A new class of drug in the diabetes toolbox

The DAWN and SEED trials demonstrate the potential of glucokinase activators for the treatment of type 2 diabetes, but how they fit in the overall treatment algorithm remains to be determined.

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For nearly three decades, scientists have searched for an orally active small-molecule activator of glucokinase (GK) for the treatment of diabetes, because of its central role in glucose homeostasis in the pancreas and the liver[1]. The first report of a potential glucokinase activator (GKA) was published in 2003, and was followed by more than 150 patents and considerable attention by the pharmaceutical industry[1–3]. Progress has been hampered by predictable adverse effects that were noted in early clinical studies; however, some have persevered, leveraging medicinal chemistry to engineer away adverse features. In this issue of *Nature Medicine*, Zhu et al. and Yang et al. report results of the SEED and DAWN studies, respectively — two phase 3 trials evaluating the GKA dorzagliatin in patients with type 2 diabetes[4,5].

The biology of GK as a molecular glucose sensor has been slowly elucidated since its discovery in the 1960s, but interest peaked at the turn of the century when mutations in GK were associated with heritable forms of diabetes and hypoglycemia. Mechanistic insights have raised concerns about adverse effects. For instance, unfettered activation of GK in the pancreatic β-cell was expected to reduce thresholds for insulin secretion, which could potentially lead to hypoglycemia — a hypothesis supported by genetic hypoglycemia syndromes. In hepatocytes, GK regulates glucose uptake and storage, generating concern that hepatic GK activation could lead to increased lipid biosynthesis and subsequent hypertriglyceridemia and hepatic steatosis[1,6]. Indeed, hypoglycemia and hyperlipidemia shut down several drug development programs[1]. Dorzagliatin is a GKA that is active in both pancreatic islets and hepatocytes, but preliminary studies suggested few adverse effects[7].

The DAWN and SEED studies, both conducted in China, evaluated longer treatment durations in larger populations of patients with inadequate glycemic control and an average BMI (body mass index) of approximately 26 kg/m^{-2}.

The SEED study examined the safety and efficacy of dorzagliatin in treatment-naive adults ($n = 463$) with relatively new onset type 2 diabetes, randomized to dorzagliatin (75 mg) or placebo twice daily, for 24 weeks. At week 24, hemoglobin A1$_c$ (HbA1c) levels (indicating average blood glucose) were reduced by 1.07% in participants randomized to dorzagliatin, compared to 0.5% in placebo-treated participants — a statistically significant estimated treatment difference (ETD) of –0.57%. Following the masked portion of the study, participants were invited to join an open-label treatment period with dorzagliatin for 28 weeks, during which the reduction in HbA1c was sustained in participants previously randomized to dorzagliatin. Those who switched from placebo to dorzagliatin exhibited a further 0.77% reduction in HbA1c and ended the 52-week study with an average HbA1c that was less than that of participants treated with dorzagliatin for the full year.

The DAWN study followed the same basic design, randomizing adults with type 2 diabetes ($n = 767$) who were receiving metformin monotherapy to either 1,500 mg metformin (divided in 2–3 times daily doses) in combination with 75 mg dorzagliatin (twice daily), or 1,500 mg metformin in combination with placebo. Although this population had a mean

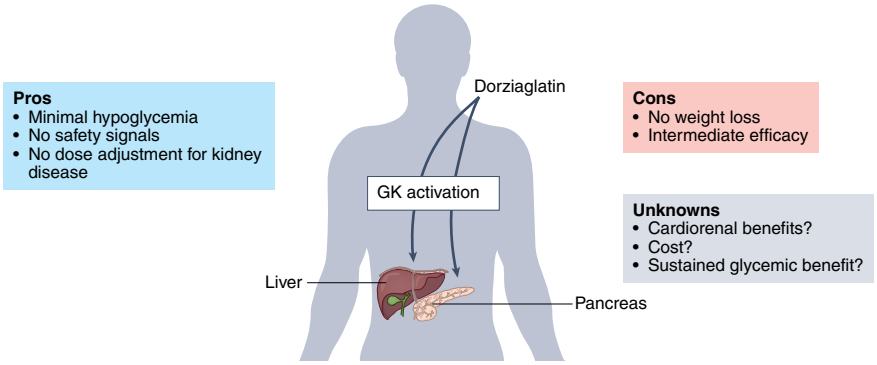

Fig. 1 | Positioning dorzagliatin in future treatment paradigms. Features of dorzagliatin that may influence future patient selection are highlighted.

