The Role of Biosimilars

Presented by Andrew D. Zelenetz, MD, PhD, and Pamela S. Becker, MD, PhD

Abstract

As biologics go off-patent, the field of oncology is grappling with incorporating biosimilars. These are highly similar (but not generic versions of) biologic agents, and they are approved based on showing "near fingerprint identity" in structure and potency. Their introduction is expected to increase competition and lower treatment costs. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Myeloid Growth Factors has incorporated the first biosimilar approved in the United States, filgrastim-sndz, into its recommendations. At the NCCN 21st Annual Conference, Andrew D. Zelenetz, MD, PhD, provided an overview of biosimilars, describing the process of their development and approval; Pamela S. Becker, MD, PhD, discussed the NCCN Guidelines recommendations for the use of filgrastim-sndz and of tbo-filgrastim, which was approved in the United States as a true biologic agent. The use of tbo-filgrastim can be somewhat confusing, as it does not have the same indications as the other growth factors.

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The Debut of Biosimilar Agents: Myeloid Growth Factors Are the First Act

As cancer biologics move off-patent, biosimilars are coming on board. In March 2015, the first biosimilar agent was approved for an oncology indication: the recombinant granulocyte colony-stimulating factor (G-CSF) filgrastim-sndz. Filgrastim-sndz is now listed in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Myeloid Growth Factors (MGFs) and is part of many drug formularies. The oncology community, therefore, must become familiar with this introductory biosimilar and its recommended use in clinical practice.

At the NCCN 21st Annual Conference, Andrew D. Zelenetz, MD, PhD, Vice Chair of Medical Informatics in the Department of Medicine, Memorial Sloan Kettering Cancer Center, and Professor of Medicine, Weill Medical College of Cornell University, described these agents. His co-presenter, Pamela S. Becker, MD, PhD, Professor of Medicine, University of Washington School of Medicine; Attending Physician, University of Washington Medical Center and Seattle Cancer Care Alliance; and Vice Chair of the NCCN Guidelines for MGFs discussed the incorporation of filgrastim-sndz within those guidelines.

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Dr. Zelenetz has disclosed that he receives consulting fees from Amgen Inc., Axess Oncology, Celgene Corporation, Gilead Sciences, Inc., GlaxoSmithKline, Hospira, Janssen Pharmaceutica Products, LP, Medscape, LLC, Roche Laboratories, Inc., Takeda Pharmaceuticals North America, Inc., and The France Foundation; he has received honoraria from Amgen Inc., Axess Oncology, Celgene Corporation, Gilead Sciences, Inc., GlaxoSmithKline, Hospira, Janssen Pharmaceutica Products, LP, Medscape, LLC, Roche Laboratories, Inc., Takeda Pharmaceuticals North America, Inc., and The France Foundation; and he has received grant/research support from Bristol-Myers Squibb Company, Gilead Sciences, Inc., GlaxoSmithKline, Janssen Pharmaceutica Products, LP, and Roche Laboratories, Inc. Dr. Becker has disclosed that she has received grant/research support from Amgen Inc.

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Functional, Equivalent Molecules

As Dr. Zelenetz, Chair of the NCCN Non-Hodgkin's Lymphoma Panel, explained, biosimilars must be proven to have no clinically meaningful differences over the already approved reference product in safety, purity, or potency.

"Biosimilars represent a functionally and equivalent molecule to the originator product and, when they become available, should be added to the NCCN Guidelines as alternatives to the originator," he added.

"Biologics have become the cornerstone of many areas of modern medicine, but they are especially important in the management of cancer," Dr. Zelenetz said, "both as supportive agents to treat cytopenias and as active therapeutic agents."

Role of Biosimilars

"Unfortunately, biologics are very expensive, and as a result, the therapeutic spending in oncology dominates all of medicine's spending," he continued, noting that approximately 50% of the biologic market is in the oncology field, with huge cost implications.

As the biologic era matures, a number of drugs are moving from patent status to patent expiration, a trend that began in Europe, with the United States now catching up, Dr. Zelenetz noted.

Although small molecules are well-defined chemically and relatively "easy" to manufacture and reproduce, biologic agents are more complicated. Over time, originator molecules are subject to drift as a result of changes in the manufacturing processes, sourcing of materials, or any of many other variables. There are guidelines in place to validate that drift is minimal as processes are changed.

Because the reference product is not even "an identical product of itself" over time, one can appreciate the difficulty in manufacturing an "absolutely identical copy" of a biologic molecule, Dr. Zelenetz said. Although an exact duplicate of a biologic medicine is not possible, an agent can be produced with differences so slight that they are not clinically relevant; biosimilars are these products, Dr. Zelenetz noted.

"Near Fingerprint Identity" Moves Product Forward

The FDA approval of a biosimilar follows the 351(k) pathway, which leads the molecule through a comprehensive set of preclinical evaluations to prove it is not meaningfully different from the reference product. The biosimilar is subject to an extensive battery of tests evaluating primary, secondary, and tertiary structure as well as preclinical functional, assays, such as receptor binding, effector function, and cytotoxicity. Once introduced into the clinic, pharmacokinetics (PK) is a critical measure in assessing the bioavailability of a "highly similar" structure; the PK must fall within predefined equivalence margins. The extent of the clinical evaluation required depends on the quality of the preclinical and PK evaluation.

The next step, a clinical trial, requires that efficacy be demonstrated only in the most clinically "sensitive" indication for the originator product. The biosimilar and originator are evaluated in a noninferiority trial.

"You don't need to prove outcomes. That's been done by the originator," Dr. Zelenetz explained. "You just have to show its clinical activity is not different from the originator."

