AGGRESSIVE TREATMENT IN NEWLY DIAGNOSED DIABETES WITH FIXED DOSE COMBINATIONS

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INTRODUCTION
The importance of early and optimal control of glycemia in diabetes is well known. The need for multiple drugs, focusing on the various pathophysiologic mechanisms that cause diabetes, is also well understood. The less-than-acceptable results of our therapy, too, are no secret. Our inability to achieve desired glycemic goals is due, in part, to poor compliance, adherence and persistence with to suggested antidiabetic therapy.

One way in which we can improve adherence and persistence to therapy, is by using appropriate fixed dose combination (FDC) preparations. Early and proactive use of appropriate FDCs is a simple and effective way of achieving glycemic and other targets.

This chapter discusses the utility of FDCs in the management of diabetes.

THE DIABETES BURDEN
The oft-quoted statistics of the diabetes pandemic are unable to quantify the burden of disease that individuals with diabetes have to face. A diagnosis of diabetes brings with it a financial, professional, social and personal load that has to be shouldered life-long. The physical, mental, time-related and economic stress of taking various tablets and injections, self monitoring of glucose, related investigations, and medical consultations are difficult to estimate.

In such a scenario, it helps the patient cope with his or her illness if the above mentioned burden is reduced by any means possible.

Of the nearly 300 million people with diabetes worldwide, over half are unable to achieve glycemic target. 85% of them are overweight or obese, and 75% are hypertensive. Many have dyslipidemia and other comorbid conditions. All these require multidrug therapy which is daunting and complex for both patient and physician.

IMPORTANCE OF TIGHT GLYCEMIC CONTROL
Ample evidence is available to prove that aggressive glycemic control in type 2 diabetes leads not only to an improvement in symptoms and short term health, but also in long term complications.

The landmark UKPDS showed that every reduction of 1% HbA1c reduced the risk of all microvascular and macrovascular chronic complications. Similar findings have been noted by other workers, including the Kumamoto study. In the UKPDS, the composite endpoint of “any diabetes-related endpoint” was reduced by 12% in the intensively treated group (HbA1c achieved = 7.0%) as compared to the conventionally treated group (7.9%).

Not only that, early glycemic control, and especially early, aggressive, intensive glycemic control, has been shown to have long term effects lasting much beyond the duration of intensive therapy. This is known as the “legacy effect” or a “metabolic memory”.

A follow up study, analyzing a cohort of the UKPDS patients after 10 years of post trial monitoring, revealed favorable reductions in any diabetes-related endpoint, microvascular disease, myocardial
infarction and all-cause mortality. These results were noted in spite of the fact that the intensively treated group had finally reached on HbA1c similar to that of the conventional treatment group. Thus, it makes sense to try and achieve tight glycemic control as early as possible in the natural history of the disease.

CURRENT STATUS OF GLYCEMIC CONTROL
The current situation of glycemic control is far from ideal. The A1Chieve study, which is the largest observational study in diabetes, has reported an average HbA1c of 9.5% in patients across the globe, as compared to the goal of 7.0% or below. Similar values are reported from every region/location. A1Chieve study, which is the largest observational study in diabetes, has reported an average HbA1c of 9.5% in patients across the globe, as compared to the goal of 7.0% or below. Similar values are reported from every region/location.7

One of the reasons for this is a reluctance to increase the “pill burden”. This reluctance is visible both on part of the physician, who worries about doctor-shopping on part of the patient, and on the patient, who is concerned about cost, convenience and potential side effects.

In an American study, only 40-44% of patients had their treatment regimes adjusted at the most recent clinic visit. An earlier study had demonstrated that the average time taken to augment or substitute treatment in metformin monotherapy patients with HbA1c >8.0% (n =354) was 14 months. The duration for sulfonylurea monotherapy patients with HbA1c >8.0% (n =2517) to receive therapy change or intensification was 20 months. These “linear” patterns of therapy reinforce the views of Kalra and Gupta, who describe four varying therapy patterns in diabetes, with the linear one representing lack of proactivism or dynamism. Therefore, we need to encourage proactive, dynamic prescription behaviour and habits, to try and improve the status of glycemic control in our patients.

