



Recent Trends of Combined Oral Hypoglycemic Agents (OHAs) with Drug Pricing

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Abstract

Recently, novel oral hypoglycemic agent (OHA) includes imeglimin (Twymeeeg) that has similar construction with Metformin. Other agents would be combination of vildagliptin and metformin (EquMet). Both Twymeeeg and EquMet are provided twice daily (bid), where blood glucose variability can be improved for 24 hours. Japanese government and Ministry of Health, Labor and Welfare (MHLW) decides National Health Insurance (NHI) drug price for long, which is influenced by the interrelationships among MHLW, pharmaceutical companies, wholesalers, pharmacies and patients. According to NHI pricing in April 2023, EquMet is lower than Equa, which seems to be at least beneficial for diatetic patients.

Keywords: Oral hypoglycemic agent (OHA); Imeglimin (Twymeeeg); Vildagliptin and metformin (EquMet); Ministry of Health, Labor and Welfare (MHLW); National Health Insurance (NHI) drug price

Introduction

In recent years, several novel oral hypoglycemic agents (OHAs) have been introduced to clinical practice. Among them, imeglimin (Twymeeeg) that has similar molecular construction has been in topic [1,2]. On the other hand, the trend of combining existing OHAs has been gradually observed. In particular, metformin has been attracted attention, which was widely used as the first-line agent for Type 2 Diabetes (T2D) in the world. One of the combined agents would be EquMet, which is vildagliptin (Equa) and Metformin. It is the combination of DPP4-i and biguanide [3,4]. Some perspectives are described in this article.

For decades, combined OHAs presented the matter of medical costs paid by the patients. From the economic point of view, long-term policies have been found by the Ministry of Health, Labor and Welfare (MHLW) [5]. In Japan, interrelationships among several organizations are important. They are i) Japanese government - MHLW - local government in each prefecture, ii) research and sales departments of pharmaceutical companies, iii) wholesalers that distribute a variety of medical agents, iv) pharmacies often located in front of the hospital, and v) each patient. These five

organizations have mutual deep relationship. Various activities are carried out based on strict regulations such as the Pharmaceutical Affairs Law [6]. However, economic competition has been continued for actual practice. MHLW determines annual prices of medical agents which are based on the research and understanding of the development and distribution of medicine.

Table 1: Several representative OHAs in topics with pharmacological price.

Type	Oral Hypoglycemic Agent	yen / 1Tab	yen / day	remarks	
Biguanide	Metformin (Metogluco) 250mg	10.1	40.4	4 Tab for monotherapy	
	DPP4-i				
DPP4-i	Vildagliptin (Equa) 25mg	65.3	130.6	2 Tab for monotherapy	
	EquMet LD	55.7	111.4	Equa + Met 2 Tab /day	
	EquMet HD	55.0	110.0	Equa + Met 4 Tab /day	
Triazine ring					
SGLT2-i	Imeglimin (Twymeeeg)	34.4	137.6	4 Tab for monotherapy	
	GLP-1RA	Ipragliflozin L-Proline (Suglat) 25mg	120.8	120.8	once in the morning
		Canagliflozin (Canagh) 100mg	168.8	168.8	"
		empagliflozin (Jardiance) 10mg	188.9	188.9	"
		empagliflozin (Jardiance) 25mg	322.6	322.6	"
GLP-1RA	Oral semaglutide (Rybelsus) 3mg	143.2	143.2	fasting in the morning	
	Oral semaglutide (Rybelsus) 7mg	334.2	334.2	"	
	Oral semaglutide (Rybelsus) 14mg	501.3	501.3	"	

Citation: Bando H (2023). Recent Trends of Combined Oral Hypoglycemic Agents (OHAs) with Drug Pricing. SunText Rev Pharm Sci 4(1): 120.

Latest topic for OHA will be shown. The author and collaborators major in diabetes and endocrinology associated with various reports for years [7]. As to these areas, imeglimin (Twymeeeg) has attracted attention [8]. It has dual function for increasing insulin secretion and decreasing insulin resistance [9,10]. The characteristic point includes the administration of this agent for twice a day (bis in die, bid). Its suppression of blood glucose levels at night is observed more than OHA once a day (quaque die, qd) [11]. Similarly, vildagliptin (Equa) also shows benefit for better clinical efficacy by bid [12]. It was confirmed by using 24-hour blood glucose fluctuations. Then, EquMet is likely to give better glucose variability, which includes vildagliptin and metformin twice a day.

Pharmacological pricing of several representative agents will be described. In certain OHA combination drugs, the drug price usually increases as the included components increase. On the other hand, a case can be found where drug price is lower than monotherapy. This interesting example would be EquMet combination Tablets LD or HD, including vildagliptin and metformin [13]. The required drug price per tablet and per day is summarized in Table 1. Among these, Equa has the advantage of significantly lowering nocturnal blood glucose levels [12]. For impressive phenomenon, Equa alone costs 65.3 yen, followed by Equa+Metformin 250 mg = 55.70 yen and Equa+Metformin 500 mg = 55.0 yen. Then, daily required expenses will be doubled up to 130.6 yen, 111.4 yen, and 111.0 yen, respectively. Considering the exchange rate between USA and Japan, 1 dollar is equivalent to 135 Japanese yen. In social medical insurance, many Japanese people are covered about 70-90% of medical expense from government or social insurance services.

Several factors may be involved in this phenomenon. MHLW in Japan has expressed continuous concern for rapid rise in total annual medical expenditures for years [14]. As one of the countermeasures, MHLW has adopted a policy suppressing medical costs by increasing the use of generic agents rather than original agents. Among them, two types of OHA have been tried to produce combined tablet, which costs less than the total price. Annual pricing by MHLW was decided for April 2023, where the price of Metformin-Equa-EquMet was changed (Table 1) [15]. These changes of National Health Insurance (NHI) drug price were influenced by the interrelationships of the five organizations mentioned above. Therefore, it requires to check the evaluation after observing future progress. At the moment, this policy seems to be beneficial, at least in part, for patients for diabetes.

In summary, latest topics about OHA were introduced. What kind of direction does this matter develop in progress? Several types of combined OHA have been introduced into clinical practice. This may be similar to the trend towards combination of several inhalers into one for bronchial asthma. After producing some combined

OHAs, their pricing will be changed. We would pay attention to pharmacological changes in the future.

Conflict of Interest

The authors declare no conflict of interest.

Funding

There was no funding received for this paper.

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