REAL-WORLD CHALLENGES IN TYPE 2 DIABETES MELLITUS: WHY A PARADIGM SHIFT IS NEEDED

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MEETING SUMMARY

Despite the increasing range of treatment options for patients with Type 2 diabetes mellitus (T2DM), there are a number of real-world barriers that prevent many patients from achieving and maintaining glycaemic control. The objective of this symposium was to provide an overview of the challenges in T2DM treatment and to discuss novel strategies that may overcome these issues. The symposium started by exploring the key barriers that prevent patients from achieving glycaemic control, highlighting patient non-adherence to treatment as the major contributor to poor glycaemic control in a real-world setting. The speakers then explored the issue of non-adherence further, focussing on patient and physician-related contributing factors, including patient perceptions of treatment value and burden, fears of hypoglycaemia, and patient–physician interactions. The symposium ended with a presentation on potential strategies to improve treatment adherence and clinical outcomes in T2DM. Clinical evidence was presented suggesting that effective methods for helping patients to attain and maintain glycaemic control include both early treatment with intensive combination therapy and treatment with fixed-dose combinations of a glucagon-like peptide 1 (GLP-1) receptor agonist and a basal insulin analogue (iDegLira and iGlarLixi). Novel drug delivery methods were highlighted as a potential strategy for improving patient adherence and treatment success, with data presented on the efficacy and safety of ITCA 650 (Intarcia Therapeutics Inc., Boston, Massachusetts, USA), a subdermal osmotic mini-pump that provides continuous delivery of a GLP-1 receptor agonist. The symposium concluded with a summary of the main points, in which the need for new strategies to address the issue of non-adherence to therapy in T2DM was emphasised.

Introduction

Professor Luc Van Gaal

Even with recent advances in treatment options, patients with T2DM still have multiple unmet needs.[1] A core issue in T2DM is attaining and maintaining glycaemic control, driven by the progressive nature of the disease leading to a decline in beta cell function over time, which in turn necessitates adaptation of treatment regimens to maintain metabolic targets. Lack of glycaemic control remains a major concern in T2DM, with the 2009 PANORAMA study[2] finding that 36.7% of patients with T2DM across nine European countries were not achieving target glycated haemoglobin (HbA1c) levels of ≤7%. Barriers to achieving glycaemic control may encompass a variety of factors, such as poor adherence to therapy, lack of adequate support in managing treatment side effects, such as weight gain and hypoglycaemia, and physician's behaviour, such as clinical inertia.[3-7]

Of all the elements that influence glycaemic control, poor adherence to treatment is a major and widespread barrier to treatment success and can be influenced by a number of factors, including medication costs, side effects, understanding of regimens, and perception of treatment benefits.[8] Poor treatment adherence is of particular concern, because it is associated with increased HbA1c levels, which leads to patients spending a high proportion of time in a hyperglycaemic state (Figure 1).[9] This in turn increases the risk of complications, hospitalisation, morbidity, and mortality.[10]

In summary, there are multiple barriers to effective treatment of T2DM. The factors contributing to these barriers provide excellent opportunities to design targeted strategies and shift the current treatment paradigm.

Real-World Challenges: Achieving Effective and Sustained Glycaemic Control

Professor Richard O'Brien

The prevalence of diabetes is rapidly increasing across the globe, with the number of diabetes patients worldwide predicted to increase from around 415 million in 2015 to around 642 million in 2040.[11]

