EDITORIAL

Canagliflozin/metformin Fixed-dose Combination: National Evidence, Global Relevance

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Diabetes is a multifactorial and multifaceted syndrome, which needs a multipronged approach to management.[1] Judicious use of rational drug combinations assists in the timely achievement of glycemic targets in persons with type 2 diabetes.[2] Fixed-dose combinations (FDCs) offer a person-friendly means of taking multiple drugs. Not only that, FDCs are physician-friendly but pharmacist-friendly as well, as they ease both prescription writing and dispensing.

In recent years, sodium-glucose transporter 2 inhibitors (SGLT2i) have created a paradigm shift in the management of type 2 diabetes.[3] Apart from good glucose control, these drugs also ensure cardiovascular and renal benefits. This has made them a preferred choice in modern algorithms. Certain guidelines suggest the use of SGLT2i, with metformin, as first-line therapy.[4] This move is welcome, as it allows persons living with type 2 diabetes to benefit from the pleiotropic advantages of SGLT2i.[5]

While randomized controlled trials (RCTs) have always provided robust evidence for the efficacy, safety, and tolerability of drugs, their applicability to large populations can be questioned. Real-world evidence (RWE),[6] therefore, is required to explore the utility of newly introduced medications. One way of doing this is to perform phase 4, or postmarketing trials. Phase 4 trials, conducted in India, allow medicines to be tested in Indian participants, with appropriate trial methodology, using clinically relevant endpoints under the robust controls associated with clinical trials. Thus, phase 4 trials offer the advantages of both phase 3 RCTs and RWE and study the safety as well as efficacy of the concerned drug.

Magdum et al. report the findings of such a prospective, multicentric, open-label, single-arm study, conducted on 276 Indian adults living with type 2 diabetes.[7] These participants, aged 18–65, were inadequately controlled on diet and exercise. They were initiated on an FDC of canagliflozin and metformin (50/500 and 50/1000 mg) twice daily. Unlike most other studies safety assessment was taken as the primary endpoint, and change in glycated hemoglobin (HbA1c) as the secondary endpoint. This methodology highlights the need to focus on the safety and tolerability of newer drugs. The inclusion criteria allowed initiation of canagliflozin + metformin in persons on glucose-lowering pharmacotherapy, as well as those who were treatment-naive. This is concordant with guidance from European as well as American professional organizations.[4]

The demographics of the study cohort are representative of patients seen in Indian diabetes practice, with a majority of relatively elder male participants. Central obesity, as well as obesity, is common and so is impaired renal function. Dyslipidemia and hypertension are the commonly reported comorbidities, followed by hypothyroidism and diabetic neuropathy.

The results reveal good tolerability of the canagliflozin + metformin FDC. As 41.6% of participants reported a treatment-emergent adverse event (TEAE), this reflects the attentiveness of the investigators. Only 10.6% of participants; however, experienced a TEAE related to the study treatment. Serious TEAEs were uncommon (1.1%), with only two persons (0.7%) reporting serious TEAE related to the study treatment. Adverse events that are commonly linked to SGLT2i include genital infection, urinary tract infection, and diabetic ketoacidosis. These were noted in 3.3, 2.6, and 0.4% of participants, respectively. Counseling regarding genital hygiene and hydration can further minimize the risk of these complications. Hypoglycemia, rarely encountered with SGLT2i and metformin, was reported by 3.3% of participants. It must be noted that these persons were those who were taking other glucose-lowering therapy as well.

Efficacy was a secondary endpoint in this study. Starting from a baseline of 8.5 ± 0.83%. Around 27.8 and 34.3% of persons were able to achieve target HBA1 c <7% at 12 and 24 weeks, respectively. A weight loss of 2.1 kg and a reduction in waist circumference of 1.73 cm were documented at week 24, along with a fall in blood pressure of 2.6/0.1 mmHg.

Canagliflozin was approved for medical use in 2013. The Canagliflozin Cardiovascular Assessment Study trial proved the cardiovascular and renal safety and benefits of canagliflozin in 2017. Along with similar findings from other cardiovascular outcome trials, these have brought about a paradigm shift in the management of diabetes SGLT2i are now used as preferred therapy not only to achieve euglycemia, but also to protect the heart and kidney, and prevent vascular and renal complications.

The pan India by Magdum et al. describes the safety and efficacy of providing reassurance that canagliflozin + metformin FDC can be used safely in a wide spectrum of patients, as monotherapy, or along with other glucose-lowering drugs. At the same time, the results caution us to practice pharmacovigilance and keep a close watch on possible adverse events. The study also adds weight to the growing data on diabetes care from India and showcases the ability of Indian investigators to conduct, and publish, good-quality RWE. We commend the authors, as well as the editor of the Journal of Physicians of India for sharing their knowledge, and for contributing to the growth of Indian diabetology.

The data, collected from across India, has not only national but international relevance.

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