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Academic oncology clinicians' understanding of biosimilars and information needed before prescribing

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Abstract

Background: With increasing numbers of oncology biosimilars in the approval pipeline, it is important to investigate oncology clinicians' understanding of biosimilars and what information they need prior to adoption.

Methods: Between January and May 2018, 77 oncology clinicians (52 physicians, 16 pharmacists, and 9 advanced practice providers) completed a survey covering three domains: clinician understanding, prescription preferences, and patient involvement. An in-depth interview was designed based on themes identified in the first 50 surveys: cost, safety and efficacy, patient preference, and disease stage. Participants were chosen to participate in the interview based on outlying responses to survey questions.

Results: When asked to define a biosimilar, 74% (57/77) of respondents could not give a satisfactory definition, and 40.3% (31/77) considered a biosimilar the same as a generic drug. The most important factor in biosimilar prescription was safety and efficacy (4.51 out of 5) followed closely by cost differences (4.34 out of 5). A 40% increase (53.2–94.8%) in clinicians' prescribing likelihood was seen after a biosimilar is designated as interchangeable. Participants in this study were split regarding the importance of shared decision-making with patients [50.7% (39/77) important or extremely important, 39.0% (30/77) somewhat or not at all important]. Clinicians were also split concerning the role that pharmacists should play in the decision to prescribe or substitute biosimilars.

Conclusion: Understanding of biosimilars is low, and educational needs are high. The information that clinicians deem important to assess, such as safety, efficacy and cost, will need to be provided before they are comfortable prescribing biosimilars.

Keywords: biosimilar, breast cancer, colon cancer, colorectal cancer, lung cancer, monoclonal antibody

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Introduction

On 14 September 2017, the United States Food and Drug Administration (US FDA) approved bevacizumab-awwb, a biosimilar to Avastin® (Genentech, South San Francisco, CA, USA), making it the first antineoplastic biosimilar to be approved.[1] This was quickly followed by a second approval on 1 December 2017 for a biosimilar to Herceptin® (Genentech), trastuzumab-dkst.[2] Biosimilars are defined by the US FDA as an 'agent that has biologically similar properties to US FDA-approved biologics.'[3,4] Biosimilars are not considered generic products, because the term generic is reserved for exact chemical copies of small molecule drugs.[5] Unlike generics, which are chemically created to be bioequivalent, biologics are proteins that are produced *via* recombinant DNA to mimic the effects of currently approved biologics, but this does not result in the creation of identical products.[3] Minor differences are allowed

in inactive components as long as no clinically meaningful differences exist between the proposed biosimilar and the reference product with regard to safety, purity, and potency.[6]

While the exact data requirements are determined on a product-specific basis, the US FDA does provide guidelines for obtaining sufficient data to demonstrate biosimilarity. Sponsors can compare the proteins' primary structures, higher order structures, enzymatic posttranslational modifications, and/or other potential variations or intentional chemical modifications.[7] They can also run comparative analyses of the pharmacologic activity, such as human pharmacokinetic (PK) and pharmacodynamic (PD) studies, using *in vitro* or *in vivo* functional assays.[7] Clinical trials, may be considered in further support to demonstrate biosimilarity, but are not required if pharmacologic data are deemed sufficient. The US FDA uses a totality-of-the-evidence approach when evaluating a sponsor's demonstration of biosimilarity and recommends that sponsors use a stepwise approach when developing evidence for biosimilarity.[7,8]

The financial burden on healthcare systems, especially for the treatment of cancer, has been increasing at a rapid rate around the world. The oncology drug market is expected to reach US $111.9 billion by 2020, while the estimated total financial burden of prescription medications was already US $1.2 trillion worldwide at the end of 2016.[9,10] The three highest grossing biologics in cancer treatment, trastuzumab, bevacizumab, and rituximab, accounted for US $19.1 billion in sales worldwide in 2015.[11] The expectation is that biosimilars will be priced lower than their respective reference drugs, thus lowering healthcare costs. Some have argued, though, that the savings are likely to be less than predicated, based on current pricing, rebates, and payment structures.[12–14]

