BIOSIMILARS

Addressing Oncologists' Gaps in the Use of Biosimilar Products

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Introduction

The availability of biosimilar products may improve access to healthcare by increasing the number of therapeutic options available at potentially lower costs.[1] As of April 2019, 18 such biological products had been approved by the FDA, including 4 biosimilars for trastuzumab, 3 each for infliximab and adalimumab, 2 each for pegfilgrastim and filgrastim, and 1 each for rituximab, epoetin alfa, bevacizumab, and etanercept. The pace of approvals has accelerated, from the first indication for a filgrastim biosimilar in 2015 to 3 approvals in 2016, 5 in 2017, and 9 through early 2019, 7 of which were announced in the 2018 calendar year.

According to a current market forecast, global sales of biosimilars will exceed $19 billion by 2023, up from just $2.5 billion in 2017, driven by their cost-effectiveness and the patent expiration of a number of biologics.[2] These products present substantial opportunities for cost savings, with one recent modeling analysis indicating an estimated 5-year US cost savings of $256 million for use of biosimilar filgrastims in patients with cancer requiring myelosuppressive chemotherapy.[3]

Physicians, pharmacists, and other healthcare providers are likely the most important stakeholders for biosimilar acceptance[4] and are expected to play a key role in their uptake.[5] In practice, however, there are few clinical practice guidelines to direct the use of biosimilars, and their introduction has been met with optimism and skepticism as clinicians ponder the efficacy, safety, and interchangeability of these products compared with their biologic originator drugs.

Clinicians appeared wary of prescribing biosimilars, according to the results of a 2018 survey from PricewaterhouseCoopers' Health Research Institute: 55% reported being unfamiliar with biosimilars and 35% reported never prescribing biosimilars.[6] In an earlier survey, Molinari and colleagues found that physicians, particularly those in the United States, lacked technical knowledge and understanding of the effects of biologics and biosimilars sharing the same nonproprietary name.[7] Another survey found that 30% of physicians would not prescribe a biosimilar to a treatment-naïve patient, assuming similar efficacy and safety, and given their current state of knowledge.[5] Barriers to prescribing among reluctant hematologists and oncologists include mistrust, issues with manufacture, and insufficient data.[8]

There is a growing consensus that educating healthcare providers on biosimilars may improve understanding of the products and instill confidence in their use.[4,9] The American Society of Clinical Oncology (ASCO) said in a 2018 statement that continuous provider education on biosimilars is "critical to inform, promote, and use biosimilar products in a medically appropriate and cost-effective way to treat cancer."[10] Examples of such efforts, according to ASCO, may include webcasts, online practice guidelines, social media updates, and educational sessions at scientific meetings.

Aim

Continuing medical education (CME) has been shown to improve clinician performance and patient health, with more positive outcomes seen in programs that include features such as interactivity or multiple methods of education.[11] Accordingly, we developed and deployed live and online expert-led, interactive CME-certified activities with the goal of better preparing medical oncologists, hematologists, nurses, pharmacists, and other clinicians to incorporate biosimilars into the treatment paradigm for patients with cancer. We hypothesized that these activities would help improve the ability of clinicians to assess the risks and benefits of biosimilars and to mitigate barriers to their adoption in clinical practice.

Methods

We developed a CME-certified educational initiative, "From Biologics to Biosimilars in Oncology Practice: A New Source of Value," intended for medical oncologists, hematologists, nurses, pharmacists, and other clinicians involved in the care of patients with cancer. The program consisted of a live series of meetings and an online course based on the same educational content. Three live meetings were held in conjunction with ASCO state/regional meetings that took place between September 15, 2017, and July 13, 2018. The online course was available for CME credit between December 22, 2017, and December 22, 2018. The program was reviewed and accredited by the Accreditation Council for Continuing Medical Education but was not reviewed by an institutional review board.

