JOURNAL OF SCIENTIFIC RESEARCH IN ALLIED SCIENCES
ISSN NO. 2455-5800
DOI No. 10.26838/JUSRES.2020.6.1.121

Contents available at: www.jusres.com

TRIPLE DRUG THERAPY AS FIXED-DOSE FORMULATION OR A COMBINATION THERAPY FOR TYPE 2 DIABETES

Sanjay Arora[1], Sanjeev Gupta[2], Santosh Kumar[3], Shankar Narayanan[4]

1. *F-85, 2nd floor, Mansarover Garden, Delhi-110015*
2. *Swastik Hospital, Sec-3, Jawahar Nagar, Jaipur -302004*
3. *Apoorva Heart Care Clinic Ballia -277001*
4. *M. L. Dhawale Hospital, Boisar Rd, Opposite S.T Workshop, Gothan Pura, Palghar, Maharashtra 401404*

ARTICLE INFO | **ABSTRACT** | **REVIEW ARTICLE**

Article History
Received: December 2019
Accepted: February 2020

Corresponding author
Sanjay Arora
Mansarover Garden, Delhi

INTRODUCTION

Type 2 diabetes mellitus is a multifactorial disease affecting multiple organ systems. It is characterized by the resistance of cells to insulin thereby causing hyperglycemia. It is associated with microvascular and macrovascular complications which in the long run can lead to morbidity and mortality. Lifestyle modifications and monotherapy with oral hypoglycemic agents are generally considered as a first-line intervention for glycemic control. Type 2 diabetes mellitus is a multifactorial disease affecting multiple organ systems. It is characterized by the resistance of cells to insulin thereby causing hyperglycemia. It is associated with microvascular and macrovascular complications which in the long run can lead to morbidity and mortality. Lifestyle modifications and monotherapy with oral hypoglycemic agents are generally considered as a first-line intervention for glycemic control[1]. Fixed-dose and combination therapies with complementary mechanisms of action provide the opportunity to achieve earlier and more sustainable glycemic control with increased patient adherence and reduced side-effect profiles[2]. Basically, combination therapy with agents having complementary mechanisms of action formulated as a single dosage form is known as "Fixed-Dose Combinations" (FDCs) while, combination therapy is con-current usage of two or more drugs having complementary mechanisms of action which may not be in a single dosage form.

Essentially, the rationality of FDCs should be based on certain aspects such as[3]:

- The drugs in the combination should act by different mechanisms,
- The pharmacokinetics must not be widely different,
- The combination should not have supra-additive toxicity of the ingredients

Various FDC involving two drugs have been approved by USFDA: Glucovance (glibenclamide +metformin), actoplusmet

(pioglitazone + metformin), janumet (sitagliptin + metformin), kombiglyze XR (saxagliptin + metformin), jentadueto (linagliptin + metformin), oseni (alogliptin + pioglitazone), invokamet (canagliflozin + metformin) and xigduo XR (dapagliflozin + metformin). A combination of nateglinide and voglibose (Basen, Japan) is approved in Japan[3].

However, healthcare professionals should be aware of the role of these products, including their advantages and disadvantages (Table 1).

Table 1: Advantages and Disadvantages of FDCs in diabetes[1]

S. No	Advantages of FDCs	Disadvantages of FDCs
1	FDCs help in formulating two drugs into a single dosage form, thereby minimizing the medication burden to the patient.	Dose titration will be difficult.
2	The relative adherence rates of type 2 diabetes patients can be improved.	A patient who is satisfied taking separate medications may not switch to FDCs.
3	It improves glycemic control showing better efficacy	There may be an increase in the number of ADRs
4	Medical expenditures due to hospitalization can be reduced	The combination may affect the bioavailability of agents
5	It decreases the frequency of drug administration in patients with type 2 diabetes	The drugs may be incompatible physically leading to the generation of undesired impurities
6	It prevents polypharmacy	Difficult to identify the drug candidate causing a side effect in the patient

