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SPECIAL REPORT

Recommendations on the Proper Use of SGLT2 Inhibitors

The Committee on the Proper Use of SGLT2 Inhibitors*

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Following the launch of the first sodium-glucose co-transporter-2 (SGLT2) inhibitor on April 17, 2014, several other SGLT2 inhibitors have followed over time, so that 6 active pharmaceutical ingredients (APIs)/7 finished pharmaceutical products (FPPs) are currently available for clinical use in Japan. Launched as a class of agents with a novel mechanism of action for the treatment of type 2 diabetes, in clinical trials, these agents have not only been associated with adverse reactions (ARs) common to conventional antidiabetic drugs, e.g., hypoglycemia; they have also been associated with those unique to this class, e.g., urogenital infections. Furthermore, their wide-ranging and complex influences on metabolism and circulation have raised concern over the occurrence of a wide spectrum of ARs associated with their use, including serious ARs. Indeed, numerous reports of ARs and adverse events (AEs) have followed soon after launch of these agents. This has led to the "Committee on the Proper Use of SGLT2 Inhibitors" ("Committee" hereafter) being launched and the "Recommendations on the Proper Use of SGLT2 Inhibitors" ("Recommendations" hereafter) being developed and published on June 13, 2014. Thereafter, the Recommendations have been revised on August 29, 2014 in light of AEs and ARs reported to date; 3-month post-marketing surveillances (PMSs) have also provided a certain amount of safety data from elderly patients 65 years of age or older receiving SGLT2 inhibitors, demonstrating that the AEs and ARs reported during these surveillances were not widely different in kind and frequency from those reported in the preceding clinical trials.

Of note, a majority of these Recommendations apply to the combination drugs (each incorporating an SGLT2 inhibitor and a DPP-4 inhibitor) that have been launched since September 2017, one after another, by pharmaceutical companies, for the treatment of type 2 diabetes.

Again, while some SGLT2 inhibitors have been granted approval for use in combination with insulin formulations in adult patients with type 1 diabetes since December 2018, reports have demonstrated an increased risk of ketoacidosis associated with this combined use. In addition, the applications filed overseas for approval of SGLT2 inhibitors in adult patients with type 1 diabetes have met with conditional (European Medicine Agency [EMA] approval limiting their use to patients with body mass index (BMI) $\geq$ 27 kg/m^2) or no (U. S. Food and Drug Administration [FDA]) approval. In light of these developments which need to be taken seriously, it appears that sufficient care, as well as emergency measures, needs to be taken when it comes to using SGLT2 inhibitors in patients with type 1 diabetes. Thus, the Committee hereby updates its Recommendations to promote the proper use of SGLT2 inhibitors

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and to ensure that these recommendations are more widely shared than ever thereby helping minimize the occurrence of ARs and AEs associated with the use of SGLT2 inhibitors.

RECOMMENDATIONS

1. Physicians should be aware that there is a certain level of risk associated with the use of SGLT2 inhibitors in patients with type 1 diabetes and consider using these agents only in those with inadequate glycemic control despite appropriate and proactive self-management including insulin therapy being implemented under the supervision of a well-experienced diabetologist.
2. Physicians should exercise sufficient care in ensuring that patients receiving insulin secretagogues, e.g., insulin and sulfonylurea (SU), in combination with an SGLT2 inhibitor, are closely monitored for occurrence of hypoglycemia; that their doses are reduced to minimize occurrence of hypoglycemia (see below for instructions on how to reduce their doses); and that patients receiving these agents concurrently are instructed on the risk of hypoglycemia associated with their use.
3. SGLT2 inhibitors should only be used with caution in elderly patients 75 years old or older or patients 65 to 74 years old with geriatric syndrome (e.g., sarcopenia, cognitive decline, and decreased activities of daily living [ADL]).
4. Care should be given to ensuring that sufficient countermeasures against dehydration associated with the use of SGLT2 inhibitors, including patient education, are implemented and that dehydration is closely watched for, particularly in patients receiving diuretics as well.
5. SGLT2 inhibitors must be discontinued in patients who have developed fever, diarrhea or vomiting or who have difficulty taking sufficient meals due to loss of appetite (e.g., during "sick days").
6. Ketoacidosis may be suspected in patients complaining of fatigue, nausea/vomiting, or abdominal pain even when the glucose levels are within or near normal levels (i.e., euglycemic ketoacidosis). In these cases, physicians should examine these patients for blood ketone body levels (or for urine ketone body levels if blood tests are not readily available) and seek consultation from diabetologists. Physicians should also bear in mind that ketoacidosis may be shown to be aggravated in patients with type 1 diabetes using insulin pumps, discontinuing insulin injections or reducing excessive dose of insulin.
7. Physicians should discontinue SGLT2 inhibitors immediately in patients who have developed skin symptoms likely to be due to drug eruption, e.g., erythema, after the start of these agents and seek consultation from dermatologists. Physicians should also watch for symptoms likely to be due to Fournier's gangrene, i.e., necrotizing fasciitis affecting the external genitalia and/or perineum, and should diligently report any ARs or AEs encountered during SGLT2 inhibitor use.
8. Physicians should be proactive about detecting urogenital infections likely to be associated with SGLT2 inhibitors through timely history taking (preferably using a questionnaire) and laboratory testing.

