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Infectious complications of newer agents in the fight against diabetes

Abstract: Infectious complications have been reported with antidiabetic medications. Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors have been associated with upper respiratory tract infections and urinary tract infections. Sodium-glucose cotransporter 2 inhibitors have been associated with lower limb amputations, urinary tract infections, genital mycotic infections, and Fournier gangrene.

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Diabetes is a major threat to health, with an estimated 10.5% overall prevalence in the US.[1] Diabetes is characterized by a deficiency and desensitization of the body to insulin, which results in an abundance of glucose in the bloodstream. This constant hyperglycemia can lead to impaired neutrophil chemotaxis and adherence to vascular endothelium, bactericidal activity, and cell-mediated immunity.[2,3] In addition to an impaired immune system, there is some debate whether patients with diabetes—especially those taking injectable medications—may be at higher incidence of colonization with *Staphylococcus aureus*, possibly due to the frequency of medical interventions.[4,5] This combination of factors may predispose patients to infections in body systems including the respiratory, urinary, and gastrointestinal

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systems; skin and soft tissues; and head and neck areas.[6]

Because immune systems of patients with diabetes are compromised, infections are often more severe and frequent than in patients without diabetes, and can pose a serious threat to quality of life.[6] In addition, patients with diabetes often have micro- and macrovasculature complications resulting in reduced blood flow, neuropathies that prevent immediate recognition of symptoms, gastrointestinal and urinary motility issues, and a greater frequency of medical interventions.[6] This can lead to prolonged time to clinical improvement and issues with antimicrobial resistance, necessitating longer courses of broad-spectrum antibiotics.

Three classes of medications used in the treatment of diabetes have been implicated in increased risk of infections: glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter 2 (SGLT2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors. This article reviews the place in therapy of these three medication classes, evaluates evidence for risk of associated infection, and discusses ensuing implications.

Methods

A literature search of MEDLINE (1966 to February 2020) using combinations of the following search terms: infection, SGLT2 inhibitor, GLP-1 RA, DPP-4 inhibitor, and individual medication names yielded 616 results. Any article type, including randomized studies, retrospective studies, observational reports, case series, and case studies were considered. References from pertinent articles and product monographs were reviewed. Fifty-five relevant English-language studies, reports, cases, and package inserts were included. The FDA provides guidance regarding labeling recommendations (see *FDA guidance for labeling recommendations*).[7]

Glucagon-like peptide-1 receptor agonists

GLP-1 RAs are FDA-approved for the treatment of type 2 diabetes as an adjunctive therapy to diet and exercise. Several GLP-1 RAs are available: exenatide (Bydureon, Byetta), liraglutide (Victoza), dulaglutide (Trulicity), lixisenatide (Adlyxin), and the newest agent, semaglutide (Ozempic, Rybelsus).[8-15] Exenatide, liraglutide, and lixisenatide are considered short-acting and administered by subcutaneous injection either once or twice daily, whereas exenatide extended-release, dulaglutide, and semaglutide (Ozempic) are long-acting and administered by subcutaneous injection once weekly; semaglutide (Rybelsus) is taken orally once daily. These considerations also apply to combination medications that include agents discussed here.

GLP-1 RAs bind to the glucagon-like peptide-1 receptor and stimulate glucose-dependent insulin release from pancreatic islets, slow gastric emptying, inhibit inappropriate postmeal glucagon release, and increase satiety and promote weight loss. Meta-analyses suggest that GLP-1 RA therapy in patients with a baseline hemoglobin A1C (A1C) of 8%-8.5% can lower A1C by 0.2%-0.3% more than insulin glargine, and

FDA guidance for labeling recommendations[7]

Section	When to Include
Contraindication	When risk from use clearly outweighs any possible therapeutic benefit
Boxed Warning	• An adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug • An adverse reaction that could be prevented with appropriate use • The drug can only be used safely with restrictions.
Warnings and Precautions	Adverse reactions that result in the following: • Death • Life-threatening adverse events • Inpatient hospitalization or prolongation of hospitalization • Persistent or significant incapacity or disruption to normal life functions • Congenital anomaly or birth defect • Otherwise clinically significant adverse reactions with implications for prescribing
Adverse Reaction	Undesirable effect reasonably associated with use of the drug; events that do not meet criteria above

