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CONQUERING THE CANCER CARE CONTINUUM™

Understanding the Value of Biosimilars in Oncology

Lillie D. Shockney, RN, BS, MAS

We all go to our local pharmacy to get prescriptions filled for ourselves or a loved one. We usually notice, primarily based on the copayment, whether the prescription drug we are getting is a trade name we may see in a television commercial or it is a generic drug. How? By the amount of the copayment. Our money goes much further when we get a generic form of a drug, as the copayment is commonly 75% less than that for the real McCoy (ie, trade name drug). People question why there is such a huge price difference between the "same thing," and they also wonder whether the drug with the long confusing name is as good as the brand advertised on television.

Lillie D. Shockney, RN, BS, MAS

Pharmaceutical companies spend millions and millions of dollars conducting research focused on drug development to get a new innovative drug, carefully and tediously researched in the lab, into human clinical trials to eventually get it approved and to the market. The time line is commonly 15 years or longer. More importantly perhaps, most of the drug development research never makes it anywhere, despite hundreds of millions of dollars being spent trying to create a drug that will be of value to those who need it. This results in the price tag on a newly FDA-approved trade name drug being very high when it finally gets to market. It is the only way for the pharmaceutical companies to attempt to recover their investments as well as offset the losses they have experienced on all the other drug research that met with a dead end. At present there is no alternate system to recover the exorbitant expenses incurred through bench and human research.

With our healthcare economic system where it is today (ie, incredibly top-heavy in expenditures on medications compared with other healthcare expenses), we have to begin embracing the concept and benefits of what are called "biosimilar" products. These are synthetically manufactured drugs that are highly similar to our already FDA-approved biological products but cost a tiny percentage of their original innovative versions. The similarity is despite a few minor differences in clinically *inactive* components, and if there are no clinically meaningful differences in safety, purity, and potency between the biosimilar and the approved biological product,[1] then it makes sense to use the biosimilar option whenever possible. The biosimilar drugs are not exactly the same as the innovator products but are considered biologically and clinically comparable.

This final issue in the series of *Conquering the Cancer Care Continuum* provides you insight into issues that pharmacologists and pharmacists face related to providing these types of drugs and understanding the differences, if any, between the original innovator drugs and the new Memorex versions of them. You will learn the dollars and cents associated with this challenge and how

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The Role of Biosimilars in Oncology: A Nurse's Perspective

Beth Faiman, PhD(c), MSN, APRN-BC, AOCN

Cindy is a 52-year-old female with non-Hodgkin lymphoma. She plans to undergo an autologous hematopoietic stem cell transplant (HSCT). When discussing the risks associated with HSCT, the oncologist warns Cindy that her white blood cells (WBCs) will become critically low as a result of high-dose chemotherapy. The low WBCs will place her at an increased risk for developing a possibly life-threatening infection. The oncologist will minimize Cindy's risk of infection by giving her an injection of a granulocyte colony-stimulating factor (G-CSF); G-CSF is a glycoprotein that will stimulate WBC production and decrease the length and severity of neutropenia.

When the oncologist leaves the room, the registered nurse (RN) arrives to provide additional education on the transplant process and information on the G-CSF that will be administered. Cindy recently read an article about biosimilars in cancer. She asks the RN if the G-CSF will be a generic or trade name compound. Cindy is concerned the generic G-CSF will not be as effective as the original, or "innovator," product in reducing her chance of a life-threatening infection, according to what she read on the Internet. The RN knows the institution prefers the generic filgrastim product to the trade name Neupogen. How should she address Cindy's concerns about the safety and efficacy of biosimilar compounds?

Beth Faiman, PhD(c), MSN, APRN-BC, AOCN

The surge in interest to develop biosimilars is expected to continue in the United States and worldwide.

Biosimilar Drug Development Is the Wave of the Future

Tremendous advances in the supportive care of cancer were seen in the 1980s and 1990s. Drugs developed prior to this period were traditionally manufactured through a well-defined pathway and chemical synthesis. In 1982, a genetically engineered form of insulin (Humulin) was approved by the FDA. In the 1990s, supportive care biopharmaceutical drugs such as erythropoietins and G-CSF compounds were developed using recombinant DNA or hybridoma technology to mimic endogenous human proteins.[1] These synthetically manufactured drugs are called biosimilars.

