ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The Benefits and Drawbacks of Biosimilars

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H&O What are biosimilars?

BC The class of pharmacologic agents known as biologics has revolutionized the way that we treat a large variety of diseases. Biologic agents generally contain proteins that are made synthetically. Now that the patents have expired on a number of these agents, pharmaceutical companies are attempting to make off-patent biologics—new agents that act the same as the biologics that are already on the market. To provide an overly simplified definition, biosimilars are roughly equivalent to generic versions of biologics.

H&O Could you describe the biosimilar that was recently approved, filgrastim-sndz?

BC Filgrastim-sndz (Zarxio, Sandoz) is a new agent that is very similar to the original biologic filgrastim (Neupogen, Amgen), a granulocyte colony-stimulating factor (G-CSF). This drug is used to prevent infections in patients who are given chemotherapeutic agents that reduce their white blood cell count.

H&O How is the development of biosimilars different from that of generic drugs?

BC Generic drugs for small molecules have a relatively simple chemical structure that can be reproduced or processed so that the chemical itself is identical. By contrast, it is not clear that any protein or peptide made, for example, in a different cell line or by a different company in a different process will be identical to the original biologic agent. For example, there can be differences in the sugar residues that are attached to the protein. There also can be differences in protein folding that are hard to predict. Therefore, even though the biosimilar may have an identical peptide chain, it may not have an identical effect. For this reason, the process of making biosimilars is not easy and can be fraught with problems.

In fact, one of the issues with biologics has been that there are significantly more lot-to-lot variations than with small molecule drugs, even among the original proteins. Even though the proteins are identical and produced in the same way, different lots can have dissimilar effects, particularly when it comes to side effects. Although this usually does not lead to problems, such problems have occurred. The best example of this is erythropoietin. A few brands of erythropoietin were on the market in Europe, and even though the protein itself was identical, one of those brands had a different toxicity. Some people developed immunity to the erythropoietin, which caused them to develop immunity to their own erythropoietin. The availability of agents with different effects led to major problems that took quite a while to sort out. This is an example of a single protein that otherwise had characteristics that were identical to those of the original, but had very different toxicities. Such variations present a challenge in developing biosimilars, and are a major concern with using them.

H&O What is required for approval of a biosimilar?

BC Companies must demonstrate that the molecule has similar characteristics and similar efficacy compared

with the original biologic agent. They must have evidence that the pharmacodynamics and pharmacokinetics of the molecule are similar in patients, and they must have in vitro evidence that the molecule has the same mechanism of action.

Europe has had biosimilars for a longer time, and has a somewhat different process for approval. In one case, the European Medicines Agency had a drug undergoing review as a biosimilar that was actually a "bio-better," that is, the newer agent had better efficacy than the original agent. This drug was not approved because it was not biosimilar. One reason for this regulation is to keep the doses consistent, so that the physicians who are used to giving the drug will know how much is required. Consistency of dose is especially important for certain agents, such as those that affect blood clotting. This is one reason why the area of biosimilars is more fraught than many people realize.

H&O What is the difference between biosimilars and bioidenticals?

BC There is a difference between biosimilars and bioidenticals or interchangeable molecules. A biosimilar is an agent that is similar, and will have roughly the same efficacy as and most other characteristics of the original molecule. However, the manufacturer of a biosimilar has not gone as far as proving that the drug is identical to the original drug in its effect in any given patient. This distinction is important. A pharmacist can substitute a generic drug for a brand-name drug, but this is not appropriate for the biosimilars because they are not identical.

H&O What is the naming convention for biosimilars and why is this topic important?

BC So far, there is no generally accepted naming convention, which is a problem. In the US Food and Drug Administration (FDA) approval notice of filgrastim-sndz, they included the suffix "-sndz" to the original protein filgrastim to indicate that it is different from filgrastim. This is very important because, as I mentioned before, there has been at least one example of a biosimilar drug having unusual and potentially lethal side effects. It is necessary to be able to track which drug the patient is receiving, so that if there are unusual toxicities or other complications, the source of the problem can be determined.

H&O What are the benefits of using biosimilars?

BC The only benefit is that they are less expensive. Otherwise, there is no particular benefit. As I mentioned before, if the drug is actually more efficacious, it is not considered a valid biosimilar.

The availability of biosimilars will have an impact on drug costs. This impact will not be as dramatic as that of generic small-molecule drugs, because manufacturing biosimilars is much more difficult. The expectation is that the price will decline by approximately one-third, or possibly by as much as one-half. With generics, by contrast, the cost often is reduced by 90% to 95%, or even more. Nonetheless, I still think that the reduced cost for biosimilars will have an overall impact on drug costs.

H&O What are the questions or concerns with using biosimilars?

BC Biologics are large and complex molecules that have very specific effects. They are antibodies in many cases, or proteins such as G-CSF. The main concern is that some modifications might occur during the manufacturing process that will be undetectable and will lead to altered efficacy, immunogenicity, or toxicity. This worry may turn out to be overblown, and these companies may be able to manufacturer biosimilars in a way that is as consistent as the original companies, with very predictable effects. However, we still do not know whether that is possible, and many people are concerned.

H&O How do physicians generally feel about the use of biosimilars?

BC I think physicians are somewhat wary. Some drugs, such as filgrastim, are not given chronically; they are given situationally. I am a rheumatologist, and the rheumatology community has been very worried because many biologic agents in this field are given for years, many of them potentially for the duration of the patient's life. Many physicians are worried that these biosimilars will be substituted for the original, and the physician will not know until the patient develops toxicity or until the drug suddenly loses efficacy.

Another worry is that different insurance companies will have contracts with different manufacturers of the biosimilar drugs. As patients change insurance companies, they will receive whichever drug their insurance company will pay for, meaning they may change biosimilars over the course of treatment.

I think physicians are very wary about changing drugs midstream like this. If a patient has rheumatoid arthritis that is very well controlled with a specific brand-name drug, physicians do not want the patient to change drugs. Most likely, the new drug will be effective and will not cause problems; however, if this is not the case, there is a chance that the patient will never respond to this type of therapy again. This is a major concern for many physicians.

H&O What do you think is the future of biosimilar use and development?

BC I think it is very clear that these will be used in the future. Everyone—even the major pharmaceutical companies—is jumping into this field with both feet. For example, Pfizer and Sandoz (a subset of Novartis) are developing biosimilar drugs. These are not specific generic drug manufacturing companies; these are major pharmaceutical companies developing drugs because, even with the diminished price of biosimilars vs the original, the companies still will make a significant profit. However, I think that we still should be cautious about biosimilar use. There are still many questions and concerns regarding the use of biosimilars, especially for long-term treatments.

Suggested Readings

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