Combination therapy for type 2 diabetes is preferred modality; however, compliance and cost-effectiveness are the two major constraints faced by combination therapy. Adherence is commonly overlooked in clinical practice, although it is an essential part of treating chronic diseases. There can be multiple reasons for non-compliance or non-adherence viz., some patients do not accept insulin treatment because of the fear of needles and injections, the fear that the complications of diabetes are caused by insulin, and other false beliefs, and are willing to take as many antidiabetic pills the doctor is prepared to prescribe. In a retrospective observational study, Rozenfeld et al. reported that for each 10% decrease in drug adherence, a 0.1% decrease in HbA1c level was observed. The adherence rate for oral antidiabetic agents ranged from 65% to 85%[4]. Guillausseau et al reported in a prospective observational study that patients were less likely to adhere to treatment as the frequency of dosing increased from once daily to 3 or 4 times per day, and treatment efficacy exhibited an inverse correlation with dosing frequency[5]. In one randomized controlled trial (the UMPIRE [Use of a Multidrug Pill in Reducing Cardiovascular Events] trial), fixed-dose combinations for aspirin, statins, and hypertension medication improved adherence and clinical outcomes (blood pressure and LDL-C)[6,7]. A meta-analysis involving >70,000 patients in 10 observational studies showed a significant 0.53% A1C reduction with FDCs compared with co-administered dual therapies associated with improved adherence, as measured by a 5.0% to 8.6% increase in medication possession ratio[8]. More recently, the retrospective GIFT study reported a 0.3% to 0.4% A1C reduction after a switch from separate metformin and DPP4 inhibitor to an FDC[8]. The greatest improvement was seen in patients with the highest pill burden (>10

pills/day), reinforcing the potential benefits of consolidating AHA therapies. This is consistent with the 2003 World Health Organization report citing numbers of medications (>5) and doses (>12) as major predictors of poor adherence, especially in elderly individuals with multiple co-morbidities[9]. Choi et al., compare the pharmacokinetic characteristics of metformin between a fixed-dose combination (FDC) of voglibose/metformin and co-administered individual voglibose and metformin tablets in healthy Korean volunteers under fasting conditions[10]. A randomized, open-label, single-dose, two-treatment, two-way crossover study with a 7-day wash-out period was conducted. In total, 7 adverse drug reactions occurred in 4 subjects during the study; of these, 3 cases were from 3 subjects in the test treatment group, and 4 cases were from 3 subjects in the reference treatment group. All adverse drug reactions had been reported previously, and all subjects recovered fully without any squeal. In conclusion, the pharmacokinetic profiles of metformin in two different study treatments, a voglibose/metformin FDC vs. the co-administration of the individual formulations, met the regulatory criteria for bioequivalence in healthy Korean subjects under fasting conditions. There was no significant difference in safety profiles between the two treatments. Thus, indicating the utility of prescribing an FDC over a loose combination of drugs as FDC would result in better compliance and adherence to the treatment[10].

Following the widespread acceptance of two drugs FDC and requirement of maintaining prandial as well as post-prandial glycemic levels for type 2 diabetes, triple FDC of sulphonylureas, metformin and pioglitazone; as well as sulphonylureas, metformin, and voglibose, have been introduced. Sulphonylureas acts by insulin release from the beta cell of the pancreas, metformin by improving insulin sensitivity at the muscle and liver and voglibose is an α-glucosidase inhibitor that acts by reducing the postprandial blood glucose by regulating glucose absorption[3].

Faruqui carried out post-marketing surveillance (PMS) in a non-randomized, open, non-comparative, mono-centric study[11]. The drug administered was an FDC of voglibose 0.2 mg; glimepiride 0.5 mg and metformin 500 mg sustained-release (SR). Fifty type 2 diabetic patients were given FDC twice daily with major meals for 3 months. It was found that there was significant decrease from baseline in HBA1c value 10.6 ± 1.3 vs. 6.6 ± 0.4 ($P< 0.0001$), FPG levels 208.33mg/dl vs. 118.06 ($P< 0.0001$), and PPHG levels 360.14 mg/dl vs. 168.36, ($P< 0.0001$) after 3 months of treatment. The combination was found to be effective in controlling both fasting and postprandial glucose levels and was well tolerated. Investigator concluded that the use of triple-drug combination is a good option in the management of type 2 diabetes which controls both fasting as well as postprandial blood glucose and ultimately HbA1c values[11]. Similar results were also reported by C Rao et al[12], concluding their findings as a triple-drug combination of voglibose, metformin and glimepiride reduce HbA1c, FPG and PPHG level in type 2 DM patients. C Rao et al in the same study reported that the above-mentioned triple-drug FDC was safe and well-tolerated in their clinical trial[12]. In another trial, the effect of addition of voglibose to the combination of glimepiride and metformin was studied and changes on various parameters i.e. FPG, PPHG, HbA1c and lipid profile [total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), very-low-density lipoproteins (VLDL), high-density lipoproteins (HDL)] were observed in type 2 DM patients[13]. It was observed that there was a significant reduction in FPG, PPHG, and HbA1c with voglibose. The reduction in these parameters was observed in chronological sequence within the duration of the study i.e. at 1st, 2nd, 3rd, 4th, 5th and 6th months. The addition of voglibose

was reported to influence serum lipids. i. e. TC, TG, LDL and VLDL and these were reduced significantly with voglibose. A comprehensive systematic review of all the publications and studies suggests that FDCs of oral hypoglycemic agents significantly reduce HbA1C and FPG values thereby efficiently reducing hyperglycemia in patients who fail to achieve glycemic control with monotherapy. However, there are some limitations for FDCs such as difficulty in dose titration, stability problems between the drugs leading to incompatibilities[1].