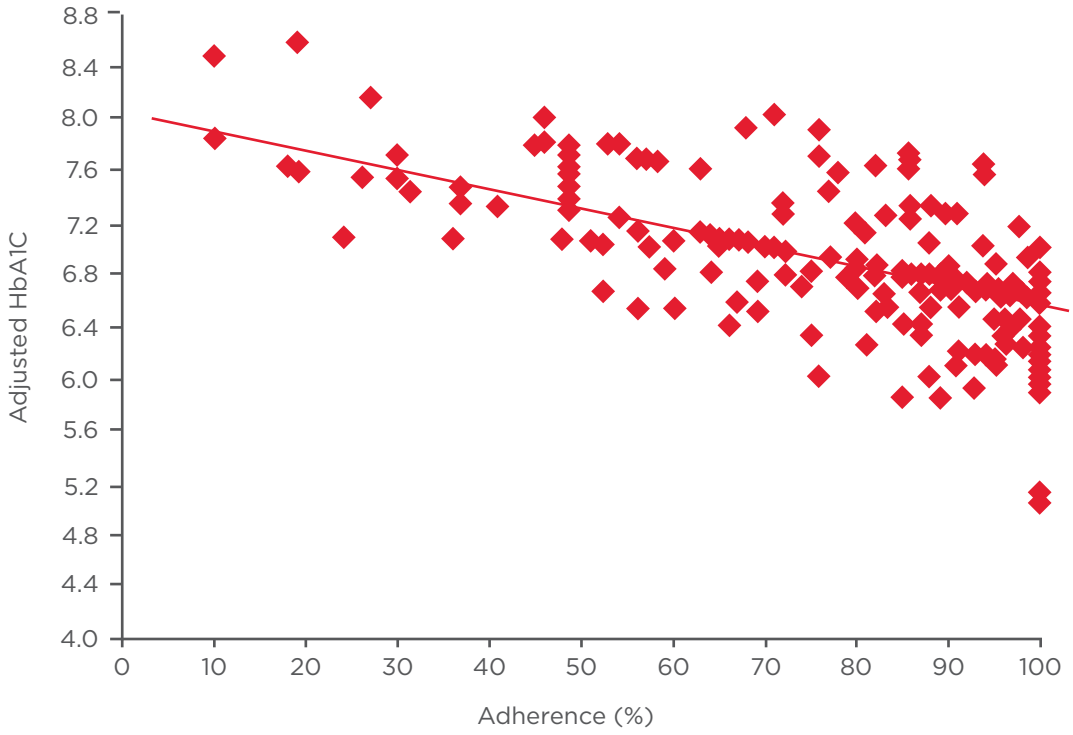

Figure 1: The association between treatment adherence and glycated haemoglobin levels in patients with Type 2 diabetes mellitus.

HbA1c: glycated haemoglobin.

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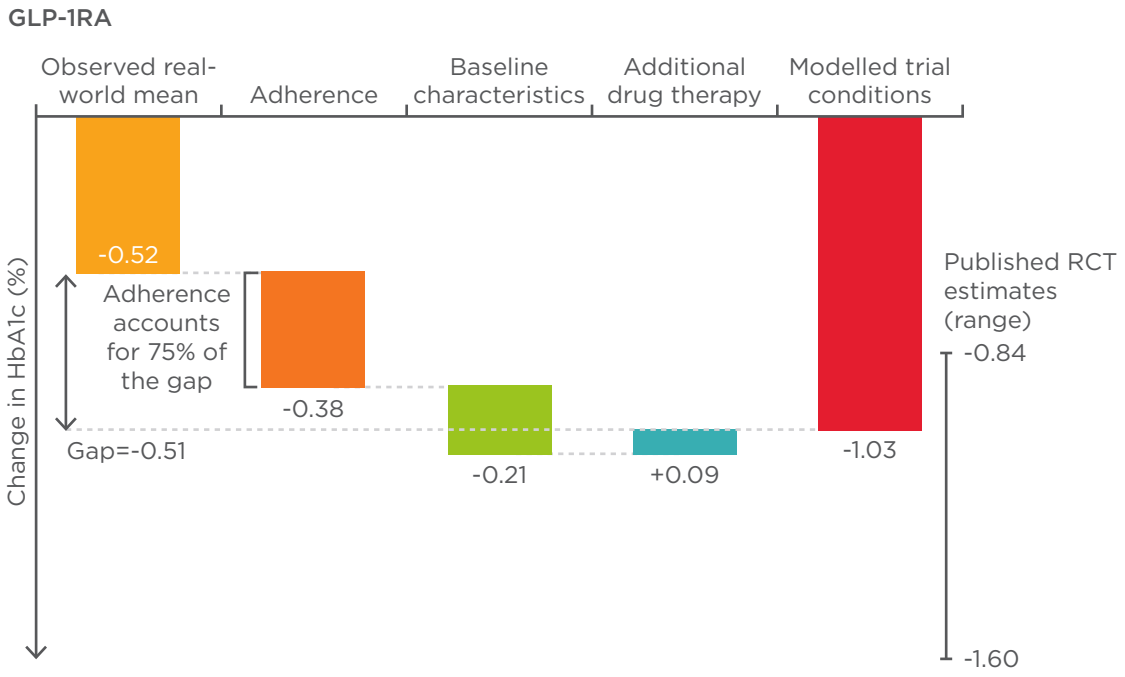

