〔短　　報〕

Evaluating Injector Preferences for Biosimilar Insulin Preparations

インスリン製剤におけるバイオシミラーの適正な選択方法の検討

Atsushi Ishimura*[a], Sayaka Okayasu[a], Yutaka Shimizu[b]
石村　淳*[a]，岡安　彩佳[a]，清水　裕[b]

[a] Department of Clinical Pharmacy, Nihon Pharmaceutical University
[b] Pharmaceutical department, Sainokuni Higashiomiya Medical Center
[a] 日本薬科大学薬学科臨床薬学分野
[b] 彩の国東大宮メディカルセンター薬剤部

Received December 2, 2021
Accepted January 17, 2022

Summary: Biosimilars, which are insulin preparations used for the treatment of diabetes, were launched successively, starting with insulin glargine in 2015, to help curb medical expenses. Since the manufacturers and distributors of biological products and biosimilars are different, it may be necessary to acquire new procedures due to changes in syringes. Thus, along with reduction in medical costs, syringe operability is also equally important. To promote appropriate biosimilars, we investigated the usage status of biosimilars and the operability issues associated with changes in insulin injectors.
As a result, in FY2019, the usage rate of biosimilars was 45.5%, and for individuals of the age of 20s to 40s, the usage rate of biosimilars exceeded that of the biological products. To assess the operability of the insulin injector, an injector similar to that currently used for treatment was selected, particularly in patients with chronic use of insulin. Therefore, when switching to biosimilars, it may be preferable to focus on curbing medical expenses for young people who have a short history of insulin use. However, for elderly patients with chronic insulin use, along with medical expenses, it is important to select a drug, considering an injector that is similar to the injector in use. This is required to ensure accurate self-injection even after switching to biosimilars.

Key words: insulin therapy, biosimilars, insulin injector, operability

要旨：糖尿病の薬物治療に用いられるインスリン製剤のバイオシミラーは，医療費の抑制に寄与するために，2015年のインスリングラルギンを皮切りに次々と発売された．先行バイオ医薬品とバイオシミラーでは，製造販売業者が異なるため注入器の変更が伴い，新たな手技の獲得が必要となることがあるため，医療費削減だけでなく注入器の操作性も重要である．そこで，適切なバイオシミラーの推進を目的に，バイオシミラーの使用状況とインスリン注入器の変更に伴う操作性の調査を行った．
その結果，2019年度では，バイオシミラーの使用率は45.5%となり，20歳代から40歳代までは，バイオシミラーの使用率が先行バイオ医薬品を上回っていた．また，インスリン注入器の操作性では，特にインスリン使用歴が長い患者において，現在，治療で使用中の注入器と類似性のある注入器を選択することが明らかとなった．したがって，バイオシミラーに変更する場合，インスリン使用歴の短い若年層には医療費の抑制を中心に考えて良い可能性がある．しかし，インスリン使用歴の長い高齢層が，変更後も正確な自己注射を実践するためには，医療費だけでなく，使用中の注入器と同様の注入器を考慮した薬剤を選択することが重要であると考えられた．

キーワード：インスリン療法，バイオシミラー，インスリン注入器，操作性

* 〒362-0806 埼玉県北足立郡伊奈町小室10281
TEL：048-721-1155
E-mail：atsushiishimura@nichiyaku.ac.jp

Introduction

For the treatment of diabetes, diet, exercise, and

drugs are used to maintain blood sugar levels within an appropriate range. Intensive insulin therapy, which is a typical drug-based treatment for diabetes, involves frequent injections of multiple insulin preparations, to replicate insulin secretion in a healthy individual. Insulin preparations are biotechnological drugs (biological products) and contribute significantly to modern medical care, but many of the biological products are extremely expensive, which puts pressure in terms of medical costs.

Therefore, in recent years, biosimilars are attracting attention of the same safety, and efficacy as the biological products [1]. The greatest significance of biosimilars is their contribution to the reduction in medical expenses, and the drug price is approximately 70% of the biological products. Insulin glargine, lispro, and aspart were launched in 2015, 2020, and 2021, respectively (Table 1). If only the control of medical expenses is emphasized, it would be viable to change from biological products to biosimilars. Indeed, the increased financial burden results in frequent interruption of treatment in diabetic patients [2]; thus, it is important to reduce the burden of medical expenses. In contrast, since most patients on insulin therapy self-administer insulin by injection, the quality, type, dosage accuracy, and operability of insulin preparations may affect treatment compliance and therapeutic effects. However, because the manufacturers and distributors of the biosimilars and the biological products are different, the injector may change, and it may be necessary to follow a new procedure. Thus, along with the reduction in medical costs, the operability of the injector is considered an important issue for promoting biosimilars for patients on insulin therapy.

