

Accelerated Approval, Ignoring Harm, is a Crime

New Direct-acting Antiviral for Hepatitis C (Epclusa)

Hemorrhage caused by an Anti-influenza Agent, Baloxavir

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Accelerated Approval, Ignoring Harm, is a Crime

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Sales of an anti-influenza agent, Xofluza (generic name: baloxavir), in 2018/19 winter is estimated to be more than 270 million US dollars, and more than 10 million people may have been treated with the agent: similar extent of use with that of Tamiflu in 2009/10 season in Japan.

At the same time, as high as 22.5% of influenza AH3N2 viruses are resistant to Xofluza in this season. Tamiflu resistant virus does not prolong the course of influenza. However, Xofluza resistant virus delays patient's recovery from influenza. High rates of resistance and delayed healing were well-known before approval (See MedCheck No. 80). In addition, toxicity tests of Xofluza showed bleeding toxicity: prothrombin time (PT) was prolonged by up to 2.4 times by fasting before autopsy. Although PT-INR was not shown, it could be dangerous enough to cause bleeding. However, the manufacturer (Shionogi & Co., Ltd.) explained that supplementation with the diet and vitamin K prevented prolongation of PT and such bleeding will not occur in humans. Japan's Ministry of Health, Labor and Welfare (MHLW) accepted such an explanation and approved the agent for marketing.

Serious hemorrhagic cases became reality in this season as described in this issue (p7). Since its launch in March 2018, 25 cases with bleeding have been reported, including 3 deaths. However, the MHLW stated that causal relationship cannot be denied in only 13 survivors and denied the causality of all other bleeding cases, including 3 deaths.

Although the manufacturer has disclosed only 3 survived cases, and the MHLW has not disclosed fatal cases either, even in some of the disclosed cases, immeasurable PT, PT-INR or prothrombin activity (below 10%) was frequently observed.

If a patient died following bleeding after taking Xofluza, it is reasonable to consider that hemorrhage was an adverse reaction to the agent and was the

cause of death. Denying the causality between Xofluza and death is a usual practice and deliberate decision by the MHLW.

Xofluza was designated as an agent for "preferential treatment system in examination" at the trial stage, and the examination period was greatly shortened and it was approved quickly. This designation requires all four criteria below to be fulfilled:

- (1) the substance is innovative with a new mechanism of action,
- (2) the target disease is serious,
- (3) the substance has extremely high efficacy and safety, and
- (4) the substance is developed and applied first in Japan.

Influenza is basically a mild and self-limiting infection and does not meet the criterion (2). Xofluza does not outperform Tamiflu in efficacy. It has unacceptable harm of bleeding, which was already detected in animal studies. Therefore, it does not meet criterion (3).

Simply because Xofluza is a product with a mechanism of action different from that of neuraminidase inhibitors and was first developed in Japan, the regulator approved it in a rush. They neglected to confirm the efficacy and safety in high-risk persons even though increased risk of harm is expected in them based on animal experiments.

Anti-influenza drugs are unnecessary for otherwise healthy people. It is the high-risk people for whom an anti-influenza drug should be effective. However, if you have severe flu symptoms, you may lose appetite and cannot eat. Then, you have to avoid using Xofluza due to the high risk of bleeding. After all, just like Tamiflu, Xofluza has no place in use for influenza infection.

Accelerated approval, ignoring harm, is a crime.

New Products

New Direct-acting Antiviral for Hepatitis C (Epclusa)

Advance in hepatitis C with prior treatment failure or decompensated cirrhosis

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MedCheck-Editorial Team

Summary

- A new antiviral targeting hepatitis C virus (HCV) (brand name: Epclusa) was launched in February, 2019. It is a combination of direct acting antivirals (DAA), sofosbuvir and velpatasvir.
- The combination yielded a sustained virological response (SVR) in all types of HCVs. In Japan, sofosbuvir + velpatasvir taken for 24 weeks in combination with ribavirin was approved for chronic hepatitis C and compensated cirrhosis in which existing DAAAs were ineffective.
- What is noteworthy is that a 12-week regimen of this combination as a single drug therapy was approved for decompensated cirrhosis (advanced cirrhosis), which was previously not subjected to antiviral treatment.
- The rate of SVR obtained by various DDAs is approximately over 90%. Therefore, no randomized controlled study has been conducted to compare the combination with placebo nor interferon therapy, and thus the effect on long-term prognosis, such as prevention of cirrhosis and hepatic cancer or overall mortality, is unknown. The recent study reported that markedly lower rate of decompensation of cirrhosis and overall mortality were observed in patients who used DAA as compared with non-DAA users. The study seems to be reliable as important baseline characteristics were well matched.
- Hypoglycemia occurred in chronic hepatitis C patients with diabetes who were treated with DAAAs and achieved SVR. This is because glucose metabolism improves when viremia resolves and hepatocellular function is recovered. This is a preferable outcome, but requires careful monitoring to prevent hypoglycemia.

Conclusion: The combination offers an advance in chronic hepatitis C with prior treatment failure or decompensated cirrhosis. It is recommended.

