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Case Report

Personalised Medicine for the Treatment of T2DM

Gilles Plourde[1, 2]*, Marie-Eve Matte[3]

[1]*Associate Professor at the Faculty of Health Sciences, University of Ottawa, Ontario, Canada

[2] Faculty of Medicine, University of Montreal, Montreal, Quebec Canada

[3] MSc Student, Department of Clinical Pharmacology, Faculty of Medicine, University of Montreal, Montreal, Quebec Canada

Correspondence to: Gilles Plourde, Drug Safety Unit – Director's Office, Health Canada, Ontario, Canada; **E-mail:** gilles.plourde@hc-sc.gc.ca; drgplourde@gmail.com

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Case Report

Introduction

Personalized medicine aims at better targeting therapeutic intervention to the individual by maximizing the benefits and minimizing harms associated with drugs. T2DM is a heterogeneous disease with an important genetic background. The underlying pathogenic mechanisms and the clinical features markedly vary among patients [1-3]. The American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) position statement on T2DM management and the American Association of Clinical Endocrinologists (AACE) clearly mention that the choice of T2DM goal therapies of reaching an HbA1c of < 7% for all patients should be replaced by a more patient-individualized approach based on attributes specific to both the patients and the medications themselves [4-6].

Individual drug response may vary due to many factors such as: 1). Individual characteristics of the patient: age, gender, BMI or comorbidities; liver and/or kidney function and others; 2). polymorphisms in genes encoding drug-metabolizing enzymes, transporters, receptors and molecules involved in signal transduction; 3). some specificities of the disease itself such as the known duration of T2DM that may influence the magnitude of the beta-cell defect, its severity as quantified by the increase in HbA1c; 4). the main components of the pathophysiology of the disease, especially the relative contributions of the defect in insulin secretion and insulin resistance; 5) the properties of the OADs especially their specific mode of action tackling the most crucial pathophysiological defects and targeting fasting and/or postprandial hyperglycaemia; and 6). the PKs parameters that may be altered by comorbidities such as renal or hepatic impairment but also by genetic background and polymorphism in enzymes or transporters playing a key role in drug metabolism leading to a true individual drug response [7-8].

However, we are at some point already going for an individualized approach in the treatment of T2DM that is based on our understanding of some of the pathophysiology of the disease such as their risk for hypoglycemia, how long the patients have had the disease, whether they have other important comorbidities, their risk of weight gain and their motivation status. We actually have very good guidelines based on outcome data to suggest how we should individualize treatment targets. Specifically, the ADA has put forward a very interesting graphical representation of individual physiologic and patient-centered aspects (https: //durobojh7gocg.cloudfront.net/content/diacare/38/1/140/F1.large.jpg) that the HCP should incorporate in the selection of our treatment target and in the selection of the appropriate medication. However, a great inter-individual variability exists in the clinical outcomes of glucose-lowering agents, especially for the OADs [7-8]. Therefore, the poor therapeutic outcomes that we often observed with a specific medication may be caused by treating patients without being concern for the individual pharmacogenetic and/or the pharmacogenomic characteristics that might influence the drug response.

Therefore, understanding the basis of this heterogeneity should provide an opportunity for better personalising treatment strategies according to individual patient clinical characteristics and the molecular characteristics of the OADs [9-11]. This case report will discuss both the opportunities and the challenges of personalised medicine and how this new treatment issue may lead to a better individualized treatment of T2DM. Although, the treatment of pediatric T2DM is rather limited to insulin and metformin, if we consider that the mean age that most pediatric patients are diagnosed with T2DM is around 14 years-old, these adolescents will become rapidly adult's patients and we believe that it is a very good opportunity to introduce this topic within this special issue to better prepare the HPC to this new era of treating T2DM.

Case Report

Joseph is a 16 year-old obese (BMI 32 kg/m^2) European-American that came to your office with her mother because he presented symptoms of T2DM. With this limited information what should be the individual characteristics and disease-related biological characteristics you need to consider in the objective of personalising Joseph's treatment in case he receive the diagnosis of T2DM?

(A) His age;

(B) His gender;

(C) His BMI;

(D) His race/ethnicity;

(E) His markers of insulin secretion (C-peptide);

(F) His markers of disease severity (HbA1c)

(G) His fasting versus postprandial hyperglycaemia;

(H) His markers of insulin resistance (metabolic syndrome);

(I) The presence or not of renal impairment.