Therefore, we investigated the operability of insulin injectors in patients with diabetes undergoing self-injection insulin therapy, using the latest biosimilars in insulin preparations. We conducted an investigation to promote the appropriate selection of biosimilars and injectors in insulin preparations.

Method

1. Survey of latest biosimilar usage in insulin preparations

Insulin glargine was investigated using open data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), published on the website of the Ministry of Health, Labor, and Welfare. The survey included biological products (Lantus® injection Solostar® and Lantus XR® Injection Solostar®) and biosimilars (insulin glargine BS injection MirioPen® "Lilly" and insulin glargine BS injection kit "FFP"). The number of injections and usage rates of the biosimilar and the biological products were calculated from the fiscal year (FY) 2014 to FY2019. Also, from the latest data of FY2019, we calculated the usage rates of biological products and their corresponding biosimilars based on the age group of patients.

Table 1　List of insulin biosimilars

Generic name	biological products	Drug price (yen)	Biosimilars	Drug price (yen)
Insulin Glargine	Lantus® Injection SoloStar®	1,685	Insulin Glargine BS Injection MirioPen® [Lilly] (Released in 2015) Insulin Glargine BS Injection Kit [FFP] (Released in 2016)	1,316
Insulin Lispro	Humalog® Injection MirioPen®	1,342	Insulin Lispro BS Injection SoloStar® HU「Sanofi」(Released in 2020)	1,203
Insulin Aspart	NovoRapid® Injection FlexTouch®	1,799	Insulin Aspart BS Injection SoloStar® NR「Sanofi」(Released in 2021)	1,418
	NovoRapid® Injection FlexPen®	1,817		
	NovoRapid® Injection InnoLet®	1,761		

(as of November 2021)

Additionally, we calculated that similar investigation at Sainokuni Higashiomiya Medical Center.

2. Investigating the operability of an insulin injector

(1) Study participants

Patients with diabetes who visited the Department of Diabetes Medicine of Sainokuni Higashiomiya Medical Center for four months, from July 20, 2021, to November 19, 2021, and who had been using a pen-type injector of Mirio Pen® (Eli Lilly: MP) or Solostar® (Sanofi: SS) for more than two months were enrolled in the study. The subjects were asked to perform a self-injection procedure using Novo Nordisk Flex Touch® (FT), Flex Pen® (FP), and Inolet® (IL). Exclusion criteria were as follows: mental or physical ineligibility, unwilling to participate, earlier history of using FT, FP, and IL, and inability to self-inject.

(2) Survey flow and survey items

The researcher explained the purpose of this research and the outline of the research in writing and verbally and obtained written informed consent. As a general rule, a survey can be used to conducted during the waiting time, until the medical examination. The participants were evaluated by an interview, and by using an independently prepared insulin injector selection confirmation table (confirmation table) (Fig.1). The confirmation table consisted of <Survey item 1>, that can be investigated from electronic

Insulin injector selection confirmation table

<Survey item 1 >
Gender : Male ・ Female
Age : ( ) years old
Disease type : Type 1 ・ Type 2 ・ Others ( )
HbA1c at the time of investigation: ( ) %
Insulin usage history： ( ) months
Insulin in use： (・)
Insulin unit： (・)
Comorbidities: Yes ・ No
[Yes ; neuropathy, retinopathy ( ) stage, nephropathy ( ) stage]

<Survey item 2>
The injection needle is not equipped with an injector
Question 1. Ease of putting on and taking off the cap ( )
Question 2. Ease of putting on and taking off the injection needle ( )
Question 3. Ease of unit setting ( )
Question 4. Easy-to-read display (number) of administration memory ( )
Question 5. Ease of hearing the sound when setting the unit ( )

The injection needle with injector
Question 6. Good stability when grasped ( )
Question 7. Ease of pressing the injection button ( )
Question 8. Difficulty of slipping of syringe during injection ( )
Question 9. Ease of understanding when the injection button is pressed all the way down ( )

Good choice
Question 10. Easy to carry and store ( )

Fig.1 Insulin injector selection confirmation table

medical record information and <Survey item 2> that the pharmacist observes and investigates. The amount of insulin in <Survey item 2> was set to the same unit as the daily dose. When basal/additional insulin was administered more than once per day, the one with the larger dose was used. The injection needle used in the survey was a BD Micro Fine Plus TM32G 4 mm needle (Becton Dickinson, Japan). The history of insulin use was calculated as 96 months (8 years) for patients who have been using electronic medical records since February 2014.

