REPORT

Integrating Trastuzumab Biosimilars and HER2-Directed Therapies into HER2-Positive Breast Cancer Management

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ABSTRACT

The approval of the humanized monoclonal antibody trastuzumab in 1998 changed the trajectory of treatment and subsequent outcomes for patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer and is now the standard of care in the neoadjuvant, adjuvant, and metastatic settings. However, as with most biologic drugs, trastuzumab comes with a relatively high price tag compared with traditional cytotoxic chemotherapy and contributes to healthcare budgets. Three engineered products related to trastuzumab—2 antibody-drug conjugates, ado-trastuzumab emtansine and fam-trastuzumab deruxtecan-nxki, as well as the subcutaneous trastuzumab/hyaluronidase—have since been approved and have expanded the treatment options for this patient population. The approval of 5 trastuzumab biosimilars as of the end of 2019 holds the promise of considerable cost savings, but challenges to integrating their use into patient care must be addressed. Barriers to their use, including physician uncertainty to switch patients from the reference drug to the therapeutic biosimilar and patients' lack of understanding about biosimilars, are common in the United States. It is also important that all stakeholders, including managed care professionals, pharmacists, and practice administrators, understand how to incorporate trastuzumab biosimilars into formulary discussions, clinical care plans and processes, and educational initiatives for healthcare providers and patients.

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For author information and disclosures, see end of text.

Introduction

An estimated 268,600 new cases of invasive breast cancer were diagnosed in women in 2019, making it the most common cancer in women in the United States. Although approximately 42,260 women died from the disease that year, the overall death rate from breast cancer has fallen by 40%, from 33.2 per 100,000 in 1989 to 20.0 per 100,000 in 2016.[1] This is due not only to earlier diagnosis through screening but also to the emergence of agents with new mechanisms of action and more targeted therapies that address the presence or absence of 3 key molecular markers in breast cancer: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2). These molecular markers are the basis for classifying breast cancer into 3 subtypes—HER2-positive, hormone receptor-positive (ER+ and/or PR+), or triple-negative—and for determining the appropriate initial treatment approach in early-stage disease.[2] Genomic and molecular testing is now standard practice in patients with advanced-stage breast cancer in order to determine the most appropriate targeted therapies based on hormone and HER2 status as well as *PIK3CA*, *BRCA1*, *BRCA2,* and *PD-L1* biomarker status.[3]

An estimated 15% to 20% of women with newly diagnosed breast cancer have tumors that overexpress HER2. These tumors tend to be more aggressive, more likely to invade lymph nodes, and more likely to recur and metastasize than other subtypes. They have also been historically associated with shorter patient survival compared with hormone receptor–positive breast cancer.[2,4] However, with the 1998 approval of trastuzumab, a humanized monoclonal antibody (mAb) that targets the extracellular domain of the HER2 protein, the trajectory of HER2-positive breast cancer shifted dramatically. Based on substantially improved outcomes in multiple clinical trials, including significant survival benefits across all stages of the disease, trastuzumab-based regimens are considered the gold standard of treatment for women with HER2-positive breast cancer.[2,3]

Trastuzumab

Cochrane Database of Systematic Reviews found that trastuzumab-based regimens in early breast cancer (EBC) improved overall survival (OS) by 33% (hazard ratio [HR], 0.66; 95% CI, 0.57-0.77; P <.00001)

and disease-free survival (DFS) by 40% (HR, 0.60; 95% CI, 0.50-0.71; $P < .00001$),[5] and in the metastatic setting improved OS by 18% (HR, 0.82; 95% CI, 0.71-0.94; $P = .004$) and progression-free survival by almost 40% (HR, 0.61; 95% CI, 0.54-0.70; $P < .00001$).[6]

Dosage and Administration

Trastuzumab has a variety of dosing regimens, with the dose, combination of agents, and duration depending on its use in the neoadjuvant, adjuvant, or metastatic setting. Trastuzumab is administered via intravenous (IV) infusion and requires a loading dose followed by a maintenance dose. The National Comprehensive Cancer Network (NCCN) lists 10 potential regimens in the preoperative and adjuvant settings.[3]