Keywords:

direct-acting antiviral, sofosbuvir, velpatasvir, Epclusa, chronic hepatitis C, compensated cirrhosis, decompensated cirrhosis, hypoglycemia

Brand name: Epclusa

generic name: sofosbuvir + velpatasvir

• sofosbuvir 400 mg + velpatasvir 100 mg per tablet

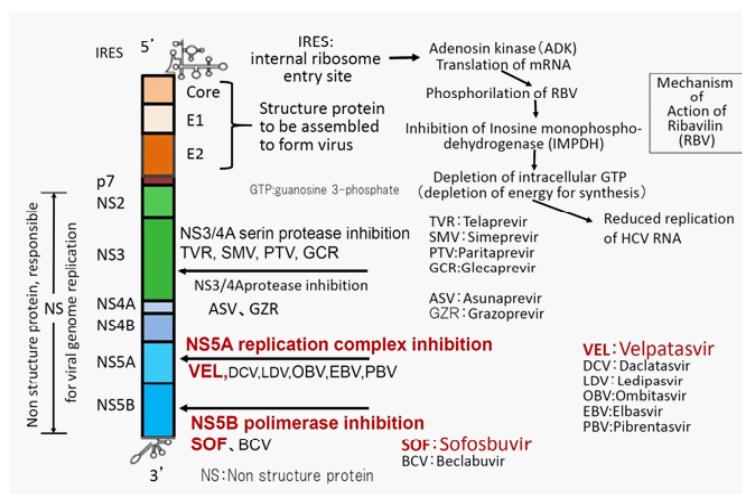
(See the figure for the mechanism of action)

■ Indication:

1. HCV decompensated cirrhosis: Usual dosage: 1 tablet/day taken orally for 12 weeks in adults.
 2. Chronic hepatitis C or HCV compensated cirrhosis in which existing DAA treatments failed: Usual dosage: 1 tablet/day in combination with ribavirin taken for 24 weeks in adults.
- Cost: about 60,000 yen (536 USD)/tablet, 5 million yen (45,000 USD)/12 weeks, 10 million yen (90,000 USD)/24 weeks

New Products

Figure: HCV genome and mechanism of action of anti-HCV agents



Known facts

Hepatitis C virus (HCV) interferes with utilization of triglyceride to form lipoprotein in hepatocytes and causes fatty liver and hepatocellular necrosis, leading to liver cirrhosis and hepatic cancer over a long period of time. **Table 1a** is a summary of direct-acting antivirals (DAAs) which have been approved in Japan in prior to the approval of the new combination: sofosbuvir (SOF) and velpatasvir (VEL) (hereafter SOF/VEL combination). It also shows whether each drug requires ribavirin in combination [1,2]. When used alone or combined with ribavirin for 12-24 weeks, they avoid the use of interferon and yield higher rates of sustained virological response (SVR).

Table 1b and **Table1c** show differences between existing DAAs and SOF/VEL combination.

However, in order to evaluate whether DAAAs are truly useful or not, prolongation of life span must be confirmed in DAA users as compared with non-DAA users in a long-term randomized controlled study. The trial conducted with DAAAs did not have non-users as control, and thus it is impossible to judge whether they are truly useful or not.

The recent study [3] retrospectively involved patients with hepatic cell carcinoma and cirrhosis which had been surgically resected or ablated between 2015 and 2018 and treated with DAAs and propensity-matched patients between 2007 and 2015 without DAA treatment. Total mortality was significantly lower in DAA group compared with No-DAA group (hazard ratio [HR]=0.39, 95% CI:0.17–0.91, $p=0.03$). A significant reduction in the

rate of hepatic decompensation was observed in DAA group compared with No-DAA group (HR=0.32; 95% CI=0.13-0.84, p=0.02). ([Table 2](#)). It is not a randomized control study (RCT), but a retrospective cohort study. However, it seems to be reliable because propensity scores of 16 baseline characteristics which are all important for prognosis of cirrhosis were well matched for the 2 groups, using previous surgical cases as control. Moreover, it may be true that virus elimination by DAAs is related to recovery of glucose metabolism and improvement of hepatocellular function.

What's new?

Velpatasvir (VEL) is effective when used alone in cases in which ledipasvir and daclatasvir are ineffective (types 3-6). When combined with sofosbuvir and ribavirin, it yields high rates of SVR in all types of HCVs. It is slightly less effective in type 3. However, an overseas study shows that when it was used for 24 weeks in combination with ribavirin, SVR was obtained in 84.6% of patients (11/13 patients).

Table 3 summarizes the result of a clinical trial conducted in Japan.

Harm

Since the clinical trial has no control, it is extremely difficult to assess causality between the test agent and adverse events.

With a 24-week SOF/VEL + ribavirin regimen for 60 patients with chronic hepatitis C or HCV compensated cirrhosis, in whom other DAA therapies had failed, 4 adverse events (\geq grade 3) occurred, including 2 hepatic cancer, 1 hepatic angiosarcoma and 1 pneumonia. In 6 cases (10%), ribavirin was discontinued or the dose had to be adjusted due to anemia. In 2 cases (3%), all regimens were discontinued.

With a 12-week regimen for 51 patients with decompensated cirrhosis, 2 adverse events (\geq grade 3) occurred (1 rectal adenocarcinoma and 1 esophageal varices). No death occurred in a single-drug therapy group while 3 deaths occurred in a ribavirin combination group due to bacterial sepsis, gastric variceal bleeding and hepatocellular carcinoma. Causal relationship has

Table 1a: DAA Regimens without interferon for patients with chronic hepatitis C or HCV compensated cirrhosis

Type of HCV ✽	Regimen	Brand name
genotype 1 (serogroup 1)	DCV + ASV comb. Tx	Daklinza+Sunvepra
	LDV/SOF comb. Tab	Harvoni
	OBV/PTV/RTV comb. Tab	Viekirax
	EBV + GZR comb. Tx	Erelsa + Grazina
genotype 2 (serogroup 2)	DCV/ASV/BCV comb. Tab	Ximency
	SOF + RBV comb. Tx	Sovaldi + Ribavirin
	OBV/PTV/RTV comb. Tab + RBV comb. Tx	Viekirax + Ribavirin
genotypes 3, 4, 5, 6	LDV/SOF comb. Tab	Harvoni
all genotypes (1-6)	SOF + RBV comb. Tx	Sovaldi + Ribavirin