Summary of FDA labeling recommendations for infections with newer antidiabetic agents

Infection	FDA Labeling Recommendations
GLP-1 RAs	
URTI	Adverse reaction (albiglutide and liraglutide)[10,13]
SGLT2 Inhibitors	
Lower limb amputation	Warnings and precautions*[21,24] (Note: this originally was a boxed warning for canagliflozin, but it was removed in August 2020)
Urinary tract infection	Warnings and precautions[21-24]
Genital mycotic infection	Warnings and precautions[21-24]
Fournier gangrene	Warnings and precautions[21-24]
DPP-4 Inhibitors	
URTI	Adverse reaction[45-48]

*Does not include dapagliflozin or empagliflozin

compared with placebo, these agents have been shown to reduce A1C by 1%.[16] In a systematic review of 17 randomized trials comparing GLP-1 RAs with placebo or another antidiabetic agent, patients demonstrated a weight reduction of about 1.5-2.5 kg over a period of 30 weeks.[16] Notably, these agents have minimal risk of hypoglycemia, unless used in combination with insulin or insulin secretagogues (sulfonylureas such as glyburide and glipizide).[10]

These agents do come with certain risks of infectious complications, particularly upper respiratory tract infections (URTIs)[10,13] (see *Summary of FDA labeling recommendations for infections with newer antidiabetic agents*). In addition, cases of nasopharyngitis and influenza have been associated with GLP-1 RA use, although much of this evidence is conflicting. In a trial of once-weekly dulaglutide in 361 patients with type 2 diabetes, nasopharyngitis was one of the most frequent adverse events (27% dulaglutide versus 26% insulin glargine).[17] In a trial comparing the efficacy and safety of 0.5 and 1 mg semaglutide against insulin glargine in 1,089 patients with type 2 diabetes, investigators found that the percentage of nasopharyngitis and URTI was the same or higher in patients taking insulin compared with those taking semaglutide (URTI incidence in patients taking insulin: 7% versus semaglutide, 3% [0.5 mg] and 4% [1.0 mg]).[18] Further evidence comes from the Liraglutide Effect and Action in Diabetes (LEAD)-6 trial of 464 patients with type 2 diabetes, which showed an overall infection rate (mainly nasopharyngitis and URTIs) of 33.2% in patients randomized to the liraglutide group and 36.6% in patients randomized to the exenatide group.[19] In a randomized controlled trial of exenatide versus placebo in 116 patients with type 2 diabetes, urinary tract infection (UTI) was one of the most frequently reported adverse events, but was similar between groups (6.7% versus 8.9%, respectively).[20] In summary, GLP-1 RAs are associated with the development of URTI, which is listed as an adverse reaction in some package inserts of this class but is not a contraindication to use and is not listed as a warning or precaution. Clinicians should screen patients taking GLP-1 RA for signs or symptoms of URTI or UTI and treat accordingly.

Sodium-glucose cotransporter 2 inhibitors

SGLT2 inhibitors are FDA-approved for the treatment of type 2 diabetes accompanied by lifestyle changes including diet and exercise. Agents currently available in the US include canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance), and ertugliflozin (Steglatro).[21-24] These are all administered orally once daily. These considerations would also apply to combination medications that include agents discussed here.

SGLT2 inhibitors reduce serum glucose by increasing glucose excretion through inhibition of the SGLT2 transporter in the kidney, which normally reabsorbs approximately 90% of the glucose from the renal filtrate. These

agents can be used as either monotherapy or in combination with other agents, such as insulin, metformin, or sulfonylureas, and can decrease A1C by 0.5%-1.5%.[25] Additional benefits of these agents include weight loss (2-3 kg due to calorie loss from renal glucose excretion), decreased BP, and very low incidence of hypoglycemic events except when added to insulin or a sulfonylurea. In addition, the benefits of SGLT2 inhibitors on body weight and BP positively impact cardiovascular risk factors.[26-28] Within this class, canagliflozin and empagliflozin have been shown to reduce the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.[26,27] Additionally, both medications reduced hospitalization for heart failure, and empagliflozin reduced death from any cause.[26-28] The FDA has added indications for canagliflozin and empagliflozin to reduce the risk of cardiovascular death in adult patients with type 2 diabetes and existing cardiovascular disease.[29,30]

Clinicians should monitor patients for signs or symptoms of UTIs while on SGLT2 inhibitor therapy and treat accordingly.

