an injection training session for just over a month ago who had very severe psoriasis, essentially covering nearly his entire body. His hands were some of the worst I've seen, and it was nearly as bad on his face with one of his eyes essentially being forced shut.

Not only was it physically torturous for him to deal with the pain and the itch and the inability to sleep or get comfortable, but to walk down the street and perceive that people are constantly giving you the 'Oh my goodness, is that contagious' look takes a severe emotional toll. He came back for his second dose just last week and I could hardly believe it was the same person, and he could hardly contain his appreciation for having started this therapy. He went from being absolutely covered to essentially being almost 100% clear just after one dose and a 4-week span. But what really struck me was to hear him describe how he can walk down the street now and people don't stare at him anymore!

I've put in a couple of pictures there just for reference. I wouldn't have believed it if I didn't document it. I had to take a picture before I did the injection training, because I had to see if he's going to be one of these people that get the miraculous benefit and when he came back, he actually hid his hands in his pockets, and you could see this, almost giddy. And when I went to shake his hand, he took his hand out, it was emotional for me because it was so emotional for

him.



MC: Yes, that's really amazing. And I'm just looking at the pictures, here, and what a huge difference the medication has made.

SB: We are exposed to similar stories to that everyday whether it be for clients that have Crohn's and have felt like a prisoner in their own home out of fear to venture outside and not be in immediate proximity to a bathroom, or horror stories of clients that refused to stay home and then had an unbelievably embarrassing incident where they've tried to request to use the bathroom at a business only to be refused and unfortunately be unable to hold it. Or for a RA [rheumatoid arthritis] patient that forgot what it was like to not have ever-present debilitating pain. Some of them describe going from essentially being relegated to a wheelchair to jumping up and down on their bed like a child when their bodies no longer betray them. The list goes on and on. When the condition is suitably controlled, the impact quite often goes beyond the physical.

[The Beatles – Here Comes The Sun]

MC: You mentioned that that patient came back for a second dose. And I understand that many of the biologics are not given daily like other medications, why is that?

SB: You don't have to take them as often as they tend to have longer half-lives meaning they stick around in the body longer and have more opportunity to do what they do over a longer period of time. The differences between the molecules determine if you have to take it weekly or bi-weekly or monthly or every 3 months etc. Great efforts are certainly taken to guard against potential immunogenicity, so our bodies are less likely to identify them as foreign, as you described previously and as a result, they don't get rid of them as fast as they would otherwise. I guess our bodies are also used to seeing many of these sorts of antibodies or these types of molecules floating around in our system and thankfully don't get too upset about it.

MC: So, are we starting to have more evidence or preferable treatment, of one drug over another?

SB: Well everyone reacts to medication differently and certainly there's a lot of effort put in place to try and identify who's going to be a responder or who's going to be a non-responder. I guess you've already mentioned the HER-2 positive breast cancer, that sort of thing. And they're also creating more antibodies now that tend to be more specific. So the medication that the patient that I just referenced, he's on an IL-23. There have been other medications around for a while

that have targeted IL-12 and 23. This new one is a little bit more specific, so it has an opportunity to have less impact on other areas of the immune system and again they're certainly looking for ways to identify who's going to be a responder and equally important, who's not going to be a responder.

We've been physically embedded inside of a clinical research facility for our first number of years, until we kind of grew out of that space and had to move on. One of the things that I know is continuously ongoing during the clinical trials is trying to identify, retrospectively, they'll do panels of bloodwork, and trying to identify after the fact, who are the people that responded or who are the people that didn't respond and trying to see if there's something that they can identify proactively going forward, to be able to more suitably target the therapy to the people who are going to get the maximum benefit from it.

MC: I think that's really great and I definitely think that there's a lot more research that's going into it and a lot more that's going to come out it in the next couple years I would say and maybe sooner. And out of curiosity, have you had someone use two biological drugs at the same time?

SB: Concurrent biologic use for the same indication is generally contraindicated but we have seen it certainly in extenuating circumstances. They don't typically recommend that it be used together not because of any direct interaction between the molecules themselves. But I guess out of potential concern of overdoing it. If you have two different therapies that are aggressively treating the immune system as an example, you don't want to completely wipe out the immune system.