The NCCN guidelines list 4 potential trastuzumab-containing regimens for metastatic treatment in premenopausal women with trastuzumab in combination with an antiestrogen, either as monotherapy or in combination with lapatinib. For postmenopausal women, the preferred regimens are pertuzumab, trastuzumab, and docetaxel (category 1) or pertuzumab, trastuzumab, and paclitaxel. Several other regimens are also recommended.[3] The NCCN notes that an FDA-approved biosimilar is an appropriate substitute for trastuzumab in all settings.[3]

Safety

Overall, trastuzumab is well tolerated and does not require any supportive care medications before or after administration. The most common adverse effects (AEs) affecting at least 5% of women in the adjuvant setting are headache, diarrhea, nausea, and chills (most grade 2 in severity), whereas fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash were the most common AEs affecting at least 10% in the metastatic breast cancer (MBC) setting.[7,8]

Trastuzumab labeling carries a black box warning of the risk of cardiomyopathy. In the pivotal phase 3 clinical trial published by Slamon and colleagues, combining trastuzumab with anthracyclines caused cardiac dysfunction and heart failure in up to 27% of patients with metastatic disease compared with 7% in the anthracycline monotherapy group.[9] Since then, large observational studies have also identified higher rates of cardiotoxicity in women receiving trastuzumab compared with anthracycline alone.[10,11] This led to a change in clinical trial design to give the 2 drugs sequentially rather than concurrently, which demonstrated a much lower rate of cardiovascular effects.[12] Whether the cardiovascular changes are reversible when trastuzumab is discontinued remains a key question.[12]

Trastuzumab/hyaluronidase-oysk

Trastuzumab/hyaluronidase-oysk received FDA approval in February 2019. The product uses a patented drug delivery technology to facilitate subcutaneous (SC) administration, with recombinant human hyaluronidase (also called rHuPH20) acting as a temporary spreading factor. It degrades hyaluronan, a large glycosaminoglycan that otherwise limits SC administration of large volumes of fluid.[13] Although delivered SC, this product is not self-administered and must be administered by healthcare professionals in an outpatient setting.

Trastuzumab/hyaluronidase-oysk was compared with trastuzumab IV in the open-label, phase 3, noninferiority HannaH (Enhanced Treatment with Neoadjuvant Herceptin) trial. Eligible patients received 8 cycles of chemotherapy with either fixed-dose SC trastuzumab/hyaluronidase-oysk (600 mg) or IV trastuzumab (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) every 3 weeks in the neoadjuvant setting. Patients received an additional 10 cycles of SC trastuzumab/hyaluronidase-oysk or IV trastuzumab (according to their initial randomization) for 1 year following surgery.[14]

Rates of grade 3 or higher AEs were similar in the 2 groups, with neutropenia, leukopenia, and febrile neutropenia most common. However, 21% of patients in the SC group versus 12% of patients in the IV group had serious AEs, primarily infections and infestations (8.1% vs 4.4%).[15] With 6 years of follow-up in the 591 women in the intention-to-treat population, the event-free survival rate of 65% (HR, 0.98; 95% CI, 0.74-1.29) with an 84% OS (HR, 0.94; 95% CI, 0.61-1.45) were similar between the SC and IV study groups.

The faster administration time provides a much improved experience for patients as demonstrated in the PrefHER and MetaspHer studies. Results of the multicenter, crossover PrefHER trial, which randomized 240 women undergoing neoadjuvant or adjuvant treatment for HER-positive breast cancer to 4 cycles each of IV trastuzumab or SC trastuzumab/hyaluronidase-oysk, found that 91.5% of women preferred the SC formulation primarily because they spent less time in the clinic.[16] Similar results were seen in the MetaspHer study, which randomized 113 women to 3 cycles of trastuzumab/hyaluronidase-oysk SC or trastuzumab IV, followed by 3 cycles of the IV formulation.[17] Several studies have been conducted outside the United States attesting to the cost-savings potential of an SC delivery approach for healthcare systems; the savings are accrued from less preparation and delivery time as well as direct medical cost savings.[18-24] However, with the quickly evolving biosimilars market, the cost-savings potential of an SC delivery approach is not yet known in the United States.