(J) The presence or not of liver disease.

(K) All of the above.

Answer: K

Explanations

A) His Age

As mentioned on many occasion in previous articles, the onset of T2DM at an early age points to a glycaemic legacy if the disease is uncontrolled for long periods of time. Many of these patients are obese at diagnosis and also have co-morbidities such as HTN, dyslipidaemia and microalbuminuria at a relatively early age which put them at risk of early CVD. Although LSI may be helpful in the management of many of these co-morbidities, pharmacotherapy with the aim of preserving β-cell function and improving insulin sensitivity should often be added. At present, metformin is the only OAD approved for use in children and adolescent. However, recent data from the Treatment Options for Type 2 Diabetes and Adolescents and Youth (TODAY) study showed that 50% of children and adolescent failed to maintain durable glycaemic control with metformin monotherapy and combination therapy or insulin was often necessary within a few years of diagnosis. Although not discussed in this article, it is possible to suggest the presence of a pharmacogenomic and pharmacogenetic components to explain this relatively poor response to metformin (See below). Therefore, agents that address insulin resistance other than metformin can potentially help to preserve β-cell function (DPP-4 inhibitors and GLP-1 receptor agonists) should be considered given that the disease will progress over many decades. The choice of medication based on Joseph genetic information will be further discussed below.

B) His gender

Differences in gender responses to therapy may be considered when individualizing treatment for people with T2DM as it is an important personal characteristic [7, 12]. For instance, females had smaller decreases in HbA1c and were less likely to reach glycaemic targets despite higher insulin doses and more hypoglycaemic events than males [7]. However, no obvious gender-related differences were reported with OADs so far. Further studies are required to clarify whether or not a gender-related difference clearly exists for OADs. However, for the reasons discussed in previous articles including those related to the puberty; in the context of clinical practice gender should always be considered in personalising treatment.

C) His BMI

When only two classes of OADs were available, metformin was preferred in obese patients while sulphonylureas were considered as a better option in non-obese patients with T2DM. Now metformin is considered as the first-line therapy in all patients with T2DM [8] in the absence of contraindications that include acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma and relevant gastrointestinal symptoms; those patients should rather be treated with insulin [13]. Currently, OADs can be separated according to their effects on body weight: some inducing weight gain (sulphonylureas, glitazones, insulin), others being weight neutral or inducing only mild weight reduction (metformin, DPP-4 inhibitors) and others associated with significant weight loss (SGLT2 inhibitors, glucagon-like peptide-1 or GLP-1 receptor agonists) [7, 14-15]. These differential weight effects may influence HCP's preferred choice according to patient's initial body weight and desire of weight change. Considering that our patient is obese, choosing a medication that has a positive effect on weight loss can be a good choice in personalising his treatment. Therefore, medications in the class of SGLT2 inhibitors or GLP-1 receptor agonist should be considered. However, other clinical and genetic considerations needs to be assessed before deciding which medication should be the best for Joseph. This will be further discussed below.

D) His race/ethnicity

Differing effects of metformin on glycaemic control by race-ethnicity have been reported. For instance, African American individuals appear to have a better glycaemic response to metformin when compared with European Americans [16]. DPP-4 inhibitors exhibit a better glucose-lowering efficacy in Asians than in other ethnic groups. However, the precise underlying mechanisms remain unknown [17] and other research are also needed to further document the impact of race/ethnicity on the choice of the most appropriate OADs to treat their T2DM. The fact that our patient is European American may indicate that his response to metformin may be reduced with time. That is why it is important to note this information in the context on personalising treatment of T2DM.