Figure 2: Variation in impact of glucagon-like peptide 1 receptor agonist therapy on glycated haemoglobin levels observed between real-world and randomised-controlled trial populations is mainly explained by adherence to therapy.

HbA1c: glycated haemoglobin; RCT: randomised controlled trial.

The number of drugs approved to treat diabetes is also increasing rapidly and there are now 11 categories of diabetes medications, including GLP-1 receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium–glucose cotransporter-2 inhibitors, and each category may contain a plethora of individual drugs.[12] However, despite the wealth of pharmacological treatment options, real-world data show that the proportion of patients with HbA1c levels >7.0% is unacceptably high in both developed and developing countries and has shown no signs of improvement over the past 10–20 years.[13,14] In parallel, the percentage of deaths attributable to high blood glucose continues to increase, with data from the World Health Organization (WHO) indicating an increase in nearly all regions of the world between 2000 and 2012.[15]

Intriguingly, real-world inadequacies in achieving glycaemic targets among patients are not reflected in data from clinical trials, where most patients are able to maintain good, long-term glycaemic control. The ACCORD study[16] showed that HbA1c could be lowered from >8% to <6.5% over 6 months. Similarly, in the ADVANCE study,[17] patients randomised to intensive glucose control involving gliclazide achieved good glycaemic control over the 2-year trial period. The reasons for this disparity in metabolic control between the clinical trial and real-world settings were analysed in a recent retrospective study.[18] This study modelled data from clinical trials and the real word to identify key treatment characteristics that contribute to the difference in efficacy between the two settings. Poor adherence to therapy was found to be the biggest cause of a lower than anticipated impact of therapy on HbA1c levels in the real world; patients treated with GLP-1 receptor agonists saw a reduction in HbA1c levels of 0.52% in the real-world setting compared to 1.30% in the clinical trial setting, with 75% of this difference accounted for by adherence to therapy (Figure 2).[18] Similar results were seen for patients treated with DPP-4 inhibitors. These data clearly demonstrate a need to address the patient and physician-related factors leading to poor adherence as a means of improving glycaemic control. As a first step, it is important to ensure that prescriptions for diabetes medicines are filled, given that it has been reported that >30% of new prescriptions for diabetes medicines are not filled in the USA.[19] Furthermore, among those who do

start taking their diabetes medications, it is critical to improve levels of maintenance of treatment; nearly half of patients are no longer taking their antidiabetic medication 1 year after initiation.[20]

In summary, while multiple treatment options exist for patients with T2DM, many patients are not achieving or maintaining their glycaemic targets, with patient adherence to treatment significantly influencing this clinical outcome. Therefore, strategies that are successful in improving treatment adherence are likely to have a substantial effect on improving glycaemic control in the real world.

The Bigger Picture: Patient or Physician Contributors to Type 2 Diabetes Mellitus Management Challenges

Professor William H. Polonsky

Three important patient-related factors contributing to treatment adherence in T2DM are forgetfulness, medication beliefs, and patient–physician trust.

Forgetfulness

Many patients report forgetfulness as the reason for non-adherence to their medication. Forgetfulness can be contributed to by cognitive impairment resulting from various factors, including dementia or depression and a lack of strong social support structures. Patients at particular risk of forgetfulness include retired persons whose lives are unstructured by external commitments, persons living in chaotic social conditions resulting from poverty, and those who may be confused about their drug regimen. A systematic review and meta-analysis has shown that forgetfulness is a complex challenge to address.[21] Clinical trials aimed at improving adherence found that the most effective strategies consisted of combinations of convenient care, information, patient reminders and self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, and manual telephone follow-up. However, even the most effective interventions did not result in large improvements in adherence and treatment outcomes.[21]