It remains unknown if trastuzumab/hyaluronidase-oysk SC delivery will pose a threat to uptake of the biosimilars, all of which are administered by IV.[25] This version of trastuzumab does increase the potential for reducing the cost of trastuzumab IV therapy by adding more market competition. In evaluating costs, stakeholders must consider the complete episode of care; these include differences in drug administration costs and in revenue potential between the 2 different routes in practice settings.

The phase 3 PERSEPHONE trial was designed to investigate the hypothesis, demonstrated in other studies, that 6-month adjuvant trastuzumab treatment is noninferior to 12-month delivery.[26] The open-label, noninferiority trial randomized 4089 patients with HER2-positive EBC to either 6-month or 12-month trastuzumab delivered every 3 weeks IV or SC in combination with chemotherapy. Switching from the IV to the SC route was allowed at the prescriber's discretion. Eighty-two percent of the trastuzumab cycles were given IV and 18% were given SC. The 6-month cohorts met the primary end point of DFS noninferiority to 12 months of treatment, with increased adherence and fewer cardiac and other serious AEs in the 6-month group.[26] A cost analysis estimated an average savings of $12,800 for 6 months of trastuzumab versus 12 months, regardless of administration route, for a 100% cost-effective approach with no decrease in quality of life.[27] If such a change were adopted as a standard of practice with biosimilars, the cost savings could be even more significant.

Economic Issues Related to Trastuzumab

As with most biologics, the cost of trastuzumab started high and has continued to climb, even as other biologics with similar mechanisms of action entered the market.[28] One potential reason for this price increase is that there has not been competition in the marketplace prior to the advent of trastuzumab biosimilar, SC trastuzumab/hyaludronidase-oysk, and antibody–drug conjugate approvals. Trastuzumab has consistently ranked in the top 20 drugs for sales revenue in the United States, with sales of $2.87 billion in 2018.[29]

Although trastuzumab's high price does not limit access for patients with the need for lifesaving treatment in the United States due to coverage of the therapy by Medicare Part B as well as Medicaid plans, there are significant financial impacts to organizations—including practices and health systems—and to patients due to out-of-pocket costs. The cost-effectiveness of trastuzumab with or without concurrent or consecutive therapies in the neoadjuvant, adjuvant, and metastatic setting has been extensively studied, but results vary depending on the setting, breast cancer stage, and treatment regimen.[30-33] In a survey of 45 US oncologists, one-third cited high out-of-pocket costs for patients as a barrier to prescribing trastuzumab in the early and curative stages, and 10% reported at least 1 instance of delaying or canceling treatment because of reimbursement issues. Reimbursement issues also played a role in 60% of instances in which physicians did not prescribe the drug in the metastatic setting.[34] In the same survey, one-third of physicians reported that they would increase the use of HER2-positive antibody therapy if a lower-cost biosimilar version of trastuzumab were available.[34]

Ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, and Other Antibody–Drug Conjugates

The impact of antibody–drug conjugates on the overall cost of care for patients with HER2-positive breast cancer is not yet known and complicates the landscape. These agents carry different indications than the reference trastuzumab product, and supportive care management also varies. **Table 1**[35,36] highlights indications and dosing of these agents.

Ado-trastuzumab emtansine is an antibody–drug conjugate. This antibody–drug conjugate links a microtubule inhibitor to a mAb. After the mAb binds with the tumor cell, the cytotoxic drug is delivered into the tumor cell where the "payload" is released. The rationale is to kill cancer cells and spare normal cells from toxicity, thereby potentially increasing efficacy and decreasing toxicity.[37]