E) His markers of insulin secretion (C-peptide)

T2DM is an evolving disease characterized by a progressive loss of β-cell function and a decline in insulin secretory capacities, which results in the progression of the disease [7]. Disease progression and interindividual response to OADs varies markedly among patients with T2DM (18). Because some OADs mainly promote insulin secretion while others rather act primarily on insulin sensitivity, the residual insulin secretion should influence the drug-related response regarding improvement of glucose control in patients with T2DM [19-20]. Therefore, measurement of plasma C-peptide has been suggested of being of clinical utility in the assessment of patients with T2DM [19]. However, there is limited evidence to support the use of C-peptide to predict treatment response in patients with T2DM [21]. Nevertheless, the recent development of incretin-based therapies may somewhat change this approach. Indeed, severe insulin deficiency as evidenced by low plasma C-peptide concentrations predicts a poor to a non-response to GLP-1 receptor agonists [22-23]. Again, this information is particularly relevant when we will have to decide which OADs is the best for our patient. For instance, the patient may have specific gene in favor of specific OADs but without the supporting clinical information the patient is no longer a candidate to receive these medications. Which means that the genetic information should be supported by the clinical information to obtain the best personalised treatment?

F) His markers of disease severity (HbA1c)

The level of HbA1c, used as a validated marker of glucose control during recent weeks, is the main marker use to guide the choice of

therapy. Initiation of insulin therapy rather than OADs is recommended in patients with T2DM who present with an initial HbA1c level > 9% (75 mmol/mol) and symptoms related to hyperglycaemia. When the HbA1c is above 8.0–8.5%, the likelihood of achieving glycaemic targets with a single OAD diminishes drastically. These patients may be better candidates for treatment with a combination of OADs as first-line therapy [24], although this is not commonly done yet in clinical practice [25]. Whatever the glucose-lowering agent used, the higher the baseline HbA1c level, the greater the reduction in HbA1c achieved [26]. However, the impact of the increase in baseline HbA1c on the clinical efficacy of a SGLT2 inhibitor is greater than that of a DPP-4 inhibitor [27]. This difference can be explained by the greater amount of glucose removed from the body by SGLT2 inhibitors at the higher plasma glucose concentration. In contrast, high HbA1c may suggest a profound defect in insulin secretion, which may limit the efficacy of DPP-4 inhibitors [28-30]. Thus SGLT2 inhibitors may be preferred to DPP-4 inhibitors in T2DM patients with high initial HbA1c [7, 27]. Knowing the initial HbA1c level is not questionable as it is one of the main characteristic that the HCP should know before initiating T2DM treatment and this has been largely discussed in previous articles. However, it is now evident that this information is essential in the selection of the appropriate OAD not only for the initial treatment of T2DM but also as a second-line treatment; for instance when patients are no longer responding to metformin as in 50% of patients in the TODAY study.

G) His Fasting versus postprandial hyperglycaemia

HbA1c value gives an integrated view of overall glucose control during the last 2–3 months, but does not allow discriminating between preponderant contributions of fasting or postprandial hyperglycaemia [31]. Some OADs are mainly active on fasting hyperglycaemia (metformin, thiazolidinediones, basal insulin) while others are mainly targeting postprandial hyperglycaemia (incretin-based therapies, acarbose, prandial insulin bolus). In a meta-analysis exploring 24-week effects on HbA1c of maximal doses of DPP-4 inhibitors, DPP-4 inhibitors appear to be more effective in patients with mild/moderate fasting hyperglycaemia [32]. Short-acting GLP-1 receptor agonists (i.e. exenatide) mainly target postprandial hyperglycaemia whereas long-acting receptor agonist (i.e. liraglutide) mainly targets fasting hyperglycaemia [33]. Thus, the individual relative contributions of fasting versus postprandial hyperglycaemia may be helpful in choosing the best OAD therapy in patients with T2DM [34, 31]. That is why it is important to get this information in the assessment of each patient with T2DM.

H) His markers of insulin resistance (metabolic syndrome)

Insulin resistance syndrome is linked to abdominal obesity and is usually associated with biological markers of the metabolic syndrome that includes HTN, abdominal obesity, dyslipidemia and dysglycemia. Therefore, the presence of atherogenic dyslipidaemia (hypertriglyceridaemia, low HDL, HTN and abdominal obesity should encourage the prescription of agents that can promote weight loss (SGLT-2 inhibitors, GLP-1 receptor agonists) and/or improve insulin resistance (pioglitazone) [13-15]. NAFLD is rather common in patients with poorly controlled T2DM and metabolic syndrome and could be improved with pioglitazone [35] or liraglutide [36]. Therefore, knowing the presence of the markers of insulin resistance may be helpful in choosing the best OAD therapy in patients with T2DM.