However, SGLT2 inhibitors are not without adverse reactions. Neal and colleagues found that use of canagliflozin increased risk of lower limb amputations by 97% versus placebo.[27,29] A retrospective cohort study with over 953,000 patients with diabetes found that initiating SGLT2 inhibitors increased risk of amputations; however, this increased risk was not significant when SGLT2 inhibitors were compared with DPP-4 inhibitors or GLP-1 RAs.[32] Consequently, these findings led to the FDA warning that canagliflozin should be discontinued if patients develop infections or ulcers of the lower limbs.[21]

Next, glycosuria resulting from SGLT2 inhibitors leads to increased occurrences of UTI.[31-38] Package inserts for agents within this class contain information on postmarketing reports of serious UTI, including cases of urosepsis and pyelonephritis.[31] A systematic review of SGLT2 inhibitors (seven trials) found that compared with the control groups, there was an 8.8% versus 6.1% rate increase of UTIs (risk ratio 1.44, 95% confidence interval [CI] 1.05-1.98).[32] In a safety evaluation of canagliflozin, UTI was reported in 2.54% of the study participants, who were subsequently removed from the study and treated appropriately.[33] In a meta-analysis of randomized controlled trials, dapagliflozin was associated with an increased risk of UTI versus comparator (relative risk [RR] 1.74 [95% CI 1.21-2.49]).[34] In contrast, two meta-analyses (105 and 86 randomized trials, respectively) found no significant difference in the risk of UTI with the SGLT2 inhibitors versus comparators except for high-dose (≥10 mg) dapagliflozin (odds ratio [OR] 1.30 [95% credible interval 1.09-1.57] and RR of 1.33 [95% CI 1.10-1.61], respectively).[35,36] Clinicians should monitor patients for signs or symptoms of UTIs while on SGLT2 inhibitor therapy and treat accordingly.

In addition to UTIs, glycosuria resulting from the SGLT2 inhibitors has been associated with mycotic genital infections such as vulvovaginal candidiasis.[31,34,36-38] A double-blind study evaluated vulvovaginal symptoms and Candida colonization in 198 women with type 2 diabetes and revealed that treatment with canagliflozin was associated with increased incidence of vulvovaginal candidiasis as compared with placebo (OR 2.8, 95% CI 1.0-7.3).[37] Three subsequent meta-analyses confirmed these findings for SGLT2 inhibitors (RR 3.37 [95% CI 2.89-3.93]; RR 3.52 [95% CI 2.06-6.03] for dapagliflozin; OR ranging from 3.21 [95% CI 2.08-4.93] for dapagliflozin 2.5 mg to 5.23 [95% CI 3.86-7.09] for canagliflozin 300 mg).[34,36,38] In these meta-analyses, the increased risk of genital infections was present regardless of medication or dose regimen. Finally, in a recent evaluation of older women and men with diabetes, SGLT2 inhibitor use was associated with an adjusted hazard ratio of 2.47 (95% CI 2.08-2.92) for genital mycotic infection versus DPP-4 inhibitors within 30 days of medication initiation.[39] Of interest, one meta-analysis found that SGLT2 inhibitors unexpectedly reduced the risk of gastroenteritis and were not associated with increased risk of UTI, or respiratory tract infections.[38] However, the randomized controlled trials were not of sufficient power to detect rare infections such as urosepsis or pyelonephritis. Clinicians should screen patients for signs or symptoms of mycotic genital infections while on SGLT2 inhibitor therapy and treat accordingly.