Ado-trastuzumab emtansine was first approved in 2013 to treat HER2-positive MBC that was previously treated with trastuzumab and a taxane. A later study in patients with EBC led to its 2019 approval for adjuvant treatment of HER2-positive EBC in patients with residual invasive disease after neoadjuvant taxane- and trastuzumab-based treatment.[35] That indication was evaluated in the KATHERINE trial, a multicenter, open-label study in 1486 patients with HER2-positive EBC previously treated with neoadjuvant taxane- and trastuzumab-based therapy. Patients were randomized to adjuvant ado-trastuzumab emtansine or trastuzumab for 14 cycles. The interim analysis at 3 years estimated 88.3% of patients in the ado-trastuzumab emtansine group were free of invasive disease compared with 77.0% in the trastuzumab group. Invasive DFS was significantly higher in the ado-trastuzumab emtansine group than in the trastuzumab group (HR for invasive disease or death, 0.50; 95% CI, 0.39-0.64; P <.001). Distant recurrence as the first

TABLE 1. HER2 Antibody–Drug Conjugates Breast Cancer Indications and Dosing[35,36]

Generic Name (Brand Name)	Indication* and Dosing	Dosing
Ado-trastuzumab emtansine (Kadcyla)	1. Metastatic disease in patients who previously have received trastuzumab and a taxane, separately or in combination 2. Adjuvant treatment**	3.6 mg/kg IV every 3 weeks until disease progression or unacceptable toxicity (metastatic) or a total of 14 cycles (EBC)
Fam-trastuzumab deruxtecan-nxki (Enhertu)	Unresectable or metastatic cancer in patients who have received ≥2 anti-HER2–based regimens in the metastatic setting	5.4 mg/kg IV every 3 weeks until disease progression or unacceptable toxicity

EBC indicates early breast cancer; HER2, human epidermal growth factor receptor 2; IV, intravenous.
*All indications include HER2-positive breast cancer.
**Adjuvant treatment of patients with HER2-positive EBC who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

invasive-disease event occurred in 10.5% of patients in the ado-trastuzumab emtansine group and 15.9% of those in the trastuzumab group (HR, 0.60; 95% CI, 0.45-0.79). The benefits were sustained across all subgroups, including patients with hormone receptor-positive or -negative disease.[38] Patients in the ado-trastuzumab emtansine cohort were more likely to discontinue therapy due to AEs or to require a dose reduction than those in the trastuzumab group. They also experienced higher rates of serious AEs (12.7% vs 8.1%). The most common grade 3 or higher events in this group were decreased platelet counts and hypertension.[38]

Although ado-trastuzumab has been incorporated into national guidelines, an economic analysis of the agent as a second-line therapy compared with lapatinib plus capecitabine found it was not cost-effective from either a payer or societal perspective at a willingness-to-pay threshold of $150,000 per quality-adjusted life-year, although there was some suggestion that it might be cost-effective compared with capecitabine monotherapy.[3,39] The United Kingdom's National Institute for Health and Care Excellence also found that it was not cost-effective and thus does not recommend its use.[40]

Fam-trastuzumab deruxtecan-nxki was granted accelerated FDA approval in December 2019 based on data from the phase 2 DESTINY-Breast01 study.[41] This agent is an antibody–drug conjugate composed of a humanized anti-HER2 immunoglobulin G1 mAb, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor called DXd.[36] The DESTINY-Breast01 study was a multicenter, single-arm trial that enrolled 184 patients with previously treated metastatic HER2-positive breast cancer. The primary efficacy end point was objective response rate, which was reported to be 60.3% (95% CI, 53.4%-68.0%), with a 4.3% complete response rate and a 56% partial response rate. Median response duration was 14.8 months (95% CI, 13.8-16.9). The most common AEs (frequency >20%) were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutropenia, diarrhea, leukopenia, cough, and thrombocytopenia.[42] The approval of fam-trastuzumab deruxtecan-nxki represents a therapeutic advancement and new option for patients with pretreated HER2-positive MBC.

Other HER2-directed antibody–drug conjugates are in clinical development, including [vic-] trastuzumab duocarmazine.[37] [Vic-] trastuzumab duocarmazine is composed of a recombinant humanized HER2 mAb covalently bound through a cleavable link to a duocarmycin prodrug, seco-duocarmycin-hydroxybenzamide-azaindole, known as seco-DUBA, which has cytotoxic activity. The safety and efficacy of [vic-] trastuzumab duocarmazine is being assessed in the open-label, randomized TULIP trial, comparing it with physician's choice treatment in women with HER2-positive, unresectable, locally advanced or MBC. In the phase 1 dose-escalation study, [vic-] trastuzumab duocarmazine was well tolerated, with ocular toxicity being the most commonly reported AE. Results from this trial are expected in 2021.[37]

The landscape of HER2-positive breast cancer continues to change with the addition of antibody–drug conjugates. These agents represent an advanced approach to cancer treatment that couples the specificity of mAbs to the cytotoxicity of classical chemotherapy agents, with potential for increased efficacy and manageable toxicity.

