Biologics and Biosimilars Step Onto the Cancer Therapy Stage

Oncologist and health economist Gary Lyman, MD, MPH, discusses a class of treatments on the rise. Will lower prices follow?

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They're used to treat everything from rheumatoid arthritis to multiple sclerosis to diabetes to cancer, prompting industry insiders to buzz about their potential with the breathless excitement once reserved for Hollywood starlets.

They're biologics, a costly class of drugs that emerged a few decades ago and is now stepping into the pharmaceutical spotlight in a big way. A slew of cancer biologics (with a total global spend of $20 billion) are poised to lose their patent protections by 2020, potentially opening up the market for greater competition — and more consumer-friendly pricing.

So what are biologics, why do they cost so much, and will their rising young "understudies," generic-ish versions called biosimilars, be just as expensive — and inaccessible — once they hit the market?

We sat down with Fred Hutchinson Cancer Research Center's Gary Lyman, MD, MPH, a national thought leader in health economics, to get the scoop. An oncologist, public health researcher and co-director of the Hutchinson Institute for Cancer Outcomes Research, or HICOR, Lyman just co-authored a New England Journal of Medicine paper on biosimilars and what their imminent debut might mean for cancer patients, the health care industry and society. He also recently led an American Society of Clinical Oncology (ASCO) panel that published a position statement on biosimilars in the April Journal of Clinical Oncology.

"We've had biosimilars for a couple of years," he said, en route to Chicago for ASCO's annual meeting, where he would give a presentation on this same topic (listen to a related podcast here). "But biosimilar *cancer* treatments have not yet hit the market in the United States. There are two that have been approved by the U.S. Food and Drug Administration [alternatives to Avastin and Herceptin] and there are literally hundreds more of these biologics and biosimilars coming down the pipeline."

The problem?

"If patients can't afford them or get access to them, they might as well stay in the laboratory," he

said.

(The following conversation has been edited for length and clarity.)

So what are biologics and biosimilars?

Most medications are simple chemicals that can be synthesized in the laboratory. We know their structure and they can be reproduced exactly the same each time as long as you have the right formula and the right chemicals. Aspirin is a good example, but there are thousands. They come in all shapes and sizes, and once the patent for a particular drug expires, you can make a generic, and that generic should be exactly the same as the original brand medication.

Biologics are different. They're generally proteins — large complicated molecules — that are produced in living cells, like bacteria or yeast. So even if you know the exact amino acid sequence, the underlying structure of that complicated protein, it cannot be exactly reproduced. When you try to make another batch of it, it may differ slightly. There will be drift due to slight changes.

A biosimilar is a highly similar version of the original biologic.

Biosimilars are sort of but not quite generics?

Correct. Once the patent for a biologic expires, the formula used for that biologic or "reference product" becomes available so a commercial company can make a biosimilar. But because they're so complex and made inside living systems, it won't be exactly the same as the reference product.

So the FDA definition for approval is that it has to be "highly similar," which sounds very subjective but it's not. They have very straightforward rules: it has to have the same amino acid sequence and the same pharmacokinetics [e.g., measures of how drugs travel and break down inside the body]; it has to look the same in the lab; it has to act the same in animal studies and there has to be some clinical data showing it functions the same as the original reference product.

If all that is satisfied, then the FDA can say it's highly similar to the reference product and it should have no meaningful clinical differences in its effect and safety.

Are biosimilars as safe as biologics?

They should be, but we don't have much experience with them here in the U.S. None of the biosimilars approved and used in Europe over the last decade have been withdrawn from the market, so that's reassuring.

But oncologists will have to remain vigilant about safety given the fact that, unlike the reference product, biosimilars did not undergo large randomized clinical trials. They had to demonstrate they were highly similar based largely on preclinical work, but there may be very little clinical data provided to the FDA to prove they're as effective and safe as the reference product.

We will need to track these agents closely for years, making sure we're getting reports on safety

concerns, adverse events, allergic reactions, or any evidence that the disease control is not as good.

These would not be random clinical trials but expanded cohorts of patients using the drugs after they're on the market. Patient reported outcomes, or PROs, will be vital. Capturing this data and showing continued benefit and no harms will go a long way to reassuring all of us that they're a safe and effective alternative for patients.

What's the good, bad and ugly of these new drugs?

