Prevalence and Economic Burden

The burden of diabetes is one of the most important challenges globally and impacts almost all the countries in the world. The IDF projects a 51% increase in the prevalence of diabetes worldwide, predominantly driven by Asia, Africa and the Middle East.¹ The projected increase in prevalence of diabetes in India is estimated to be ~65% from 61.3 million in 2011 to 101.2 million by 2030.¹ Globally, there were 4.6 million deaths (20-79 years of age) due to diabetes in 2011, which accounts to 8.2% of all-cause mortality in this age group.² In India, there were 0.11 million deaths due to diabetes in 2004 which increased drastically to 0.98 million deaths in 2011.³³ There were 1.157 million years of life lost and 2.263 million disability adjusted life years (DALYs) in India during 2004.³⁴ The costs associated with diabetes include increased use of health services, lost productivity, and disability which can be a considerable burden to the individual, to families and to society. The Indian Council of Medical Research–INdiaDIABetes (ICMR– INDIAB) study, an ICMR collaborative study was initiated to estimate the prevalence of diabetes and pre-diabetes in India. The results suggested that increase in the numbers of people with diabetes in India is directly associated with increased urbanisation, growth of the middle class and ageing of the population.³ These results when extrapolated to India as a whole, the estimates translated to 62.4 million individuals with diabetes.⁵ Several studies across India have reported interesting differences in the patterns of complications. The prevalence of retinopathy, nephropathy, and peripheral vascular disease appear to be lower, while that of neuropathy and cardiovascular disease reported higher prevalence rates.

Addressing Unmet Needs in Diabetes Management

It can take up to five years to initiate insulin therapy, even in the presence of elevated HbA1c.⁶ DiabCare India 2011, a cross-sectional study to investigate the relationship between diabetes control, management and complications in a subset of urban Indian diabetes population treated at referral diabetes care centres screened 6168 subjects whose mean age was 51.9 years and the mean duration of diabetes was 6.9 years. One of the key findings were that type 2 diabetes sets in early in Indians and the glycaemic control is often sub optimal. The mean HbA1c was 8.97 ± 2.19 in these patients and only 19.7% of type 2 diabetes patients had HbA1c < 7%.⁷ A good long-term glycaemic control and reduction in the risk of secondary complications is possible with the initiation of insulin in the early years of diabetes. However, clinical inertia defined as ‘recognition of the problem, but failure to act’ is the principal cause for poor glycaemic control. Increased prevalence of diabetes, limited access to specialist care for complications and poor glycaemic control are shifting the responsibility of ‘insulin initiation’ from specialists to primary care physicians.⁸ Unfortunately, many patients are reluctant to begin insulin and may delay starting insulin therapy for significant periods of time. The complexity of therapy and healthcare resources has kept insulin as last resort of therapy for physicians. In one of the studies it was found that one-quarter of patients may refuse insulin therapy once it is prescribed.⁹¹⁰ Little is actually known about this phenomenon, often termed “psychological insulin resistance” (PIR), how common it may
be, or why patients feel this way. What makes the problem more complex is the emerging concept of “insulin paradox” (Figure 1). Patients report that fear of hypoglycaemia and restrictiveness are major barriers to using insulin. Similarly, physicians agree that hypoglycaemia is a barrier to effective glycaemic management and that 75.5% of them would treat patients’ diabetes more ambitiously if there was no concern over hypoglycaemic events. Another major concern is the fixed administration time for basal insulin administration. In a study evaluating 28% of patients said they find it difficult to take insulin at the prescribed time daily or with meals every day while 22% of patients said they planned their daily activities around insulin injections. Finally, forgotten or omitted insulin injections are an important contributing factor to poor glycaemic control in people with diabetes. A mathematical modelling using simulation has indicated that forgetting 2.1 meal-related injections per week may lead to an increase in HbA1c of at least 0.3-0.4% points, and missing 2.1 basal insulin injections per week can increase in HbA1c of 0.2-0.3%.