But like so many therapeutic decisions, it comes down to a risk versus reward situation. Depending on the severity of the condition, the therapeutic options that have already been tried, the potentially limited options remaining and then weighing the potential pros and cons of all of that. We would certainly take extra precautions and monitor much more closely but thankfully it isn't a common occurrence. Much more often, if a given biologic isn't cutting the mustard after a suitable trial period they would want to consider an alternative therapy and allow a suitable washout period from the previous biologic based on lengthy half-life that we discussed previously, before starting a new one.

CB: And you mentioned risk and reward, so when it comes to risk, we certainly have to talk about the safety of these drugs. And I understand this is a generalized statement, but I get the question a lot. How do they affect the immune system?

SB: Well I'm glad to say that for most of the biologics that we deal with, most people don't have any, don't experience any downside at all certainly a lot of people get freaked out at the thought of getting a needle or getting an infusion, they automatically assume that must be serious or dangerous or something like that. But ultimately, it's just another way to get a medication into the body. As you're both aware, anything you take by mouth has to be able to survive the acidic environment of the stomach. If it survives that, it has to be able to survive the basic environment of the small intestine. If it can survive that, it has to be small enough to be absorbed through the small intestine and I guess your small intestine has to be functioning appropriately to allow it to be absorbed. And if it can do that, it has to be able to survive first pass metabolism in the liver before it ever can get to the bloodstream to get pumped around the body and do what it supposed to do. So, by taking an injection, be it subcutaneous or

intramuscular or intravenous you get to bypass a lot of those potential hurdles which I guess are also opportunities for issues.

Many of these drugs do target the immune system and it's because many of the issues in the target conditions are a result of an overactive immune system that for whatever reason has gotten turned on and forgot how to shut off and thus continue spew out extra inflammatory cytokines that can wreak havoc on our own healthy cells. I stole a sink analogy from a specialist in town a couple of years ago that I find a lot of patients can, you know make it real for them I suppose. So, if you think of your immune system like a sink normal if you want to wash the dishes, you turn on the tap, you run so much water in the sink, you wash the dishes, you turn off the tap and away you go.

And you can kind of think of that's sort of how our immune system would typical work. We're exposed to a bug, a virus, bacteria, our immune system gets activated, we generate these inflammatory cytokines, deal with the infectious pathogen. Once we deal with it we kind of, our immune system kind of goes back into a resting mode and away we go. But in one of these autoimmune conditions in particular, the immune system's gotten turned on, so this tap has gotten turned on, but unfortunately, we don't know how to shut it off anymore.

So eventually the sink not only fills up with water, but the extra water starts to pour over onto the floor and you got a flooded kitchen now and you're getting rot around the floorboards and that's a similar idea, your body is producing extra inflammatory cytokines that are now just flooding your whole body and where they kind of hang out and wreak their havoc kind of determines what the condition is. So, if it's in your joints, rheumatoid arthritis, if it's in your spine, ankylosing spondylitis, gastrointestinal tract, Crohn's and colitis and so on and so forth. And you can kind of think of these medications like mops.

A lot of the medications bind up or soak up the extra inflammatory cytokine, but unlike a traditional pain pill, let's say you take and you might notice of benefit a half an hour later. If you think about one of these medications, it can quite often take a lot longer than that for you to really start noticing the benefit. And the way I describe that to clients is, right now your kitchen is probably flooded before they start therapy. So, coming in with one mop is probably not going to be enough to get it cleaned up.

Quite often, these medications have an induction period, where they get either more medication or more doses closer together, so I say we're coming in with more mops early on to try and get the floor clean and then once we get the floor clean we'll come back on our regular interval, be it monthly or every two months try to keep the floor clean because unfortunately we still don't know how to turn off that tap. There's always going to be that trickle onto the floor, so we have to come back regularly and make sure that we're doing that touch up work as well.

I usually emphasize that the dose that get you well tends to be the dose that keeps you well. Because unfortunately some people once they start doing well and go 'ah I'm cured', some of them, we are, but unfortunately for a lot of these conditions we're not there yet, you have to continue to take to them to continue to stay well and unfortunately if you don't the condition sometimes can come back with a vengeance and be much more difficult to get under control subsequently.