I) The presence or not of renal impairment

As discussed in article number 2, CKD is a frequent complication in patients with T2DM, especially after a long duration of hyperglycaemia, especially when HTN is present. The presence of renal impairment has to be taken into account when selecting both the type and the dose of the OADs in patients with T2DM [12]. More particularly, this is the case for metformin [13], incretin-based therapies (DPP-4 inhibitors and GLP-1 receptor agonists) [16] and SGLT2 inhibitors [37]. The risk of hypoglycaemia is also increased in T2DM patients receiving most sulphonylureas in the presence of renal insufficiency [12]. Again, it is essential to know whether or not we are in presence of renal impairment before choosing the best OAD therapy in patients with T2DM.

J) The presence or not of liver disease

Severe liver disease is much less frequent than CKD in patients with T2DM. If present, it should impose cautious selection of both type and dose of OADs to minimize the risk of adverse drug reactions [38]. However, NAFLD is common in patients with T2DM. Some OADs have proven to be more efficacious to reduce hepatic fat content than others, especially thiazolidinediones (pioglitazone) [35] and GLP-1 receptor agonists (liraglutide) [36]. The presence of a liver disease can easily be found by simply doing a liver profile. This will also permit to screen for the presence of NAFDL. Again, this information is relevant before prescribing the most appropriate medication for a specific patient.

You have completed the investigation and you found that this patient had T2DM. It was then treated with insulin and LSI for few months. After one year with this treatment he was transfer to metformin and LSI. He lost 5 kg of body weight, which means that he is no longer obese but still have difficulties controlling his weight and his blood glucose and had some gastrointestinal intolerance on metformin despite being highly compliant to the HCP and diabetic nurse recommendations. His blood pressure was normal as well as his lipid profile and his liver profile was normal too suggesting the absence of NAFDL and liver diseases. His last HbA1c has increased to 7.8% recently added to his digestive symptoms with metformin consequently he had to return on insulin but does not want to stay on insulin for a long period of time. His C-peptide is at 1.7 mmol/L (0.2-1.0mmoll) suggesting the presence of insulin resistance but not insulin deficiency. His ACR is of 0.88 mg/mmol (<3.5 mg/mmol); and his eGFR is of 118 ml/min (90-120 ml/min) suggesting the absence of renal impairment. Joseph has no problem with fasting or post prandial hyperglycemia in the past few months as seen on his SBGM. After 6 months, you are planning to change his insulin for a new medication since he is now18 years-old but before that you decided to send him to a research center for a genetic consult in order to determine which medication should be the most appropriate for him. You got the following results from the genetic consult. The patient had OCT1 variants encoded by the gene

SLC22A1; variant alleles in TCF7L2 and IRS-1 genes; the presence of the SLCO1B1*1B (c.388G-c.521T) haplotype; the presence of PPAR-γ. 12Ala carriers; variants of the transcription factor 7- like 2 genes (TCF7L2) and the rs6923761 variant of the GLP-1R gene. Based on this genetic information what should be the treatment of choice?

(A) Biguanides (metformin);
(B) Sulphonylureas;
(C) Meglitinides (repaglinide, nateglinide);
(D) Thiazolidinediones (TZD) (pioglitazone, rosiglitazone);
(E) Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins);
(F) Glucagon-like peptide-1 (GLP-1) agonist (Liraglutide, Exenatide)
(G) Sodium–glucose cotransporters type 2 (SGLT2) inhibitors (gliflozins)
(H) Only C, D and F are correct

Answer: H

Explanations

A) Biguanides (Metformin)

Metformin has been a cornerstone in T2DM management even if its mechanism of action remains unclear [7]. At the moment, it seems to lower blood glucose through hepatic diminution of glucose production and an increase of peripheral insulin sensitization [39]. Despite its wide and, generally, well tolerated utilisation, according to the TODAY study, 50% of patients are poor responders and up to 63% are experiencing important gastrointestinal adverse reactions [39]. Because of its positive charge, metformin is, most likely, transported by organic action transporters (OCTs); plasma membrane monoamine transporter (PMAT), OCT1 and OCT3 may be responsible for its intestinal absorption, OCT1 and MATE1 for its transport to the liver and biliary excretion, respectively whereas OCT2 seems implicated to its transport to the kidney and MATE1/2 for its secretion [39]. However, some of them were found, by GWAS, to possibly have genetic variants implicated in response variability to OADs [7].