The FDA has defined a biosimilar product as being highly similar to an already approved biological product. The similarity is notwithstanding minor differences in clinically inactive components, as well as no clinically meaningful differences in safety, purity, and potency between the biosimilar and the approved biological product.[2] The biosimilar drugs are not exactly the same as the innovator (trade name) product, but they are considered biologically and clinically comparable to the innovator product. As of 2010, worldwide sales of biopharmaceuticals were in excess of $100 billion.[3] Worldwide sales and use of biological agents in cancer and other areas such as rheumatology, immunology, and neurology are expected to increase dramatically and could rise by 75% by 2025.[4]

The high cost of drug development and innovation has led to an interest in developing drugs that are biologically similar to products already approved by the FDA. The surge in interest to develop biosimilars is expected to continue in the United States and worldwide. The interest is based on financial considerations to decrease healthcare costs and is also fueled by current legislation. The Patient Protection and Affordable Care Act was signed into law by President Barack Obama on March 23, 2010, and specifically addresses the topic of biosimilars. The Affordable Care Act created an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. As of March 2013, statutory conditions for the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) have been drafted. At present, investigational compounds can be considered biosimilar if data show that, among other things, the product is highly similar to existing compounds.[2]

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.[5] In accordance with pharmacovigilance, the drug development process for new medicines and biosimilars requires an extraordinary amount of time and effort. The process of drug development does not stop after the approval of a drug. Ongoing evaluation and postmarketing data need to be collected to prove the long-term effects of these drugs to be similar and safe.[6] Postmarketing pharmacovigilance will be necessary to establish the true safety and efficacy of biosimilar drugs.

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Biosimilar filgrastims have been launched in the United States and across Europe with Neupogen as the reference or innovator product. Biosimilar filgrastims such as tbo-filgrastim (Teva Pharmaceuticals), approved by the FDA on August 29, 2012, are indicated for prevention and treatment of chemotherapy-induced neutropenia, mobilization of peripheral blood progenitor cells for HSCT, patients with acute myeloid leukemia, patients undergoing HSCT, and patients with severe chronic neutropenia.[7] The approval was based on the results of studies presented for marketing authorization. The data indicate therapeutic equivalence and safety of filgrastim biosimilars in the prophylaxis of complications related to neutropenia caused by chemotherapy.[8,9]

How Would You Respond to Cindy's Concerns?

There are many ways to respond to Cindy's concerns. One approach would be to reinforce that the hospital's decision to use biosimilars is based on evidence. There are sufficient data to support the role of a biosimilar form of Neupogen in the prophylaxis of complications related to neutropenia caused by chemotherapy. The RN can also provide additional education and ways Cindy can be proactive to decrease her risk of infection, such as good hand-washing techniques and avoidance of people with colds or illnesses. Cindy may have additional financial or psychosocial concerns the RN may explore regarding the transplant process to alleviate concerns as well.

Conclusion

The number of biosimilar drugs in oncology will continue to increase over the next few decades. Current government legislation supports the development of biosimilars as outlined in the BPCI Act. The use of biologically similar drugs in cancer can dramatically decrease costs to the patient and the healthcare system. Additional surveillance for long-term side effects should be conducted. All adverse events or unintended side effects must be reported to the FDA to ensure long-term safety and efficacy of each compound. ■

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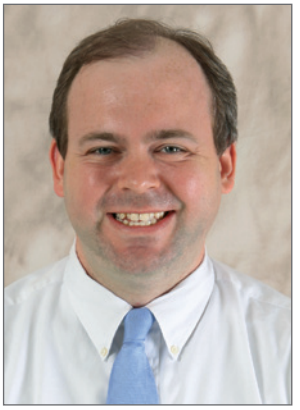
The Role of Biosimilars in Oncology: A Pharmacist's Perspective

Steve Stricker, PharmD, MS, BCOP

CJ is a 62-year-old female beginning chemotherapy with doxorubicin and cyclophosphamide for stage III breast cancer. To minimize the risk of neutropenia-associated complications, it is planned for CJ to return to the clinic daily following chemotherapy for injections of a colony-stimulating factor (CSF) until her absolute neutrophil count exceeds 10,000 × 10^6/L. As the oncology pharmacist on the team, you are asked which CSF to recommend considering the recent development of biosimilar CSFs. Additionally, you are asked if biosimilar options are safe and efficacious for patient use. How would you answer?



