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RESEARCH ARTICLE

THE KNOWLEDGE, OPINIONS, ATTITUDES OF PHYSICIANS ABOUT BIOSIMILAR DRUGS: A UNIVERSITY HOSPITAL DATA

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ABSTRACT

Purpose: To evaluate the knowledge, opinions and prescribing attitudes of physicians working in an university hospital about biosimilar drugs and analyse the factors affect these parameters.
Methods: In this descriptive, cross-sectional study, data was collected using a questionnaire consisting of 5 sections and 41 questions evaluating the knowledge, opinions and prescribing attitudes of physicians about biosimilar drugs. Descriptive statistics was used to report the findings; relationship between dependent and independent variables were examined using the t-test for parametric data, and Mann Whitney U and Kruskall Wallis analysis for nonparametric data. P <0.05 was considered statistically significant.
Results: Questionnaire response rate was 61.9% (n=114). Physicians mean knowledge score about biosimilar drugs was 7.6 ± 2.5 out of 14 points. Have heard the concept the biosimilar drug, had training towards biosimilar drugs and high academic level were increased the mean knowledge score. Of the respondents, 45.2% of the physicians stated that biosimilar drugs are not as effective as biological reference drugs, and 35.9% thought that they aren't safe. More than half of the physicians (56.6%) stated that they did not hesitate to prescribe biosimilar drugs.
Conclusions: Physicians' general knowledge level on biosimilar drugs was low and they had doubts about the efficacy and safety of biosimilar drugs. This might be related with lack of knowledge. Therefore structured training programmes related in this area, might increase the knowledge level and might positively affect physicians' opinions and attitudes on biosimilar drugs

Keywords: Biosimilar drug, level of knowledge, opinion, attitude, pyhsicians

INTRODUCTION

Biosimilar drugs (BSD) are defined by the World Health Organization as biotherapeutic products similar in quality, safety and efficacy to biological reference drugs (BRD) manufactured or extracted from a biological source. BSDs are popular products all over the world in terms of their potential to reduce health expenditures to low levels (1). All biotechnological drugs, including BRDs and BSDs, have great differences from chemical drugs produced by chemical synthesis because their molecules are large and their structures are very complex. The main differences of biotechnological drugs from chemical drugs are that the production technologies are complex, the risks of immunogenicity are high, the product produced in each batch is not exactly the same as the other. In addition, BRDs with high production and development costs are very expensive and place a significant burden on the health economy. Therefore, it is important in terms of health economics that the BSDs of BRDs whose licenses have expired, reduce the cost, albeit to some extent (2).

BSDs are also used in the treatment of many diseases and are frequently prescribed by different specialties in medicine such as internal medicine, dermatology, neurology, oncology. In various studies investigating the knowledge level and/or awareness of physicians regarding the concept of BSDs, it was found that the physicians who are frequently used biological drugs have heard of the concept of BSD, but their knowledge on BSD is low. The BSD is a product with clinical effects similar to the original product on any patient and that can be replaced with the original reference product but it is reported that the physicians do not trust BSDs sufficiently, and they think that BSDs are not structurally identical to the BRD. Additionaly physicians think BSDs may be insufficient also in terms of efficacy and safety (3,4). It is of great importance to follow and implement innovations by physicians in health. Therefore, in this study, we aimed to determine the knowledge, opinions and attitudes of physicians working in departments that prescribe the BSDs that are comparatively new products introduced in the late twentieth century and evaluate the factors affect these parameters.

MATERIALS AND METHODS

In this descriptive and cross-sectional research; the data were collected through a questionnaire from physicians working in Internal Medicine, Cardiology, Dermatology, Chest Diseases, Neurology, Physical Therapy and Rehabilitation Departments who frequently prescribe BSDs in a University Hospital. Questionnaire has been applied to the physicians between September 2018-May 2019. The study was started after the approval of Dokuz Eylul University Ethics Committee for Non-Interventional Research (Date: 07.06.2018, Number:2018/14-14) and conducted in line with the principles of the Declaration of Helsinki.

