Surfing the Vildagliptin Tsunami

Sir,

The latest buzz in the Indian diabetes drugs scene is the loss of exclusivity (LOE) of vildagliptin. This can potentially bring down the daily cost of vildagliptin under Rs. 10. This puts vildagliptin in the same "low cost category" (operationally defined in this paper as, cost of therapy per day less than Rs. 20 when given with metformin 2000 mg/day) as

- Modern sulphonylreas (glimepiride and gliclazide)
- Teneligliptin
- Alogliptin
- Alpha-glucosidase inhibitors (acarbose and voglibose)
- Pioglitazone,

Among others.

Against this backdrop, the recently published VERIFY trial[1] which looked at early combination therapy versus sequential therapy in patients with treatment naïve diabetes with HbA1c 6.5 to 7.5% assumes particular significance.

- In the past, such combination therapy, regardless of what it offered in terms of glycemic or other benefits, would have been prohibitively expensive for most Indian patients
- Indian doctors see patients later in the course of the disease—so only a minority of our patients fit into the early diabetes inclusion criteria for VERIFY trial—thus limiting our ability to extrapolate to majority of our patients
- In contrast, preliminary evidence suggests DPP4 inhibitors (and incretin therapies in general) may work better in Indians. This raises the tantalizing possibility that even at higher baseline HbA1c salutary effects can be expected with gliptins, thus making extrapolation of VERIFY results to the average Indian patient possible.

To extrapolate the results of VERIFY trial to Indian setting, some key questions need to be answered:

1. Do all or most Indian patients with diabetes require early combination therapy?
2. Is the durability of therapy a drug-specific effect or class specific effect?
3. How does vildagliptin compare to other members in the same "cost category" with respect to the CV benefit and glycemic durability?
4. Quality of the generic vildagliptin—should the endocrinologist worry?

I shall try to answer these questions in this paper.

Upfront combination therapy—rationale

Indian patients are often diagnosed late and have a high prevalence of microvascular and macrovascular complications at diagnosis.[2] The mean HbA1c is also higher in Indian patients—with epidemiological studies showing the average HbA1c of 9%.[3,4] The ADA guidelines suggests that upfront combination therapy should be considered in patients with baseline HbA1c 1.5% above the target range, thus making at least 50% of newly diagnosed Indian patients candidates for upfront combination therapy. The question is which drug to combine with metformin.

Glycemic durability—comparison of low cost drugs

The glycemic durability of different classes of antidiabetic drugs (and drug classes) cannot be compared directly, since such head-to-head comparison studies are lacking. Furthermore, there are no retrospective cohort studies or network meta-analysis to even indirectly compare the durability. The drug used to treat diabetes is not the only or even the major determinant of glycemic durability. One must be cautious in interpreting retrospective non-randomized studies which are marred by confounding by indication. For instance, a patient with poor glycemic control may be started upfront with insulin or sulphonylurea, and the observed glycemic durability may be a marker of the underlying poor β-cell function, not the drug given.

During the phase 1 of VERIFY trial,[1] in which upfront combination therapy versus metformin alone was given, 43.6% of patients failed (two consecutive HbA1c >7% done 13 weeks apart) with vildagliptin + metformin compared to 62.1% in the metformin plus placebo arm. Hence, the final results of VERIFY should be interpreted, taking this into account.

Table 1: Summarises the glycemic durability gleaned from randomized controlled trials of the different "low cost" drugs

Drug	Trial	5 year Durability
Metformin	ADOPT[5]	79%
Vildagliptin	VERIFY[1]	~60%
Gliclazide	ADVANCE ADVANCE-ON	Number could not be determined, but the Gliclazide arm essentially remains flat for 5 years
Glimepiride	CAROLINA[6]	60.3%
Alpha Glucosidase inhibitors	-	Data on glycemic durability not available
Pioglitazone	ADOPT[5]	85%
Alogliptin	EXAMINE[7]	Maximum follow-up 40.7 months. Five-year durability data not available.
Teneligliptin	-	Data on glycemic durability not available

Table 1 summarizes the glycemic durability gleaned from randomized controlled trials of the different drugs in the same "cost category" as vildagliptin.

A shown in Table 1, nearly every low cost drug has more or less similar glycemic durability. Thus the observed benefit of VERIFY trial cannot be considered either a drug effect or class effect.

Thus, glycemic durability is unlikely to be a differentiating factor of vildagliptin, especially when compared to the other commonly used second line agents—sulphonylureas. While some meta-analyses suggest gliptins are superior to sulphonylureas in glycemic durability,[8] others show that the glycemic response wanes significantly in the second year.[9] This suggests that the cohort studied influences glycemic durability of the drug.

Upfront combination therapy—the "tangible" cost

Unlike a single payer healthcare system, the complexity and variability of Indian healthcare precludes any universally applicable cost benefit analysis. Hence what is "cost-effective" depends on the context.

For the sake of simplicity, if we assume that the average cost of Metformin per day is Rs 5 per day (for 1,000 mg immediate release metformin twice daily) and Vildagliptin + Metformin therapy Rs 20 per day (for 50/1,000 twice daily) the difference in cost when given for 5 years is Rs 5,475/year (or Rs 456/month). Whether this additional cost is worth it, is an individual doctor/patient's decision. The lack of data on hard end points makes this decision difficult, since it is not immediately apparent what we get for the additional cost incurred. Unlike in the VERIFY trial, where the two drugs were given separately, the availability of generic FDCs (fixed drug combinations) potentially allows a patient to be on twice daily tablet for upto 5 years.

Drug quality—things to consider

With the loss of exclusivity, it is expected that an increasing number of generic makers will manufacture vildagliptin. Since the requirement for generics is pharmacological equivalence—bioavailability within 80—120% of the originator molecule. Vildagliptin is produced as an S-isomer, with R-enantiomer being an impurity. Enantiomers of drugs often differ in their pharmacological action. Other gliptins such as linagliptin,[10] alogliptin,[11] and sitagliptin[12] and teneligliptin also show chirality. However, with the exception of teneligliptin—all the other gliptins are manufactured by a single company. This can potentially reduce the difficulties associated with drug quality control. Enantiomeric separation of S-enantiomer in bioequivalence studies may therefore be needed, when multiple companies manufacture the same compound and where bioequivalence may depend on more than just dissolution and reaching a particular concentration in plasma. However, Indian regulatory agencies do not insist on chiral purity. Whether the "generic" vildagliptins work as well as the innovator molecule, remains to be seen.

Conclusion

The Indian endocrinologists need to balance costs of therapy with an array of clinically relevant variables (efficacy, CV safety, weight, hypoglycemia, adverse effects). The lowered cost along with recent evidence for glycemic durability may make upfront combination therapy with gliptins (like vildagliptin) a rational choice for many patients. At the same time, the generic drug quality is likely to be the elephant in the room. The lowered cost will result in a tsunami of "generic" vildagliptins, but patient centric drug selection will help us not just survive, but surf this tsunami with ease.

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Conflicts of interest

There are no conflicts of interest.

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