Trastuzumab Biosimilars

Five trastuzumab biosimilars have been approved in the United States for HER2-positive breast cancer as of late 2019: trastuzumab-anns, trastuzumab-qyyp, trastuzumab-dttb, trastuzumab-pkrb, and trastuzumab-dkst, although only 2 are available.[43] All major clinical trials for biosimilars demonstrated equivalence or noninferiority between the biosimilar and the reference drug with similar safety signals (**Table 2**).[44-53] However, the trials used different equivalence margins and were of relatively short duration in the adjuvant or MBC setting, which may be of some concern to clinicians.[54] These biosimilar trastuzumab studies used certain clinical end points, such as pathologic complete response (pCR) or overall response rate, which are ideal because they are sensitive enough to determine if a difference exists in terms of activity. In particular, pCR is important because the FDA has accepted it has a surrogate marker for survival; conversely, OS, a traditional end point, is not ideal because it accounts for all causes of death, not just those that are therapy related. Table 2[44-53] highlights key clinical efficacy and safety data.

As of 2019, trastuzumab-anns and trastuzumab-dkst are the only 2 biosimilars in this class that have been launched. Trastuzumab-anns entered the market just a few months after FDA approval without any patent settlement with trastuzumab manufacturer Genentech. Trastuzumab-dkst became available in late 2019.[55] The other 3 biosimilars have settled with Genentech and are expected to launch in 2020.[56]

The lag in launch of approved trastuzumab biosimilars has resulted in an estimated $140 million in savings lost in 2018.[57] However, once more biosimilars are on the market, the competition has the potential to increase the cost differential between the reference and biosimilar drug to more than the 15% discount at which trastuzumab-anns launched.[56] In Europe, the entrance of 3 trastuzumab biosimilars captured 38% of market share after just 10 months on the market, with sales of the reference product falling 16%.[56]

The true value of the trastuzumab biosimilars remains unclear. Just 1 study has been published on the potential cost-savings benefit of trastuzumab, and it was based on the Croatian healthcare system. It found that at a 15% lower cost than the reference drug, 14 additional patients could be treated; at a 35% discount, an additional 47 could be treated.[58] Nonetheless, it is important to consider analysts' expectations for cost savings from biosimilars overall. A 2017 RAND report estimated a potential $54 billion cost savings from biosimilars

TABLE 2. Trastuzumab Biosimilars: Indications, Trials, Efficacy, and Safety[44-53]