Biosimilars have gained more market share in Europe, and as of May 2018, the European Medicines Agency (EMA) has approved 41 biosimilars, including 10 for cancer.[15] The first anticancer biosimilar approved by the EMA was a biosimilar for rituximab in February 2017.[16] European researchers have also conducted studies into the concerns and understanding of biosimilars among patients and physicians.[17–20] Studies by Peyrin-Biroulett and Jacobs concluded that there is a need for patient education; while Hemmington and O'Callaghan determined that medical specialists are generally familiar with terminology and hold positive attitudes, but would need guidance on how to explain biosimilars to patients.[17–20] The study conducted by O'Callaghan also found that the majority of physicians opposed pharmacist-led substitution of biological medicines, but some thought it could be appropriate if agreed to in advance.[20] A similar study conducted in Lebanon and other Middle Eastern and North African countries found that the majority of participants were aware of biosimilars 77/117 (54.8%), but only 48 of the 77 (62%) have a sophisticated understanding of them.[21] Again, more education is needed.

Overall, three prior studies have assessed clinicians' perceptions and knowledge of biosimilars in the US.[6,12,22] Of these, two were conducted prior to oncology biosimilar approval, and found a lack of provider knowledge and a need for continuing pharmacovigilance and for education about the approval process, safety profiles, and what constitutes interchangeability.[6,22] A third report, which polled community oncologists after the approval of the first two oncology biosimilars, also found that more education was needed before they would prescribe biosimilars.[12] The American Society of Clinical Oncology recently released a statement emphasizing that prescribers should always be consulted before a pharmacist substitutes a biosimilar for a reference product,[23] and a recent article argues that the successful introduction of biosimilars into the clinic will depend in part on clinician and patient education and confidence.[24]

With an increasing number of biosimilars in the approval pipeline in the US, it is important to extend the past research and assess the understanding and views of academic oncology clinicians, including oncologists, pharmacists and advanced practice providers. This study aimed to investigate oncology clinicians' understanding of biosimilars and the information and data they deem important to assess before prescribing them.

Methods

Between January and May 2018, oncology clinicians who practice at a single academic healthcare system in the US were contacted to complete a survey regarding their understanding of oncology biosimilars and perceptions regarding their use. The 12 question survey, based on previous research conducted on biosimilars,[6,17–20,22] covered three domains: clinician understanding (questions 1–5), prescription preferences (questions 6–9, 12) and

how/if patients should be involved (questions 10–11). A total of six demographic questions were appended (refer to Table 3 for the 12 survey questions).

The survey was cognitively tested with three non-oncology clinicians knowledgeable about biosimilar use. The survey could be completed online *via* SurveyMonkey (SurveyMonkey Inc., Palo Alto, CA, USA; www.surveymonkey.com) or in hard-copy form. A definition of 'biosimilar' was provided after the five knowledge questions, to inform the remaining opinion questions. Both formats were completed in two steps, before and after the definition of biosimilar, so that knowledge questions were not influenced by the definition.

After the survey was completed by 50 participants, the research team performed descriptive analyses of the responses to identify themes in which there was wide variability. An in-depth interview was then designed based on the identified themes: cost, safety and efficacy, patient preference, and disease stage. Interview guides were interactive and included open-ended probes to further elicit participants' views. The in-depth interview was cognitively tested with two experts in qualitative research and revised. Questions were added to the interviews as new topics were introduced by clinicians. The interviews were conducted by two trained interviewers, JC and MM. In-depth interview participants were chosen based on outlying responses to questions regarding the four themes. Recruitment continued until saturation was reached with no new information, codes, or themes noted.[25] The study was approved by the Emory University Institutional Review Board (#IRB00100513). The surveys were accompanied by an information sheet explaining the study and consent was documented by completion of the survey. Written consent was obtained for the in-depth interviews.

Analyses

The open-ended definition of 'biosimilar' was scored from 0 to 4 with one point given for mentioning each of the following components provided by RDH: a biosimilar is biologic, is manufactured differently from the reference product, has similar efficacy and safety, and has the same mechanism of action. For question 4, naming one or two of the cancers for which a biosimilar is approved was scored as partially correct, naming all three was scored as correct and naming a cancer with no approved biosimilar resulted in an incorrect score. A composite understanding score was created to summarize the five questions in the first domain. Each of the five questions were re-scaled to a score of 0 to 1, where 0 demonstrated poor and 1 demonstrated good understanding (Table 1).