This study was approved by the Japan Pharmaceutical University Ethics Committee (approval number: Nichiyakurin 3-3) and the Higashiomiya Sainokuni Medical Center Ethics Committee (approval number: 38).

3. Analytical method

For statistical analysis, js-STARXR release 1.1.1j was used, along with unpaired Welch's t-test; the significance level was set at 5%.

Results

1. Usage of biosimilars in insulin preparations

The number of insulin glargine injections used is shown in Fig.2. In FY2014, before the launch of biosimilars, the total number of biological products was 6,525,315. In FY2015, when biosimilars were released, their usage rate was 547,223 (8.5%) out of a total of 6,448,460. Following this, the usage rate of biosimilars increased from FY2016. In FY2019, the usage rate of biosimilars was 2,776,407 (45.5%) out of a total of 6,101,489. Additionally, at the Sainokuni Higashiomiya Medical Center, the switching of biosimilars has been carried out since FY2015. In FY2019, the usage rate of biosimilars was 381 (100%) out of a total of 381 patients.

Further, Fig.3 shows the usage rate by age group in FY2019. In the age group of 20-40 years, the usage rate of biosimilars exceeded that of the biological

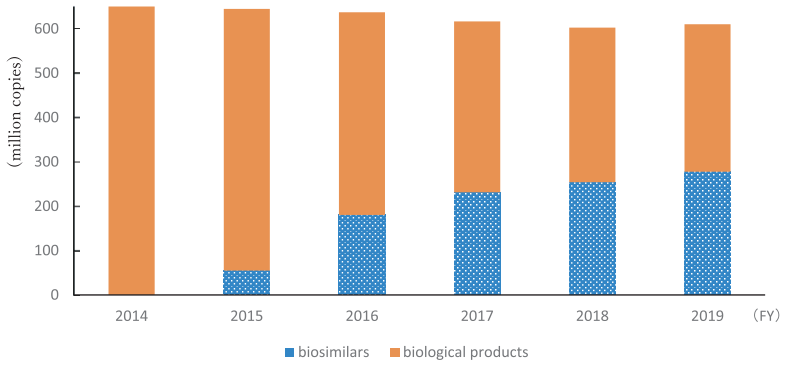

Fig.2 Usage of biosimilars for insulin preparation (insulin glargine)
FY: Fiscal year

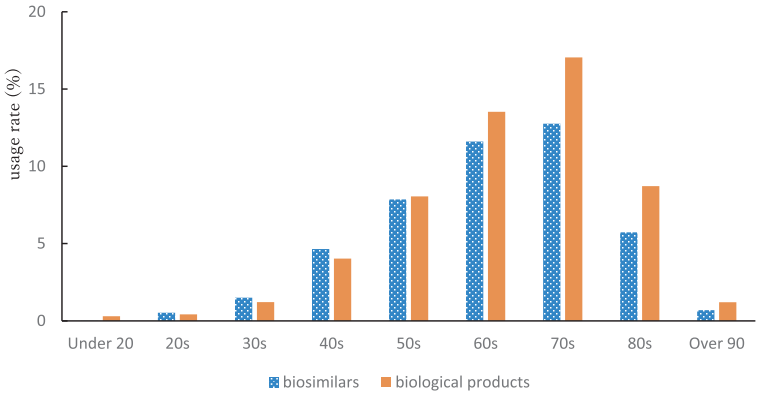

Fig.3 Usage rate of insulin glargine by age group in FY2019

products. However, after the age of 50-60 years, the predecessor biopharmaceutical exceeded the usage rate of biosimilars, and the usage rate of the biological products was the highest in individuals aged 70 years and above. Also, at Sainokuni Higashiomiya Medical Center, unlike NDB data was switched to 100% biosimilars.

2. Operability due to change of insulin injector for patients with diabetes

The survey included 83 patients with diabetes (type 1 diabetes, n=5; type 2 diabetes, n=73, other illnesses, n=5). Table 2 lists the attributes of the study participants. Table 3 shows the number of people who chose the insulin injector for each question in the confirmation table. For most of the questions, the majority of the people selected FP, except for questions 6 and 8, where FT was selected by majority of the participants. For six or more of the 10 questions, FP was the most frequently selected injector by the participants at 43 (51.8%), followed by FT 11 (13.3%), and IL 2 (2.4%). The remaining 27 (32.5%) participants chose various injectors, depending on the question.