CONCLUSIONS

FDCs of oral hypoglycemic agents significantly reduce HbA1C and FPG values thereby efficiently reducing hyperglycemia in patients who fail to achieve glycemic control with monotherapy. Diabetes is a chronic disease that requires life-long therapy. Thus, patient compliance and therapy adherence are two major constraints for achieving desired glycemic control in type 2 diabetics. FDCs help to improve patient compliance and therapy adherence. With the acceptance of two drugs anti-diabetic FDCs, triple-drug FDCs have been introduced to further maintain the prandial as well as post-prandial blood glucose levels. Studies have shown that triple combination of voglibose, metformin and glimepiride have been able to maintain fasting and postprandial glucose level with in the desired levels.

REFERENCES

1. Vijayakumar TM, Jayram J, Meghana Cheekireddy V, Himaja D, Dharma Teja Y, Narayanasamy D. Safety, Efficacy, and Bioavailability of Fixed-Dose Combinations in Type 2 Diabetes Mellitus: A Systematic Updated Review. *Curr Ther Res - Clin Exp*. 2017;84:4-9. doi:10.1016/j.curtheres.2017.01.005
2. Schlosser R. Fixed-Dose and Fixed-Ratio Combination Therapies in Type 2 Diabetes. *Can J Diabetes*. 2019;43(6):440-444. doi:10.1016/j.jcjd.2019.05.005
3. John M, Gopinath D, Kalra S. Triple fixed drug combinations in type 2 diabetes. *Indian J Endocrinol Metab*. 2015;19(3):311-313. doi:10.4103/2230-8210.152739
4. Rozenfeld Y, Hunt JS, Plauschinat C et al. Oral antidiabetic medication adherence and glycemic control in managed care. *Am JManagCare*. 2008;14:71–75.
5. PJ G. Influence of oral antidiabetic drug compliance on metabolic control in type 2 diabetes. A survey in general practice. *Diabetes Metab*. 2003;29:79–81.
6. Thom S, Poulter N, Field J E. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. *JAMA*. 2013;310:918–929.
7. Kim JD, Park CY, Cha BY, et al. Comparison of Adherence to Glimepiride/Metformin Sustained Release Once-daily Versus Glimepiride/Metformin Immediate Release BID Fixed-combination Therapy Using the Medication Event Monitoring System in Patients With Type 2 Diabetes. *Clin Ther*. 2018;40(5):752-761.e2. doi:10.1016/j.clinthera.2018.04.002
8. Han S, Iglay K, Davies MJ, Zhang Q RL. Glycemic effectiveness and medication adherence with fixed-dose combination or coadministered dual therapy of antihyperglycemic regimens: A meta-analysis. *Curr Med Res Opin*. 2012;28:969-977.
9. Organization. WH. *Behavioral Mechanisms Explaining Adherence*.
10. Choi HK, Oh M, Kim EJ, et al. Pharmacokinetic study of metformin to compare a voglibose/metformin fixed-dose combination with coadministered voglibose and metformin. *Int J Clin Pharmacol Ther*. 2015;53(2):147-153. doi:10.5414/CP202197
11. Faruqui AA. Safety and Efficacy of Fixed-Dose Combination of Voglibose, Glimepiride and Metformin in Indian Type

2 Diabetes Mellitus Patients. *Adv Diabetes Metab*. 2016;4(3):49-54. doi:10.13189/adm.2016.040302

12. C Rao AAF. Efficacy and safety of oral triple-drug combination (voglibose, glimepiride and metformin) in the management of type 2 diabetes mellitus, International Journal of. *Curr Res Rev*. 5(16):20-26.
13. Amita Jindal, Mahesh Jindal, Mandeep Kaur, Mr. Raj Kumar MRSB. Efficacy and safety of voglibose as an add-on triple-drug in patients of type two diabetes mellitus uncontrolled with glimepiride and metformin in Punjabi population, *Indian J Basic Appl Med Res*. 2014;3(3):111-116.