



Latest Characteristic and Trend of Oral Hypoglycemic Agents (OHAs) With Drug Pricing

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Abstract

Some oral hypoglycemic agents (OHAs) exist for type 2 diabetes (T2D), such as metformin (Metgluco) and imeglimin (Twymeeg). For combined OHA, vildagliptin-metformin hydrochloride (EquMet) has been known for clinical effect. The Ministry of Health, Labor and Welfare (MHLW), Japan decides National Health Insurance (NHI) drug price for years. According to NHI pricing in April 2024, Metgluco as 250mg and 500mg became the same price of 10.1 Japanese Yen (JY). EquMet HD (high dose)/LD (low dose) is lower than Equa as 50.2, 51.0, and 60.6 JY, respectively. This trend comes from the MHLW policy for intending decreasing national medical expenses.

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

Commentary Article

For the treatment of type 2 diabetes (T2D), metformin has been the first-line pharmacological agent from most previous research algorithms [1]. Its characteristic points include efficacy, safety and also affordability. In addition, clinical application of monotherapy and/or concomitant usage with other OHAs would be beneficial [2]. However, recent novel OHAs have changed the situation, including glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i). Both agents indicate renoprotective and cardioprotective benefits with various evidence [3]. In comparison with metformin, SGLT-2i showed lower rate of heart failure (OR 1.51), myocardial infarct (OR 1.45) and similar event ratio for stroke (OR 1.03) [3]. Then, first-line treatment of metformin for youth-onset T2D will be suboptimal in more than half patients within 2 years [4]. From clinical evidence point of view, it may be applicable for changes of first-line agent for T2D as mentioned above. However, when considering the actual clinical practice with various factors of cost-effectiveness and drug-naïve populations of T2D, actual significance of metformin for convenient management of T2D

patients with low CV risk can remain solid in our usual medical practice [5].

Ministry of Health, Labor and Welfare (MHLW), Japan has continued medical management for long in Japan. Cost accounting system has conducted according to adding up material cost, manufacturing expenses, and so on [6]. The principle for deciding each cost for medical agent consisted from several factors. They include i) manufacturing (importing) cost such as material cost, personnel expenses, and manufacturing expenses, ii) sales cost with research cost, etc. iii) operating profit, iv) distribution cost, and v) consumption tax. Among these process, operating profit may vary drastically in the broad range of -50% to +100%. It depends on the degree of the novelty, efficacy or safety in comparison with the existing treatment so far. The determination method for drug price for the follow-on biologics. There are principles for two cases as follows: a) case of follow-on products by biotechnology. The drug price will become 0.7 multiplication of that of the original product. b) case of chemically synthesized products. The drug price will be calculated as 0.5 multiplication of that of the original product. Concerning a) and b), when the medicine is > 10 items 0.6 (for a) or 0.4 (for b) will be multiplied for the calculation [6].

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Furthermore, recent topics about drug pricing of OHA in Japan will be introduced. The first is the pricing of Metformin. Two kinds of tablets for 250mg and 500mg had different prices until March 2024. New fiscal year starts in April 2024 in Japan. Both tablets were decided to have the same cost, which is 10.1 Japanese yen for one tablet of 250mg or 500mg [7]. Its price was set at the minimum

level among all medical agents in Japan (Table 1). Metformin has been prescribed very frequently across the world. When it is provided 500mg, 1500mg, or 2250mg/day, the drug price cost would be 10.1, 30.3, 50.5 Japanese Yen (JY) per Tablet. The exchange rate would be 1 USD= about 150 JY.

Table 1: Several representative OHAs in topics with pharmacological price in 2024.

Type	Oral Hypoglycemic Agent	yen / 1Tab	yen / day	remarks
Biguanide	Metformin (Metgluco) 250mg	10.10	40.4	4 Tab for monotherapy
	Metformin (Metgluco) 500mg	10.10	20.2	2 Tab for monotherapy
DPP4-i	Vildagliptin (Equa) 25mg	60.60	121.2	2 Tab for monotherapy
	EquMet LD	51.00	112.0	Equa + Met 2 Tab /day
	EquMet HD	50.20	100.4	Equa + Met 4 Tab /day
Triazine ring	Imeglimin (Twymeeg)	34.10	136.4	4 Tab for monotherapy
SGLT2-i	Ipragliflozin L-Proline (Suglat) 25mg	113.90	113.9	once in the morning
	Canagliflozin (Canaglu) 100mg	158.50	158.5	''
	empagliflozin (Jardiance) 10mg	188.90	188.9	''
	empagliflozin (Jardiance) 25mg	322.60	322.6	''
GLP-1RA	Oral semaglutide (Rybelsus) 3mg	139.60	139.6	fasting in the morning
	Oral semaglutide (Rybelsus) 7mg	325.70	325.7	''
	Oral semaglutide (Rybelsus) 14mg	488.50	488.5	''

The second is the pricing of combined OHA of vildagliptin (Equa) and metformin (Metgluco). The brand names are Equmet LD (low dose) and EquMet HD (high dose) [8]. Thus, there are several types of vildagliptin/metformin related agents, which are Equa, EquMet LD, and Equmet HD [9]. The impressive fact will be presented in Table 1 [7]. As the contained medical agents increases, the drug price decreases. Although this policy is rare, certain purpose may exist from administrative and pharmaceutical law. Monotherapy of metformin and combined therapy of vildagliptin/metformin have been prevalent with clinical efficacy. Furthermore, this combination has been known as most economical for patients and also MJLW of Japanese government [7]. Then, this policy seems to be beneficial in a broad sense.

The background behind this status can be observed related to Japan's recent medical policies [10]. In September 2023, the Ministry of Health, Labor and Welfare (MHLW) announced national medical expenses and demographic trends. National medical expenses for fiscal year 2021 (2021.4-2022.3) were 45,035.9 billion yen, an increase of 2,069.4 billion yen (4.8%) from the previous year. During the same period, the ratio to gross domestic product (GDP) also gradually increased to 8.18%.

According to a study by the Organization for Economic Co-operation and Development (OECD), Japan's medical expenditure as a percentage of GDP was 25th among OECD member countries in the 2011 report, which was below the average. However, it rose to the 4th rank in the 2023 report in OECD countries, which seems to keep higher standard level at present. Regarding the population, the total fertility rate decreased from 1.30 in the previous year to 1.26, the lowest on record (2022.1-2022.12) [11].

Given the current state of medical administration, MHLW is concerned about the present situation where total medical expenses are rapidly increasing every year [11]. As one of the countermeasures, MHLW continued the policy of using generic medicine more frequently than brand-name medicine and controlling drug costs in medical expenses. Among these, two types of OHA are combined as a combination drug, and the drug price is set lower than the combined drug price of the two OHAs. These trends are expected to continue in the future. As our prediction in medical area, there will be strong points and weak points. However, at least in part, it can also be considered a beneficial direction from the patient's perspective.

In conclusion, latest topics concerning OHA and drug pricing were described. Metformin with a dose-dependent hypoglycemic effect can be easily increased in dose, where improving HbA1c will be expected associated with great economic benefits. Several kinds of combined OHA were used in clinical practice. This trend may come from the policy of MHLW, and will be continued thereafter. Drug pricing will be changed annually. It is expected that this article will become a useful reference in future practice.

Conflict of Interest

The authors declare no conflict of interest.

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