CB: And I hope you don't mind but I'm probably going to end up stealing that sink analogy while I'm trying to explain to patients how these things work.

The role of pharmacies and pharmacists

CB: And you know it's definitely a new process for patients, you know it's a specialty pharmacy that involves infusions and needles and there may be a fear of the injection side of things but also the whole process and then the fear of any potential side effects. So how do you help patients through this whole kind of new experience and new process?

SB: Well we take a lot of time up front to make sure the clients are well informed, comfortable and hopefully excited with the proposed treatment plan. An objective weighing of the risks versus benefits of most of these medications would typically make the choice clear but ultimately the client decides what goes into their body and they need to be comfortable with that prospect. Many of them have suffered for long enough that they are willing to try just about anything but others that have heard somebody say that a friend read something on-line and they'd never put that stuff in their body. Rationally addressing those apprehensions can be challenging and time consuming but I think well worth the extra investment upfront to help them get off on the right foot.

We realize that there is often a lot of information coming at them from a lot of different angles and it can be hard to absorb or digest it all, so I always tell clients that if I leave them with nothing else, I want it to be with the comfort and confidence knowing that they can give us call with any questions or concerns that they might have at any point in time. Furthermore, we follow-up with clinical and logistical touch points on a regular basis to help address any potential issues and help support adherence, etc. We often get accused of coddling or handholding clients, but I believe the extra time and effort is often needed to help keep clients from slipping through the cracks as they go forward.

CB: I can certainly appreciate that you guys are out there and that you offer this service for these patients and I'm sure your patients appreciate it too.

SB: And I fully realize as well, that, I used to manage regular community pharmacies and I recognize the demands that they face. You have to know something about everything and I always felt that unfortunately, I never had the luxury of having enough opportunity to be exposed to these things, to learn about them to the extent that I would like. So now, we were conscious in our set up of the business model to be able to spend the time required to not just make ourselves familiar and confident with these therapies but be able to impart that to clients as well.

CB: That's excellent. Thanks!

MC: Speaking about how pharmacists help patients, I was looking through a book in the library. This is one of the perks of having an office in the library. This book is called Biotechnology and Pharmacy by Pezzuto et al. It was published in 1993 and lists only 16 marketed biologic or biotech derived drugs in the USA.

They write, "Biotechnology will dictate drug therapy in the future; therefore, it is critical for pharmacists to become familiar with these products as well as their impact on patient care.

They also add, "Pharmacists can potentially be involved in all aspects of the biotechnology drug use process including product distribution, patient and physician education, clinical monitoring, administration, research, and social and ethical policy-making decisions."
(Pezzuto et al., 1993)

CB: So again, I'm going to turn to you Sheldon for some answers. That sounds like a lot, so what do pharmacies actually do when it comes to biologics?

SB: Certainly, we try and help iron out any number of wrinkles that could cause clients to get tripped up and fail to realize the full benefit of these incredible products and unfortunately, a lot of these wrinkles have historically caused far too many patients to get sub-optimal results. Quality control is a big responsibility and one of BioScript's original claims to fame was our commitment to quality assurance; being able to guarantee that these incredibly expensive, temperature sensitive medications were always stored & handled under ideal conditions to be able to ensure that what gets into a client's body was at its absolute best and thus had the best chance of providing the maximum benefit. We've invested heavily in our refrigeration quality and capacity as well as in constant monitoring and detailed multi-level alerts to make sure the medications never are in jeopardy.

Most pharmacies have to consider the balance of the overhead and potential liability that goes along with stocking these expensive medications versus the potential for patient inconvenience or therapeutic delays if the client has to request them explicitly and have them be ordered in on demand. The unforgiving and unpredictable nature of the weather in Newfoundland, which can put power supply at risk, along with the challenging logistics that can be associated with getting these sensitive medications to the required point of care, all of these things serve to throw or introduce a few extra wrinkles into the mix, but I'm glad to say that we keep the iron hot when it comes to keeping these things cold at BioScript.

CB: That's excellent. And where are we now in terms of the pharmacist's role?