ARS LIKELY TO BE ENCOUNTERED AND THEIR COUNTERMEASURES

Severe hypoglycemia

Severe hypoglycemia continues to be reported in patients receiving SGLT2 inhibitors, with the incidence shown to be highest among those receiving concurrent insulin and then among those receiving concurrent insulin secretagogues, e.g., SU. The incidence of severe hypoglycemia varies between DPP-4 inhibitor users and SGLT2 inhibitors and has been characterized as being most frequent among SGLT2 inhibitor users receiving concurrent insulin versus among DPP-4 inhibitor users receiving concurrent SUs, suggesting that resolution of glucotoxicity with SGLT2 inhibitors may lead to enhancement of insulin potency thus resulting in hypoglycemia among SGLT2 inhibitor users receiving concurrent insulin. Thus, addition of an SGLT2 inhibitor is thought likely to cause severe hypoglycemia in patients receiving insulin, an SU or a rapid-acting insulin secretagogue, suggesting that consideration needs to be given to reducing the dose of either agent used in combination with an SGLT2 inhibitor. It should also be borne in mind that these hypoglycemic episodes may occur in not only elderly but relatively younger patients receiving an SGLT2 inhibitor as add-on to insulin.

In patients with type 2 diabetes starting on SGLT2 inhibitors as add-on to insulin, the insulin dose should be reduced beforehand with sufficient care given to the occurrence hypoglycemia. Again, in patients with type 1 diabetes receiving an SGLT2 inhibitor as add-on to insulin, the insulin dose should be carefully reduced beforehand (see below for instructions on how to reduce insulin doses) with sufficient care given to the occurrence of ketoacidosis associated with excessive insulin dose reductions.

1-a. In patients with type 1 diabetes showing favorable glycemic control (HbA1c $< 7.5\%$), consideration should be given at baseline to reducing their basal/bolus insulin doses by 10-20%.

1-b. In patients with type 1 diabetes showing poor glycemic control (HbA1c $\geq 7.5\%$), care should be given to ensuring that their basal/bolus insulin doses are not reduced or only minimally reduced.

2-a. Patients with type 1 diabetes should be instructed on how to reduce their basal/bolus insulin doses on their own, based on self-monitoring of blood glucose (SMBG) or continuous glucose monitoring (CGM) results demonstrating that their glycemic control has been improved but hypoglycemia has become manifest during treatment with an SGLT2 inhibitor as add-on to insulin.

2-b. In all cases described above, however, patients with type 1 diabetes should be instructed not to reduce their basal/bolus insulin doses too much, specifically, not to reduce their basal insulin dose by 20% or more compared to baseline and to reduce their basal/bolus insulin doses with utmost caution.

Again, in patients receiving an SGLT2 inhibitor as add-on to SU, consideration needs to be given to reducing the SU dose beforehand as specified below, as in patients receiving a DPP-4 inhibitor as add-on to SU.

- In patients receiving glimepiride more than 2 mg/day, the glimepiride dose should be reduced to 2 mg/day or less.
- In patients receiving glibenclamide more than 1.25 mg/day, the glimepiride dose should be reduced to 1.25 mg/day or less.
- In patients receiving gliclazide more than 40 mg/day, the gliclazide dose should be reduced to 40 mg/day or less.

Ketoacidosis

Following approval of SGLT2 inhibitors for use in patients with type 1 diabetes, ketoacidosis has been increasingly reported in patients receiving SGLT2 inhibitors. Given that it is thought likely to be due to insulin discontinuation, excessive carbohydrate restriction, and excessive soft drink intake, patients with type 1 diabetes should be carefully interviewed prior to initiation of an SGLT2 inhibitor to ensure that SGLT2 inhibitors are not used in those who have experienced repeated ketoacidosis, show the initial symptoms of ketoacidosis or are on carbohydrate restriction diet. Of note, attention should be given to problems with insulin pumps and to discontinuation of basal insulin due to the use of a predictive low-glucose management (PLGM) system as potential causes of ketoacidosis in patients with type 1 diabetes. In clinical trials, ketoacidosis has been reported to be increased with heavy drinking, infections, and dehydration and among women and non-obese/lean (BMI < 25 kg/m^2) individuals. Of note, among patients with type 1 diabetes receiving SGLT2 inhibitors whose blood glucose levels may not be increased even after insulin discontinuation, ketoacidosis may often be detected late and aggravated at diagnosis. Again, unlike typical diabetic ketoacidosis, this type of ketoacidosis (i.e., euglycemic ketoacidosis) calls for sufficient glucose supplementation from an initial stage of treatment onwards. Thus, patients with type 1 diabetes should be sufficiently informed about ketoacidosis-associated symptoms (e.g., fatigue, nausea/vomiting and abdominal pain), and those with suspected ketoacidosis should be instructed to consult diabetologists immediately.