Importantly, studies have suggested that in most cases non-adherence is intentional and that often patients who claim forgetfulness actually have underlying concerns and beliefs surrounding their medication that contribute to non-adherence.[22]

Medication Beliefs

A key influencing factor in treatment adherence is how worthwhile a patient believes their medication to be and whether the patient considers the benefits to outweigh the burden and potential harm. In T2DM, the benefits of medication are often not immediately tangible, as many medications are prescribed to reduce the risk of health issues later in life.[23] In contrast, there are many immediate burdens associated with taking medication, including cost and the logistics of following complex regimens that involve taking multiple pills and/or injections.[23] Patients can also associate their medication with feelings of failure or punishment, due to previous interactions with healthcare professionals in which starting medication has been explained as a future consequence of failing to make lifestyle changes.[24] In some cases, patients observe their medication as potentially harmful, especially if they have experienced a hypoglycaemic event, and feel that avoiding or stopping their medication is the safer and healthier option.[22] Many patients associate taking fewer medicines with having less severe disease, regardless of their metabolic results, and require education surrounding the direct relationship between a lack of glucose control and increased likelihood of experiencing future health problems.[23,24]

Patient–Physician Interactions

Adherence rates are also impacted by the quality of patient–physician interactions.[23] Patients who have confidence that their physician involves them in decisions, understands their issues with their treatment, and puts their needs first are more likely to adhere to their medication regimen.[25] Time is an important factor in ensuring that physicians can build trust with their patients and fully address their concerns, and is also important in overcoming clinical inertia. Longer consultation times have been found to increase the proportion of patients who receive a change in medication after presenting with poorly controlled disease.[26] Thus, in many situations, what can be perceived as inertia among some physicians to alter treatment regimens may actually be a result of consultation times that are too short to accurately assess treatment requirements.

In summary, treatment adherence rates can be influenced by both patient-related issues, including patient perceptions of the balance between treatment benefits and burden, and the quality and duration of patient–physician interactions.

Shifting the Paradigm: New Strategies to Overcome Barriers to Type 2 Diabetes Mellitus Treatment Success

Professor Eduard Montanya

It is clear that new treatment approaches are required to improve clinical outcomes for patients with diabetes. Early combination therapy, fixed-dose combination therapy, telemedicine, and new ways of delivering medicines represent four potential strategies to overcome barriers to treatment success.

Early Combination Therapy

Traditionally, treatment regimens for patients with T2DM sequentially escalate in intensity as the disease progresses. Patients may first be advised to undertake a change in lifestyle, followed by treatment with oral antidiabetic drug (OAD) monotherapy, OAD combination therapy, injectable antidiabetic drugs (generally GLP-1 receptor agonists), and, finally, insulin-containing treatment regimens.[27] In the typical stepwise treatment approach to T2DM, treatment is changed only when HbA1c levels rise above the target, which can lead to patients experiencing repeated and sustained periods of poor glycaemic control.[27] An alternative treatment option is the early combination approach, in which patients receive intensive OAD combination therapy soon after diagnosis, and each subsequent therapy is introduced when HbA1c levels start to rise, but before they have exceeded the target level.[27] In the early combination approach, patients spend less time overall in a hyperglycaemic state compared with the traditional approach, therefore, they are less likely to experience complications associated with hyperglycaemia.[27,28]

Clinical studies have suggested that early and intensive combination therapy is more successful at reducing and maintaining HbA1c levels compared with a more traditional approach.[29,30] In addition to improved glycaemic control, the early combination approach has the potential to target multiple pathophysiological factors that contribute to the progression of T2DM, including lowering the rate of beta cell failure, and may also help overcome the challenge of clinical inertia, as intensification is less frequently needed.[31]

Fixed-Dose Combination Therapy

Another emerging treatment option is fixed-dose combination therapy, which can reduce the treatment burden by combining multiple medicines into one pill or injection. Of particular interest in advanced-stage disease are fixed-dose combination therapies, in which a GLP-1 receptor agonist and basal insulin are combined in a pre-filled pen device. These treatments combine the HbA1c, fasting plasma glucose, and postprandial glucose-lowering abilities of each individual drug, while also balancing the positive and negative side effects of each therapy.[32] Clinical studies have shown these fixed-dose therapies to be more effective at lowering blood glucose, reducing the risk of hypoglycaemia, and enabling weight loss, compared with basal insulin alone.[32] Currently, two such therapies exist, both of which are approved for use in T2DM in the European Union (EU) and USA: iDegLira, a combination of insulin degludec and liraglutide and iGlarLixi, a combination of insulin glargine and lixisenatide.[33]