CURRENT MANAGEMENT STRATEGIES
Current guidelines for diabetes management by the International Diabetes Federation (IDF), American Diabetes Federation (ADA) and others tend to suggest initial monotherapy, along with lifestyle modification, followed by combination therapy only if monotherapy fails.11,12

The American Association of Clinical Endocrinologists (AACE), however, has broken fresh ground by categorizing patients according to their initial HbA1c. Patients with an initial HbA1c of 7.6-9.0%, who form the majority in every practice, are recommended initial dual therapy. Those with an HbA1c > 9% can be started on triple therapy. Thus, the logic of early, aggressive combination therapy has received expert backing, based on pathophysiological logic and clinical evidence.

Based on the individual clinical picture, one can choose an appropriate combination regime/ a combination of two insulin sensitizers, or one sensitizer and secretagogue, or one sensitizer and one α-glucosidase inhibitor can be used to initiate therapy in patients with an HbA1c of 7.6-9.0%. The choice of combination will depend on duration and degree of hyperglycemia, relative fasting and postprandial hyperglycemia, risk of hypoglycemia, meal habits and lifestyle, comorbid conditions and tolerability of drugs. For patients with a higher HbA1c (>9.0%), more options are available: two sensitizers and one secretagogue, in varying doses.

The IDF guidelines recommended that target glycemic goals be achieved within 180 days. To do so, one needs to practice proactive management strategies, using early combination therapy.

CURRENT TRENDS IN OTHER DISEASES
Combination therapy is not limited to diabetes mellitus alone. Similar trends in prescription and management are noted in other metabolic, non- infectious diseases. These include hypertension, dyslipidemia, acute coronary syndromes, rheumatoid arthritis, cancer, HIV/AIDS, and various bacterial infections.

Combination therapy, based on the rationale of a multitargeted approach, is being used earlier in the natural history of these diseases. This helps achieve, and maintain, desired therapeutic targets.

IS ‘EARLY’ THERAPY ACTUALLY EARLY?
There is an ongoing and never-ending debate, as to how early should be early? Some experts suggest the use of the term ‘timely’ (Dr. Alok Gupta, Gorakhpur; personal communication). This is because β-cell destruction tends to precede the clinical diagnosis of type 2 diabetes by up to 9-12 years.13,14 By the time the diagnosis is made, and treatment begun, as much as 80-85% of β-cell function is already lost.15

Hence, all that we can offer to the patient is ‘timely’, rather than ‘early’ therapy. The best possible strategy would be to begin a multipronged treatment as soon as possible, focusing on all risk factors and pathophysiological mechanisms. There should be no delay in trying to achieve eumetabolic status.

RATIONALE FOR EARLY COMBINATION THERAPY
Over the past few decades, we have moved from a simplistic insulin-based pathophysiologic model of diabetes (insulin deficiency and insulin resistance) to a deeper understanding of the disease. De Fronzo listed eight players in the diabetic orchestra, calling them the ominous octet: the beta-cell, cell, liver, adipose tissue, skeletal muscle, brain, liver and gastrointestinal tract.

Added to this is dopamine, the forgotten felon, which modulates glycemia through the autonomic nervous system. Including potential links being unravelled with testosterone,
renin-angiotensin system, and vitamin D, the term ‘Dirty Dozen’ has been proposed to club the pathophysiologic mechanisms of diabetes.\textsuperscript{10}

In view of multiple pathophysiologic pathways being involved in diabetes, there is a rationale to prescribe multiple pharmacologic interventions as well, to ensure comprehensive management and achieve optimal therapeutic outcomes.

Unfortunately, we do not have any oral drug which acts on all aspects of the Dirty Dozen, or even for that matter, the Ominous Octet. Hence, there is a need for combination therapy to achieve the desired results.