Table 1b: Regimen for chronic hepatitis C or compensated HCV cirrhosis with previous DAA treatment failure

type of HCV ✽	Regimen	brand name
all genotypes (1-6)	SOF/LEP comb Tab + RBV comb Tx (24w)	Epcrusa + Ribavirin

Table 1c: Regimen for patients with decompensated HCV cirrhosis

type of HCV ✽	Regimen	brand name
all genotypes (1-6)	SOF/LEP comb Tab (12w)	Epcrusa

Table 2: Effect of DAAs on overall mortality, progression to decompensated cirrhosis and recurrence of HCC

Endpoints	DAA		Hazard Ratio (HR)		
	User n=102	non-user n=102	HR	95% CI	P value
Follow-up months mean (range)	21.4 (1-37)	17.5 (1-37)			
All-cause mortality	7	18	0.39	0.17-0.91	0.03
Progression to decompensation	6	14	0.32	0.13-0.84	0.02
Recurrence of HCC	28	38	0.70	0.44-1.13	0.15
SVR by DAA is predictors for endpoints					
All-cause mortality	-	-	0.02	0.00-0.19	<0.001
Progression to decompensation	-	-	0.12	0.02-0.38	<0.001
Recurrence of HCC	-	-	0.25	0.11-0.57	<0.001

Table 3: Rates of SVR by treatment duration and combination with/without ribavirin

Subjects	Combination of ribavirin	12 week		24 week		P value
		n	SVR %	n	SVR %	
Chronic Hepatitis C or compensated HCV cirrhosis in which previous treatment with DAAs was ineffective	with	57	82.5	60	96.7	0.011
	without	51	92.2	-	-	
Decompensated HCV cirrhosis	with *	51	92.2	-	-	1.0

been denied. However, it cannot be denied in some cases, such as gastric variceal bleeding.

In clinical trials, no hypoglycemia was reported. However, after marketing, it occurred frequently in patients with diabetes who were on hypoglycemic agents. HCV inhibits utilization of triglyceride to synthesize lipoprotein in hepatocytes, and causes fatty liver. As a result, hepatocellular function and glucose metabolism are impaired, leading to hepatocellular necrosis [4,5]. When HCV turns negative, hepatocellular function and glucose metabolism improve. Therefore, if hypoglycemic agents are not reduced or discontinued, hypoglycemia might occur.

Cited from Ref.1 and revised by MedCheck
DAAs: direct-acting antivirals comb Tab: combination tablet, comb. Tx: combination therapy
ASV:Asunaprevir, BCV:Beclabuvir, DCV: Daclatasvir, EBV:Elbasvir, GCR:Clecaprevir, GZR: Grazoprevir, LDV:Ledipasvir, OBV:Ombitasvir, PBV:Pibrentasvir, PTV:Paritaprevir, RBV: Ribavirin, RTV : Ritonavir, SMV:Simeprevir, SOF: Sofosbuvir, TVR:Telaprevir, VEL:Velpatasvir
✽ Types of HCVs: Genotype is a classification of HCVs determined by differences in their genes. There are genotypes 1 to 6, and there are also subclassifications, such as 1a and 1b. Genotype 1b comprises 70 - 80% of Japanese patients while genotype 2a and 2b comprise 10 - 20% and below 10%, respectively. There is another classification called serogroup, which is determined by differences in antibody. Genotypes 1a and 1b correspond to serogroup 1, and genotypes 2a and 2b to serogroup 2. Japan's national health insurance covers a test to identify serogroups, but not genotypes.

Cited from Ref.3, SVR: Sustained virological response (viral response is sustained for 12 weeks or over), HCC: Hepatic cell carcinoma, DAAs: Direct-acting antivirals, 95% CI: 95 % confidence interval, -: no data
The study covered 163 DAA users and 328 non-users, who underwent surgery for initial hepatic cell carcinoma in 2015-2018 and 2007-2015, respectively. Propensity scores of 16 baseline characteristics, which are important in determining prognosis of cirrhosis and hepatic cell carcinoma, were matched. From each group, 102 patients, whose propensity scores were well matched, were followed.

SVR: sustained virological response rate (viral response is sustained for 12 weeks or over), HCV: hepatitis C virus, -: no data

*: Total 3 deaths occurred in combination with ribavirin

In practice

In patients with chronic hepatitis C or HCV compensated cirrhosis who failed previous treatment with existing DAAs, SOF/VEL combination taken for 24 weeks in combination with ribavirin is recommended for all types of HCVs.

Furthermore, in patients with advanced, decompensated cirrhosis, SOF/VEL combination taken for 12 weeks is recommended for all types of HCVs.

In many patients with diabetes who are on hypoglycemic agents, as viral load decreases, glucose metabolism may improve and glucose level may drop. Therefore, it is necessary to carefully monitor changes in viral load and glucose level, and the dose of hypoglycemic agents should be adjusted.

New Products

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Adverse Reactions

Hemorrhage caused by an Anti-influenza Agent, Xofluza Serious toxicity necessitating suspension of its use

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Nakanishi T and Hama R

Keywords:

baloxavir marboxil, Xofluza, hemorrhage, prothrombin time, INR, vitamin K, fresh frozen plasma, fasting, influenza

Introduction:

On March 1st, 2019, Japan's Ministry of Health, Labor and Welfare (MHLW) requested Shionogi, the manufacturer of Xofluza (baloxavir marboxil), to revise "Precautions" in its package insert [1]. The MHLW also announced that 25 cases of hemorrhage, including 3 deaths, had been reported since the drug was launched in March, 2018 [2].