The format for both the live and online activities consisted of a slide-based lecture with interactive multiple-choice questions developed in collaboration with a steering committee including Gary H. Lyman, MD, MPH, of the Fred Hutchinson Cancer Research Center, Seattle, Washington, and first author of the aforementioned ASCO biosimilars statement[10]; and Jeffrey Crawford, MD, of Duke Cancer Institute, Durham, North Carolina. The online activity was also presented by Drs. Lyman and Crawford. The live meetings, which took place in Harrisburg, Pennsylvania; Newark, Delaware; and Miami, Florida; were presented by Gary I. Cohen, MD, of Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, Maryland.

The activities were developed within the framework of Moore's conceptual model for planning and assessing continuous learning for physicians.[12] Specifically, the activity addressed Moore's levels 1 (participant demographics), 2 (participant's assessments of educational activities), 3 (knowledge acquisition and attitude change), 4 (competence), and 5 (performance).

A standardized evaluation tool was used to characterize participant demographics, satisfaction, perception of bias, perception of enhanced clinical effectiveness, and overall assessment of activity format and any educational materials provided. Assessment also included attitude, confidence, practice, and barrier questions (open-ended, multiple choice, or Likert scale). Barriers to the use of biosimilars in managing patients with cancer were rated by participants using a Likert scale of 1 (not a barrier) to 5 (extreme barrier). We considered major barriers to be the proportion of learners choosing 4 or 5 on the scale.

To measure change from baseline to postactivity knowledge, multiple-choice questions were developed and posed to participants at the live event through interactive web-based polling technology for the online course. To measure the impact of the education, each question was posed twice: once before exposure to the education and once immediately after exposure. Live activity participants were invited to complete an electronic follow-up survey including the same questions, at 6 to 8 weeks after the event, in order to measure knowledge retention over time. Each of the questions corresponded to 1 learning objective in order to measure change in (1) understanding of the biosimilar approval process, (2) awareness of currently approved biosimilars, and (3) familiarity with the evidence supporting approval of a trastuzumab biosimilar. For the live activity, these questions were incorporated into the content, while for the online activity, they were administered as standard online pre- and postactivity surveys.

Statistical Analysis

Data management, extraction, and statistical analyses were performed using Educational Trak (Educational Measures, 2003, Centennial,

Colorado). Because all questions were not answered by every attendee before and after the activity and upon follow-up, the preactivity, postactivity, and follow-up data were compared as independent samples (*t* test). Significant differences between the responses to the pretest and posttest and follow-up were assessed at $P < .05$.

Effect-size calculations using Cohen's *d* were performed to measure the magnitude of the difference in scores between pretest responders (ie, naïve to the education) and posttest responders (ie received the education). Results are expressed as the percentage of nonoverlap between those 2 measures, with higher percentages (eg, increasing proportion of correct answers in the posttest group) reflecting more effective education. A measure of patient impact was also calculated by extrapolating these results to the broader pool of participants for the live and online activities. Effect size was calculated on randomly selected unmatched responses from 30 participants for the regional meetings on randomly selected matched responses from 50 participants for the web course.

Results

Demographics

A total of 9599 individuals participated in the activities, including 114 at the regional meetings and 9485 in the web course. Attendees at the live meetings were predominantly physicians (MD/DO, 66%; 14%, NP/PA; 12%, RN/BSN; 9%, pharmacist), while the web course participants were predominantly nurses (RN/BSN, 58%; MD/DO, 17%; 17%, pharmacist; 6%, NP/PA; 2%, other).

Physicians attending the live meetings were predominately oncologists (76%) and hematologists (11%), have been in practice more than 10 years, and see more than 25 patients with cancer per month. Web course participants reported their specialty as hematology/oncology (10%), primary care (45%), surgery (27%) and other (19%); have been in practice more than 10 years (57%); and see at least 1 patient with cancer per month (69%).

Impact on Knowledge, Competence, and Attitudes

Following completion of the activity, significantly more participants understood the level of evidence needed for biosimilars to be approved by the FDA (**Table 1**), representing 68% and 66% absolute increases among live meeting and web course attendees, respectively. The 10% of regional meeting attendees prior to the activity who understood that for FDA approval, a biosimilar must demonstrate no clinically meaningful differences with the reference biologic in terms of safety, purity, and potency, indicates the level of unfamiliarity with the biosimilar process among community oncologists.