These scores were then summed such that the maximum composite score was 5 and minimum was 0. The importance questions (colleague and expert opinion, cost differences, safety and efficacy, PK similarities, chemical/physical) were evaluated on a scale of 1 (not important) to 5 (very important), with the mean score for each question determined. Clinician characteristics captured included sex, profession, age ($\leqslant$44, $\geqslant$45), and clinical experience (0–10 years, $>$10 years). Descriptive statistics were reported for each variable. Categorical biosimilar variables were compared across clinician characteristics using Chi-squared tests or Fisher's exact tests, where appropriate. Numeric biosimilar variables such as the composite score and the importance scores were compared across clinician characteristics using analysis of variance. Differences in level of importance (1 to 5) between questions (cost *versus* safety and efficacy, for example) were evaluated using a mixed model, with a subject-specific random intercept. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and statistical significance was assessed at the 0.05 level.

The qualitative interviews were audio-recorded and transcribed verbatim. *A priori* codes were based on the four themes identified from the surveys. Inductive codes were generated independently by three investigators (JC, MM, RDP) by reviewing four interviews. The three investigators compared codes and created a final code book. The interviews were then qualitatively coded in MAXqda (VERBI GmbH, Berlin, Germany; http://www.maxqda.com/) by JC using multi-level semantic content analysis.[26] One third of the interviews were randomly chosen and independently double coded by MM. Discrepancies (n = 27) between the two coders were resolved by consensus.

Results

A total of 98 oncology clinicians were contacted for the survey. Of these, 6 started but did not complete the online survey, 1 refused due to maternity leave, and 14 could not be reached for

Table 1. Scaling for composite score.

Question	Score
1. Familiarity	Extremely familiar = 1
	Moderately familiar = 0.75
	Somewhat familiar = 0.5
	Slightly familiar = 0.25
	Not at all familiar = 0
2. Definition of biosimilar	Satisfactory (2, 3 or 4 of the definition components) = 1
	Unsatisfactory (0 or 1 of the definition components) = 0
3. True/false	True = 1
	False = 0
4. Cancers approved for	Correct = 1
	Partially correct = 0.5
	Incorrect = 0
5. What biosimilar must demonstrate to be an interchangeable:	Correct = 1
	Incorrect = 0

a total of 77 participants and a response rate of 78.6% (77/98). A total of 56 completed the survey online and 21 in paper form. Table 2 lists the participant demographics.

The majority of survey participants stated that they were moderately to somewhat familiar with current developments in oncology biosimilars. Analysis of the open-ended definitions found that 57 (74%) participants could identify only one or none of the components of the definition, with only one participant's definition including all four components. An example of a definition receiving a 0 was 'almost identical version of an original drug' and 'no idea'. The best definition we received was 'a biological product that has same biologic/therapeutic activity as a licensed product but differs in manufacturing or structure'. The definition given to the participants for the true/false question was that of a generic; however, 31 (40.3%) of respondents incorrectly chose true. Overall, 21 (28.4%) participants correctly selected at least 1 of the current indications (lung, renal, and colorectal) and 48 (62.3%) correctly identified safety and efficacy as the single requirement that a biosimilar must meet to become interchangeable. The mean composite understanding score of all participants was 2.02 (minimum 0.05; maximum 3.50).

When asked about their likelihood of biosimilar use in the clinic, 41 (53.2%) selected likely or highly likely, and 73 (94.8%) would prescribe an interchangeable biosimilar to patients. The most important factor in deciding to use a biosimilar was safety and efficacy (4.51 out of 5), followed closely by cost differences (4.34 out of 5). PK similarities, colleague and expert opinion, and chemical/physical characteristics were all considered less important than safety and efficacy ($p < 0.001$). As one participant stated, 'I think knowing the background and, I guess, the research support and the mechanism of action of the drug and they have similar adverse effect profiles and that sort of the confidence that there's not going to be a major difference between that and branded drug.' Another interviewee said, 'Preservation of efficacy is going to be important and the second thing is it should be economically a more appealing option.'