In response to this request, on March 25th, the package insert was revised. The revised Important Precautions say that the risk of hemorrhage, which might occur a few days after administration, should be explained to patients and their families. Moreover, under Clinically Significant Adverse Reactions, it was added that in case of hemorrhage, an appropriate management must be done. Under Drug Interactions, prolongation of prothrombin time (PT) (Note 1), which implies bleeding tendency, due to interaction with warfarin was included.

As mentioned in MedCheck No. 80 [4], there is no difference in efficacy between Xofluza and Tamiflu although the former is a one-dose treatment due to its long half-life. However, more viruses resistant to Xofluza have been detected, and in toxicity studies, coagulopathy was observed, suggesting the risk of hemorrhage. This will be discussed later on.

Total 4 cases are discussed here. They include a case reported in the adverse reaction monitoring by Japan Federation of Democratic Medical Institutions (MIN-IREN) [7] as well as 3 hemorrhage-related cases published in the "notice about the revised precautions" issued by Shionogi [8]. Particularly, in cases 1 and 2, serious hemorrhage could have occurred anytime. The MHLW

denies the causality between Xofluza and 3 deaths, but it cannot be trusted. (See page 2) Moreover, hemorrhage occurred on the first day of treatment even without interaction with warfarin.

This article gives warning that high-risk patients, such as the elderly and those in fasting, have markedly high risk of hemorrhage, and thus they should avoid using the agent.

Case 1: Potential risk of serious hemorrhage due to interaction with warfarin

The patient was a woman in early eighties who were on warfarin 1 mg and other medications. Drip infusion was given intravenously on the following day of Xofluza treatment as the patient complained of difficulty in dietary intake. Fever resolved on the next day. Hematuria was observed 6 days after the treatment. It aggravated after 8 days, and warfarin was discontinued. On day 9, PT was markedly prolonged (PT83.3 seconds) (Note 1) and PT-INR (hereafter INR) was 8.06 (INR exceeding 3.0 suggests extremely high risk of hemorrhage). Vitamin K1 10 mg × 2 was intravenously administered.

On day 10, both PT and INR were immeasurable. Vitamin K1 10 mg × 2 was intravenously administered, but it was ineffective. On the following day, after total 5 units (80mL × 5) of fresh frozen plasma were administered intravenously. INR improved and returned to 1.13.

Activity of coagulation factors in prior to the administration of fresh frozen plasma was AT III=75%, factor V=100%, factor X=37% and factor X III=86%. Decreased activity of factor X was observed.

Adverse Reactions

Note1: PT stands for "prothrombin time". The standard time is 12 ± 1.5 seconds. It is a test commonly used to measure activity of several coagulation factors comprehensively. PT ratio is a ratio to control time and the normal ratio is 1. Prolongation of PT comprehensively indicates abnormality in extrinsic coagulation factors (I, II, V, VII, X). Hepatic disorders and warfarin treatment can cause prolongation. PT and PT ratio greatly vary among those computed in various institutions. PT-INR is an internationally normalized PT ratio. In presence of warfarin, appropriate PT-INR is 1.5-2.2 [9]. Warfarin suppresses vitamin K, which activates factors II, VII, IX and X, and prolongs PT

Case 2: Interaction with warfarin

A 61-year-old woman showed PT immeasurable due to more than 60.0 seconds, and INR was also immeasurable on 7 days after the treatment with Xofluza..

Warfarin was discontinued. Eight days after the treatment, bruises, which seemed to be subcutaneous hemorrhage, were observed and INR was 5.43. On day 11, INR was 4.07. Warfarin was resumed at a lower dose. On day 13, INR was 4.01 and warfarin dose was reduced further. On day 17, INR recovered to 2.30. Warfarin dose was returned to the initial level. On day 32, INR was 2.66.

Case 3: Melena on the day of Xofluza treatment

A 22-year-old woman presented with diarrhea every 30 minutes in the evening on the day of the treatment with Xofluza. Later it led to melena. Tenderness was felt on the left lower quadrant of the abdomen on palpation. The symptoms resolved after 6 days.

Case 4: Intraoral bleeding after 3 hours

A 73-year-old woman presented with bleeding in the mouth 3 hours after Xofluza treatment. Bleeding was from the whole mucosa of oral cavity. Hemostatic agents, including tranexamate, were given, and the symptom relieved on the following day.

Immediate and delayed bleeding reactions:

Locations of bleeding seem to include all kinds of organs, such as oral, gastrointestinal, urinary mucosa

and skin. It should be noted that there are cases in which bleeding occurred on the day of the treatment (cases 3 and 4) and those in which bleeding occurred and abnormality in coagulation factors was detected several days after the treatment (cases 1 and 2). In the latter, PT and PT-INR were immeasurable and there were increased potential risks of irreversible hemorrhage and death.

Xofluza is metabolized by esterase (**Note 2**) into an active form. In most people, an unchanged form is metabolized into an active metabolite so rapidly that it is not detected in the blood. Then within a few hours, blood concentration of the active metabolite reaches its peak. In cases 3 and 4, bleeding occurred within relatively short period time. The time of bleeding coincides with the time of maximum concentration. It suggest that bleeding might be induced by the direct action of Xofluza metabolite.

On the other hand, in cases 1 and 2, why did bleeding tendency emerged after several days? It may be related to the large interindividual variability of esterase activity. In an extremely poor metabolizer, concentration of the active metabolite increases very slowly. In addition, as the effect of Xofluza persists with a single-dose treatment, its half-life is extremely long: average for 4 days. This is probably related to why bleeding can occur even a few days after the treatment.

Moreover, in both cases, patients were treated with warfarin. It interferes with vitamin K reductase, inhibiting vitamin K cycle and activation of vitamin K-dependent coagulation factors II (fibrinogen), VII, IX, and X, and works as an anticoagulant.

Note2 : An enzyme which hydrolyzes ester. There are various kinds of esterase.