Table 2　Background of study participants

Sex	Male：46　Female：37
Age	30s：1
	40s：4
	50s：13
	60s：22
	70s：27
	80s：16
Disease type	Type 1 diabetes：5
	Type 2 diabetes：73
	Other illnesses：5
Insulin usage history of participants	Less than 12 months：18
	12–60 months：30
	60 months or more：35
Insulin unit (Survey implementation unit)	Less than 10 credits：34
	10 credits or more：49
HbA1c at the time of investigation(%)	6.9% or less：26
	More than 7%：57
Complications	Neuropathy：13
	Omentum：19
	Nephropathy：45

(Number of people)

3. Comparison of patient backgrounds between those who chose FP and those who chose injectors other than FP

Of the 10 questions, 43 (51.8%) participants selected FP for 6 or more questions and 40 (48.2%) selected other questions, and the patient background (age, insulin usage history, insulin usage) was compared. It was observed that those who chose FP had a significantly longer history of insulin use than those who chose FP ($p<0.004$) (Table 4).

Discussion

In this study, we first examined the use of biosimilars for insulin preparations using NDB open

Table3　Number of people who chose insulin injectors for each question

	FP	FT	IL
Question 1	37	24	22
Question 2	57	24	2
Question 3	48	21	14
Question 4	38	21	24
Question 5	60	17	6
Question 6	36	40	7
Question 7	41	30	12
Question 8	29	47	7
Question 9	39	34	10
Question 10	60	14	9
Question (6/10) or more	43	11	2

FP : Flex Pen®, FT : Flex Touch®, IL : Inolet®

(Number of people)

Table 4　Comparison of patient backgrounds between those who chose FP and those who chose other injectors

	FP	Other than FP	*p-value*
Age	69.8 ± 11.3	66.8 ± 11.3	0.243
Insulin usage history	58.5 ± 33.7	36.5 ± 32.5	0.004
Insulin unit	12.9 ± 7.3	13.3 ± 10.8	0.851

(mean ± standard deviation)

data. When comparing data from FY2014, before the launch of glargine biosimilars, with the latest data in FY2019, the total number of patients initially using biosimilars was almost nil, which increased annually up to 45% by FY2019. In the younger age group (up to 40 years), the usage rate of biosimilars was higher than that in the biological products. This is because there is no difference in the time-action profile, effect, and patient blood glucose fluctuation after administration, between the biological products of insulin glargine and its biosimilar [3,4]. The data from continuous glucose monitoring confirmed these results [5]. Therefore, it could have been recommended to gradually switch to biosimilars, because these would be cheaper for young people, who have a large amount of out-of-pocket insurance, while warranting that the effect of drug changes on treatment would be small. In terms of the operability of the injector, SS of the biological products and MP of the biosimilars were also evaluated for the "ease of operability" of the injector among healthcare professionals and patients with diabetes [6], which was found to be similar. The only difference was the retention time after injection, but since the retention time of SS is 10 s or more and that of MP is 5 s or more, the retention time of the biosimilar was shorter. From this data, it could be concluded that the switch to biosimilars was encouraged as a result of the reduction of resistance to switching patients, in addition to acceptance by medical professionals for reasons such as drug efficacy, drug price, and operation method.

The number of insulin lispro and insulin aspart biosimilars released in recent years is not yet listed in the NDB open data, owing to a more recent launch. However, based on clinical practice, the switch is not progressing in a manner observed with insulin glargine. The reason may be that there is a limit to the number of days that a newly launched drug in Japan can be prescribed, but it was speculated that this was due to a different syringe change than that for insulin glargine. Unlike once-daily injection of glargine, lispro and aspart need to be administered three times daily, but the injectors for both these biosimilars are SS; thus, the post-injection retention time is longer than MP, FT, or FP. It is speculated that such changes in the injector may affect the psychological burden on the patient.