Telemedicine

While new treatment approaches and therapies have demonstrated efficacy in clinical trials, improving patient adherence to treatment is key to unlocking their potential in a real-world setting. Telemedicine involves using electronic communication to deliver health services to patients and has been suggested as a potential strategy to increase treatment adherence in patients with diabetes. These interventions can utilise tools such as text messages, DVD, and web-based applications, with >1,000 applications currently available for smartphones and tablet computers that are specifically targeted towards people with diabetes.[34] These applications can facilitate consultations and diagnosis, while also providing treatment reminders and links to further information and resources. While these tools have the potential to improve disease management and clinical outcomes, current evidence on their efficacy in diabetes is insufficient and unconvincing; in a meta-analysis, the use of telemedicine tools was associated with only modest, short-term improvements in glycaemic control and had no clear effect on quality of life or mortality.[35]

Novel Drug Delivery Methods

An innovative way of tackling treatment non-adherence could be new drug delivery methods that remove the need for patients to physically take their medicine, thereby circumventing adherence issues. The ITCA 650 device is an osmotic mini-pump the size of a matchstick that is inserted subdermally, where it delivers a continuous

dose of the GLP-1 receptor agonist exenatide for up to 6 months (Figure 3).[36] ITCA 650 is currently under US Food and Drug Administration (FDA) review for use in patients with T2DM.[36]

A complete clinical development plan involving >5,000 patients with T2DM has been completed with ITCA 650 to support regulatory filings in the USA, EU, and other territories. The clinical efficacy and safety of ITCA 650 was evaluated in a Phase II and a Phase III programme (FREEDOM) designed to assess whether the addition of ITCA 650 to current standards of care results in improved outcomes, and whether ITCA 650 is superior to the leading branded oral therapy for the treatment of T2DM.[37-40]

In the FREEDOM-1 study,[39] a Phase III, randomised, placebo-controlled study in 460 patients with T2DM, ITCA 650 was significantly superior to placebo at reducing mean HbA1c levels and mean body weight when added to OAD. In the FREEDOM-2 study,[40] a Phase III, head-to-head study in 535 patients with T2DM uncontrolled on metformin, ITCA 650 was superior to sitagliptin at reducing mean HbA1c levels from Week 0 to Week 52 (1.5% reduction versus 0.8% reduction, respectively; $p<0.001$). Treatment with ITCA 650 was generally well-tolerated. The safety profile was consistent across the Phase I, II, and III studies and comparable with that previously observed for exenatide and GLP-1 receptor agonists. Gastrointestinal effects, including nausea, typically occurred early after implantation and were generally transient. Overall, the ITCA 650 mini-pump was well-tolerated and effective, and offers an innovative approach to address the adherence issue and improve the convenience of T2DM treatment in clinical practice.

In summary, numerous strategies with the potential to overcome barriers to effective treatment of T2DM have been approved or are currently under development. These include innovative treatment approaches using existing medicines, electronic tools to support patient adherence, and novel drug delivery methods.

Figure 3: The ITCA 650 osmotic mini-pump containing exenatide.
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Concluding Remarks

- T2DM remains difficult to control, despite the increasing availability of many new pharmacological treatment options.
- Poor patient adherence to medication constitutes a major barrier to the treatment of T2DM.
- Low adherence to treatment worsens glucose control and increases the risk of complications and associated healthcare costs.
- Treatment adherence is influenced by multiple patient and physician-related factors, including perception of benefits, fear of hypoglycaemia, side effects, regimen complexity, and clinical inertia.
- Each of these factors represents an opportunity for targeted efforts to improve treatment adherence.
- New approaches are needed to overcome the barriers to success in diabetes treatment; among those currently under development is the ITCA 650, a novel drug delivery device that has the potential to improve long-term therapeutic outcomes by ensuring 100% adherence to therapy.

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