Hemorrhage could be predicted based on the results of animal tests:

The package insert explains that mechanism of onset and risk factors of hemorrhage due to interaction with warfarin are unknown [3,8]. However, at least vitamin K deficiency is related (**Note 1**). In the results of toxicity studies [5,6], PT was prolonged with fasting while no abnormality was observed in animals that were given food and vitamin K. This coincides with the fact that factor X was lacking in Case 1.

Blood products for bleeding cases in which vitamin K is ineffective:

In Case 2, INR improved after warfarin was temporarily discontinued, but it was immeasurable at one point. In Case 1, not only INR was immeasurable, but vitamin K was also ineffective. Only after fresh frozen plasma was used, INR improved.

In cases in which PT and INR are immeasurable, serious hemorrhage can occur anytime. This is a serious situation that may lead to life-threatening events, such as intracranial hemorrhage and intraperitoneal hemorrhage, or sequelae from falls.

Regarding the mechanism of action, in Case 1, it cannot be denied that factor X was directly inhibited or other coagulation factors were lacking. Since human prothrombin complex (Kcentra) contains coagulation factors II, VII, IX and X, and proteins C and S, it could have been effective. However, because there might have been unknown factors, the use of fresh frozen plasma was an appropriate choice. As of now, the mechanism of hemorrhage caused by Xofluza is not understood. Therefore, there might be no treatment other than blood product (Kcentra) or blood transfusion (fresh frozen plasma). The use of blood or blood products is associated with increased risk of unnecessary infection (Kcentra is partly produced from blood from non-donors). Another problem is that they are valuable medical resource that can be obtained only from blood donations. In case of emergency, they are not easily accessible. It also requires consent from patients (their families) prior to treatment. The MHLW denies causality between the drug and deaths, but this cannot be trusted [10-12]. High-risk patients are essentially the ones who need an effective antiviral agents, but the risk of hemorrhage is higher in such patients. Xofluza was subjected to "preferential examination designation system" and was approved too quickly (4 months) [12-13]. There are various issues involving this drug (see page 2).

Harm outweighs benefits. Do not use Xofluza.

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Annual theme: Critical appraisal series for treatment guidelines (6)

Critical Assessment of Diabetes Guidelines

Do not aim at normalizing glucose level with medicines

Translated from Med Check (in Japanese) Nov 2018 : 18 (80):134-138

MedCheck Editorial Team

Summary

- Patients are supposed to lead a comfortable life even with diabetes when they receive treatments based on the guideline, if it gives truly useful guidance. Moreover, their lifespan should be lengthened by the treatments.
- However, hypoglycemic attacks and cardiovascular diseases may occur frequently and lifespan might be shortened when blood glucose is lowered with drugs to the "excellent" level ($\text{HbA1c} < 6.2\%$) recommended by the 2010 guideline of the Japan Diabetes Society (GL2010). Moreover, by following the 2016 guidelines (GL2016) ($\text{HbA1c} < 7.0\%$), the same harms may be induced, as well.
- Recently, the American College of Physicians (ACP) has released an excellent guidance statement (ACP guidance). It recommends clinicians to "achieve an HbA1c level between 7% and 8% in most patients with type 2 diabetes", and to "consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA1c levels less than 6.5%". This guidance is based on the findings that the recommended treatment would greatly reduce hypoglycemic attacks and cardiovascular diseases and increase lifespan, as compared with the treatment recommended by the Japanese Diabetes Society ($\text{HbA1c} < 6.2\%$ or 7.0%).
- When the ACP guidance is followed, only 11.6% of the diabetes patients in Japan would need additional treatment. However, if GL2010 or GL2016 is followed, 84.6% or 46% of the patients would be subjected to the additional treatment, respectively. In other words, 7.3 times or 3.8 times more diabetes patients would have to receive additional treatments, respectively, as compared with the ACP guidance.
- According to the ACP guidance, when HbA1c levels less than 7.0% are achieved, pharmacologic therapy could be deintensified, and when HbA1c levels are reduced to less than 6.5%, it should be deintensified. This means that 27% of the diabetes patients may choose milder treatment, and 7.5% of them should deintensify their pharmacologic therapies.
- The recent diabetic medicines are all costly. If the guidelines of the Japanese Diabetes Society are followed, high drug costs and medical costs would be needed. In addition, hypoglycemic attacks and cardiovascular diseases would occur frequently and life expectancy would be negatively affected, as well. On the other hand, the ACP guidance would reduce medical costs and improve health and life expectancy of patients with type 2 diabetes.
- Type 2 diabetes may develop and aggravate by persistent exposure to strong stress, such as sleep deprivation, continuous intake of excessive carbohydrate and intake of low-quality vegetable oil. The basic therapy is the low-carb diet based on the severity of the disease. Furthermore, enough sleep time should be ensured without depending on hypnotics, specific causes of excessive stress for individual patient should be identified and resolved, and high quality fat should be taken. These measures would reduce dependence on diabetes drugs as much as possible.
- In case medication is needed, the only useful drug is insulin.

