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Pharmacology Consult

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Sodium-Glucose Cotransporter 2 Inhibitors and Fournier Gangrene

A Rare and Lethal Adverse Event

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In 2018, the US Food and Drug Administration issued a warning for a serious and rare infection, necrotizing fasciitis of the perineum, also called Fournier gangrene (FG) associated with sodium-glucose cotransporter 2 (SGLT2) inhibitors.[1] A rare infection, occurring more likely in males, FG destroys tissue in the perineal or perianal areas and/or the external genitalia.[2,3] Only 6 cases of FG (all men) were identified in other antidiabetic drug classes for a period of more than 30 years with an average of 1.6 infections for 100 000 males aged 50 to 79 years.[3] However, in the August 29, 2018, US Food and Drug Administration warning, 12 persons (7 men and 5 women) developed FG within months of beginning an SGLT2 inhibitor. All 12 patients were hospitalized and required surgery. Several patients required disfiguring surgical procedures and experienced complications, and 1 patient died.[3]

Sodium-glucose cotransporter 2 inhibitors are a new class of antihyperglycemics for the treatment of type 2 diabetes mellitus (T2DM) and are described in Table 1.[4] First introduced in 2013, SGLT2 inhibitors work in the proximal renal tubule blocking SGLT2 protein activity in glucose reabsorption. The result is increased renal excretion of glucose with concomitant decrease in blood glucose. Additional benefits include increased insulin sensitivity, improved insulin release from beta cells in the pancreas, and reduced gluconeogenesis. Patient outcomes include improved glycemia, glycated hemoglobin level reduction, and, for some persons, modest reductions in weight and blood pressure.[4,5] In addition to reductions in fasting and postprandial hyperglycemia, SGLT2 inhibitors promote increased endogenous glucose production and increased pancreatic glucagon secretion. Higher glucagon levels result in vasodilation in the kidney, which results in favorable cardiac effects leading to improved glomerular blood flow. These effects may be kidney protective, a benefit much desired considering the rise of diabetic kidney disease, which is the leading cause of end-stage kidney disease in the world and occurs in nearly half of patients with T2DM.[6] While the long-term efficacy and safety of SGLT2 inhibitors remain unknown, SGLT2 agents are a promising treatment for reducing the risk of cardiovascular disease and death and improving clinical outcomes for T2DM patients at risk of diabetic kidney disease and for those with heart failure.[6]

The most common adverse effects for both men and women are genital mycotic infections, the majority of which are caused by *Candida*.[6,7] Less common adverse effects are increased risk of fractures and lower limb amputations especially in patients with history of previous amputations. At this time, benefits of therapy appear to outweigh risks, and SGLT2 inhibitors can be safely administered with commonly used diuretics with close monitoring at the beginning of therapy particularly for patients receiving loop diuretics.[7] Use SGLT2 inhibitors with caution in hypovolemia to prevent renal insult. Glycosuria increases risk of genital and urinary tract infections as well as urosepsis and pyelonephritis. Patient education on signs and symptoms of infection and careful assessments are crucial to minimize adverse events.[8]

Results from multiple clinical trials are both favorable and neutral with respect to reductions in cardiovascular death and heart failure hospitalization with SGLT2 therapy.[8] It remains unknown whether benefits of therapy apply to all SGLT inhibitors in T2DM, not only for those at increased cardiovascular risk. Lower rates of death reported in observational studies with SGLT2 inhibitors may be a function of immortal time bias and time-lag biases also called survivor treatment selection bias, which is common in observational cohort studies.[9–11] Favorable outcomes may have occurred

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Table 1. Sodium-Glucose Cotransporter Type 2 Inhibitors for Treatment of Type 2 Diabetes Mellitus[4]

Year	Agent	Trade Name	Company	Website
2013	Canagliflozin	Invokana	Janssen Pharmaceuticals, Titusville, New Jersey	http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf
2014	Dapagliflozin	Farxiga	AstraZeneca, Wilmington, Delaware	http://www.azpicentral.com/farxiga/pi_farxiga.pdf
2014	Empagliflozin	Jardiance	Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Connecticut	https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf
2014	Ipragliflozin	Suglat	Astellas Phama Tokyo, Japan	Available only in Japan. For information in Japanese, see *Nihon Yakurigaku Zasshi* 2015;145(1):36–42
2017	Ertugliflozin	Steglatro	Merck & Co, Inc, Whitehouse Station, New Jersey	https://www.drugs.com/pro/steglatro.html or https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209803s000lbl.pdf

because patients who survived longer were more likely to receive care and not because the receipt of the drug intervention extended survival.[12] Certainly, more research is needed.