Biosimilar Generic Name (Brand Name)	Indication	Phase 3 Trial Design	Study End Points (Biosimilar vs Reference Product)	Most Common Serious AEs (Biosimilar vs Reference Product)
Trastuzumab-anns* (Kanjinti)	• Treatment of HER2-overexpressing breast cancer • Treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	• LILAC N = 725; EBC • Neoadjuvant therapy followed by adjuvant treatment up to 1 year	pCR: 48.0% vs 40.5%	• Neoadjuvant phase: 15% vs 14% (neutropenia most common) • Adjuvant phase: 9% vs 6% (neutropenia, infection most common)
Trastuzumab-dkst* (Ogivri)	• Treatment of HER2-overexpressing breast cancer • Treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	• HERITAGE n = 500; MBC • Biosimilar or reference drug plus taxane for 24 weeks then either alone until disease progression or loss of tolerability	• ORR: 69.6% vs 64.0% • TTP at 48 weeks: 41.3% vs 43.0% • PFS: 44.3% vs 44.7% • OS: 89.1% vs 85.1%	• Neutropenia (all grades): 57.5% vs 53.3% • Peripheral neuropathy (all grades): 23.1% vs 24.8% • Diarrhea (all grades): 20.6% vs 20.7%
Trastuzumab-pkrb (Herzuma)	• Treatment of HER2-overexpressing breast cancer	• N = 549; EBC • Neoadjuvant therapy with biosimilar or reference product plus docetaxel followed by adjuvant period up to 1 year; trial continuing	• Neoadjuvant: bpCR: 46.8% vs 50.4% • Adjuvant (24 mo): OS 97% vs 98%	6.6% vs 7.6%
Trastuzumab-qypp (Trazimera)	• Treatment of HER2-overexpressing breast cancer • Treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	• REFLECTIONS n = 707; MBC • First-line treatment with biosimilar or reference product plus paclitaxel	• ORR (week 33): 62.5% vs 66.5% • Median PFS: 12.16 mo vs 12.06 mo	34.4% vs 36.5% (neutropenia most common)
Trastuzumab-dttb (Ontruzant)	• Adjuvant and MBC • Metastatic gastric cancer	• N = 875 EBC or locally advanced • Adjuvant setting • Biosimilar or reference drug plus docetaxel and then FEC; in the adjuvant setting received drug only, some with radiotherapy/hormone therapy per local practice	• bpCR equivalent • CR: ER-negative and/or PR-negative (60.% vs 53%); ER+ and/or PR+ (46.9% vs 33.9%) • tpCR: 45.8% vs 35.8% • OS: 96.3% vs 91.2% • EFS at median follow-up (437 days for biosimilar and 438 days for reference product): 92.2% vs 91.6%; OS: 99.8% vs 98.9%	10.5% vs 10.7%

AE indicates adverse effect; bpCR, breast pathologic complete response; CR, complete response; EBC, early breast cancer; EFS, event-free survival; ER, estrogen receptor; FEC, fluorouracil/epirubicin/cyclophosphamide; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; PR, progesterone receptor; tpCR, total pathologic complete response; TTP, total time to progression.
*Indicates currently available.

in direct spending over a 10-year period. The report estimated that oncology mAbs would account for 13% of savings.[59]

Extrapolation

One area of significant concern among clinicians is the extrapolation of a biosimilar to all indications of the reference drug.[60] Currently, the FDA biosimilar approval process does not require separate clinical trials for each indication; however, manufacturers have to provide sufficient scientific evidence to support the determination of biosimilar status, such as knowledge of the structure, mechanism(s) of action, pharmacokinetics, and pharmacodynamics in each of its approved indications.[61] Clinically equivalent studies are required only if uncertainty remains. As shown in Table 2,[44-53] 4 biosimilars share the same indications for the reference drug, whereas trastuzumab-pkrb is indicated only for breast cancer. All indications are based on clinical trials for that disease rather than extrapolation.

Trastuzumab Biosimilar Uptake: Issues for Physicians, Payers, and Pharmacists

With trastuzumab biosimilars having been on the market for just a few months, it is difficult to predict how payers will incorporate them into formularies. For instance, infliximab remained on most formularies in 2017 despite the availability of a biosimilar at a 15% lower wholesale price. This suggests that payers must consider multiple factors other than cost in evaluating biosimilars for formulary decisions, which is usually of utmost importance when small-molecule generics enter the market. Considerations also include provider and patient relationships as well as concerns about efficacy and safety when the issue of switching to the biosimilar arises.[62]

However, the environment may be changing. As of October 1, 2019, UnitedHealthcare began requiring the use of trastuzumab-anns prior to the use of trastuzumab and other trastuzumab biosimilars.[63] Medicare Advantage plans are now able to use step therapy for Part B drugs, so it is possible they could institute similar requirements.[64]

Another factor that may slow adoption of the trastuzumab biosimilars is that federal and state laws allowing substitution (interchangeability) for generics do not apply to biosimilars. Only biosimilars with an interchangeable designation can be substituted for the reference product automatically. In most states, that substitution requires that the prescriber receive notification. In addition, rebates and discounts offered by the reference manufacturer may make the biosimilar discount less attractive.[62] However, payers could require therapeutic substitution as part of the formulary process.[65]