Therefore, in this study, we evaluated the effect of changing the injector on the difference in operability by making patients using MP or SS use FP, FT, and IL, which they had never used. As a result, in the comprehensive patient operability evaluation, the improved syringe (FT) was not selected, and most of them chose a syringe (FP) that has the same morphology as the in-use syringe. FP accounted for more than half of the total injections. In addition, those who chose the conventional injector (FP) had a long history of insulin use. Previous studies have compared FT with conventional injectors and reported that FT is preferred over MP or SS [7,8]. Certainly, FT has the characteristic that the length of the injector and the injection pressure do not change compared to that in MP and SS [9,10]. In addition, it is thought that the thickness and shortness of the injector can be improved, and the ease of grip can be evaluated. In the results of this study as well, FT was selected by most of the people in questions 6 and 8 of "Stability when gripped". In contrast, for questions 7 and 9 of "Easy to push", most people chose FP instead of FT. In many conventional prefilled pen type injectors such as MP and SS, the length of the injector changes when the injection button protrudes, depending on the dose setting. The force of the thumb pushes the injection button, resulting in injection of the drug solution; thus, accurate administration cannot be performed unless the injection button is pushed all the way with a force greater than the maximum injection resistance [11]. The developed FT does not protrude the injection button, and semi-automatically injects it using an internal triple spring [12], making it possible to inject the drug solution without relying on the force of the thumb [6]. However, the operation of injectors such as MP, SS, and FP has been left to the patient's own control. Therefore, the semi-automatic operation of the FT may make it difficult for the patient to understand how long the injection button should be pressed. Additionally, Japanese people inject a lower

daily dose of insulin than that by Westerners; thus, it is possible that they have less resistance to pushing out the injection button. Therefore, it can be inferred that the conventional habitual injector may be preferred over the improved injector.

Thus, when switching from biological products to biosimilars, it is expected to guarantee the quality of medical care, such as drug efficacy. When switching to biosimilars, it may be possible to focus on curbing medical expenses for young people who have a short history of insulin use. However, for elderly people with chronic insulin use, along with medical expenses, it is important to select a drug considering an injector that is similar to the injector in use, to practice accurate self-injection even after switching.

In summary, insulin injectors are used daily by diabetics, and diabetics' preferences, ease of use, and confidence in the injector can affect treatment adherence and efficacy. Therefore, for patients who have switched to biosimilars, to practice accurate self-injection, it is necessary to select an injector suitable for the patient, to allow accurate operation. We expect that the results of this survey will be useful for selecting an accurate injector.

Conflicts of Interest

The authors have no conflicts of interest to disclose concerning this article.

References

1) Takayasu Y, Tsukamoto T, Development and perspective for the biosimilar medicines, *Folia Pharmacologica Japonica*, 2016; 147: 303-9.
2) Tanaka M, Ito H, Oshikiri K, et al. Factors that hinder the characteristics and reverse referrals of diabetic patients in illness diagnosis and illness cooperation. *Practice*, 2013; 30: 641-8.
3) Blevins TC, Dahl D, Rosenstock J, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. *Diabetes, Obesity and Metabolism*, 2015; 17: 726-33.
4) Rosenstock J, Hollander P, Bhargava A, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). *Diabetes, Obesity and Metabolism*, 2015; 17: 734-41.
5) Kondo K, Kato R, Kida M, et al. Validity of CGM and examination of equivalence by comparing fluctuation of blood glucose between glargine and glargine biosimilars. *Japanese Journal of Pharmaceutical and Diabetes*, 2017; 6: 201-6.
6) Asakura T, Hyllested-Winge J, Hoshino T. Usability and preference evaluation on prefilled insulin devices: FlexTouch®, SoloSTAR® and MirioPen® among diabetic patients and health care professionals in Japan. *Japanese Journal of Pharmaceutical and Diabetes*, 2014; 3: 147-56.
7) Oyer D, Narendran P, Qvist M, et al. Ease of use and preference of a new versus widely available prefilled insulin pen assessed by people with diabetes, physicians and nurses. *Expert Opinion on Drug Delivery*, 2011; 8: 1259-69.
8) Bailey T, Thurman J, Niemeyer M, et al. Usability and preference evaluation of a prefilled insulin pen with a novel injection mechanism by people with diabetes and healthcare professionals. *Current Medical Research and Opinion*, 2011; 27: 2043-52.
9) Wielandt JO, Niemeyer M, Hansen MR, et al. An assessment of dose accuracy and injection force of a novel prefilled insulin pen: comparison with a widely used prefilled insulin pen. *Expert Opinion on Drug Delivery*, 2011; 8: 1271-6.
10) Hemmingsen H, Niemeyer M, Hansen MR, et al. A prefilled insulin pen with a novel injection mechanism and a lower injection force than other prefilled insulin pens. *Diabetes Technology and Therapeutics*, 2011; 13: 1207-11.
11) Asakura T, Seino H. Comparison of infusion resistance of commercial insulin injectors with that for infusion using special injection needles, and cautions in instructing patients on injection technique. *Iryo Yakugaku*, 2006; 32: 723-8.
12) Asakura T. Function and clinical usefulness of flextouch®, a prefilled insulin injector with a semi-automatic injection mechanism. *Progress in Medicine*, 2015; 35: 585-94.