duration of diabetes of nearly 5 years, they were required to have C-peptide levels above the lower limit of normal at screening, thereby limiting exposure to patients with preserved insulin secretory capacity. At week 24, HbA1c was reduced by 1.02% in participants randomized to dorzagliatin, compared to 0.36% in placebo treated participants — a statistically significant ETD of –0.66%. In the 28-week open-label portion of the study, HbA1c increased slightly (0.21%) in participants who had already received dorzagliatin for 24 weeks. By contrast, those switched from placebo to dorzagliatin after the initial 24 weeks sustained a further 0.6% reduction in HbA1c and, as was observed in SEED, ended the study with an average HbA1c that was less than that of participants treated with dorzagliatin for the full 52 weeks.

The safety profile was favorable in both studies, with no substantial concern for hypoglycemia, hyperlipidemia or hepatic toxicity. Dorzagliatin was weight neutral. Although rigorous monitoring for asymptomatic hypoglycemia was not conducted in either study, only seven episodes of clinically significant symptomatic hypoglycemia were recorded in dorzagliatin-treated participants, with none recorded in placebo-treated individuals. All episodes were self-limited. An increase of ~20% in triglycerides was reported in both studies, in participants randomized to dorzagliatin at week 24, but triglycerides did not rise further in the extension phases. Adverse events were largely balanced between the active drug and placebo, suggesting overall safety of dorzagliatin.

Consistent with the mechanism of action, β-cell function and insulin resistance were improved in both studies; however, whether the primary effect of dorzagliatin is due to activity within the β-cell or the hepatocyte is uncertain. Increased insulin secretion may be particularly favorable in early type 2 diabetes, due to loss of first-phase insulin release. As with other insulin secretagogues, dorzagliatin has the potential to cause progressive β-cell stress. The numerically greater HbA1c reduction at 52 weeks among those treated with placebo for the first 24 weeks in both studies suggests that this may be the case with dorzagliatin. However, the hepatic activity of this non-selective GKA could maintain long-term efficacy of dorzagliatin, even if it does induce β-cell decline. Another GKA under development, TTP399, is hepatoselective and does not affect β-cell function. Phase 2 studies with TTP399 demonstrate improved glycemic control in patients with both type 2 and type 1 diabetes[8,9]. These data provide hope that GKAs will provide long-term glycemic benefit.

Many questions remain. For example, additional studies will be necessary to determine if dorzagliatin can demonstrate long-term efficacy, provide the same benefit and safety in the setting of sulfonylurea and insulin therapy and in more obese populations, and confer cardiorenal benefits. It will also be necessary to determine whether dorzagliatin causes accelerated β-cell dysfunction or has clinical benefit in individuals without substantial β-cell function. Combining dorzagliatin with agents that could provide β-cell protection — such as glucagon-like peptide 1 (GLP-1) receptor agonists or thiazolidinediones (TZDs) – may allow for β-cell preservation and a synergistic mechanism of action[10].

The DAWN and SEED trials capitalize on more than five decades of basic and translational research to demonstrate the potential of GK activation for the treatment of diabetes. It seems unlikely that dorzagliatin will become standard first- or second-line therapy after metformin for the patients with type 2 diabetes and obesity. Generally, such patients would benefit from weight loss and therapeutics that offer cardiorenal protection, such as the GLP-1 receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors. As dorzagliatin requires no dose adjustment for kidney disease, there may be a niche for this GKA in patients who have diabetes and advanced kidney disease, for whom antihyperglycemic therapy options are currently very limited[11]. Indeed, as more is understood about the heterogeneity of diabetes and precision medicine becomes a reality, it is likely that various populations will benefit from pharmacotherapies specific to the metabolic and genetic abnormalities responsible for their hyperglycemia. Regardless, the DAWN and SEED trials demonstrate that GKAs should have a place in the antihyperglycemic armamentarium (Fig. 1)[12], although further studies will be needed to fully elucidate their role. Drug regulators and market forces will define the pace and scale of adoption of what could be the first fundamentally new class of diabetes medications in nearly a decade. ❐

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Competing interests

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