Table 2. Survey participant demographics.

Survey participants demographics (*n* = 77)		
	N	**%**
Sex		
Male	47	61.0%
Female	30	39.0%
Profession		
Physician	52	67.5%
Pharmacist	16	20.8%
Advanced practice provider	9	11.7%
Ethnicity		
White	52	67.5%
Latino or Hispanic	2	2.6%
Black or African American	7	9.1%
Native American	1	1.3%
Asian/Pacific Islander	10	13.0%
Other	5	6.5%
Age		
25–34	21	27.3%
35–44	21	27.3%
45–54	22	28.6%
55–64	10	13.0%
65–74	3	3.9%
Years of clinical experience		
0–5	17	27.0%
6–10	20	31.7%
11–15	15	23.8%
16–20	11	17.5%
20+	14	22.2%
Primary oncology clinic		
Brain	7	9.1%
Breast	7	9.1%
Gastrointestinal	8	10.4%

(Continued)

Table 2. (Continued)

Survey participants demographics (n = 77)		
	N	**%**
Genitourinary	7	9.1%
Head and neck	5	6.5%
Melanoma	5	6.5%
Lung	5	6.5%
Myeloma	4	5.2%
Lymphoma	8	10.4%
Leukemia	5	6.5%
Stem cell transplant and cellular therapy	3	3.9%
Other hematology	4	5.2%
Other (5 general oncology, 2 phase 1, 1 sarcoma, 1 resident)	9	11.7%

Saturation of themes was reached with 15 in-depth interviews. Interview participants were representative of all survey respondents and included all three professions.
Responses to all questions can be found in Table 3.

Statistical analyses found that respondents who were younger (p = .005) or had less experience (p = .007) considered colleague and expert opinion more important. Younger (p = .041) and less experienced (p = .014) also thought safety and efficacy were more important than their older, more experienced colleagues. On the flip side, those who were older with more years of experience tended to get the true/false question correct more frequently (p = .056; not statistically significant), though they did not do better on the other understanding questions. No other significant correlations were found.

Participants did not show any difference in confidence in prescribing biosimilars to more and less medically complicated patients, with 31 (40.3%) somewhat confident for the uncomplicated patient and 29 (37.7%) somewhat confident for the complicated patient. However, for both patients, about one third said they were undecided about whether they would prescribe biosimilars [24 (31.2%) and 22 (28.6%), respectively]. Clinicians were split on the importance of disclosing to patients that they were being prescribed a biosimilar. A total of 36 (46.8%) indicated that it was important or extremely important, while 33 (42.9%) believed that it was somewhat or not at all important. This trend was seen to a lesser degree regarding sharing decision-making with patients. Overall, 39 participants (50.6%) said it is important or extremely important, while 30 (39.0%) believed that it was somewhat or not at all important. One participant said in an in-depth interview, 'I think that it is always the patient's choice when it comes to what they do.' This view was not shared among all interviewees: 'I think if you give a patient a choice, it's hard for them to fully understand the implications of the choice.'

Clinicians were asked during the in-depth interview what role they felt pharmacists should play in prescribing biosimilars. A total of 10 believed that pharmacists should be involved in the decision-making process, but the pharmacist should never make the decision alone. One provider said, 'That [decision] should be a prospective decision made by the group not an *ad hoc* decision made by the pharmacist.' Another participant stated, 'The pharmacist could make the decision with the understanding of the team approach, you know informing the patient as well as the physician before making the final decision.' A total of seven providers stated specifically that pharmacists should not act unilaterally or outside of the provider's approval: 'Not that they can't, it's that they don't have the background to make those decisions.'

Table 3. Survey questions and responses.