Steve Stricker, PharmD, MS, BCOP

Until recently, the selection of biological therapies for any indication was limited to the availability of the originator or reference product. For a patient like CJ, this would result in the prescribing of filgrastim (Neupogen) or pegfilgrastim (Neulasta) for prophylaxis of neutropenia and/or neutropenia-associated complications from chemotherapy. However, with patent expiration looming for many of these highly specialized medications, healthcare professionals are now facing the introduction of the biological therapy equivalent (referred to as biosimilars) of the chemical generic drug product. Because biologics are far more complex than their small molecule drug counterparts, often comprising large molecular weight proteins or peptides developed from living cells or organisms, minor differences in structural assembly or protein folding may theoretically translate into differences in activity not previously observed with the development of other generic drug products. As a result, many healthcare professionals have expressed concern and uncertainty regarding the similarity of clinical efficacy and safety between these new biosimilars and the corresponding reference biologics. Therefore, education of clinicians regarding biosimilars should address the major concerns/barriers to use of these drug products in clinical practice.

The paradigm that biosimilars are "similar but not identical" to the reference biologic is both what some clinicians find appealing from a pharmacoeconomic perspective and what other clinicians fear from a clinical utilization perspective. These concerns are what have led naysayers to erroneously conclude that biosimilars are of lower quality than the innovator drug and may not achieve therapeutic outcomes as effectively. To refute this notion, it is necessary to briefly address the development process of these drugs. First, because the manufacturing processes for biologics are proprietary, it is impossible to exactly replicate the structure of the innovator product. Small differences in amino acid sequence or protein folding will result in a new and unique biologic molecule.[1] As such, biosimilars cannot be regarded as true generic versions of innovator compounds. It is also important to recognize that the concern related to the intrinsic variability in biologic systems often cited for biosimilars also results in minor variations from batch to batch in the production of innovator biologics so that no 2 batches will be identical. However, the quality controls imposed for both innovator biologics and biosimilars ensure the creation of a product that is within an acceptable range of variability and strives to eliminate any difference in clinical efficacy.[2] Thus, the goal of biosimilar production becomes the desire to create a product that is highly similar to the innovator drug with regard to physicochemical and functional characteristics. If successful, clinical efficacy and safety must be addressed but is allowed by the FDA, to some degree, to be extrapolated from clinical trials and experiential utilization of the innovator drug. Some may find the FDA's compressed approval pathway for biosimilars to be a cavalier approach for a unique drug molecule. However, Weise and colleagues address this directly by suggesting, "a repetition of the entire development program of the reference product is scientifically not necessary and could even be considered unethical."[2]

Therefore, if we correctly conclude that an approved biosimilar product is structurally very similar to the innovator product, and the FDA allows the extrapolation of some clinical efficacy and safety data from clinical trials conducted for the innovator drug, are we

ready to accept biosimilars for all patients and all indications? The answer should be...not yet, there's more we must first consider!

Whereas products that share structural similarity should reasonably be expected to share adverse event profiles, concerns do still remain regarding immunogenicity. While major issues in product variation may be detected by ultrasensitive analytical methods, human immunogenicity data are required prior to approval of a biosimilar product. This is especially true for biologic compounds known to induce immune responses resulting in significant patient safety issues.[2] Here, we may learn a lesson from our colleagues across the globe. The European Medicines Agency (EMA) was the first to develop guidelines for biosimilars in 2005 and followed with the first worldwide biosimilar approval in 2006. With 13 biosimilars approved by EMA to date, issues with immunogenicity have been observed and addressed for some products. In one example, EMA noted excessive immunogenicity with a biosimilar somatropin due to a high level of host cell proteins that could be removed through an additional purification step added to the manufacturing process.[2,3] In the European model, pharmacovigilance and postmarketing studies for biosimilars are often recommended and tailored to the individual drug product and any perceived drug-specific issues that may exist.

Therapeutic interchange also remains an important consideration in the use of biosimilar medications. For standard generic drug products, the FDA's *Orange Book* provides guidance for substitution for an innovator product. Those products deemed identical are assigned an AB rating allowing a pharmacist to dispense, without medical authorization, a generic in place of a prescribed innovator drug. As established here, biosimilars are not identical to the reference product, thus resulting in issues with therapeutic interchange. The FDA has delineated a pathway by which a biosimilar may be labeled as interchangeable with an innovator compound. This pathway requires data in addition to what is expected for a product to simply be recognized by the FDA as biosimilar. Here, a manufacturer must demonstrate that a product may be expected to produce the same clinical outcomes in any patient as that observed for the innovator compound. Additionally, it must be demonstrated that the risk of switching therapy between the biosimilar and the innovator product is no greater than using the innovator product alone without changing therapies.[4] Simply put, this process holds manufacturers to a higher standard of demonstrating biosimilarity, clinical efficacy, and human safety data than what would typically be required for FDA approval alone.