In the pretest, participants were most likely to underestimate the number of FDA-approved biosimilars when asked to specify a range (**Table 2**). The number of participants correctly selecting 6 to 15 approved products (as of November 2018) increased 36% in the live meetings and 56% in the web course ($P < .05$) for both comparisons).

The proportion of participants with correct knowledge about the details of a specific biosimilar approval increased significantly as a result of the activity (**Table 3**). In the pretest, only about one-third knew that in a comparison trial of patients with ERBB2 (HER2)-positive metastatic breast cancer, the biosimilar MYL-1401O (trastuzumab-dkst) demonstrated comparable immunogenicity, pharmacokinetics, safety, and efficacy to trastuzumab.[13] Almost all live meeting participants knew this evidence following the activity. Among web course participants recognition of this evidence increased 45% ($P < .05$).

In aggregate, scores on these practice impact questions improved from 22% in the pretest to 78% in the posttest, with similar trends seen in the web course (23% to 78%) and the regional live meetings (27% to 81%), and 47% in the follow-up survey.

Self-reported familiarity with the biosimilar approval process increased from 21% at baseline to 69% immediately following the activity, while confidence in utilizing biosimilars increased from 25% to 36% in pre- and postactivity measurements.

Barriers to Optimal Patient Outcomes

None of the 6 barriers to the use of biosimilars that were queried were rated as major barriers by most participants. Institutional or formulary restrictions were most often cited as a major barrier (15%), followed by patient reluctance to use biosimilars (12%), lack of familiarity with the biosimilar approval process (12%), lack of efficacy data (11%), lack of safety data (11%), and other, including lack of time, cost of therapies, and insurance (10%). In written comments captured as part of the activity evaluations, one participant said, "I use biosimilars for my kidney transplant population. Have a lot of insurance approval barriers though efficacy is there."

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COA Releases Biosimilars Position Statement

Kelly Davio

THE COMMUNITY ONCOLOGY ALLIANCE (COA) recently released a position statement[1] about biosimilars, saying it will work with stakeholders to support the acceptance of biosimilars and to close knowledge gaps, given the burdensome cost of cancer care.

The statement comes from COA's Biosimilars Committee, which was formed in January[2] to begin educating oncologists and to assess the prevalence of biosimilars in the current market as an appropriate treatment option.

COA said it will work with manufacturers of biologics and biosimilars to reduce the cost of care, improve access, and reduce financial toxicities while continuing to provide logistical support for innovation in cancer treatment.

US total spending on cancer care has increased from $27 billion in 1990 to $124 billion in 2010, with a projection of around $174 billion by 2020, the organization said; this increase will happen across all phases of care.

Besides higher spending on cancer care, the other piece that is different from years ago is that patients are shouldering an increasing share of these rising costs as health plans restructure benefits to include high-deductible health plans that shift costs to beneficiaries. The financial consequences can be devastating to patients and families.

The fastest-growing drug classes within oncology are biologics, accounting for more than 40% of US oncology spending. Sales figures in 2015 for 3 of the top 20 global products—bevacizumab, rituximab, and trastuzumab, all of which have FDA-approved but not-yet-launched biosimilars—were $6.2 billion, $6.3 billion, and $5.6 billion, respectively.

In addition, the increased prevalence of cancer, earlier treatment initiation, and improved patient outcomes all contribute to the growing use of oncology and supportive care biologic agents, as well as the overall high cost of cancer care.

By 2020, a range of biosimilars for biologic agents used in oncology treatment are expected to receive FDA approval.

COA cited Congressional Budget Office (CBO) estimates that the sales-weighted market average discount on biosimilars would be 20% to 25% relative to reference agents in the first year. In the fourth year, the CBO estimates this would reach about 40%. The RAND Corporation estimates that savings to the US healthcare system resulting from the use of biosimilars over biologics range from an estimated $13 billion to $66 billion over the 10-year period between 2014 and 2024.