Keywords:

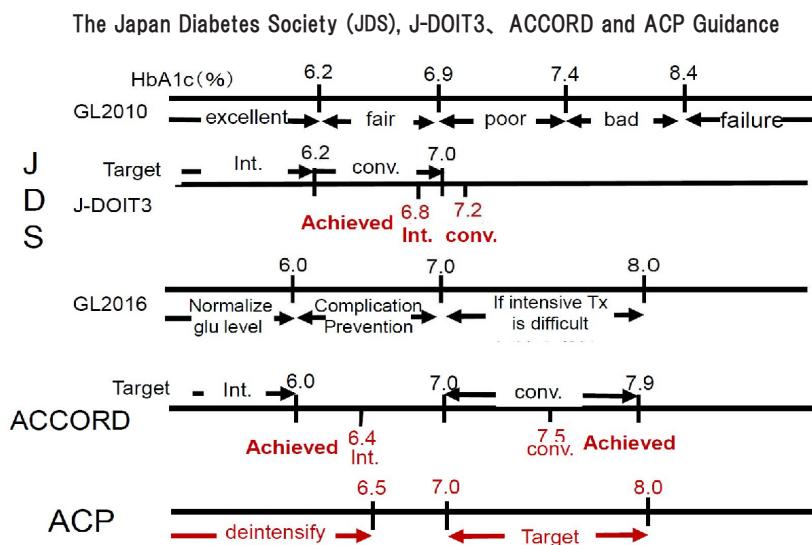
Guideline of the Japanese Diabetes Society, ACP guidance, HbA1c, blood glucose level, glycemic control, cardiovascular disease, total mortality rate, sleep time, stress, low-carbohydrate diet, VK2-osteocalcin inhibitory vegetable oil, insulin, hypoglycemic agent

Introduction

The "MedCheck" No. 45 (Feature: Diabetes, Part 2, 2012) [1] explained that "if the guidelines are really useful, patients are supposed to have a comfortable life by receiving the recommended treatments, and their lifespan should be lengthened. However, if we follow the guidelines, the lifespan would be shortened." The guideline of the Japanese Diabetes Association (GL 2010) [2] targeted strict glycemic control, and hemoglobin A1c (HbA1c) levels were evaluated as follows; less than 6.2 (excellent, thereafter % is omitted: Note 1), less than 6.2-6.9 (fair), 6.9 and over (poor), 7.4 and over (bad), and 8.4 and over (failure). The guideline followed this classification of HbA1c levels, even though the ACCORD study [3] had already confirmed that intensive glycemic control increased cardiovascular deaths, leading to increased total mortality, and the classification was flawed (this will be discussed in details later).

The guideline was revised in 2016 [4]. Has the existing policy been revised? This article critically evaluates the guidelines referring to the ACP guidance [5] published by the American College of Physicians (ACP) in March, 2018, and other new research findings.

Figure 1: Comparison of Target and Achieved HbA1c Levels in Some Guidelines:



JDS: The Japan Diabetes Society, int.: intensive therapy, conv.: conventional or standard therapy
GL2010[2], ACCORD [3], GL2016[4], ACP Guidance [5], J-DOIT3 [6]

Note1: In order to avoid confusion of % used to describe HbA1c levels with % for incidences of adverse events and proportions of patients, % for HbA1c levels is omitted after the summary.

Differences in HbA1c levels targeted by various guidelines (Figure.1)

Figure 1 compares target HbA1c levels set by various guidelines and clinical trials and the actual levels achieved.

As mentioned above, GL 2010 [2] targeted the intensive glycemic control, using the following classification of HbA1c levels; less than 6.2 (excellent), less than 6.2-6.9 (fair), 6.9 and over (poor), 7.4 and over (bad) and 8.4 and over (failure). Although this guideline was revised after the results of ACCORD study were published, it persisted on this classification. GL 2016 [4] changed the description and stated that HbA1c level less than 6.0 should be targeted "only if it can be achieved solely by appropriate diet and exercise therapies or by pharmacologic therapies without side effects, including hypoglycemia". Practically, it gave up on achieving the intensive target level with medication. However, it still

recommends HbA1c level less than 7.0 as a target level for preventing complications (Figure. 1).

On the other hand, J-DOIT3 study [6] published in 2017 targeted HbA1c level less than 6.2 for the intensive therapy group because it was launched in 2006. However, actually, only HbA1c 6.8 (median value) was achieved. Even for the standard care group, only HbA1c 7.2 was achieved while the target was less than 7.0.

Review

Intensive target levels were hardly achieved

Table summarizes the main results of the ACCORD study and the J-DOIT 3 study. The ACCORD study is a randomized controlled trial (RCT) comparing intensive therapy group targeting HbA1c level less than 6.0 and standard therapy group targeting a HbA1c level from 7.0 to 7.9. Among the participants who targeted HbA1c less than 6.0, a half of them achieved only less than 6.4. Less than one-fourth of them achieved HbA1c level less than 6.0 (quartile range 6.1-7.0: Note 2). Another one-fourth of them achieved HbA1c level above 7.0. Meanwhile, in the standard therapy group, a half of the participants nearly achieved the target value of 7.0-7.9 (quartile range 7.0-8.1).

As a result, hypoglycemia requiring any assistance occurred frequently in the intensive therapy group; 16.2% of the participants; while it occurred in 5.1% of the participants in the standard therapy group (odds ratio 3.6). Moreover, hypoglycemia requiring medical assistance was 10.5% versus 3.5%, and odds ratio was 3.2.

If the targeted HbA1c level, less than 6.0, is achieved, hypoglycemia would occur more frequently.

Note2: When you arrange the values in order from lowest to highest and divide the whole into four, three boundaries are created. The boundary between the lowest quarter and second quarter (the 25th percentile) is the first quartile. The boundary between the third and fourth quarters (the 75th percentile) is the third quartile. The quartile range of 6.1-7.0 refers to the range between the first quartile, 6.1, and the third quartile, 7.0.

Difference in total mortality rate by achieved HbA1c value

The incidences of cardiovascular diseases and total mortality were higher by 35% and 22% in the intensive therapy group than in the standard therapy group, respectively. If the intensive control is continued for 3.5 years, additional 1 person in 95 persons would die as compared with those who receive the standard therapy (NNTH=95: Table). This is a frightening outcome.

