Precision Medicine with Sulfonylureas: From Clinical Studies to Bedside Practice

V Mohan¹, Mathew John², Soumik Goswami³, Mohan Magdam⁴, Saket Kant⁵, MV Vimal⁶, S Amarnath⁷

Abstract

Precision medicine is part of personalized therapy that is based on an individual’s genetic/epigenetic imprints, lifestyle, and environmental characteristics. Recent advances in understanding of the genomic landscape in diabetes mellitus have identified genetic polymorphisms associated with the risk of diabetes mellitus along with other related complications such as cardiovascular risk or hypoglycemia, in turn, spurring the development of precision medicine in prevention and management of diabetes mellitus. Here we will discuss the various genetic polymorphisms that are currently being explored for the development of precision medicine with sulfonylureas, such as glimepiride, for management of people with diabetes.

Sulfonylureas (SUs) in Precision Medicine

Sulfonylureas undergo metabolism in the liver mainly by the CYP2C9 enzyme. Gene polymorphisms of the CYP2C9 enzyme lead to impaired metabolism of SUs, which, in turn, might lead to hypoglycemia. In a case study it was shown that a marked sensitivity to SUs was observed in patients with diabetes with HNF1A mutation. This finding was later validated in a randomized controlled trial that served as the first example of personalized medicine in the treatment of diabetes mellitus. It has been suggested that the SU-induced closure of the ATP-sensitive potassium (K<sub>ATP</sub>) channel bypasses the key sites of beta-cell dysfunction that are upstream of the K<sub>ATP</sub> channel, thereby, leading to increased insulin secretion. SUs serve as the first-line treatment due to the presence of activating mutations in ABC8 and KCNJ11 genes that prevent the closure of K<sub>ATP</sub> in response to glycolysis-generated ATP in case of some specific people with neonatal diabetes mellitus. Therapeutic response to SUs is also affected by genetic polymorphisms in the TCF7L2 gene, which increases the risk of type 2 diabetes mellitus. The underlying mechanism involves impairment of incretinogenic role of incretin hormones. In fact, a study by Srinivasan et al, indicated that altered integrin signaling is an important underlying mechanism for increasing risk of type 2 diabetes mellitus through TCF7L2 variation. This gene variation in turn, affects acute response towards SU and metformin treatments. In the following sections, we will discuss the genetic variations that have been explored for precision medicine in patients with diabetes.

Gene Variation Mimicking SU Therapy

ABCC8 p.A1369S is a common missense mutation in the gene encoding a component of the SU receptor, which promotes closing of the target K<sub>ATP</sub> channel during SU therapy and leads to enhanced secretion of insulin, thereby, mimicking the effects of SU therapy. Based on individual data from 1,20,286 participants in the UK Biobank, Emdin et al. studied the association of this gene variant with type 2 diabetes mellitus, cardiometabolic traits, and coronary heart disease. It was found from the study that this gene variant was associated with lower risk of type 2 diabetes mellitus, increased body mass index (BMI), and lower waist-to-hip ratio adjusted for BMI. In addition, it was also associated with reduced risk of coronary heart disease, which indicated that genetic mutation that mimics SU therapy might reduce the risk of coronary heart disease.

This adds to the long-term efficacy, benefits beyond glycemic control and safety data for SUs.

¹Chairman and Chief Diabetologist, Dr. Mohan’s Diabetes Specialities Centre, Chennai, Tamil Nadu; ²Consultant Endocrinologist and Managing Partner, Providence Endocrine and Diabetes Specialty Centre, Trivandrum, Kerala; ³Consultant Endocrinologist, Department of Endocrinology, NRS Medical College, Kolkata, West Bengal; ⁴Consultant Endocrinologist, Poona hospital and Aditya Birla Hospital, Pune, Maharashtra; ⁵Sr. Consultant, Department of Endocrinology, Max Super Speciality Hospital, Shalimar Bagh, New Delhi; ⁶Consultant Endocrinologist, Aster MIMS, Calicut, Kerala; ⁷Medical Affairs, Diabetes and Cardiovascular, Sanofi India Ltd.
Table 1: Gene mutations/polymorphisms associated with the safety and efficacy of SUs

<table>
<thead>
<tr>
<th>Gene mutation</th>
<th>Involvement of SUs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF1A</td>
<td>Marked sensitivity to SUs</td>
</tr>
<tr>
<td>ABCC8 p.A1369S</td>
<td>Mimics the effect of SU therapy, increasing insulin release</td>
</tr>
<tr>
<td>KCNJ11</td>
<td>Neonatal patients can be switched over from insulin to SU therapy</td>
</tr>
<tr>
<td>HNF4A</td>
<td>Can be managed with SU therapy</td>
</tr>
<tr>
<td>CYP2C9p3 and</td>
<td>At higher risk of hypoglycemia when treated with SUs, such as glimepiride</td>
</tr>
<tr>
<td>CYP2C9r2</td>
<td></td>
</tr>
<tr>
<td>POR*28</td>
<td>Shows better response to SU treatment by affecting CYP2C9 alleles</td>
</tr>
<tr>
<td>HNF1A</td>
<td>Hepatic Nuclear Factor I Alpha; ABCC8p.A13695: ATP binding cassette subfamily C member 8, with A1369S mutation; KCNJ11: Potassium Voltage-Gated Channel Subfamily J Member 11; HNF4A: Hepatic Nuclear Factor 4 Alpha; CYP2C9p3 and CYP2C9r2: Genetic variants of Cytochrome P450 2C9 (CYP2C9); POR*28: Genetic variant of Cytochrome P450 Oxidoreductase (POR).</td>
</tr>
</tbody>
</table>