Dehydration/cerebral infarction and other dehydration-associated complications

While the data reported to date from large-scale clinical trials and PMSs show no evidence for increased incidence of cerebral infarction with SGLT2 inhibitors, SGLT2 inhibitors are shown to be associated with body fluid loss (dehydration) early after their initiation. Thus, patients receiving SGLT2 inhibitors should be encouraged to drink an appropriate amount of water regularly and informed that dehydration may lead to the onset of thromboembolism, e.g., cerebral infarction. Dehydration may also lead to the onset of acute renal failure, which needs to be watched for particularly in patients concurrently receiving diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs) and non-steroidal anti-inflammatory drugs (NSAIDs). Again, SGLT2 inhibitors should be used with utmost caution in elderly patients 75 years of age or older, patients 65 to 74 years of age with geriatric syndrome (e.g., sarcopenia, cognitive decline, and decreased ADL) or patients likely to be associated with body fluid loss, e.g., those receiving concurrent diuretics), with attention also given to monitoring these patients closely for body fluid loss (particularly early after initiation of SGLT2 inhibitors), while ensuring that they drink an appropriate amount of water regularly, during the course of treatment with these agents. Of note, dehydration has also been reported to be associated with hyperglycemic hyperosmolar nonketotic syndrome. Furthermore, given that dehydration and cerebral infarction have been reported in not only elderly but younger patients receiving SGLT2 inhibitors, these conditions need to be closely watched for in all patients receiving SGLT2 inhibitors. Caution should be exercised against dehydration not only in patients starting on SGLT2 inhibitors but in those who have developed fever, diarrhea or vomiting or who have difficulty taking sufficient meals due to anorexia (e.g., during "sick days") while on SGLT2 inhibitors, i.e., those in whom SGLT2 inhibitors be discontinued. Again, all patients receiving SGLT2 inhibitors should be sufficiently instructed beforehand to exercise due caution while on these agents.

Additionally, given that dehydration represents an major risk factor for biguanide-associated lactic acidosis, caution needs to be exercised against both dehydration and lactic acidosis in patients receiving SGLT2 inhibitors as add-on to biguanides (see also "Recommendations on the Proper Use of Metformin" available from http://www.jds.or.jp).

Skin symptoms

While numerous case reports show that SGLT2 inhibitors are associated with various skin symptoms (e.g., itching, exanthema, and erythema), these are non-serious in a majority of cases. Skin symptoms are reported with all SGLT2 inhibitors, including some judged to be serious ARs based on their severity (e.g., those shown to be systemically spread or those requiring steroid treatment). Skin symptoms associated with SGLT2 inhibitors are shown to occur within about 2 weeks from one day after their initiation, indicating that these symptoms need to be closely watched for from early on, including the day of initiation of treatment. Given that some patients who developed rash

while on an SGLT2 inhibitor may develop rash with another SGLT2 inhibitor, it may be advisable to consider switching to a different class of agents other than SGLT2 inhibitors. In any case, it is critically important to seek consultation from dermatologists about skin symptoms developing in patients receiving SGLT2 inhibitors. Particularly, consultation must be sought immediately from dermatologists about any rash (redness or erosion) affecting the mucosa (e.g., conjunctiva, lip, external genitalia) thought likely to be a serious drug eruption such as Stevens-Johnson syndrome.

Additionally, it is shown in studies reported overseas that SGLT2 inhibitors are associated with Fournier's gangrene, i.e., necrotizing fasciitis affecting the external genitalia and/or perineum, which is also reported to be a cause of death in some cases. Given its rapid clinical course, Fournier's gangrene calls for immediate surgical and antibiotic treatment. Again, since delays in its diagnosis are likely to place affected patients at risk of dying from it, attention should be given to detection of redness, swelling and pain in the external genitalia/perineum and around the anus, and to ensuring that dermatologists or any other specialists capable of surgical procedures are consulted about any patient suspected of having Fournier's gangrene.

Urogenital infections

An increased incidence of urogenital infections (especially genital infections) is reported with SGLT2 inhibitors in clinical trials conducted in not only patients with type 2 but those with type 1 diabetes. Indeed, to date, numerous cases of urogenital infections have been reported with SGLT2 inhibitors. Urinary tract/genital infections reported to date mainly include pyelonephritis and cystitis/vulvovaginal candidiasis. Overall, it is shown that urogenital infections affect more women but do affect men as well, occurring 2-3 days or 2 months after initiation of treatment with SGLT2 inhibitors in some cases. Given that serious urogenital infections (e.g., pyelonephritis) continue to be reported, care should be taken to detect these infections using a questionnaire or laboratory testing as required and to seek consultation from urologists/gynecologists about any infection detected in patients receiving SGLT2 inhibitors.

In summary, the Committee has thus updated some of its major recommendations on the use of SGLT2 inhibitors in light of ARs reported, as well as PMS results reported for elderly users of SGLT2 inhibitors, during the five years after the launch of the first SGLT2 inhibitor, where the PMS data appear to suggest that a certain level of caution should be exercised in ensuring the safe use of SGLT2 inhibitors in patients 75 years of age or older.

CONFLICT OF INTEREST STATEMENT

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with human or animal subjects performed by any of the authors.

APPENDIX

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