International Journal of Medical Research and Practice

IntJMRP

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LETTERS

Oral anti-diabetics: What after metformin

Submission: 00-00-2016 **Revision: 00-00-2016** **Publication: 00-00-2016**

INTRODUCTION

Diabetes has become a global burden now and India has unfortunately secured the second position in the world. For years we have gone through the same debate about the medication in type 2 diabetics after failing of lifestyle intervention. Metformin has become the gold standard to start with but we are in a dilemma what to start after that. In the past 15 years there have been tons of new drug inventions in the field of diabetes. Individualization of drugs has been stressed for many years. It has been seen that too tight control in moribound patients with increased age might in fact be detrimental and those with newly diagnosed diabetes of young age, tight glycemic control gives a good glycemic memory, and finally less microvascular complications. Hence the patient group selection is very important.

There are advantages and disadvantages of every group of drug. On the basis of these and balancing the advantages and disadvantages, one has to take decision about the selection of right drug for the right patient at right time with right dose, at right route and at right interval. Sulfonylureas (SUs) are cheap, easily available, and have good initial efficacy. But chance of hypoglycemia is a major drawback of these drugs. Weight gain, poor long-term efficacy are other drawbacks. Some studies have highlighted that SUs have relation with increased destruction of beta cells. Even cardiac safety of these drugs has been questioned (although most studies have been carried out with glibenclamide).

Thiazolidinediones have certain advantages like low risk of hypoglycemia and are cheap. Another very important advantage is that it targets insulin resistance. But again these drugs cause weight gain. Heart failure is another complication. Increased risk of bone fracture often restricts the use of these drugs in elderly population, particularly female. Some studies have highlighted its relationship with bladder cancer, though it is still debatable.

Dipeptidyl peptidase 4 inhibitors (DPP4 inhibitors) are unique group of drugs which does not have potentiality for hypoglycemia. There is no effect on body weight. In hypoglycemia it promotes increased glucagon response. Its efficacy is sustained. From US FDA good cardiovascular safety data is available. However increased risk of hospitalization due to heart failure by saxagliptin is quite particular as the savor group selected very high risk individuals with some already having increased pro-BNP levels but the hazard ratio is seen to be coming down after the initial phase. DPP4 inhibitors decrease inflammatory markers and decreased carotid intima thickness (spike trial of Sitagliptin). Dedicated study shows that some gliptins have favorable results in nephropathy and can be used in all eGFR. These are safe in elderly. Main disadvantage of gliptins are that they are costly (except the US-FDA and European body non-recognized molecules). They cannot be used in patients having history of pancreatitis.

SGLT2 inhibitors are another new group of drugs. They work by novel mechanism of action sparing pancreas. They also have no risk of hypoglycemia. Four years efficacy data of these drugs are satisfactory. They promote weight loss. They have excellent cardiovascular safety data (in fact superiority data available). They address insulin resistance by promoting visceral fat loss. They promote increased uric acid excretion though its significance yet to be known. It has nephro-protective theoretical hypothesis. In spite of all these advantages there are certain disadvantages: they are costly. As they promote increased fluid loss, so they are to be avoided in aged and in very young patients. They should be used very cautiously with loop diuretics. There is increased chance of genitor urinary infections; though recurrence rate is low. There is increased chance of euglycemic diabetic ketoacidosis (DKA) if wrong group of patient is selected. Another restriction of these drugs is that long-term safety data is yet to be available. There is increased risk of bone fracture and increased chance of potassium imbalance with canaglifozin. These drugs cannot be used in low eGFR (particularly if it is less than 45 ml/min).

CONCLUSION

Based on the available data the clinicians have to choose an agent depending on the economic status, profession, age and existing co-morbidities of an individual. Every patient is unique and hence the same glycemic targets should not be set for all. Diabetes management is changing each day. Newer drugs addressing the underlying pathologies and acting in a novel mechanism are always welcome.

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How to cite this article: Roy S. Oral anti-diabetics: What after metformin. IntJMRP 2016;1(2):pp–pp.

Source of Support: None declare. **Conflict of Interest:** None.