	Answers	Percentage
Question 1		
Please rate your overall familiarity with developments in biosimilars in oncology		
Extremely familiar	3	3.9%
Moderately familiar	31	40.3%
Somewhat familiar	26	33.8%
Slightly familiar	10	13.0%
Not at all familiar	7	9.1%
Question 2		
A biosimilar is: _____		
None of the 4 components of a correct definition mentioned	34	44.2%
1 component	23	29.9%
2 components	17	22.1%
3 components	2	2.6%
4 components	1	1.3%
Question 3		
A biosimilar agent has the same chemical structure and manufacturing process as the reference brand name agent		
True	31	40.3%
False	46	59.7%
Question 4		
Biosimilars are currently approved for the treatment of which of the following cancers? (Bone, pancreatic, **lung*, kidney*, colorectal***, liver)		
Incorrect	53	71.6%
Partially correct	13	17.6%
Correct	8	10.8%
Missing	3	
Question 5		
What must a biosimilar demonstrate in order to be given the designation of being interchangeable by the US FDA?		
a. It must have the same amino acid sequence as reference drug b. ***It can be alternated with reference product with no change in safety or efficacy** c. The cost must be similar to the reference drug d. It is given the designation by the US FDA when approved as a biosimilar		
Incorrect	29	37.7%
Correct	48	62.3%

(Continued)

Table 3. (Continued)

	Answers	Percentage
Question 6		
Once approved by the US FDA, what is the likelihood you will use biosimilars in your practice setting?		
Highly likely	15	19.5%
Likely	26	33.8%
Somewhat likely	13	16.9%
Not likely	8	10.4%
Never	15	19.5%
Question 7		

As more information on biosimilars becomes available, how important are the following types of information in helping you decide to use biosimilar products? (1 = not important 5 = very important)

	Colleague and expert opinion	Cost differences	Safety and efficacy	Pharmacokinetic similarities	Chemical/physical similarities
Mean	3.69	4.34	4.51	3.92	3.40

Question 8		
Situation 1: Patient is a 54-year-old woman with stage 2 HER2-positive breast cancer. No history of other medical problems except surgery to repair a medial malleolus fracture while in high school. She will receive adjuvant therapy		
How confident are you in using a biosimilar rather than a reference biologic in this patient?		
Very confident	9	11.7%
Somewhat confident	31	40.3%
Not very confident	10	13.0%
Never switch	3	3.9%
Undecided	24	31.2%
Question 9		
Situation 2: Patient is a 65-year-old female with relapsed stage 3 (now stage 4) breast cancer. She has an extensive history of medical problems including, high blood pressure, diabetes, and chronic renal insufficiency. She has been previously treated with surgery and adjuvant chemotherapy.		
How confident are you in using a biosimilar rather than a reference biologic in this patient?		
Very confident	10	13.0%
Somewhat confident	29	37.7%
Not very confident	14	18.2%
Never switch	2	2.6%
Undecided	22	28.6%

Table 3. (Continued)

	Answers	Percentage
Question 10		
How important is it to disclose to the patient that you are prescribing a biosimilar?		
Extremely important	15	19.5%
Important	21	27.3%
Moderately important	8	10.4%
Somewhat important	16	20.8%
Not at all important	17	22.1%
Question 11		
How important is it for the patient to participate in shared decision-making when deciding to use a biosimilar?		
Extremely important	14	18.2%
Important	25	32.5%
Moderately important	8	10.4%
Somewhat important	14	18.2%
Not at all important	16	20.8%
Question 12		
If the US FDA approved a biosimilar as an interchangeable, would you use it interchangeably with the reference brand agent?		
Yes	73	94.8%
No	4	5.2%

*Correct at time of writing.
US FDA, United States Food and Drug Administration.

Discussion

In order to introduce biosimilars into oncology care, it is important to assess both academic clinicians' current understanding of biosimilars and what data and information they need before they will prescribe biosimilars. The majority of survey participants stated that they were moderately to somewhat familiar with the current developments in oncology biosimilars. However, only 20 (26.0%) participants could give a satisfactory definition of a biosimilar and 31 (40.3%) participants thought incorrectly that a biosimilar is the same as a generic drug. We found, as did previous studies, that oncologists require more education regarding biosimilars before they are extensively introduced into a clinical setting.[6,12,21,22]