Physician Barriers to Trastuzumab Uptake

One of the greatest barriers to trastuzumab biosimilar uptake will be physician and patient reluctance to switch from the reference drug to a biosimilar, given the relatively modest cost reduction (most of which the payer accrues). Other barriers are concerns about efficacy and safety.[66]

Results from an online survey of 297 US physicians who prescribe biologics found that 84% did not favor a nonmedical switch to a biosimilar, despite the potential cost benefits. Physicians also expected that switching would negatively impact patient mental health, drug efficacy and safety, and physician office management.[67] Most physicians reported trying to avoid switching between biologics unless medically necessary. Those who did switch for nonmedical reasons (primarily payer requirements) did so to avoid higher costs; however, such switches can disrupt and delay treatment for patients who must deal with administrative issues through their insurance company.

Abundant data exist that appear to indicate no compromise of efficacy or safety when switching from a reference drug to a biosimilar. In a meta-analysis conducted by Cohen et al, 90 studies were evaluated in which more than 14,000 patients switched from a reference product to a biosimilar.[68] Cohen et al concluded that switching from reference product to biosimilar is not inherently dangerous, and patients and healthcare professionals should not be concerned about such switching. The authors did acknowledge that, as with all biologics, pharmacovigilance is important to monitor for rare safety events and for unexpected changes in efficacy or safety profiles. Of note, only 4 studies that were included in this meta-analysis were cancer-related trials, and those were primarily filgrastim studies.[68]

Numerous surveys report deficits in healthcare provider understanding of biosimilars. Results of one conducted among 376 US physicians and about 900 from European and Latin American countries found significant knowledge gaps regarding the effects of biologics versus biosimilars and whether they are structurally and therapeutically identical. The authors recommended educational initiatives "to dispel the misconception that biologics and biosimilars are structurally and therapeutically identical, and to promote a better understanding of their differences in order to improve patient care."[69]

In a survey of 1201 US physicians, including oncologists, 45% thought that biosimilars were safe and appropriate for both treatment-naïve and previously treated patients, 36% thought that biosimilars were not as safe as the reference biologic, and just 12% of physicians were comfortable with extrapolation of indications. The authors also noted the need for physician education.[60] The need for additional education to providers has been noted through multiple surveys. Regulatory bodies, including the FDA as well as oncology and pharmacy professional societies, offer courses, webinars, and presentations about specific aspects of biosimilar use from development of biosimilars to education that providers can use to educate their own patients.[70,71]

Results from a 2018 survey of 77 oncologists, pharmacists, and advanced practice providers found that 74% of respondents could not define a biosimilar or differentiate it from a generic drug. For these oncology clinicians, the most important attributes of a biosimilar were safety and efficacy, followed by cost differences. Clinicians disagreed about the importance of shared decision making with patients when it came to biosimilars.[72]

Meanwhile, a survey of more than 500 US hematologists and oncologists found that[73]:

- 58% (153 of 263 total respondents) said a biosimilar would have to be priced between 11% and 30% less than the reference drug for them to prescribe it.
- 66% (126 of 191 total respondents) said it was extremely important or very important to save costs by prescribing biosimilars versus reference products.
- 34% (20 of 59 total respondents) believed that the patient's financial responsibility would be lower for a biosimilar than an originator product all of the time, whereas 58% (34 of 59 total respondents) believed it would be lower some of the time.

Although respondents were initially "uncomfortable" about the regulatory process, the majority expressed a "reasonable" level of comfort after they received education about it. They also said they would like practice guidelines for when to prescribe a biosimilar versus a reference product, which are already available in current NCCN guidelines.[3,73]

Challenges for Pharmacists

As more trastuzumab biosimilars become available, pharmacists also may experience challenges; these might include operational issues, such as storing multiple biosimilars, updating electronic medical record order sets, documenting accurately, and billing correctly. Patient safety challenges also exist, as there is the potential to inadvertently prescribe, dispense, or administer an incorrect product. A recent survey of 300 managed care and specialty pharmacy professionals found that respondents had a generally favorable view of the safety and efficacy of biosimilars, even when switching from a reference product; however, just 54% supported extrapolation.[74]