Most infections associated with this class occur more frequently in women or uncircumcised males.[31] Infections are usually mild or moderate, for the most part easily treated with antifungal agents, and usually

do not require medication discontinuation.[29] The incidence of infection is higher within the first 6 months of initiation, but frequency decreases over time. The possibility of more severe infections should be taken into account when considering adding an agent from this class to a patient's regimen—especially if the patient has a history of genital infections, as such patients are more susceptible. Combining antidiabetic agents generally increases the risk of adverse reactions; however, one meta-analysis found that combination therapy of a DPP-4 inhibitor with SGLT2 inhibitors may actually reduce the frequency of genitourinary tract infections in comparison to an SGLT2 inhibitor alone.[40]

When counseling patients on SGLT2 inhibitors, special care should be taken to ensure that the patient is aware of the signs and symptoms of a UTI or mycotic genital infection, such as dysuria, urinary urgency and frequency, swelling, vaginal itching, or abnormal discharge. In most cases, these infections can be eradicated using standard treatment and seldom necessitate discontinuing the SGLT2 inhibitor.[41] Topical or oral antifungal treatment as appropriate for mycotic infections or appropriate antibiotics for bacterial UTI can be used for treatment, with consideration of prophylaxis of mycotic infection if warranted.[41] Despite the prevalence of infection with use of these agents, there appears to be no clinical consensus regarding when to discontinue an SGLT2 inhibitor or switch to another medication within the class due to recurrent genitourinary infections, so it is up to the healthcare provider and patient to make that decision with the patient's best interests, including quality of life and optimized therapeutic outcomes, in mind.[39,41]

In August 2018, the FDA issued a warning regarding occurrence of a rare but serious infection of the perineum called Fournier gangrene.[42,43] This is a life-threatening bacterial infection of the tissue under the skin that surrounds the muscles, nerves, fat, and blood vessels of the perineum and genital areas. Between 2013 and 2019, 55 cases of Fournier gangrene were identified in patients taking SGLT2 inhibitors compared with 19 cases between 1984 and 2019 in all other antihyperglycemics.[31,44] In one case involving empagliflozin, this necrotizing fasciitis was diagnosed 14 months after initiating the medication.[45] The patient recovered after aggressive surgical debridement of the necrotic tissue and use of I.V. broad spectrum antibiotics for 2 weeks, followed by oral antibiotics. Risk factors in addition to diabetes are thought to include obesity, immunosuppressed states, smoking, alcohol use disorder, and end-stage renal or liver failure.[46] The FDA requires a warning stating this risk on all SGLT2 inhibitor prescribing information and patient medication safety guides. Patients should immediately seek medical attention if they experience any tenderness, redness, or swelling of the genitals or perineum and have a fever above 100.4°F (38°C) or malaise.[42] In addition to referring the patient to the ED, the SGLT2 inhibitor should be immediately discontinued and alternative therapy should be provided.

In summary, SGLT2 inhibitors are associated with development of UTIs, including serious UTIs such as urosepsis and pyelonephritis; mycotic genital infections; and Fournier gangrene. This class is also associated with lower limb amputation. The infections are listed as warnings and precautions. The lower limb amputations are listed as warnings and precautions for canagliflozin and ertugliflozin. Canagliflozin had lower limb amputation listed as a boxed warning, but this was removed in August 2020.[21] These warnings are not contraindications for use. Patients should be educated about the importance of routine foot care.[21,24] Clinicians should screen for signs and symptoms of infection, new pain or tenderness, or ulcers of the lower limbs, signs and symptoms of UTIs and genital infections, and signs and symptoms of Fournier gangrene while patients are taking SGLT2 inhibitors and treat accordingly.

Dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors are FDA-approved as monotherapy in patients intolerant to or with contraindications for metformin, sulfonylureas, or thiazolidinediones. They can also be considered as add-on therapy for patients with subtherapeutic responses for glycemic control already on the aforementioned agents.

Four agents are available in the US, including sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), and alogliptin (Nesina).[46-49] Most are administered once daily without regard to food, and all agents are available in combination with metformin. The considerations discussed here would apply to combination agents as well.