Our data also suggest that there is a disconnect between what the US FDA and academic clinicians deem most important before a biosimilar is approved and used in a clinical setting. In the guidelines for approval, the US FDA states that data demonstrating biosimilarity may be derived solely from analyses of the pharmacologic activity, such as human PK and PD studies.[7] Additional studies, including clinical studies, are not required if pharmacologic data are deemed sufficient. Hence, the approval process laid out by the US FDA does not make it mandatory for clinical trials to be conducted on biosimilars prior to approval. Our data show that academic clinicians place the greatest amount of importance on data showing the safety and efficacy of the drugs when deciding whether or not to prescribe biosimilars. When we probed in the in-depth interviews about what information was most important to demonstrate safety and efficacy, the most frequently mentioned factor was US FDA approval (interestingly regulatory

approval by the US FDA or EMA and established safety and efficacy were also most important in the Middle East[21]) followed by clinical trials and then real-world data. Even though the US FDA does not require clinical trial data, to date some phase III clinical data have been submitted for the approved biosimilars, though the studies are relatively small in size and number and do not cover all indications of use. Clinicians' who judge that the clinical trial data are crucial will need to be astute in analyzing the smaller trials and appropriately extrapolating the available data to other indications. PK similarities between the biosimilar and reference were not judged by our participants to be as important as other information.

One clinician stated in the in-depth interviews that 'I'll be honest with you in the ideal world the thing that would keep me from prescribing it would be lack of clinical efficacy. Just the pharmacokinetic data isn't enough… having good pharmacokinetic data and good clinical outcomes that we think are reasonable endpoints, I don't have a problem with that. I do have a problem if there is no good clinical data.' With this is mind; pharmacovigilance will be of the utmost importance after approval in order to quell any concerns that clinicians may have regarding the safety and efficacy of biosimilars

More data on safety and efficacy of biosimilars could have an impact on the frequency with which biosimilars are prescribed. There was almost a 40% increase (53.2–94.8%) in clinicians' likelihood of prescription after a biosimilar is designated as an interchangeable, a designation that requires that the biosimilar demonstrate the same safety and efficacy as the reference drug using clinical data. Clinical data could be the most important information that companies produce in order for clinicians to be comfortable using these new drugs in clinic. This increase in clinical data could also increase conformability of prescribing biosimilars to patients with various comorbidities and medical history. In both the survey and the in-depth interviews, clinicians expressed that they are currently undecided about prescribing biosimilars to patients with varying and complex medical histories. An increase in data regarding safety and efficacy could decrease the amount of uncertainty that clinicians have towards prescribing this new class of drugs.

As biosimilars begin to be used more frequently in clinics it will be important to understand the roles that each member of the decision-making team plays. Participants in this study were split (46.8% important or extremely important, 42.9% somewhat or not at all important) regarding the role that patients should play in the decision process and how much information the patients should be given about the use of biosimilars. As seen in the study conducted by O'Callaghan, clinicians views varied on the roles that they feel pharmacists should play.[20] In the in-depth interviews, 10 responded that pharmacists should be involved in the decision-making process, and 7 stated that the pharmacist should never make the decision alone, while 4 said their primary role was to answer patients' questions. While these sentiments may change as additional information becomes available and education increases, it will be important for physicians to rely on pharmacists and their knowledge of these new drugs as these drugs begin to be prescribed. It will also be important to educate patients on their current treatments' especially when switching them to new agents and regimens.

There are some limitations to this study. It is to be expected that hospitals and insurance companies will play a central and pivotal role in the use of biosimilars and patients' and clinicians' access to them. This role and the place of cost in determining the frequency of biosimilar prescription is outside the scope of this study. Additionally, this study was conducted at a single academic institution, which limited the number of respondents and the generalizability of the findings. Expanding this research to assess the views of other professions, such as nursing, is a future goal.

Conclusion

This study provides an overview of academic oncology clinicians' current understanding of biosimilars and the data and information they deem important to assess before prescribing them. Currently, understanding of biosimilars is low, and the need for education regarding biosimilars is high. The data that clinicians deem important to assess, such as demonstration of safety and efficacy and cost, will need to be provided before clinicians will comfortably prescribe biosimilars to their patients.

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R. Donald Harvey is a consultant for Genentech, South San Francisco, CA, USA.

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