**CURRENT STATUS OF ADHERENCE**

This however, is easier said than done. Most patients find it difficult to adhere to, and persist with, the suggested therapy for diabetes and comorbid condition. The complexity of therapy - number of tablets, injections, types of drugs, and varied times of administration (30 minutes before meals; immediately before meals; after meals; at night), methods of administration (with meals; sublingually), and frequency of administration (once, twice or thrice daily), - leads to difficulty in following advice.

This impacts therapeutic outcomes adversely.

Observational studies indicate that the adherence of patients is inversely proportional to the number of tablets prescribed.\textsuperscript{17}

Similar results are reported in studies analyzing the rate of persistence\textsuperscript{18} There is a great need, therefore, to reduce the pill burden on the patients, while ensuring that combination of drugs is given to them.

**CURRENT STRATEGIES TO IMPROVE ADHERENCE**

Poor adherence to medical therapy has multiple causes. It stands to reason, therefore, that more than one strategy will be required to improve adherence.

Better patient-physician communication, focus on soft skills and counseling ability of doctors, enhanced patient education, awareness and empowerment all help increase concordance with therapy. Apart from these patient-related and physician-related factors, however, drug-related factors need to be addressed if therapeutic targets are to be achieved.

Drug-related factors which affect adherence include number of tablets/injections, frequency of dosage, flexibility of time of administration, ease of instructions to be followed during administration, and cost of therapy. Strategies are required which will reduce complexity of therapy while ensuring adequacy of management.

**FIXED DOSE COMBINATIONS**

This can be achieved by prescribing fixed dose combinations (FDCs).

FDCs are pharmaceutical formulations which contain fixed amounts of more than one active pharmaceutical ingredient. FDCs have been used for long to treat infectious disease (trimethoprim+ sulfamethoxazole, for example). Their use in metabolic disease, such as diabetes and hypertension, however, is a relatively recent phenomenon.

FDCs classically include oral drug combinations. One can make a strong case for including premixed insulin and insulin analogues as FDCs. These formulations contain a fixed ratio of two drugs, as opposed to the split: mix regime, in which varying proportions of insulin are mixed. Premixed insulins can more accurately be termed fixed drug ratio combinations (FDCs), and facilitate target achievement by improving patient convenience and compliance.

**CURRENT FDCS (TABLE 1)**

**METFORMIN + SULFONYLUREA**

The most commonly prescribed antidiabetic FDC in India, Met+SU targets both insulin resistance and deficiency. Metformin suppresses hepatic gluconeogenesis to reduce fasting glyemia, and also increases peripheral glucose uptake sulfonfonylureas increase insulin release from the β-cells, and work as long as same amount of β-cell residual function is present. This therapy has been shown to provide synergistic effect in many studies and meta- analysis. There is a risk of hypoglycemia, weight gain, and potential cardiovascular risk with this combination.

Theoretically, because of the potential of sulfonfonylureas to deplete β-cell insulin stores and induce β cell apoptosis, the use of initial early Met+SU FDC “does not appear to be particularly attractive”.\textsuperscript{14}

Practically, though, this economical and effective FDC is the mainstay of diabetes management in India.

**METFORMIN + PIOGLITAZONE**

Pioglitazone increases insulin sensitivity in the liver and adipose tissue, and potentially inhibits β-cell loss, thus providing synergistic effect with metformin. Thus FDC of two insulin sensitizers provide reasonable efficacy, with safety and tolerability. An FDC of 7.5 mg pioglitazone and 500 mg metformin is also available. This combination avoids the adverse effects such as weight gain, congestive cardiac failure and osteoporotic fractures that are noted with high dose pioglitazone.