OCT1 encoded by the gene SLC22A1, has been the focus of many studies and results of its variants have been ambiguous about its influence on drug response [7]. Overall, it seems that there is a lower efficacy of metformin with individual having one or more variants associated with reduced function and gastrointestinal intolerance was significantly higher in individual showing reduced function in both alleles [39-40]. OCT2 has been studied mostly in Asian populations and heterozygous GT alleles individuals appear to be associated with better PKs results [39]. As for MATE1 and MATE2, fewer results are available, however, homozygous for minor allele in some variants showed higher and lower, respectively, HbA1c reduction [39]. Also, genetic variants found in OCT1, OCT2 and MATE1 were associated with lower incidence of T2DM or protection effects after metformin treatment [39]. In a large GWAS, ATM gene was linked to better HbA1c reduction for its minor allele but was not found to reduce T2DM progression [60, 84]. Finally, two variants in and around transcription factors gene SP1 were associated with lower HbA1c diminution and lower clearance [39]. Hence, from these equivocal results emphases the need for further studies but also, the important role that genetic profiling could have in metformin treatment, its response and better control over its adverse effects [7]. Therefore, the OCT1 variants encoded by the gene SLC22A1 may at some point explain why this patient became less responsive to metformin therapy and explain his gastrointestinal intolerance. Finally A is not a good answer.

B) Sulphonylureas

Used as first-line and add-on therapy, SUs are known to activate ATP potassium channel in pancreatic β-cell thus leading to a release of glucose-independent insulin. Ten to twenty percent of patient under SU treatment will have a small fasting plasma glucose reduction [39]. Therefore, genetic studies which focused on SU mostly targeted genes that are linked to insulin secretion. Numerous genes and cytochrome P450 (CYP450) were associated to genetic variants that could influence SUs response in T2DM patients [7]. Polymorphisms in CYP enzymes are widely studied, CYP2C9 and CYP2C19 variants have been implicated in T2DM that could altered SU metabolism and response [23, 38, 42]. Asian carriers of a defective allele of CYP2C9 (*3) and CYP2C19 (*3) seems to be particularly affected by SU administration leading to increase PKs parameters whereas Caucasians with affected alleles (*2 or *3), though ambiguous, were associated to higher risk of hypoglycaemia and lower clearance of glucose [23, 38, 42].

ABCC8, KCNJ11, TCF7L2 and IRS-1 are some the genes that were associated to impact SUs response. Two variants in ABCC8, S1369A and E23K, reported higher fasting plasma glucose and HbA1c reductions in Chinese using gliclazide and higher therapy failure associated to K allele when glibenclamide was taken, respectively. As for KCNJ11, results are ambivalent; some studies showed no difference and others implied that K allele was linked to higher HbA1c reduction, lower risk of hypoglycaemia and fasting plasma glucose (39). Variant alleles in TCF7L2 and IRS-1 genes have been associated with treatment failure; first and second SUs treatments for TCF7L2 and secondary treatment for IRS-1 [39, 43-45]. Therefore considering the presence of these variant alleles in TCF7L2 and IRS-1 genes sulphonylureas are not appropriate OADs for Joseph.

C) Meglitinides (repaglinide, nateglinide)

Possible reasons for interindividual variability in response to meglitinides may result from polymorphisms in organic anion transporting polypeptide 1B1 (OATP1B1) gene (SLCO1B1) or the metabolizing enzyme of the CYP family [46]. Nateglinide is metabolised by CYP2C9 whereas repaglinide is metabolised by CYP2C8 [42, 47]. Moderate dose adjustments based on CYP2C9 genotypes may help in reducing interindividual variability in the antihyperglycaemic effects of nateglinide. CYP2C8*3 carriers had higher clearance of repaglinide than carriers of the wild-type genotypes. Although genetic variants in metabolizing enzymes of the CYP family may alter the PK of the medications of the meglitinide family, they do not appear to have major effects on the glucose levels of T2DM patients [7-8, 46].