The lifespan of people who achieved “excellent” level of HbA1c in the GL2010 standard was shortest while that of people with “poor” or “bad” levels was longer. The result was totally opposite of what was expected. Therefore, the study, which was originally planned for 5 years, was discontinued after 3.5 years as a result of the interim analysis. The patients on the intensive therapy switched to the standard therapy later on. Other three studies (ADVANCE [7], UKPDS [8-10], VADT [11-12]) that were used for assessment by the ACP guidance were all flawed. Furthermore, their results did not show significant improvement in total mortality rate.

The J-DOIT3 study conducted in Japan involved interventions not only for diabetes, but also for controlling blood pressure and cholesterol level. However, because the participants' blood pressure was around 120-129/80 mmHg, and their LDL cholesterol levels were around 120 mg/dL, they required almost no interventions for their blood pressure and cholesterol level, and their main concern seemed to be glycemic control. When people who achieved “excellent” and “fair” HbA1c levels in the GL2010 standard are compared, the hazard ratio of total mortality was 1.01 and there was no significant difference. The biggest reason may be that the difference between achieved HbA1c levels in the two groups was only 0.4.

Table: Comparison of target and achieved levels of HbA1c and total mortality in ACCORD study and J-DOIT3 study

Study name	Groups	Number of participants	HbA1c (%)*a			Total mortality		HR (95%CI)	P value (NNTH)
			Baseline	Target	Achieved	Number	%		
ACCORD	intensive	5,128	8.1	<6.0	6.4	257	5.0	1.22 (1.01-1.5)	P=0.04 (95)
	standard	5,123	8.1	7-7.9	7.5	203	4.0		
J-DOIT3	intensive	1,269	8.0	<6.2	6.8	49	3.9	1.01 (0.7-1.5)	P=0.95 —
	conventional	1,271	8.0	<7.0	7.2	48	3.8		

* a: The baseline and achieved levels of HbA1c are expressed as median. HR: Hazard ratio. 95% CI: 95% confidence interval. NNTH: number needed to treat to harm: NNTH=95 indicates that when 95 persons receive the intensive therapy for 3.5 years, 1 additional death would occur as compared with those who received the standard therapy. In the ACCORD study, the hazard ratio of cardiovascular death was as high as 1.35 (95% CI: 1.04-1.76, p=0.02).

The authors of the J-DOIT3 study highlighted that morbidity of cerebrovascular diseases (stroke) decreased significantly, but stroke alone was not the primary endpoint. Furthermore, myocardial infarction + stroke was originally set as the primary endpoint, but they were not able to collect an adequate number of such events. Then, they added cases of revascularization and set the complex event as the primary endpoint in the middle of the study, but no significant difference was observed. That is why statistically significant difference in stroke cannot be claimed ([Note 3](#)). The study reported that renal impairment was reduced, but for the same reason, significant difference cannot be claimed. Moreover, the incidences of hypoglycemia and edema increased by 2 times and 1.6 times, respectively. This contradicts with other findings, and undermines the credibility of the study.

Note3: As for efficacy of a drug, significant differences can be claimed only by predefined endpoint. Roughly speaking, if p value of the primary endpoint is sufficiently small, and it is less than 0.05 in total when it is combined with p value of the secondary endpoint, significant difference can be claimed by the secondary endpoint, as well. In the case of the J-DOIT3 study, p value exceeded just with the primary endpoint, and significance cannot be claimed with the secondary endpoint. This is sometimes expressed as "p value is consumed by the primary endpoint".

Even for severe cases, milder control is better

Not only the ACCORD study, but also other studies suggest that the intensive control leads to higher risk of death. Among the RCTs that evaluated the effect of intensive control in hyperglycemia by using insulin, NICE-SUGAR study was the largest and most appropriately planned study, and produced a similar result [13].

The study was conducted with 6140 patients with severe hyperglycemia who were hospitalized in ICU. In the conventional control group, insulin was administered if the blood glucose level exceeded 180 mg/dL. Insulin administration was reduced and then discontinued if the blood glucose level dropped below 144 mg/dL (8.0 mmol/L). Glucose level stayed at average 140-149 mg/dL range (median 142 mg/dL). For an intensive treatment group, insulin injection was administered to maintain

glucose level between 81-108 mg/dL, and it stayed at average 110-119 mg/dL (median 107 mg/dL) [13].

The incidence of severe hypoglycemic attacks with glucose level less than 40 mg/dL was 0.5% in the conventional control group and 6.8% in the intensive control group, and significant difference was observed (odds ratio 14.7, 95% CI 9.0-25.4, p<0.001).

In this study, the hazard ratios for death at day 90, comparing cases of moderate and severe hypoglycemia with those with no hypoglycemia, were 1.4 and 2.4, respectively (p<0.001 for both) [14].

In type 2 diabetes, increased risk of death due to hypoglycemia was reported, as well. According to the analysis in the ACCORD study [3] (discontinued after 3.5 years), the adjusted hazard ratio for death in hypoglycemia cases which required any assistance at least once was 1.3-2.9 [15]. The other study also reported that clinical symptomatic hypoglycemia (mild or severe) demonstrated higher hazard ratios (propensity score, adjusted) for all-cause hospitalization (2.51 [2.00-3.16]) and total mortality (2.48 [1.41-4.38]) [16].

ACP guidance and guidelines by various societies

Giving weight to the results of the ACCORD study, The American College of Physicians (ACP) reviewed guidelines by various societies and announced the statement. The points are as follows; ① HbA1c level can be between 7.0-8.0; ② If it is less than 6.5, pharmacologic therapy should be deintensified; ③ hypoglycemia should be minimised and pharmacologic therapy should be avoided in people whose life expectancy is below 10 years as harm may outweigh benefit, but the treatment should focus on improving their symptoms only.