A consensus meeting of diabetes experts in India recommended that ultra-long acting (one shot a day) insulins with a flexible dosing (taken at any time of the day) through a painless delivery device (and injections) should be the attributes of an ideal basal insulin. The experts also concluded that lower risk of hypoglycaemia, specifically nocturnal hypoglycaemia, lower mitogenic potential and less weight gain are also important safety attributes of an insulin for successful management of diabetes.

Opportunities from Designer Proteins: An Introduction to Insulin Degludec

Reducing variability and extending duration of action can reduce the incidence of hypoglycaemia without compromising glycaemic control. Lower rates of hypoglycaemia with newer insulins will allow a physician to get closer to target. Since the 1970s, with the introduction of recombinant DNA technology, rapid-acting and long-acting insulin analogues have helped to deliver much more physiological action profiles more suited to the basal requirements and postprandial peaks. These modifications to the insulin molecule have focussed on areas of the molecule that are distant from those involved in receptor interaction. This is to maximise the chance that more desirable PK parameters can be achieved, whilst at the same time causing minimal alteration of binding affinities to the insulin and IGF-1 receptors.

Insulin degludec is a new-generation basal insulin with an ultra-long duration of action. Insulin degludec consists of recombinant DesB30 human insulin acylated at the LysB29 residue with a Hexadecadienoyl-y-L-Glutamate side-chain. Due to its structure and formulation, insulin degludec forms stable and soluble multi-hexamers upon injection. Insulin monomers will then slowly and gradually dissociate from the multi-hexamers and subsequently be absorbed into the bloodstream, providing an ultra-long duration of action.

In this issue, Mohan and colleagues further describe the molecular designing and structure of insulin degludec (Figure 2). A number of clinical pharmacological studies have shown that insulin degludec exhibits flat and stable steady-state pharmacokinetic and pharmacodynamic profiles in patients with diabetes. An euglycaemic glucose clamp study conducted in patients with type 1 diabetes demonstrated that insulin degludec presents a four times lower within-patient day-to-day variability in blood glucose-lowering effect than insulin glargine. As molecular size is known to influence the rate of insulin absorption from the injection site, the principle of self-association was applied to design an insulin capable of forming large molecular weight multi-hexamers from which active monomers could be slowly and steadily released. An insulin with a prolonged, steady release from depot into the circulation will achieve a stable and flat steady-state glucose-lowering effect over a dosing interval, and should furthermore exhibit a low within patient day-to-day variability in glucose-lowering effect. The clinical pharmacology of insulin degludec has been described by Unnikrishnan et al. in this issue.
Clinical Development of Insulin Degludec

Two global phase 2 studies were conducted to provide proof of concept and to explore the efficacy and safety of insulin degludec in type 1 and type 2 diabetes. In type 1 diabetes, a treat-to-target phase 2 trial comparing the efficacy and safety of insulin degludec once daily with insulin glargine once daily, both combined with mealtime insulin aspart over a 16-week period, found that both basal insulins provided comparable glycaemic control. In this basal–bolus trial, mean rates of both confirmed and nocturnal confirmed hypoglycaemia were lower with insulin degludec than with insulin glargine. In type 2 diabetes, a treat-to-target phase 2 trial comparing the efficacy and safety of insulin degludec once daily versus insulin glargine in insulin-naïve patients showed that insulin degludec combined with metformin lowered blood glucose levels to an extent similar to insulin glargine with metformin. When combined with metformin, insulin degludec once daily was associated with a numerically lower rate of confirmed hypoglycaemia than insulin glargine once daily in insulin-naïve patients with type 2 diabetes. The promising results from these phase 2 studies laid the foundation for the BEGIN® phase 3 study programme.

In this issue, Wangnoo et al. present published results from BEGIN®, in type 1 diabetes (two trials) and type 2 diabetes (six trials). Comparators to insulin degludec included insulin glargine (seven trials), and sitagliptin (one trial). The duration of the trials was from 6 to 12 months, with some trials having extension arms of 6 to 12 months. The extent and breadth of the BEGIN® clinical trial programme provides an excellent overview of the potential of insulin degludec in the treatment of patients with type 1 and type 2 diabetes compared with other available basal insulin analogue treatment regimens. Mithal et al. discuss further clinical insights from BEGIN® clinical trial programme in this issue.