DPP-4 inhibitors inhibit the enzyme DPP-4, which rapidly deactivates the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. Thus, when this enzyme is hindered, endogenous

GLP-1 continues to lower serum glucose by stimulating insulin secretion and suppressing glucagon secretion in a glucose-dependent manner.[50]

These agents do not offer as many secondary benefits as compared with other classes of antidiabetic agents, although they do not cause weight gain and result in modest glycemic improvements according to clinical data. One head-to-head trial reported a 0.52%-0.62% reduction in A1C in patients taking saxagliptin or sitagliptin plus metformin compared with metformin alone.[51]

Unfortunately, inhibiting DPP-4 may have more consequences than intended.[52,53] The lymphocyte cell surface protein CD26, which plays an integral role in the immune system, especially in T-cell activation, includes DPP-4 activity. It is involved in maintaining lymphocyte composition/function, T-cell activation and costimulation, as well as memory T-cell generation. Because of its DPP-4 activity, CD26 may also be suppressed by DPP-4 inhibitors, resulting in immunomodulation. Consequently, DPP-4 inhibition may result in a greater glycemic-immunosuppression balancing act than initially realized.[54] Therefore, the extent of selectivity from varying agents on the DPP-4 enzyme may influence the chance for infection-related adverse reactions.

Patients on GLP-1 RAs, SGLT2 inhibitors, and DPP-4 inhibitors should be made aware of the signs and symptoms of associated infections.

The most common infection-related adverse reactions of DPP-4 inhibitors are nasopharyngitis and URTI.[52] One meta-analysis comparing DPP-4 inhibitors with placebo found a small increased risk of nasopharyngitis (RR 1.13 [95% CI 0.99-1.29]), mostly with sitagliptin.[54] In a pooled analysis of linagliptin, nasopharyngitis occurred slightly more frequently (5.9%) than placebo (5.1%).[55] In contrast, more recent meta-analyses found no significant difference in infection versus placebo. [53] Of note, in an evaluation in patients with HIV, sitagliptin reduced inflammatory markers such as high-sensitivity C-reactive protein, potentially indicating an anti-inflammatory effect.[56] In another study evaluating patients with HIV, sitagliptin compared with placebo did not demonstrate significant change in immunologic biomarkers, including CD4, IL-6, TNF-alpha, or on T-cell activation.[57] While nasopharyngitis or URTIs can occur, these are typically self-limiting and do not require a change in DPP-4 inhibitor therapy.

In summary, DPP-4 inhibitor therapy can cause nasopharyngitis or URTIs as an adverse reaction, but URTIs are not listed as a contraindication or as a warning/precaution for DPP-4 inhibitors. URTIs are usually self-resolving without the need to switch from the DPP-4 inhibitor class. The impact of long-term DPP-4 inhibition on immunologic response is hypothetical, and postmarketing surveillance of immune-related issues from DPP-4 inhibitors would seem prudent.

Relevance to patient care and clinical practice

When evaluating and counseling patients on GLP-1 RAs, SGLT2 inhibitors, and DPP-4 inhibitors, special care should be taken to monitor for and ensure the patient is aware of the signs and symptoms of associated infections. In most cases, these infections can be eradicated using standard treatment and seldom necessitate discontinuing the medication. In cases of severe or life-threatening infections, clinicians should refer patients to the ED and counsel them to discontinue therapy immediately. The healthcare provider and patient should evaluate the benefits versus risks of therapy with these agents to decide whether to continue therapy if infection does occur during or resulting from therapy.

Conclusion

Several medications used to treat diabetes have been associated with potentially serious infections. Healthcare providers should make informed decisions utilizing evidence-based knowledge to provide optimal care while minimizing risks to patients. In cases of serious, life-threatening reactions, the FDA could consider Phase IV prospective clinical trials to evaluate postmarketing drug safety. Otherwise, clinicians may consider using existing databases such as the FDA Adverse Event Reporting System (FAERS), Medicare or Medicaid databases, or insurance company claims in order to identify adverse reactions that are less common. NP

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