**METFORMIN + REPAGLINIDE**

Metformin and repaglinide FDCs are also available. There is a lesser risk of hypoglycemia and weight gain as compared to Met+ SU FDC. The shorter duration of action means that the FDC has to be prescribed with each major meal, i.e., twice or thrice daily. It is also used as a lunch-time add-on to twice daily premixed insulin.
METFORMIN + ALPHA–GLUCOSIDASE INHIBITORS

This FDC has a synergistic effect: metformin acts on hepatic gluconeogenesis to target fasting glycemia, while acarbose/voglibose reduce intestinal glucose absorption to control postprandial glycemia. The efficacy is offset by lack of tolerability amongst a few patients who complain of gastrointestinal symptoms. Some endocrinologists feel that this FDC is more relevant in rice-eating than in wheat-consuming populations.

METFORMIN + DPP (IV) INHIBITORS

One of the most popular FDCs, metformin+ DPP (IV) inhibitors has a strong pathophysiologic rationale, robust efficacy, demonstrated safety and tolerability. The mechanism of action makes this FDC a drug of choice for early, aggressive combination therapy in type 2 diabetes.

Numerous studies and meta-analysis have been performed, which are reviewed elsewhere. Sitagliptin is available as a 50 mg combination with 500 mg or 1000 mg of metformin. Vildagliptin is available as 50+500, 50+850 and 50+1000 mg combinations with metformin. Saxagliptin is available with metformin in a 5+500 mg FDC. While efficacy is undoubted, there are analyses which highlight the occurrence of pancreatitis in patients on sitagliptin.

The bulk of evidence, however, proves that acute pancreatitis occurs more often in diabetes per se, irrespective of the drugs being used for treatment.

Weight gain does not occur with this FDC and hypoglycemia is rare. Vildagliptin has the advantage of reducing free fatty acid levels and having low variability of action. Linagliptin, which will soon be available in India as monotherapy and in FDC, is safe for use in renally compromised patients.

ADVANTAGES OF FDCS

FDCs do help improve adherence as compared to corresponding free combinations of single-drug tablets (known as “dual” therapy).

Patients switched from metformin or glibenclamide monotherapy to FDC have been shown to achieve a significantly higher adherence rate than those prescribed dual therapy (77%). Those shifted from dual therapy to FDC showed further improvement in adherence from 71% -87%. Similar results have been reported by authors studying thiazolidinedione + metformin FDC.

Observational studies using healthcare databases, studying the data retrospectively, have revealed better outcomes with FDCs. A study of 950 patients taking metformin/glibenclamide as either FDC or dual therapy revealed a greater reduction in HbA1c in the FDC group (-2.0%) vs. the dual therapy group (-1.5%). Another study demonstrated a -0.6% fall in HbA1c (-1.3% in those with baseline HbA1c ≥ 8%) in patients who were switched from dual therapy to FDC.

Thus use of FDCs, as compared to use of combination to use of combination therapy in general, carries advantages of improved efficacy, which may be explained by greater adherence.

The advantages of FDC use are listed in Table 2.

NEWER FDCS

Newer FDCs are being developed by pharmaceutical...
Table 2: Advantages of FDCs

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<tbody>
<tr>
<td>Efficacy</td>
<td>Synergistic effect</td>
<td>Complementary mechanism of action</td>
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<tr>
<td>Tolerability / safety</td>
<td>Less side effects (with low dose)</td>
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<tr>
<td>Economy</td>
<td>Cost containment</td>
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<td>Psychological</td>
<td>Reduced pill burden</td>
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Researchers. These include injectable combinations of basal insulin and GLP-1 analogues, such as detemir+ liraglutide, and glargine+ lixisenatide.

Oral combinations of antidiabetic drugs with antihypertensives and lipid lowering drugs are also available. The umbrella term ‘polypill’ is used to describe such combinations.

CONCLUSION

Diabetes is a chronic disease which is usually diagnosed after onset of cell destruction. Early, and multipronged, intervention is required in order to prevent chronic microvascular and macrovascular complications. The management of diabetes needs to address all relevant pathophysiological abnormalities in order to be successful. To do so, multiple drugs are needed, which increase the pill burden and financial burden on the patient, thus reducing adherence. FDCs, when used early on in the natural history of the disease, in optimal combination and dosage, after a practical means of improving therapeutic outcomes in diabetes.

REFERENCES


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