When asked about strategies to improve provider updates of biosimilars, the majority (91%) selected educational programs for prescribers focused on switching strategies. The least favored strategy was requiring therapeutic drug monitoring for patients who switch in order to address concerns about immunogenicity. More than half (62%) cited concerns about safety and efficacy among patients as a difficult or somewhat difficult barrier to uptake, whereas half cited formulary management issues.[74]

In addition, the survey demonstrated significant variation in payer uptake of biosimilars, with about one-third of respondents reporting that biosimilar preferences were based primarily on contracting rebates. Nearly one-fourth revealed that their organizations have not established policies or preferences for biosimilars, pending additional safety and efficacy evidence.[74]

Pharmacists often lead discussions and preparation for formulary discussions on the inclusion of therapeutic oncology biosimilars and biologics. In addition to reimbursement and contractual agreements, multiple factors for biosimilar inclusion, such as whether the data support extrapolation of use for certain indications, safety profiles, and post-approval pharmacovigilance reports, must be considered.[75] For HER2 antibody–drug conjugates, it's important to consider not only efficacy data but also comparison of differences in safety and administration as well as how the biologic may replace use of existing formulary agents.

Patient Barriers

Patient attitudes are also key to biosimilar adoption, with surveys demonstrating mixed results. Results of a 2015 PricewaterhouseCoopers study found that 67% of consumers did not know what a biosimilar was, and just 17% were able to choose the correct definition from several choices.[76] Another survey administered to 3198 patients (including 76 with breast cancer), caregivers, advocates, and individuals in the general population in Europe and the United States found that just 6% of the general population had basic awareness of biosimilars; up to 70% of patients had never heard of them. Patients who were aware of biosimilars were more likely to believe that they were safe and more willing to switch to a biosimilar, indicating that increasing patient awareness could help increase uptake of these agents.[77] Patient acceptance may improve if collaborative relationships are established with patient advocacy groups. Patient advocacy groups such as CancerCare and Susan G. Komen have patient-centered online education and workshops on biosimilars. These online workshops often feature oncologists, healthcare providers, pharmacists, and oncology social workers on their panels.[78,79]

Another risk with patients is the nocebo effect, in which a negative effect of a medical treatment occurs because of the patient's expectation but is unrelated to the physiologic effects of the treatment. This can be particularly prevalent when switching medications and is expected to be a barrier to biosimilar switching.[80] One useful strategy for overcoming the nocebo effect is positive framing, which emphasizes benefits while maintaining transparency about the risks of switching to a biosimilar.[80] Training clinicians to use this kind of enhanced communication strategy has been shown to improve acceptance and persistence after switching to a biosimilar in rheumatology patients.[81] A provider who is knowledgeable about biosimilars and communicates well with patients can help overcome patient concerns as well. Providers can also use numerous tools, including patient-facing resources from the FDA, to direct patients to information that will help them understand the risks and benefits of biosimilars.[82]

Conclusions

With 5 trastuzumab biosimilars either currently on or entering the market, there is the potential for significant impact in the treatment of HER2-positive breast cancer. The approval of SC trastuzumab/hyaluronidase-oysk with modifications in route and administration as well as trastuzumab antibody–drug conjugates with differences in efficacy and safety are rapidly changing the landscape. The effects of these additions to the market share, and their subsequent cost implications, is not yet known. The complexity and cost of managing HER2-positive breast cancer continues to evolve. Biosimilars represent an opportunity to reduce cost of care without compromising quality of care. Pharmacists have an integral role in the appropriate use of these agents by leading discussions about formulary decisions and helping to balance clinical with financial considerations; these discussions would include such issues as interchangeability, extrapolation of indications, pharmacovigilance, immunogenicity, inventory management, and affordability. Pharmacists are critical in guiding healthcare providers and patients through transitions from reference biologic to biosimilar, whether starting with the biosimilar or switching from a branded biologic. Most importantly, they have an essential role in educating patients, other healthcare professionals, and payers on the clinical efficacy and safety of HER2-targeted therapy, as well as their potential to extend life-saving treatment to patients with HER2-positive breast cancer. ■

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