The American Diabetes Association (ADA) quickly argued against this statement [17,18]. However, the ADA standard focuses on improving surrogate endpoints for complications of diabetes while the ACP guidance emphasizes life expectancy. Therefore, the ACP guidance is much more reliable.

Why do the guidelines by various societies persist on low glycemic levels? ([Figure. 2](#))

[Figure 2](#) shows a distribution of HbA1c levels of type 2 diabetes patients in Japan in 2016 [19]. This figure also shows the percentage of patients who would need

additional treatment, comparing when the ACP guidance and the guidelines of the Japan Diabetes Society are followed.

If the ACP guidance is followed, only 11.6% of the diabetes patients in Japan would need additional treatment, but with GL2010 (J-DOIT3), 84.6% of them would need additional treatment. This suggests that surprisingly, 7.3 times more patients would be subjected to additional treatment as compared with the ACP guidance. Even if the standard of GL2016 (HbA1c less than 7.0) is targeted, 44% of them would need additional treatment; 3.8 times more patients as compared with the ACP guidance.

In the ACP guidance, when HbA1c level is less than 7.0, glycemic control can be deintensified. The guidance also recommends that it should be deintensified when HbA1c level is below 6.5. Patients with HbA1c level below 7.0 (27% of the diabetes patients) may have milder pharmacologic therapy, and those with HbA1c below 6.5 (7.5% of the diabetes patients) should deintensify the pharmacologic therapy.

The recent agents for diabetics

As MedCheck-TIP has thoroughly investigated the recent diabetes medications, they lower glucose level, but do not increase life expectancy, and they have almost

no benefits, except for insulin. There are some clinical trials that claim that the drugs improve life expectancy, but none of them are reliable [17,18].

Because the recent diabetes drugs are expensive, high costs for drugs and medical care are needed. In addition, they might cause hypoglycemic attacks and cardiovascular diseases frequently, leading to shorter life expectancy.

On the contrary, if the ACP guidance is followed, medical costs can be reduced, and improved lifespan and health can be expected.

Diabetes societies in Japan and the U.S. are led by those who have conflicts of interest with pharmaceutical companies. This is probably because why they persistently promote the use of medications to lower glucose level as much as possible.

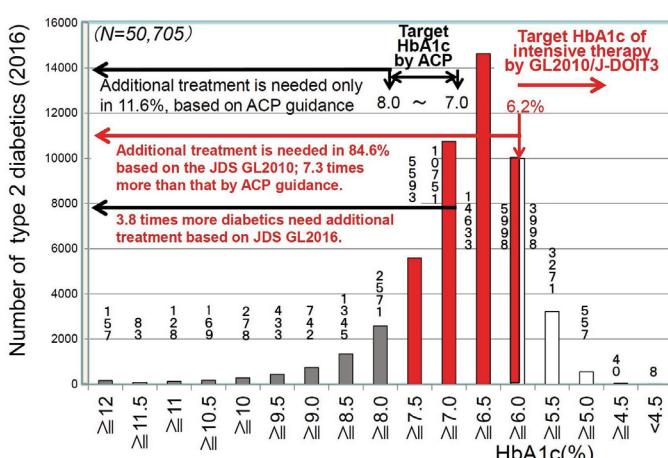
Non-pharmacotherapy is the first-line treatment for type 2 diabetes.

Diabetes is caused by an absolute and relative lack of insulin secreted by cells in the pancreas (β cells) [17,18]. Insulin is secreted according to the load of carbohydrate. It also contributes to metabolism of lipids and protein and cell proliferation as well. When these cells are continuously overloaded with excessive carbohydrate and are exposed with ischemic stress due

to systemic stress, absolute and relative deficiency of insulin secretion may occur. In particular, persistent exposure to systemic stress, such as sleep debt, excessive intake of carbohydrate [20,21] and intake of vegetable oil that inhibits vitamin K2 [22,23] may reduce secretion of necessary insulin, cause or aggravate diabetes, and promote arterial calcification.

The basic treatment for diabetes is to follow low-carbo diet according to the severity of the disease. Moreover, sufficient sleep hours should be ensured without depending on hypnotics, and causes of stress should be identified and resolved. High-quality vegetable oil should be included in the diet. With these measures, diabetes can be treated

Figure 2: Distribution of HbA1c levels of type 2 diabetes patients (2016, Japan)



Only 11.6 % of the patients ($\text{HbA1c} \geq 8$) would need additional treatment with the ACP standard. Total 84.6 % of the patients ($\text{HbA1c} \geq 6.2$) would need additional treatment with the GL2010. As compared with ACP guidance, 7.3 times more patients would need additional medications. With GL2016 ($\text{HbA1c} \geq 7$), 3.8 times more patients would need additional medications as compared with ACP guidance. The data of the distribution of HbA1c levels were taken from Japan Diabetes Clinical Data Management Study Group [19], GL2010 [2], GL2016 [4], ACP: American College of Physicians Guidance Statement [5], J-DOIT [6].

without medication or the use of pharmacologic therapy for diabetes can be minimized.

A study that reviewed epidemiological studies from all over the world on carbohydrate intake suggests that people whose carbohydrate intake accounts to 40-43% of total calorie intake live the longest [24]. The current amount of intake of vegetable oil that inhibits vitamin K2 is almost equivalent to the amount that induced complications of diabetes, such as stroke, renal impairment and testis toxicity, in animal studies, and this cannot be taken lightly [25]. Moreover, it is noteworthy that the most appropriate proportion of calorie intake from carbohydrate is 40% [24]. This may not be coincidence that it is very similar to the carbohydrate content in breast milk; 44% by calorie [26].

If medication is needed, the only useful drug is insulin [17,18].

The intensive control of glucose level, which might cause hypoglycemia, must be avoided. Choose non-

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