The majority of genital infections associated with SGLT2 inhibitors are mild cases and easily treated. However, caution is required for the diabetic patient and for persons with obesity, immunosuppression, end-stage renal disease, liver failure, smoking, and alcohol abuse because these patients have significant risk of more severe infections such as FG.[13] Patients should be instructed to seek medical attention right away for signs and/or symptoms of tenderness, redness, or swelling of the genitals or in the area from the genitals back to the rectum, a fever 100.4°F or greater and for just feeling unwell. Table 2 describes additional early and late signs of necrotizing fasciitis.[14] If FG is suspected, discontinue the SGLT2 inhibitor, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.[3]

Table 2. Progression of Signs in Necrotizing Fasciitis[14]

Early Signs
• Red/swollen areas that spread quickly
• Pain, usually severe and occurs beyond the area that is red or swollen
• Fever
Late Signs
• Ulcers, black spots on skin
• Skin color changes
• Pus, drainage from infected area
• Dizziness
• Fatigue
• Diarrhea
• Nausea

Rarely contagious, FG can lead to sepsis, shock, and organ failure with lifelong complications from scarring and amputations. Six of 10 persons with necrotizing fasciitis and streptococcal toxic shock syndrome at the same time usually die.[14] The SGLT2 medication guide should be reviewed every time the prescription is filled for any new warnings that have occurred since the last prescription.[1] Finally, monitor closely for genital fungal infections especially in women with previous genital fungal infections. In a recent study of 1049 patients (476 women, 573 men) receiving dapagliflozin, fungal infections were monitored. Baseline measures included mean age 56.7 ± 10.2 years, body mass index 35.5 ± 6.9 kg/m^2, and glycated hemoglobin 9.4% ± 1.5%. Only gender (13.2% women vs 3.3% men) and prior history of genital fungal infection (21.6% vs 7.3%) were associated with development of genital fungal infections after treatment with dapagliflozin (adjusted odds ratios [4.22; 95% confidence interval, 2.48–7.19; $P < .001$] and 2.41 [confidence interval, 1.04–5.57; $P = .039$], respectively).[15]

GOING FORWARD

Fournier gangrene is a rare necrotizing fasciitis of the perineal or perianal areas and/or external genitalia. Diagnosis of FG is an emergency with a high mortality. The best weapons are early recognition and immediate treatment with broad-spectrum antibiotics and surgical debridement. Considering the increasing prevalence of diabetes and an aging population, more clinical attention is needed on the early diagnosis and treatment of this life-threatening event especially in persons receiving SGLT2 inhibitors. Alternative FG treatment interventions such as hyperbaric oxygen therapy, vacuum-assisted closure, and unprocessed honey as a topical antimicrobial for now have limited supporting evidence due to the lack of controlled clinical trials.[2]

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References

1. US Food & Drug Administration (FDA). SGLT2 (sodium-glucose cotransporter-2) inhibitors for diabetes: drug safety communication - regarding rare occurrences of a serious infection of the genital area. US Department of Health and Human Services. August 29, 2018. https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm618908.htm; https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm. Accessed November 14, 2018.
2. Singh A, Ahmed K, Aydin A, Khan MS, Dasgupta P. Fournier's gangrene. A clinical review. *Arch Ital Urol Androl*. 2016;88(3):157–164.
3. US Food & Drug Administration (FDA). FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes. US Department of Health and Human Services. August 29, 2018. https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm. Accessed November 14, 2018.
4. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. *Drugs*. 2015;75(1):33–59.
5. Nair S, Joseph F, Ewins D, et al. From history to reality: sodium glucose co-transporter 2 inhibitors- a novel therapy for type 2 diabetes mellitus. *Pract Diabetes Int*. 2010;27:311–316.
6. Alicic RZ, Johnson EJ, Tuttle KR. SGLT2 inhibition for the prevention and treatment of diabetic kidney disease: a review. *Am J Kidney Dis*. 2018;72(2):267–277.
7. Opingari E, Partridge ACR, Verma S, Bajaj HS. SGLT2 inhibitors: practical considerations and recommendations for cardiologists. *Curr Opin Cardiol*. 2018;33(6):676–682.
8. Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72(15):1845–1855.
9. Suissa S. Response to comment on Suissa. Lower risk of death with SGLT2 inhibitors in observational studies: real or bias? *Diabetes Care* 2018;41:6-10. *Diabetes Care*. 2018;41(6):e109–e110.
10. Shariff SZ, Cuerden MS, Jain AK, Garg AX. The secret of immortal time bias in epidemiologic studies. *JASN*. 2008;19(5):841–843.
11. Ho AM, Dion PW, Ng CS, Karmakar MK. Understanding immortal time bias in observational cohort studies. *Anaesthesia*. 2013;68(2):126–130.
12. Goto M, Perencevich EN, Ohl ME. Immortal time bias in assessing evidence-based care processes for *Staphylococcus aureus* bacteremia—reply. *JAMA Intern Med*. 2018;178(2):296.
13. Kumar S, Costello AJ, Colman PG. Fournier's gangrene in a man on empagliflozin for treatment of type 2 diabetes. *Diabet Med*. 2017;34(11):1646–1648.
14. Centers for Disease Control. *Necrotizing fasciitis: all you need to know. October 18, 2018*. Atlanta, GA: National Center of Immunizations and Respiratory Diseases, Division of Bacterial Diseases: Available at: https://www.cdc.gov/groupastrep/diseases-public/necrotizing-fasciitis.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Ffeatures%2Fnecrotizingfasciitis%2Findex.html. Accessed November 14, 2018.
15. Thong KY, Yadagiri M, Barnes DJ, et al. Clinical risk factors predicting genital fungal infections with sodium-glucose cotransporter 2 inhibitor treatment: the ABCD nationwide dapagliflozin audit. *Prim Care Diabetes*. 2018;12(1):45–50.

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