At the time of the study conducted, there were 184 physicians working in departments that prescribe BSDs frequently in the university hospital. The sample was not selected and it was aimed to reach all physicians. Physicians who could not be reached during the first visit were tried to be reached in their own study areas three more times at different times. Physicians who read the information text at the beginning of the questionnaire and give verbal consent and answer the questions were included in the study. Fifty four (29.3%) of the physicians did not want to participate in the study, and 16 (8.6%) of them could not be reached despite three visits.

The questionnaire which formed of five parts and 41 questions was prepared according to published articles related the topic (5). In the first part, physicians' demographics and professional characteristics (12 questions), in the second part, BSD knowledge (14 questions), in the third part, physicians' opinions about BSDs (6 questions), in the fourth part, BSD prescribing attitudes of the physicians (5 questions) and in the fifth part, physicians' BSD prescription status, replacement BRD with its biosimilar, experiencing adverse reaction (AR) or ineffectiveness due to BSD, and reportation this status to the National Pharmacovigilance Center (4 questions) were questioned.

The knowledge level was determined by questioning the definition of BSDs, production technologies, indications of BSDs, clinical trials and ARs of them with true /false /no idea options. The correct answers were evaluated as 1 point, false and no idea answers

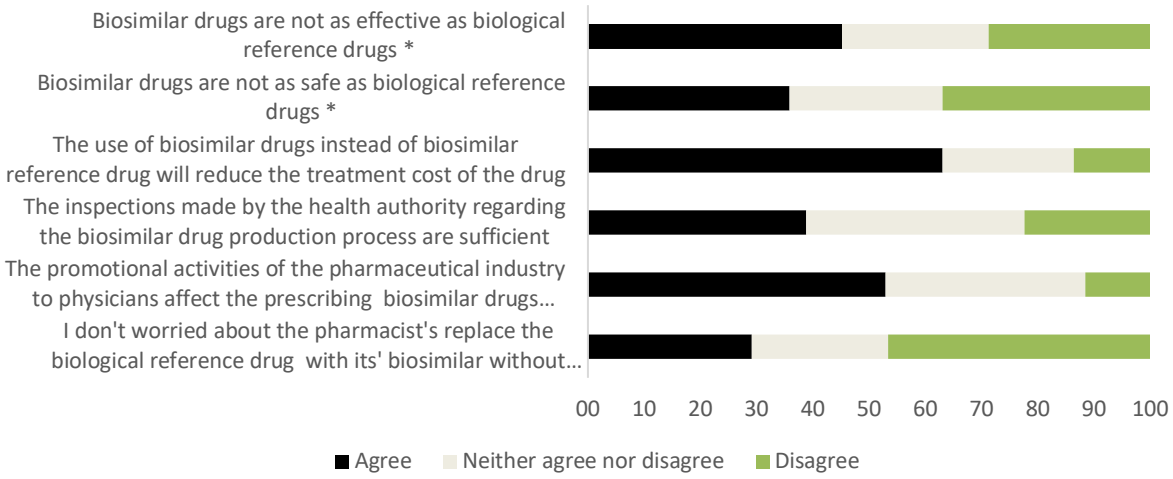

Figure 1. Physicians opinions about biosimilar drugs * negative expression

were evaluated 0 points, and the maximum possible score for physicians who answered all questions correctly was 14. Physicians' opinions on BSDs and their attitudes towards biosimilar prescribing were also questioned with a 5-point Likert scale (strongly agree, partially agree, undecided, disagree, strongly disagree). The answers were combined and evaluated in three groups as "agree/undecided/disagree".

Statistical analysis

Descriptive data were presented as numbers(n) and percentages (%) for categorical variables and as means and standard deviations (mean± SD) for continuous variables. The level of knowledge was the dependent variable of the study, and the independent variables were demographic characteristics of the physicians. The relationship between dependent and independent variables were examined using the t-test for parametric data, and Mann Whitney U and Kruskall Wallis analysis for nonparametric data. The data were analyzed with Statistical Package for the Social Sciences (SPSS-24,SPSS INC. Chicago, IL, USA). P <0.05 was considered statistically significant.

RESULTS

Questionnaires answered by 114 physicians (69.1%) who volunteered to participate in the study were evaluated. The proportion of male physicians was 52.6%, the average age of all physicians was 31.9±9.3 (25-63) and most of the physicians (69.3%) were in research assistant in medicine. The rate of physicians in internal medicine was 71.9%. Of all physcians, 86.8% had a professional experience in their area of 1-2 years. Most of the physicians (94.7%) had heard about the concept of BSD. The rate of physicians trained in BSDs was 21.9%. Seventy-two percent of the physicians were stated the prescription number was between 1-20 a day (Table 1).