Improving Efficacy without Increasing the Risk of Hypoglycaemia

In healthy people, low blood glucose is counteracted by the secretion of gluco-hormone regulatory hormones. In patients with type 1 diabetes this response is impaired, and in patients with type 2 diabetes the counter-regulatory function becomes progressively more ineffective over time. Hypoglycaemia can cause an array of symptoms including autonomic symptoms, caused by physiological changes due to low blood glucose. In addition, neuroglycopenic symptoms are brought about by the effects of hypoglycaemia on the nervous system. Nocturnal hypoglycaemic events are the most feared and potentially consequential. Repeated hypoglycaemia can lead to hypoglycaemia unawareness, in which patients cannot perceive the symptoms of fall in blood glucose. Hypoglycaemia also affects the cardiovascular system and is associated with an increased risk of cardiovascular-related events. The initiation of insulin therapy in patients with type 2 diabetes may be delayed due to the physician’s and patient’s fear of hypoglycaemia. In addition, insulin titration in pursuit of improved
glycaemia may not be optimal and insulin doses may be delayed or omitted to avoid a hypoglycaemic event.32

Results from the hypoglycaemia meta-analysis indicated that insulin degludec was associated with significantly lower rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia, compared with insulin glargine, in patients with type 2 diabetes and in the pooled type 1 and type 2 patient population.33 This advantage was most marked during the maintenance period (i.e. from 16 weeks to end of trial). The hypoglycaemia benefit was also observed for confirmed and nocturnal confirmed hypoglycaemia rates in subjects with type 2 diabetes aged ≥ 65 years. The reduced risk of hypoglycaemia with insulin degludec may have significant implications for the treatment of diabetes, potentially improving insulin regimen adherence and glycaemic control. These implications from clinical trials of insulin degludec have been highlighted by Ramachandran et al. in this issue.

Health Related Quality of Life

Patient reported outcome (PRO) measures provide insight into the way patients perceive their health and the impact that treatments have on their health-related quality of life (HRQoL). The symptoms of hypoglycaemia negatively affect patient HRQoL. Patient HRQoL declines with increasing frequency and severity of hypoglycaemic episodes. Patients express fear of hypoglycaemia, which may be an impediment to effective diabetes management.34

Insulin degludec has been associated with improved patient HRQoL using the SF-36 v2™ questionnaire, which is a validated PRO measure, in patients with type 1 diabetes and in patients with type 2 diabetes on either basal–bolus or basal–oral therapy. Insulin degludec is associated with a modest, but statistically significant, improvement in health utility compared with insulin glargine.35 The PROs demonstrate improvements in social functioning and mental health with insulin degludec likely due to reduced anxiety or concern about hypoglycaemia.

FlexTouch®: New Insulin Delivery Device for Insulin Degludec

Insulin degludec will be available in FlexTouch® pens. FlexTouch® (Novo Nordisk A/S, Bagsvaerd, Denmark) is a new prefilled insulin injection pen that has been designed with a unique spring-loaded injection mechanism instead of a push-button extension.36 In studies among patients with diabetes and both patients with diabetes and healthcare professionals (HCPs), most respondents preferred FlexTouch® and rated it as easier to use and to inject with than comparator pens.37

Summary

Ideally, the insulin therapy must aim at the creation of a near normal glycaemic profile without the barriers of unacceptable weight gain or hypoglycaemia. Provision of a flexible insulin regimen would further enhance adherence to the prescribed therapy and positively impact glycaemic control. Insulin degludec addresses many of the aspirations of ideal basal insulin. Long duration of action, flat pharmacodynamic profile, low day-to-day variability translate into benefits of predictable glucose excursions, lower risk of hypoglycaemia at same glycaemic level and effective glycaemic with one daily injection in individuals. In conclusion, insulin degludec represents an important advancement in the treatment of type 1 and 2 diabetes.

References