SB: I would suggest that nearly as, if not more important is setting the client up for success by providing detailed counselling and support, coordinating with other health care professionals, helping navigate the reimbursement waters, tapping into copay support etc. as well as training, if not physically administering these medications and being there as a trusted resource for the patients on their journey forward, helping to detect and, or mitigate any potential issues that may arise to hopefully ensure the best possible outcomes.

Being there to help guide clients through the entire process and minimize the stresses that can go along with facing these new therapies, especially when the costs involved being unimaginable for most. And stress can be a huge contributor to flares in many of the autoimmune conditions in particular that we're treating, so we try and shoulder as many of those hassles and stressors and help navigate the often, daunting waters so clients can focus on getting better.

CB: And you've mentioned stressors and you've also mentioned a little bit about the expense of these medications. So, speaking of cost and coverage, let's talk dollars and cents, and I'm talking a lot more dollars than cents here.

[Our Lady Peace – All You Did Was Save My Life]

The money: a fortune to make, a fortune to buy

MC: One of the large electronic adjudicators of health claims, Express Scripts Canada issues a report of drug claims every year. The 2016 report states that 30% of the drug spending was from high cost specialty drugs including biologics.
(Express Scripts Canada, 2017)

CB: In Canada, the top expenditure in public drug programs in 2016 were those TNF-alpha inhibitors we mentioned, costing 8.2% of the total spending, a dollar amount of just over $800 million. These are drugs like Humira and Enbrel. But, the use is only half a percent of all people in these programs. For some perspective, the cholesterol lowering medications, the 'statins' accounted for $230 million but 26% of people were using them.

MC: These are some really big numbers, but how much does the typical biologic actually cost to the patient?

SB: Thankfully most of our clients have very little if any out of pocket costs associated with these therapies. As you're aware though, the overall costs involved can be formidable. It can cost between 1 to 2 billion dollars to bring one of these meds to market and when you consider having to cover the R&D expense for not just this product, but the hundreds of other molecules that were being investigated but never did make it to market, the overhead that the pharmaceutical companies are shouldering is considerable.

Thankfully for payers, Health Canada helps to regulate the prices of most of these products and I get the impression that most of them wind up being priced considering what the market deems 'reasonable' to treat a particular condition over the course of a year and then the cost per dose depends on how often you need to receive the treatment. It wouldn't be uncommon for a typical therapy to cost $20,000 or more per year and we have some that cost that much or much more per dose.

MC: Wow, that's a lot of money and honestly, I don't think people could pay for it. So, the million-dollar question is, who pays for it?

SB: Thankfully for patients, we are normally able to coordinate with private and, or public payors and, or patient support programs to help minimize if not completely eliminate any patient out-of-pocket cost. Even a small percent co-pay when it comes to some of these expensive meds could still be a huge financial burden for clients and an undue stressor when we've already noted that that can have therapeutic consequences.

Financial barriers though, are probably still the most common block to treatment access, but unfortunately the costs associated with not suitably treating many of these conditions has to be considered as well. Not only are there significant impacts in terms of direct dollars and cents to

the health care system, which is probably where the 'reasonable cost to treat condition X in a year' comes. That along with the societal costs in terms of lost productivity and what not, but I would suggest it's hard to put a 'price' on the new lease on life many of these clients feel they've been given when on one of these therapies as well. The prospect of continued suffering and disease progression versus the optimism and the hope for the future that often accompanies these therapies, many would say is priceless.

MC: And you mentioned earlier that a lot of these products are about controlling the disease. Do patients have to use it lifelong? Because that would be really expensive too.

SB: Currently, most of the therapies we are talking about manage the conditions, but often to the point where the issues become a memory versus an ongoing reality, provided they continue to take as prescribed. Thankfully, some specialty products that we deal with are curative and I anticipate that will continue to be the trend.

I think many people are skeptical of the drug companies and that they aren't motivated to cure a condition, that they'd rather sell clients and have them stuck on the med for the rest of their lives, but they've now proven that there is indeed money in cure. The kicker is, they just have to charge that much more per dose as they have to get all their money back over a shorter period of time. Even with these incredible costs, they usually still result in significant overall savings to the health care system as the cost of inadequately controlling these conditions can be much higher, not just in terms of the patient's quality of life, but in real dollars and cents that we would be spending on escalating health care interventions.