Knowledge level of physicians on BSDs

The correct response rates of physicians to the questions asked about BSDs were varied between 2.8% and 89.9%. The rate of correct answers to questions asked by physicians about the definition of BSDs, production technologies and BSDs' ARs were quite high (between 52.3% and 85.3%), but the rate of correct answers to questions on clinical trials of BSDs were low (between 2.8% and 34.9%) (Table 2). The mean knowledge score calculated considering the correct answers given to answers to 14 questions related BSDs was 7.6±2.5. The mean knowledge score of the physicians who heard the concept of BSD was (7.9±1.9) significantly high compared to those who did not hear the concept of BSD (2.5±3.9) (p=0.002). Similarly, the mean knowledge score of the physicians' who received training on BSDs (8.7±1.4) were significantly higher than those who did not receive education (7.3±2.6) (p=0.024). Mean knowledge score of the lecturer and consultant physcians (8.3±1.6) were higher compared to research assistant in medicine (7.2±2.7) (p=0.010) (Table 3).

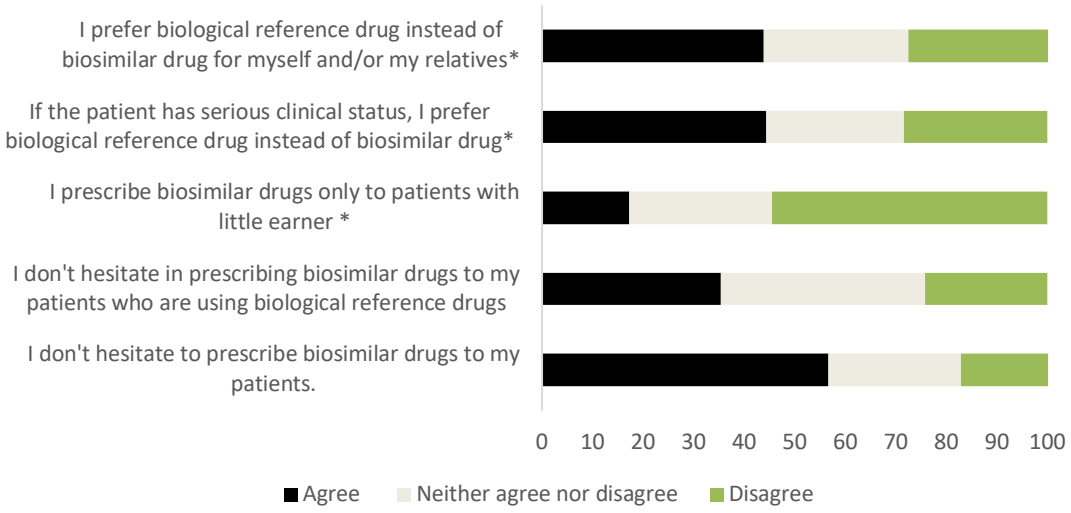

Figure 2. Physicians attitutes about prescribing biosimilar drugs * negative expression

Physicians' opinions on BSDs

Nearly half of the physicians (45.2%) had been thought that BSDs were not as effective as the BRDs, and less than half of them (35.9%) thought that they were not as safe as BRDs. Most of the physicians (63.3%) opinion was the choice of BSDs instead of BRD were decreased the cost of the treatments.

Approximately half of the physicians (52.9%) thought that the the promotional activities of the pharmaceutical industry in BSDs to physicians have been a positive effect about BSD prescribing. About one third of the physicians (38.8%) thought that the controls made by the health authority related the BSD production were sufficient. The rate of physicians who agreed with the statement “I don't worried about the pharmacist's replace the BRD with its' biosimilar without consult to physician” was quite low (29.1%) (Figure 1).

Physicians' prescribing attitudes on BSDs

More than half of the physicians (56.6%) stated that they did not hesitate to prescribe BSDs. The rate of physician who stated that not to hesitate prescribing BSDs to their patients who are using BRD was 35.4%. The majority of the physicians (54.5%) did not agree with the statement of the BSD prescribing for patients with low income. The proportion of physicians who preferred BRDs for themselves and/or their relatives in case of serious condition of the patient was 44.3% and 43.9%, respectively (Figure 2).