Cost as a Driver and a Concern

As biosimilars are entering the clinic, Dr. Zelenetz has observed that some clinicians are still skeptical. "At least in the early days of approval, they want more clinical validation, more data on efficacy, safety, and reimbursement," he said.

"From NCCN surveys, we see that there is concern that biosimilars will be forced on physicians; that they won't have a choice and that everything will be about cost." Education, such as via this session at the NCCN Conference, "is critical," he said.

From an industry perspective, biosimilar development is complex, but it is much less expensive than manufacturing a novel biologic agent. Although not as affordable as generic medications, biosimilar agents are expected to cost 20% to 40% less than the reference product (Figure 1). This "should be enough to provide some cost competition," Dr. Zelenetz suggested.

FDA Indications for MGFs

Dr. Becker described the use of G-CSFs in cancer, and showed how filgrastim-sndz and tbo-filgrastim fit in the NCCN Guidelines for MGFs. Filgrastim-sndz

Are Biosimilars Generic Versions of Biological Products? No

Generics	Biosimilars
• Copies of brand-name drugs • The *same* active ingredient • The *same* as the brand name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use • The brand-name and the generic are bioequivalent	• Complex macromolecules • *Highly similar* to the reference product they were compared to, but have allowable differences because they are made from living organisms • No clinically meaningful differences in terms of safety, purity, and potency from the reference product

Figure 1. Comparison of generic and biosimilar agents.

is approved for the same indications as filgrastim: to treat patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia (FN); patients with acute myeloid leukemia receiving induction or consolidation chemotherapy; patients with cancer undergoing bone marrow transplantation or peripheral blood progenitor cell collection and therapy; patients with severe chronic neutropenia; and patients with HIV infection.

"Filgrastim-sndz is interchangeable for all indications with filgrastim," Dr. Becker emphasized.

Among the other MGFs, pegfilgrastim (pegylated form of filgrastim) is approved for the first indication (above) only, and for acute radiation syndrome. Tbo-filgrastim was approved in Europe as a biosimilar but as a true biologic in the United States, and it has only one indication: for reducing the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive agents associated with a clinically significant incidence of FN.

NCCN Guidelines Recommendations Regarding Biosimilars

In the NCCN Guidelines, the term "G-CSF" includes filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim. In some settings, any of these is acceptable; in others, more specific recommendations are made, Dr. Becker said. As prophylaxis during chemotherapy, G-CSF has a category 1 recommendation for patients who are at high-risk of developing FN (>20%). For patients who are at intermediate-risk (10%–20%), G-CSF should be considered based on patient's risk factors, and G-CSF is not recommended for patients at low-risk (<10%) of developing FN.

Patients should be evaluated for risk of FN before their second and subsequent chemotherapy cycles. In patients experiencing FN or a dose-limiting neutropenic event during the previous cycle of chemotherapy with the use of a G-CSF, chemotherapy dose reduction or change in treatment regimen is recommended.

Among patients presenting with FN, those who are already on prophylactic pegfilgrastim need no additional G-CSF, whereas those who are receiving any other prophylactic G-CSF should continue that same agent. Patients with FN not on prophylactic G-CSF should be assessed for risk. Growth factors are not recommended in the absence of risk factors for infection-associated complications but should be considered when patients are deemed at risk.

"For prophylaxis of FN, we have category 1 evidence for filgrastim, tbo-filgrastim, and filgrastim-sndz," Dr. Becker noted.

Growth Factors in Transplantation

The use of tbo-filgrastim in stem cell mobilization and after hematopoietic stem cell transplantation has been debated. It is not FDA-approved in the autologous transplant setting or for mobilization.

Addition of tbo-filgrastim as an acceptable option for the following:	
• Mobilization of hematopoietic progenitor cells in the autologous setting	2A
• Following combination chemotherapy pre-autologous transplant with the goal of mobilization during count recovery	2A
• In combination with plerixafor for mobilization of hematopoietic progenitor cells in the autologous setting	2A
• Mobilization of allogeneic donors	2B
• For granulocyte transfusion in the allogeneic setting	2B

Category 2A: Based upon lower level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B: Based upon lower level evidence, there is NCCN consensus that the intervention is appropriate

Figure 2. NCCN Categories of Evidence and Consensus for tbo-filgrastim in various settings: recommendations from the NCCN Guidelines Panel for Myeloid Growth Factors.

Role of Biosimilars

"The problem is that over the past couple of years, our NCCN institutions were reporting that some insurance companies were only going to approve tbo-filgrastim," Dr. Becker said.

In a study of 185 patients, no significant differences were seen between filgrastim and tbo-filgrastim in the total collection of CD34(+) cells, which was the primary end point. Furthermore, no clinically meaningful differences were seen in secondary efficacy and safety end points, and tbo-filgrastim was less expensive.[1]

In another study involving 182 patients with myeloma undergoing autologous hematopoietic stem cell transplantation who received either filgrastim or tbo-filgrastim, there were no differences in the CD34(+) cell dose and time to neutrophil recovery,[2] leading the authors to conclude there was "no material difference" between the 2 growth factors in this setting. Based on these studies and polling of the NCCN Member Institutions, the NCCN Guidelines have included tbo-filgrastim in various settings of transplantation, as outlined in Figure 2.

In conclusion, Dr. Becker pointed out that both filgrastim-sndz and tbo-filgrastim are recommended in the NCCN Guidelines for mobilization of hematopoietic progenitor cells for transplantation (category 2A for autologous transplant and category 2B for allogeneic transplant) and supportive care after transplantation.

References

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