CB: And you certainly mentioned the research and development side of things and we know that medications take a lot of money to develop. The Fraser Institute, a Canadian research group issued a report in 2016 quoting 1.2 billion as preapproval cost for biologics. The pharmaceutical industry quoted up to 2.6 billion dollars. Overall, there are way too many variables to consider, with overestimates and underestimates from various groups. But either way, we are looking at numbers in the billion-dollar range and a decade of investment time.
(PhRMA, 2016, Lybecker, 2016)

MC: I often wonder though, if the biology is there, what is the rate of failure relative to chemical drugs? Maybe it's a shorter development cycle. And what about the cost to make them once they are on the market? The manufacturing cost.
(Lybecker, 2016)

CB: There is considerable overhead in terms of the manufacturing facilities, which one source states at up to a $500 million price tag for a biologics facility. After that initial investment there are production costs. When it comes to production of many small molecules, this becomes a very, very small number, pennies per pill. The cost for biologics is considerably more, with one consultant firm's article saying ranges of $100 to $1000 per gram in terms of the antibody and casually stating potentially $50 to $500 per dose.
(Rader, 2016)

MC: Trying to find a reliable estimate is nearly impossible and probably very difficult to calculate but overall, drug prices like Sheldon mentioned, are not reflected by the manufacturing cost, but rather the argument of recuperating the research and development costs and to have capital to

further fund new research. For medications that are widely used, this could mean lower costs, but for the biologics which are arguably less used, pricing can be a challenge. And if they're treating life-threatening conditions like cancer, it becomes even more muddled. So how do we try to make these medications more affordable? One answer may be biosimilars.

The rise of biosimilars

CB: Our talk wouldn't be complete without mentioning the biosimilars, which, similar to generic drugs is to provide cost savings and be an equivalent alternative to the single brand product. But the problem is that biosimilars are not like your traditional generic drugs. It's produced by different cells or biotech processes! So, unlike a chemical, the antibody will be slightly different but still quite structurally and molecularly similar between brands. Hence the name!

SB: We have entered a very interesting era in the world of biologics with the advent of biosimilars. As the moniker suggests, they are 'similar' to their reference product, and as such, are not currently interchangeable. Most of these therapies are absolutely massive proteins that have to fold up in a particular tertiary and quaternary confirmation or 3 dimensional shapes in order to impart their biological activity. You can have the exact same sequence of the thousands upon thousands of amino acids that might make up a given protein, but if you can't get it to form a 'suitably similar' 3 dimensional shape, then it won't behave the same in the body.

Much of that 3 dimensional modeling is heavily dependent on the manufacturing process itself and thus potentially vulnerable to even slight alterations in that process. Hence the phrase 'the process is the product' that some people might have heard and referenced to biologics and unfortunately or fortunately depending on how you look at it companies never have to divulge their 'process' to potential competitors. Patent protection is on the product itself, so when it expires, another company is free to try and make a copy, but the innovator company never has to lift the curtain on all of their manufacturing secrets.

MC: The European Medicines Agency approved their first biosimilar, somatropin, a growth hormone in 2006. Canada is a little late, with the same one, and our first, approved in 2009. Named Omnitrope, it is made by Sandoz, a traditionally generic pharmaceutical company, but who's parent company is Novartis, a well-established brand pharmaceutical company.

SB: There are already several biosimilars on the market. Many people are familiar with the brand name, Enbrel. Might be soon hearing about Brenzys or Erelzi. Someone familiar with Remicade, might be hearing Inflectra, Remcima or Renflexis just recently got approved as well. But there are many, many more in the pipeline or on the dartboard that are nearing the bullseye of approval.

MC: Before we look at the cost of biosimilars, I think it's important to know briefly how drugs are priced in Canada. First, brand or patented drugs are priced through the Patented Medicine Prices Review Board, a federal body. However, as healthcare is generally part of provincial jurisdiction, drug prices were traditionally negotiated directly between companies and the provincial governments. To help drive uniformity and consistency, the Pan-Canadian Pharmaceutical Alliance, a joint initiative from the provincial and territorial governments was formed to conduct national negotiations of drug prices.