Therapeutic interchange also remains an important consideration in the use of biosimilar medications.

Over time, the pharmacoeconomic benefits of using a less expensive biosimilar have been estimated to generate significant cost savings.

Even for products that have sought interchangeability, concerns still linger regarding traceability of biosimilar products in the clinical setting. This is perhaps the most compelling argument against automatic substitution rules for biosimilars. Here again we must point out the paradigm of "similar but not identical." As such, for patients developing an adverse event or an immune-mediated safety issue to a biosimilar, the exact product dispensed must be able to be appropriately and accurately identified. Root cause analysis and reporting to the FDA's MedWatch program require specific drug information, including product name and lot number. To streamline this process, the FDA appears to have taken a proactive stance in biosimilar nomenclature that ties the manufacturer name to the drug product instead of using the chemical name alone as is done with small molecule generics. For example, Teva Pharmaceutical's filgrastim biosimilar will be recognized as tbo-filgrastim rather than filgrastim alone. These higher standards of interchangeability and unique nomenclature may initially limit the market share for these new biosimilars as prescribers will be required to specify which drug product their patient will receive. Over time, the pharmacoeconomic benefits of using a less expensive biosimilar proven to have similar safety and efficacy profiles have been estimated to generate significant cost savings in an era where healthcare spending is spiraling out of control. In fact, some have estimated that the availability of a biosimilar product will replace 80% or more of prescriptions for some innovator products within 1 year of commercial availability.[5]

For those biosimilar products that meet the standards we have discussed, the FDA allows their use in the same treatment regimens at the same doses and

using the same schedule as the innovator product. However, clinicians must be aware that commercial availability of a biosimilar does not automatically equate approval for all indications for which an innovator product is currently prescribed. Clinicians are encouraged to exercise appropriate judgment in choosing a biosimilar for an off-label use despite the fact that once clinical efficacy and safety have been demonstrated, substitution of a biosimilar will likely prove to be clinically appropriate in these scenarios.

As a cancer center, we have not yet been forced to make policy decisions regarding formulary inclusion of biosimilars, substitution of biosimilars in our treatment protocols, or in how we monitor patients for adverse reactions or immune-mediated complications following treatment with a biosimilar. I predict that we will observe characteristic patterns of early adopters eager to utilize a cheaper biologic to contain costs and late adopters determined to wait until additional data emerge for patients treated with biosimilars outside the highly controlled confines of a clinical trial. Ultimately, prescribers must feel comfortable that these new products are not jeopardizing the health, well-being, or prognosis of their patients with cancer.

In the case of CJ, we pondered the question of whether biosimilars were safe and efficacious for patient use. With the issues we have considered here, I believe the answer is yes, these FDA-approved drugs are safe and efficacious for our patients, and providers should give serious consideration to use of these products as an alternative to more costly innovator products. However, until we have more long-term safety data, patients should be monitored closely for tolerance, and providers should have a low threshold for converting patients back to the innovator drug if issues arise. ■

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Understanding the Value of Biosimilars in Oncology *(continued from page 1)*

it impacts the future of oncology care in the United States. There is also a thought-provoking article about these drug comparisons and the complexities that nurses and other healthcare providers face in trying to explain to patients why they are receiving what they believe to be "brand X," whether it is really as good as its original form, and why they should be accepting the biosimilar drug.

Research has by no means ended when it comes to this debate. There will always be ongoing research to validate the accuracy of the effectiveness as well as side effect comparisons long-term, going well beyond 5 years of study.