Some of these biologic agents are miracle drugs — they save lives and can make dramatic impact on a patient's quality of life. We've seen some astounding effects with cancer drugs like Herceptin and Rituxan. Others are providing far more modest benefit, improving median survival by only a month or by weeks or days.

Cost is definitely the ugly. The cost of biologics has gone up astronomically. It's grown every year. Part of that is fed by the excitement with these agents because they're targeting critical areas in the cancer cell that in the past we could only hit nonspecifically with things like chemotherapy.

But with each new biologic approved by the FDA — and there are many more coming down the pipeline — the price seems to go up and up.

Why are biologics so expensive?

Biologics are complicated to make and reproduce. In addition, part of the high cost is because they're targeting less common tumors or subtypes of tumors. The biologic trastuzumab — Herceptin — just targets HER2+ breast cancer, for instance. And then there are rarer tumor types where companies feel that to recoup their cost of developing and manufacturing the drug, they have to charge an arm and a leg for it.

But biologics are also being marketed directly to patients. Pharmaceutical companies spend hundreds of billions of dollars putting ads on TV and on the web and in newspapers and magazines asking patients to talk to their doctor about their drug.

Most major professional organizations like ASCO believe we need to end this kind of direct-to-consumer advertising. It's not good for patients and it accounts for a huge portion of the annual budgets within these companies which then charge these high prices to pay for advertising. That makes no sense. If they got rid of that part of their budget, they could pass the savings onto the patient.

Will biosimilars, like generics, cost less?

Biosimilars are a promising way to increase competition, make biologics more accessible and potentially bring down costs, but it's complicated.

When there is more than one version of a biologic and the guidelines say you can use any of them because they should be equally effective, payers as well as health systems will negotiate prices. They'll try to get the drug makers to compete with one another, lower the price or give them some kind of deal, and then they'll say that's our preferred form of the biologic therapy.

Nevertheless, time will tell.

A biologic/biosimilar used for supportive care is one thing. Cancer treatment is another. Cancer raises the anxiety level and the desperation. And often with it, the price. Patients don't really have a good alternative choice to forgo therapy in most instances. Therefore, the healthcare market is not actually a "free-market."

Are you seeing any of what FDA Commissioner Scott Gottlieb, MD, called "shenanigans," pharma practices that might keep these drugs expensive?

Some of these biologics have several patents, not just one. So pharmaceutical companies can keep the patent infringement litigation going for years and prevent other companies from making a biosimilar in the U.S.

Also, biologic manufacturers are now getting into the biosimilar space, arguing "Who better than us to make them?" That means they're in competition with themselves and they're not going to automatically lower the price.

Can we make the field more competitive?

With biosimilars, the whole idea is to foster competition. That idea was even highlighted by the recent President's Cancer Panel Report. But they're still complex molecules that require a major cost investment, so there's a concern that competition will not be enough to substantially lower the escalating price of these products.

Competition is certainly needed because clearly these companies know that cancer patients and their families will often pay whatever it takes to get access to a new therapy. We can't just leave it to market forces to limit the cost.

One proposal is to put a cap on how much pharmaceutical companies can charge for "me-too-biologics" [biologics that target the same molecular pathways but are developed independently]. And putting a cap on what biosimilars can charge might begin to blunt that vicious cycle. The challenge is you can't make it so draconian that companies decide it's not worth it because there will be no competition.

Are there other things that can be done to bring down costs?

We need to find a way. There needs to be some regulation, or else the only ones not profiting in all of this will be the patients — and it's their lives that are at stake.

Again, some of these agents are miracle drugs, but others may only improve median survival by a month or weeks, days, or not at all. Yet they're being priced as the market will bear so patients are paying top dollar for nominal benefit. Value-based pricing — allowing the Centers for Medicare and Medicaid Services to set or negotiate prices with manufacturers, to set or negotiate the price with the company in proportion to the drug's benefit, its value to patients and the system — makes so much sense.

But it takes political will, it takes determination, and it takes vocal patient advocates and providers. Industry isn't going to do this on its own, and Congress doesn't seem compelled to do much either.

The ballot box is always there, but the voice of the patient and those in the health care field can be influential. We have to be far more vocal — it's not just about cost, it's about doing what's right and assuring appropriate access to these exciting, potentially curative drugs.

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