Physicians' BSD prescribing and AR or ineffectiveness reportation situation

Most of the physicians (76.2%) were declared that, they prescribe BSDs, less than half of the physicians (33.0%) were declared that they replace the BRD with its’ biosimilar. The rate of experience in AR and ineffectiveness related BSDs were 12.2% (n=12) and 7.2% (n=7), respectively. One of the physicians' (14.3%) who declared that observe AR related BSD and one of the physicians' (8.4%) who declared that observe ineffectiveness related BSD had reported to the situation to National Pharmacovigilance Center.

DISCUSSION

In this study, it was evaluated the knowledge, opinions, and attitudes of physicians’ related BSDs. It was concluded that the physicians’ who were in specialty areas prescribing BSDs were not sufficiently knowledgeable about BSDs and the number of physicians who think that BSDs are effective and safe is quite low.

The physicians’ who frequently prescribe BSDs were young and their professional experience was about one or two years. This finding was consistent with the fact that most of the physicians participating in the questionnaire were research assistant in medicine. Although physicians working in fields that frequently prescribe BSDs have heard about the concept of BSD substantially, the rate of those who received training on BSD was quite low. In fact that the low rate of physicians who received training on BSDs suggests

that it is inevitable that physicians' knowledge about BSDs is also limited.Only half of the physicians were able to correctly answered the question related description of BSD. In studies with similar design and conducted in England and Russia physicians were defined BSDs correctly 72% and 46%, respectively (6,7). In this study, although the rate of physicians who correctly define BSD was lower than stated in some studies in the literature, it was within the limits reported. Difference in defining BSD by the physicians in different studies may be related the training status of them. The rate of true answers of the physicians' about the questions related production technologies, indications and ARs of BSDs were more than fifty percent. But the rates of true answers of the physicians' about the efficacy, cost of the BSDs, and the possibility that pharmacist can give BSD instead of BRD were quite low. All these data suggesting that although physicians correctly define BSDs, they do not have detailed information. Low knowledge level of physicians' about BSDs was compatible with majority of them not to receive on training on this subject like reported in the literature (5, 8, 9).

Table 1. Demographic characteristics of the physicians

n=114	**n (%)**
Gender	
Female	54 (47.4)
Male	60 (52.6)
Academic level	
Lecturer	20 (17.5)
Consultant physician	15 (13.2)
Research assistant in medicine	79 (69.3)
Departments	
Internal medicine	82 (71.9)
Cardiology	9 (7.9)
Dermatology	8 (7.0)
Physical Therapy and Rehabilitation	7 (6.1)
Chest disease	4 (3.5)
Neurology	4 (3.5)
Professional experience (year)	
1-2	99 (86.8)
≥ 3	15 (13.2)
Hearing the concept of biosimilar drugs	
Yes	107 (94.7)
No	6 (5.3)
Training status in biosimilar drugs	
Yes	25 (21.9)
No	88 (77.1)
Number of prescriptions per day	
1-20	75 (72.1)
≥21	29 (27.9)

Clinical trials of BSDs are conducted at the end of the patent expiry of the biologic reference drug. There is no study comparing the knowledge level of physicians related clinical trials of BSDs. However, in studies investigating the knowledge level of physicians on clinical research; it is obvious that physicians have a lack of knowledge about clinical research (10,11). Therefore, it is an expected result that the rate of correct answers to three questions asked about the conduction of BSDs' clinical trials is low. This situation was presented for the first time with the data.

Although it was determined that to hear the concept of BSD, receiving training on BSDs and academic level were increased the general knowledge of the physicians' about BSDs, even so still their level of knowledge was not very high. The reason of this may be that although the rate of physicians' who hear the concept of BSD was high, the rate of physicians who have received training on this subject is quite low. The knowledge level of physicians about BSDs does not differ according to age, gender, professional experience, number of daily prescriptions, and knowledge level was higher in physcians' received training on BSDs shows the importance of education (7). Therefore it is important to getting lessons on BSDs in both the Faculty of Medicine education and in the residency education for the physicians who prescribe BSDs, in order to eliminate the lack of knowledge.