The SLCO1B1*1B (c.388G-c.521T) haplotype is associated with enhanced hepatic uptake and decreased plasma concentrations of some OATP1B1 substrates. The SLCO1B1 c.521CC genotype has been associated with increased and the SLCO1B1*1B/*1B genotype

with decreased exposure to repaglinide. Accordingly, SLCO1B1 genotyping may theoretically help in choosing the optimal starting dose of repaglinide [48]. In Chinese individuals, the SLCO1B1 c.521C allele has been associated with increased plasma concentrations of nateglinide, but the association could not be replicated in Caucasians [48]. Other studies are warranted to examine the association between repaglinide or nateglinide efficacy and safety and different polymorphisms. The presence of the SLCO1B1*1B (c.388G-c.521T) haplotype may have a beneficial effect in the response to meglitinides. Therefore C is a good answer.

D) Thiazolidinediones (TZD) (pioglitazone, rosiglitazone)

CYP2C8 and CYP3A4 are the main enzymes catalyzing the biotransformation of pioglitazone (and troglitazone, a TZD withdrawn because hepatotoxicity), whereas rosiglitazone is metabolized by CYP2C9 and CYP2C8 [42, 49]. SLCO1B1 genotype has had no effect on the PK of rosiglitazone, pioglitazone or their metabolites [48].

The genes coding for CYP2C8 and PPAR (peroxisome proliferator activated receptor)-gamma (γ) are the most extensively studied to date and selected polymorphisms may contribute to respective variability in pioglitazone PK and PDs, which may impact both efficacy and toxicity of the drug [50]. CYP2C8*3 was associated with lower plasma levels of rosiglitazone and hence a reduced therapeutic response but also a lower risk of developing oedema, which suggests that individualised treatment with rosiglitazone on the basis of the CYP2C8 genotype may therefore be possible [51]. However, the studies that looked at the association between CYP polymorphisms and TZD toxicity were inconsistent and generally did not produce statistically significant results. Therefore, it can only be speculated that polymorphisms in TZD-metabolizing enzymes are associated with toxicity [46].

Specific genetic variations in genes involved in the pathways regulated by TZDs could also influence the variability in treatment with these drugs [52]. A first study showed that the Pro12Ala variant in the PPAR- γ gene does not affect the efficacy of pioglitazone in patients with T2DM, suggesting that the glucose-lowering response is independent from pharmacogenetic interactions between PPAR-γ and its ligand pioglitazone [53]. However, in a more recent meta-analysis, which synthesized the currently available data on the PPAR-γ. Pro12Ala polymorphism, PPAR- γ. 12Ala carriers had a more favourable change in fasting blood glucose from baseline as compared to patients with the wild-type Pro12Pro genotype [50]. In a study investigating the influence of the S447X variant in lipoprotein lipase (LPL) gene on the response to therapy with the TZD pioglitazone, the S447X genotype conferred a statistically significant reduction in glucose-lowering response rate to pioglitazone as well as a less favourable lipid lowering response relative to the S447S genotype (54). In a study in Chinese patients with T2DM, the adiponectin gene polymorphism rs2241766 T/G was associated with pioglitazone efficacy [55]. Therefore, pharmacogenomics and pharmacogenetics may be an important tool in drug individualization and therapeutic optimization when prescribing TZDs in patients with T2DM [52]. The presence of PPAR- γ. 12Ala carriers indicates that this drug might be a good choice in the treatment of Joseph's T2DM. Therefore, D is a good answer.

E) Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)

DPP-4 inhibitors (gliptins) are increasingly used in the management of patients with T2DM, essentially because of a good safety profile [56]. The liver is not important for the elimination or action of sitagliptin, vildagliptin and saxagliptin [57]. Therefore, SLCO1B1 polymorphism unlikely affects the response to these OADs. ABCB1 polymorphisms (ABCB1 CGC/CGC, CGC/TTT, and TTT/TTT diplotypes) did not influence sitagliptin PK in healthy volunteers [59]. Cytochrome P450 (P450) enzymes CYP3A4 and CYP3A5 metabolize saxagliptin and 5-hydroxy saxagliptin (M2), its major, active metabolite. Kinetic experiments indicated that the catalytic efficiency for the CYP3A4 was approximately 4-fold higher than that for the CYP3A5. Therefore, it is unlikely that variability in expression levels of CYP3A5 due to genetic polymorphism will impact clearance of saxagliptin [60].