If we don't embrace the value of these synthetically created products, soon we will not be able to afford treating patients with cancer no matter what drugs are or aren't available. Recognizing that the incidence of cancer continues to grow steadily and will continue to do so with baby boomers now in midlife, and our current healthcare economic structure being incredibly out of control, we need to look at this as being one of the solutions to reining in cost so we have the drugs available and can afford to use them to get more people to become cancer survivors. ■

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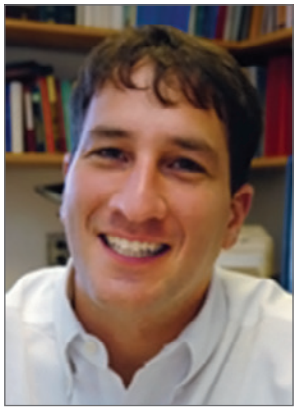
The Role of Biosimilars in Oncology: A Physician's Perspective

Jeffrey A. Meyerhardt, MD, MPH

In April 2011, the National Comprehensive Cancer Network (NCCN) convened a summit of key stakeholders regarding the issues surrounding biosimilars in oncology care. The working group subsequently published a sentinel white paper outlining the regulatory, scientific, and patient safety issues surrounding the development and expansion of biosimilars in oncology care.[1] A fundamental rationale for figuring out the biosimilars issues relates to costs. Of the nearly 200 agents listed in the NCCN compendium in 2011, 15% were classified as biologics,[1] and this number is continuing to grow each year. Of the top 20 anticancer drugs in terms of expenditures in 2010 (not including supportive care medications), 5 (25%) were biologics (bevacizumab, rituximab, trastuzumab, cetuximab, and panitumumab), but they led to 55% of the total costs.[2]



Jeffrey A. Meyerhardt, MD, MPH

Beth Faiman and Steve Stricker both focus on filgrastim in their very well-written and thought-provoking articles. Filgrastim, a growth factor stimulant, is a key supportive medication in the care of many oncology patients. Usage varies by disease type, chemotherapy regimen used (ie, febrile neutropenia potential), and stage of disease. The considerations for accepting filgrastim biosimilars are similar to many of the issues surrounding antineoplastic biosimilars. As discussed in the previous articles, biosimilars are "similar but not identical." When considering use of biosimilars that are not identical to the original drug, we would like to say they are equal in efficacy. However, demonstrating true equivalence in clinical research is a near-impossible task, but clearly, as providers, we want to be sure that substituting one drug for another drug leads to nearly equivalent drugs, accepting that some small margin of difference is likely inevitable. And while this is certainly important with supportive medications like filgrastim, it may be an even higher concern with antineoplastic therapies.

At the NCCN 16th Annual Conference in March 2011, 277 conference attendees were surveyed on their knowledge of biosimilars.[1] Approximately 50% of these were physicians, 25% nurses, 14% pharmacists, and 11% other. Only 4 questions were asked of respondents, but the answers were telling. Fifty-four percent were not familiar or only slightly familiar with the recent developments in biosimilars (ie, the recent legislation outlining an abbreviated approval pathway). The group most familiar with the changes was pharmacists, and the group least familiar was nurses, with physicians in the middle. Interest in prescribing biosimilars was high (>60% had high and moderate interest). Multiple data pieces were very or somewhat important to respondents, with >80% indicating the importance of studies showing chemical/physical similarities, studies showing pharmacokinetic similarities, inclusion in compendium, data on cost differences, understanding of payer decisions and requirements, and colleague and/or expert opinions. For each top-used biologic available at the time, approximately 20% of respondents would immediately use the biosimilar if available today, ~60% would require review and discussion prior to using, and 5% to 8% would not use the biosimilar if available today.

As providers, we want to be sure that substituting one drug for another drug leads to nearly equivalent drugs.

This last question may raise some of the most telling issues related to this subject. Sixty percent of respondents required further review of a biosimilar prior to using. The question is what data would they want? What data would be compelling? Efficacy alone? Safety? Costs? These are key questions to understand in how these biosimilars will be incorporated into clinical practice. I think also telling is that 5% to 8% of providers will not use the biosimilar despite being approved and available. Why? This issue is raised by Steve Stricker in his article – one presumes it is primarily

driven by concerns for efficacy and safety, although some providers are also considering the potential lower reimbursement and margin for biosimilars. This latter point remains an issue in oncology (as well as other fields of medicine) that requires further scrutiny as attempts are made to bring down healthcare costs.

In summary, I think many of us assumed that when drugs like filgrastim and rituximab (as 2 examples) entered the market 22 and 15 years ago, respectively, generics would come down the pike just as we have seen for traditional chemotherapies. However, as discussed in this issue of *Conquering the Cancer Care Continuum*, issues around biosimilars are many and complex in nature. However, all stakeholders involved realize that we cannot ignore the issue anymore. Biosimilars are essential to continuing to provide high-quality, cost-effective, and compassionate care to our patients. ■

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