In the opinions of the physicians' about BSDs, in terms of efficacy nearly half of the physcians' and in terms of safety almost one third of the physcians' had negative and undecided approaches to BSDs. Compatible with these findings, 55% of the physicians working in the Lombardy region in Italy thought that BSDs were less effective and less safe. While 63% of physicians working in different branches in the United States of America (USA) thought that biosimilars were as effective as BRDs, 57% of physicians thought that biosimilars were caused similar ARs like BRDs (5,12). In contrast with these findings, 15.9% of hematologists and oncologists in Tunisia had an opinion that BSDs are less effective and safe than BRDs(13). Most of the physicians in this study agreed that the use of BSDs would reduce the cost of treatment like previosly reported in different studies (5,14). It is known that biosimilars, which are located on the market after the patent of the BRD is expired, have reduce treatment costs and allow patients to access treatment easily (15,16). Physicians participating in this study were substantially aware of

Table 2. The frequency of correct response to each knowledge question and the mean knowledge level score of the physicians'

Biosimilar drug definition and production technologies	True answer	n (%)
Biosimilar drug is a product manufactured or extracted from a biological source (n=109)	T	57 (52.3)
Biosimilar drug has high level of similarity with the reference licensed biological drug (n=109)	F	93 (85.3)
In order for the biosimilar drug to be produced, the license of the biological reference drug must be expired (n=108)	T	63 (58.3)
Production technologies of biosimilar drugs are simple (n=107)	F	67 (62.6)
A biosimilar drug is a copy of the licensed biological reference drug (n=108)	F	81 (75.0)
Knowledge level score (mean±SD)	3.4±1.3	
Indications of biosimilar drugs		
The biosimilar drug is used for the same indication as the licensed biological reference drug which get referenced (n=109)	T	98 (89.9)
A biosimilar drug is as effective as a licensed biological reference drug in the treatment of diseases (n=109)	T	20 (18.3)
Knowledge level score (mean±SD)	1.1±0.5	
Clinical trials of biosimilar products		
In clinical trials of biosimilar drugs, it is necessary to prove that they are bioequivalent with the biological drug (n=108)	F	3 (2.8)
During the development of the biosimilar drug, it is mandatory to conduct all clinical trials (Phase I-Phase II-Phase III) as with the reference biological drug (n=109).	F	38 (34.9)
Phase III clinical trials of biosimilar drugs are conducted separately for each indication they will be used (n=107)	F	15 (14.0)
Knowledge level score (mean±SD)	0.5±0.7	
Adverse reactions of biosimilar drugs		
Biosimilar drugs are also have risk in terms of immunogenicity like biological reference drugs (n=108).	T	81 (75.0)
All adverse reactions associated with biosimilar drugs should be reported to the National Pharmacovigilance Center (n=108).	T	92 (85.2)
Knowledge level score (mean±SD)	1.6±0.7	
Other		
Biosimilar drugs are more expensive than biological reference drugs (n=109)	F	69 (63.3)
The pharmacist may, on her/his own initiative, give biosimilar drug instead of biological reference drug (n=114)	T	34 (29.8)
Knowledge level score (mean±SD)	0.9±0.8	
Total knowledge level score (mean±SD)	7.6±2.5	

this situation. Less than half of the physicians thought that the audits made by the health authority regarding the BSD production process were adequate. It is known that the adequacy of the audits, the guidance of the health authorities on the biosimilar product and the pharmacovigilance data studies increased the trust of the physicians in the BSD (17). Therefore conducting of evidence- based clinical studies on BSDs, implement new policies and training by the Ministry of Health to physicians might be important to increase the trust to the BSDs.

In this study, the rate of physicians who were not worried about the pharmacist's own initiative to replace the BRD prescribed by the physician with its'biosimilar was low. Mostly, physicians are of the opinion that the pharmacist should consult the

physician when replacing the BRD with its biosimilar in similar studies (9, 18).

Pharmacists should inform physicians about the replacement of the BRD, prescribed in eight states in the USA, with its biosimilar. In Europe, this situation is specific to each country and there are different practices(19). When all these data are evaluated together, although it may be deemed reasonable for physicians to be worried about the replacement of BRD with BSD, it should be kept in mind that physicians have limited knowledge about the BSDs.