The organization also cited the role that biosimilars will play in value-based care models, such as the Oncology Care Model and the Medicare Shared Savings Program.

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Table 1. Lack of Knowledge of Biosimilar Approval Process

For FDA approval, a biosimilar must demonstrate:	Live Meetings		Web Course	
	Pretest (n = 41)	Posttest (n = 36)	Pretest (n = 5712)	Posttest (n = 5940)
No clinically meaningful differences with the reference biologic in terms of structure, safety, purity, and potency	15%	3%	35%	5%
No clinically meaningful differences with the reference biologic in terms of structure, safety, purity, potency, and efficacy	17%	8%	36%	8%
No clinically meaningful differences with the reference biologic in terms of safety, purity, and potency	**10%**	**78%[a]**	**15%**	**81%[a]**
No clinically meaningful differences with the reference biologic in terms of safety, purity, potency, and efficacy	59%	11%	14%	7%

The best evidence-based response is bolded.
[a]Indicates a statistically significant difference ($P < .05$).

Table 2. Current State of Approved Biosimilars

How many biosimilar products are currently approved by the FDA for use?[a]	Live Meetings		Web Course	
	Pretest (n = 53)	Posttest (n = 54)	Pretest (n = 5712)	Posttest (n = 5940)
a. 1-5	49%	24%	43%	2%
b. 6-15	34%	70%[b]	36%	92%[b]
c. 16-25	**8%**	**4%**	**16%**	**3%**
d. 26-35	9%	2%	5%	3%

The best evidence-based response is bolded.
[a]As of November 2018.
[b]Indicates a statistically significant difference ($P < .05$).

Table 3. Lack of Knowledge of Clinical Evidence Supporting the Use of a Trastuzumab Biosimilar

In comparison clinical trials of patients with ERBB+ breast cancer, the biosimilar MYL-041A demonstrated:	Live Meetings		Web Course	
	Pretest (n = 50)	Posttest (n = 47)	Pretest (n = 5712)	Posttest (n = 5939)
a. Comparable immunogenicity to trastuzumab	0%	0%	32%	3%
b. Comparable immunogenicity and PK profile to trastuzumab	6%	0%	29%	6%
c. Comparable immunogenicity and PK and safety profiles to trastuzumab	58%	4%	22%	29%
d. Comparable immunogenicity, PK and safety profiles, and efficacy to trastuzumab	**36%**	**96%[a]**	**17%**	**62%[a]**

The best evidence-based response is bolded.
ERBB+ indicates cancer tissue positive for the c-erbB tyrosine kinase; PK, pharmacokinetics.
[a]Indicates a statistically significant difference ($P < .05$).

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However, any projected cost savings depend on how biosimilars are embraced and used. Numerous surveys have found a lack of awareness about biosimilars among providers.

Patient education is also key to increasing acceptance of biosimilars, COA notes.

The authors of the COA statement are Kashyap Patel, MD, a practicing medical oncologist at Carolina Blood and Cancer Care in South Carolina, chair of the COA Biosimilars Committee, and an advisory board member for The Center for Biosimilars® and the associate editor for Evidence-Based Oncology; Edward "Randy" Broun, MD; Leslie "Les" Busby, MD; Steve D'Amato, BScPharm; Marsha DeVita, NP; Michael Diaz, MD; Kathy Oubre, MS; Bob Phelan; William "Bud" Pierce, MD; and Jeff Vacirca, MD, FACP.

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2. DiGrande S. Community Oncology Alliance forms biosimilars committee aimed at educating providers. *The Center for Biosimilars®* website. centerforbiosimilars.com/news/community-oncology-alliance-forms-biosimilars-committee-aimed-at-educating-providers. Published January 7, 2019. Accessed April 16, 2019.

Effect Size and Patient Impact

For the regional meetings, there was a large effect size, based on a 73.1% nonoverlap between scores measured at baseline and at the end of the activity. Based on these results, it is estimated that the 114 clinicians who participated in the activity are 73.1% more likely to deliver evidence-based care for cancer, positively affecting the care of patients seen during 2641 visits each month. Similarly, the web course was associated with a large effect size, with 81.1% nonoverlap between pretest and posttest scores. It is estimated that the 9485 clinicians who participated in the activity are 81.1% more likely to deliver evidence-based care for cancer, positively affecting the care of patients seen during 55,345 visits each month.