CB: In 2016, they issued the first principles for Subsequent Entry Biologics (SEBs), which we've been calling the more familiar term biosimilars. Part of the principles are that biosimilars must offer cost savings relative to reference biologic.
(pCPA, 2016)

But, even though it is a fraction of the cost of a novel biologic, biosimilars can still cost hundreds of millions to develop. We can compare this to under $10 million to bring a generic drug to the market. This means that the overall cost savings of a biosimilar will be considerably lower than a generic. In fact, generic drugs can be priced at 25% or less of the brand equivalent but for biosimilars, sometimes it may only be as low as 80%. But, for a $10,000 per year drug, 80% is still $2,000 in savings.
(NPDUIS, 2017)

MC: In the approval process, generic drugs need to show that they achieve the same blood concentration levels in people compared to the brand. In contrast, biosimilars have to show some proof that they are safe and effective, or just as effective as the reference drug. This means that they need to conduct some more extensive clinical trials.

What happens when there are multiple indications for a drug as we mentioned before? One major advantage of biosimilars is that they can use a concept called extrapolation to extend their use to additional indications. The government looks at the overall scientific evidence of their similarity and may approve them for expanded use. This means they don't need to conduct clinical trials for all the indications, a considerable cost saving.
(Health Canada, 2016)

SB: For there to be a real, meaningful cost savings realized, the tremendous expense that goes along with clinical trials would need to be minimized which is probably at least part of the reason why indication extension is permitted. There also seems to be a push to try and establish 'similarity' more in the lab than in the real world going forward. If they can eventually suitably ascertain via assays and what not, that a new biosimilar will behave the same or suitably similar in the body and not have to reproduce the safety and efficacy clinically via costly trials, then you should be able to maximize the savings, but as you've noted, the manufacturing infrastructure and processes tend to be much more costly than traditional molecules as well, so they will still probably wind up being fairly expensive.

The other factor to consider is clinician comfort with the evidence or lack thereof supporting the alternatives. This is something that will continue to evolve but currently most clinicians aren't particularly comfortable with the thought of non-medical switching. Meaning, the patient being switched from one molecule to another for non-medical reasons but for payor reasons, etc. If someone is well established and maintained on a particular therapy, then you don't want to mess with it. If it ain't broke, don't fix it as the old saying goes. However, some payors will probably suggest that it is broken and potentially try and 'fix it'.

Many already mandate the biosimilar for a patient that's naïve to treatment with the innovator drug, for example if someone with NLPDP (Newfoundland and Labrador Provincial Drug Program) hasn't been on infliximab before then NLPDP is not going to pay for Remicade but rather the biosimilar. There have been countries in Europe that have forced switches regardless of indication, length of time on therapy, how well they were maintained and what not. And the

data is continuing to roll in regarding how appropriate that may be, but many payors are eager to potentially realize any savings in this area of their drug spend and prospect of forcing patients to switch from innovator biologic to a biosimilar is a tempting one, even though they aren't currently considered interchangeable.

[Bon Jovi – It's My Life]

CB: As the industry and our science develops and matures, hopefully we can make these medications more affordable to patients. If we can go from extracting insulin from animals to making it in cells 50 years later, the possibilities in the next 50 years are very promising.

MC: I wish we had more time to talk about these drugs! I feel we've barely scratched the surface. But know this: the history of biological drugs dates back to the 17th century! What we've learned to do is manipulate living biology through technology to create new medications for conditions that we were unable or ineffectively treating with pharmaceutical chemistry.

CB: We'd definitely like to thank our guest from BioScript, Sheldon for his insightful experiences. It's been a pleasure learning from you.

SB: Thank you for the invite, it's been a pleasure to be here. I'm very excited that a podcast like The Med Thread is on the go now and if any of the listeners haven't checked out their previous ones, please do and I'll be subscribing to it going forward to be sure.

MC: Thank you so much!

CB: As always, you can find our references and notes on our webpage at www.mtsclinic.ca and if you have questions, comments or things you want to hear about, send us a message on Facebook via the School of Pharmacy or email medthread@mun.ca.

Thanks for listening, I'm Cathy,

MC: and I'm Mike. Tune in next month when we get into the school year and talk about ADHD and stimulants.

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