In this study, more than half of the physicians stated that they did not hesitate to prescribe BSDs. In a study conducted in Canada, this rate was around 90% (20). Contrary, in a study conducted in the USA, physicians declared that they had a concern about BSD, and replace reference BRDs to its biosimilars may be dangerous because of the BRDs are not structurally identical with their biosimilars (5). Approximately 20% of physicians were agreed with the statement that "I prescription BSDs for patients with low income levels", this suggests that the cost may play a role in the physicians' preference of BSDs in the group we studied.

Table 3. The mean knowledge score of the physicians according to demographic, professional and educational characteristics.

	Knowledge score (Mean±SD)	p
Gender		
Female (n=48)	7.4 ± 2.3	0.420ǂ
Male (n=53)	7.8 ± 2.7	
Professional experience (year)		
1-2 (n=87)	7.4±2.6	0.189*
≥ 3 (n=14)	8.4±1.7	
Academic level		
Lecturer and consultant physician (n=33)	8.3±1.6	**0.010ǂ**
Research assistant in medicine (n=68)	7.2±2.7	
Hearing the concept of biosimilar drugs		
Yes (n=95)	7.9**±**1.9	**0.002***
No (n=6)	2.5**±**3.9	
Training status in biosimilar drugs		
Yes (n=22)	8.7**±**1.4	**0.024***
No (n=79)	7.3±2.6	
Number of prescriptions per day		
1-20 (n=65)	7.7±2.2	0.188ǂ
≥ 21 (n=26)	7.0±2.8	

*:Mann Whitney U; ǂ:Student' t test

However, the BSD preference was lower when the seriously ill patients or when the question of using biosimilar medicines for themselves or their relatives was questioned. This situation suggests that physicians still approach with BSDs hesistantly and may be related with lack of training on BSDs.

Three quarters of the physicians were found to prescribe BSD, nearly 30% of them were replaced BRD with its BSD in this study. The rate of BSD prescription of physicians' in various studies are nearly 50% (21, 22). According to our findings, although physicians were hesitate the use of BSDs, they prescribed BSDs in high rate. This may be related the low cost of BSDs. The rate of physicians who observed ineffectiveness or ARs due to BSD was nearly 10%. But, the rate of physicians notifiying national pharmacovigilance center in case of ineffectiveness or AR was very low. Although this data based on the statements of physicians this finding may support that biosimilars do not cause ineffective or frequent ARs as thought. There are also studies reporting that BSDs are as effective as BRDs being compatible with this finding but future studies are needed on this subject (23,24). BSDs are included in the list of drugs subject to additional monitoring and the observed ARs and ineffectiveness must be unconditionally reported. These notifications are of great importance in order to update information on drugs. The majority of the physicians answered the question asked about reporting ARs related to BSDs correctly. The reason for the low rate of AR reporting may be the timelessness.

CONCLUSION

Physicians correctly answered the questions asked about the definition of BSDs, indications, ARs and costs in highly. On the other hand, the rate of correct answers to the questions asked about clinical trials of BSDs and the pharmacist replacing the BRD with its BSD and the general knowledge levels of physicians on BSDs was low. Additionally, physicians have doubts about the efficacy and safety of BSDs and this might be related with lack of knowledge. Education of the physicians on BSDs has the potential to positively affect their opinions and attitudes about prescribing BSDs. The fact that sufficient knowledge about BSDs of physicians may cause them to use the BSDs in their daily routines. As a consequence common use of BSDs might be decrease the health expenditures because of their lower costs than BRDs.

Limitations

The research universe consists of physicians working in the departments of Internal Medicine, Cardiology, Dermatology, Chest Diseases, Neurology, Physical Therapy and Rehabilitation in a university hospital in a city, so generalization cannot be made to all physicians. Since the number of physicians in different departments is low, evaluation couldn't made according to the departments. At the same time, the fact that the participation rate is around 60% may have affected the physician representation in the relevant departments.

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Conflict of interest: There is no conflict of interest
Ethical approval: The study was approved by Dokuz Eylul University Ethics Committee for Non-Interventional Research (Date: 07.06.2018, Number: 2018/14-14).
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