Individuals carrying variants of the transcription factor 7-like 2 gene (TCF7L2) are at increased risk for T2DM and may have diminished pancreatic islet-cell responsiveness to incretins. Linagliptin significantly improved hyperglycaemia in T2DM patients both with and without the TCF7L2 gene diabetes risk alleles, although HbA1c response was significantly reduced in TT compared with CC patients [61]. Thus, diabetes susceptibility genes may be a contributor to the inter-individual variability of treatment response to DPP-4 inhibitors. In a large primary care database recently analyzed to assess the variability in response to a DPP-4 inhibitor, HbA1c reductions were significantly lower with increased T2DM duration, in agreement with a defective insulin secretion [28]. These data are in agreement with previous studies having measured insulin secretion in T2DM patients treated with sitagliptin [29] or vildagliptin [30]. Because this patients is carrying variants of the transcription factor 7- like 2 genes (TCF7L2), he may have diminished pancreatic islet-cell responsiveness to DPP-4 inhibitors (gliptins) is not a good choice for him. Therefore, E is not a good answer. However, we should consider that the genetic studies focusing on the variability of response to DPP-4 inhibitors are scarce and poorly contributive.

F) Glucagon-like peptide-1 (GLP-1) agonist

GLP-1 is an incretin that is known to induce insulin secretion of the β-cells. GLP-1 receptors (GLP-1R) agonists sustain insulin secretion consequently increasing the efficacy in the treatmet of T2DM. Encoded by GLP1R gene, GLP-1R is logically listed as one of the target that could affect treatment's response. Studies associated to GLP-1R agonist have found that there are three genetic variants that might influence its response. However, still unclear results ensue from these researches [62-64]. T allele of rs3765467 and rs761386 were linked to lower and higher standard deviation in plasma glucose in response to exogenous GLP-1, respectively. The rs6923761 variant has shown an increased response from β-cells. Since this patient is carrying the rs6923761 variant of the GLP-1R gene he may have increased pancreatic β-cells responsiveness to GLP-1. Therefore F is a good response and according to Joseph clinical presentation a GLP-1 agonist is probably the better choice for him and this is consistent with the most recent Canadian Clinical Practice Guideline http: // guidelines.diabetes.ca/bloodglucoselowering/pharmacologyt2.

G) Sodium–glucose cotransporters type 2 (SGLT2) inhibitors (gliflozins)

SGLT2 inhibitors is a glucose transporter situated in the kidney, it blocks the reabsorption of filtered glucose, leading to glucosuria [7]. The SGLT2 gene (SLC5) has been mapped to chromosome 16 p11.2, and up to 50 different mutations of this gene have been reported in the context of familial renal glucosuria [63]. SLC5A2, a gene implicated in glucose transport, holds a genetic variant, rs9934336, from which the G allele was associated with increased exposure to the drug [64]. SGLT-2 inhibitors are eliminated by uridine diphosphate glucononyltransferases (UGTs) and as for CYPs, they are known to be associated with genetic variant that can alter their function [7]. So far, there have been no definitive studies of patients with T2DM regarding the genetic variants and SNPs associated with response to the SGLT2 inhibitors.

Conclusion

According to the pharmacogenetic assessesment performed on Joseph, we now know that he could have a very good response in his T2DM treatment by using one of the following OADs: Meglitinides (repaglinide, nateglinide); Thiazolidinediones (TZD) (pioglitazone, rosiglitazone); and Glucagon-like peptide-1 (GLP-1) agonist. This information is particularly pertinent for the HCPs in deciding which OAD he will prescribe to Joseph. However, the HCPs cannot only use the information from genotypic markers for selecting and adjusting T2DM therapy and still need to corroborate this information with the clinical information obtained by the clinic and still need to follow the recommendation from clinical practice guidelines Understanding variations in genetics, environment and lifestyle in order to adapt care to each individual is the ultimate objective of precision medicine. As seen in this case report, pharmacogenomics and pharmacogenetics holds a great deal of opportunities toward that goal of personalized care. The cost of personalised medicine should be compensated for by better efficacy, less adverse drug reactions and ultimately less complications associated to T2DM, leading to improved quality of life and increased life expectancy. Eventually, the developments in the field of personalised medicine for T2DM will likely translate, into clinical practices to individualise therapy that will improve both patient outcome and public health.

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