Discussion

Results of this study reinforce the lack of knowledge, competence, and confidence among oncologists and other healthcare providers regarding biosimilars and suggest that education improved clinician understanding of the biosimilar approval process, awareness of currently approved products, and familiarity with evidence supporting approved biosimilar products. Similarly, self-reported measures of confidence and commitment to change practice were positively impacted by increased confidence in using biosimilars in practice and a strong commitment to engage patients in decision making regarding biosimilars. Finally, effect size analyses suggested an increased likelihood that participants would deliver evidence-based care with regard to biosimilars in patients with cancer.

In particular, familiarity with the biosimilar process improved 3-fold, from 21% preactivity to 69% postactivity, while confidence in using biosimilars increased a relative 44%, from 25% preactivity to 36% postactivity) in these learners, many of whom had been in practice for 10 years or more

Table 4. Perceptions Regarding Biosimilar Products

A. Familiarity With the Biosimilar Approval Process

How familiar are you with the approval process for biosimilars	Pretest (n = 5768)	Posttest (n = 5176)
a. Not familiar	48%	12%
b. Slightly familiar	31%	19%
c. Familiar	15%	37%
d. Very familiar	5%	22%
e. Expert	1%	10%

B. Confidence in Using Biosimilars

How confident are you in utilizing biosimilars in practice?	Pretest (n = 5763)	Posttest (n = 5177)
a. Not confident	46%	22%
b. Slightly confident	28%	41%
c. Confident	19%	29%
d. Very confident	5%	6%
e. Expert	1%	1%

Perceptions regarding biosimilar products: a) familiarity with the biosimilar approval process and b) confidence in using biosimilars. The best evidence-based response is bolded.

and reported seeing a substantial number of patients with cancer each month, particularly when considering live meeting attendees.

Interestingly, most participants did not perceive lack of evidence, patient reluctance, or formulary restrictions as major barriers to using biosimilars. However, barriers to practice should be further evaluated as biosimilars become more prevalent in clinical practice and clinicians have more experience navigating institutional, insurance, or patient-related issues that could present impediments to appropriate biosimilar prescribing.

It is also worth noting that although familiarity with the biosimilar approval process increased significantly, only a small rise in confidence in using biosimilars was observed, suggesting that healthcare providers remain somewhat hesitant to integrate biosimilars into practice. This further suggests that additional exposures to biosimilar education in this specific learner group should result in even greater uptake of knowledge, comprehension, and competence, based on educational literature.[14]

Study Limitations

These findings should be viewed in light of some limitations that are common in evaluation of CME-certified activities. We utilized a quasi-experimental design (ie, a nonrandomized intervention study with a comparison of pre- and postactivity groups), to quantify education-related change. The 3 specific pre-post questions evaluated are considered surrogate markers of educational uptake within specific domains of learning, as opposed to a more comprehensive multiquestion examination that many clinicians would find impractical in the context of their participation in a CME activity. Finally, the improvements in clinician confidence are based on self-reported data and thus need to be interpreted with caution—although the results of this particular study are consistent with education delivered in other domains of oncology that have produced encouraging results with regard to confidence and change.

Conclusions

These interactive live and online CME-certified activities improved measures of clinician knowledge and competence regarding their understanding of the biosimilar approval process, awareness of approved biosimilar products, and recognition of safety and efficacy data supporting the approval of a trastuzumab biosimilar. Moreover, participants reported greater confidence in biosimilars and a commitment to change practice following participation in a biosimilar-focused educational activity. However, the postactivity level of confidence in using biosimilars suggests further education is needed in this rapidly moving field to ensure that clinicians have the knowledge and competence they need to appropriately use newly approved biosimilars and to stay informed on the evolving approval process and regulations regarding these products. ◆

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