Precision Medicine with SUs in Neonatal Diabetes Mellitus

The occurrence of diabetes mellitus under six months of age is defined as neonatal diabetes, which mostly occurs due to an underlying monogenic defect, i.e., resulting from mutation(s) in a single gene. At present, more than 20 genetic causes are accountable for neonatal diabetes mellitus. In a large international cohort study on 1020 neonatal diabetes patients, more than 80 percent cases had a known genetic diagnosis. Mutations in KCNJ11 and ABCC8 account for 40% of these patients. The KCNJ11 and ABCC8 genes, encode Kir6 channel, and are found in majority of neonatal diabetes mellitus patients. This, in turn, leads to impairment of endogenous insulin release by preventing beta-cell depolarization that results from the closure of the K_ATP channels. The earliest cost-effectiveness analysis in precision medicine focused on the use of SU therapy in permanent neonatal diabetes mellitus patients. It was estimated that genetic testing in such cases would implement significant quality of life benefits at ten years. In a clinical study on 49 patients with diabetes mellitus under six months of age harboring heterozygous activating mutations in KCNJ11 gene, 44 patients (90%) could be successfully switched over from insulin to SU therapy. Sulfonylurea therapy can be initiated in infants with newly diagnosed neonatal diabetes mellitus, in case the test results of molecular genetic diagnosis are delayed.

Precision Medicine with SUs for MODY

Maturity-onset diabetes of the young (MODY) is caused by a range of single gene defects, each of such defects is responsible for one of the 11 types of MODY, such as MODY3 results from mutation in hepatocyte nuclear factor (HNF)-1a while MODY1 results from mutation in HNF-4a genes, respectively. Insulin secretion is impaired in MODY1 and MODY3 and they are often misdiagnosed as type 1 diabetes mellitus. Under such circumstances, exogenous insulin therapy is prescribed. However, it has been found that treatment with SUs restores the secretion of endogenous insulin. Furthermore, switching to SUs from insulin is preferred for a number of reasons, including safety and reduced treatment burden. In fact an additional advantage of SU mediated insulin release is the decrease in glucagon secretion and this endogenous insulin reaching portal circulation being more effective for decreasing hepatic glucose output. It has been found that MODY1 can be managed with SU treatment, although eventually insulin therapy may be required. In case of MODY3, insulin therapy is not required as the genetic defect can be rectified with SU therapy, which makes the beta-cell to secrete insulin. It has been observed that the MODY subtypes with dysregulation in beta-cell function (like HNF4A, HNF1A) or ATP-sensitive potassium channel (ABCC8) are most sensitive to SU treatment.

Gene Polymorphism of CYP2C9 Enzyme and Precision Medicine With SU

Primarily metabolism of SUs takes place in the liver by the cytochrome P450 2C9 enzyme encoded by the CYP2C9 gene. Although a majority of the population carries a normal version of this enzyme, some carry polymorphisms of the gene with reduced function, termed *2 and *3. Overall, 6% of the population carries two reduced-function polymorphisms, as a result of which they are predicted to poorly metabolize SUs.

A clinical study by Ragia et al revealed that when people with type 2 diabetes mellitus carrying the CYP2C9*3 polymorphism are treated with SUs, including glimepiride, they are at increased risk of hypoglycemia, possibly due to the impaired metabolism of SUs. The study proposed that CYP2C9 could be used as a tool for predicting the adverse effects of SUs in people with type 2 diabetes mellitus. In another similar study by Dujic et al on 1770 patients, the effects of a P450 oxidoreductase (POR) gene variant, POR*28 were studied on CYP2C9 (combined CYP2C9*2 and CYP2C9*3 genotypes) activity in the context of SU-induced hypoglycemia and the efficacy of SUs in the treatment of type 2 diabetes mellitus. The results indicated that the interaction between POR and CYP2C9 genes may be important determinants of both adverse effects and efficacy of SU therapy.

Genetic Basis for Resistance/ Poor Response to SU Therapy

It has been observed that Glu23Lys polymorphism (E23K) in KCNJ11 gene is associated with increased risk of therapeutic failure of SUs. Another variant of the ABCC8 gene with SNP at Ser1369Ala has been reported to be associated with altered antidiabetic efficacy of SU in Chinese population. Again, SNPs of the ABCC8 gene in exon 16 ( -3C/T) and exon 31 (Arg1273Arg) are reported to affect SU efficacy in European Caucasians. KATP channels with K23/A1369 risk haplotype were significantly less responsive to SU therapy including glimepiride. Carriers of the risk GG genotype of rs163184 variation in KCNQ, and the Arg (972) variant of IRS-1 also associated with increased risk of SU therapy failure.

Table 1 enlists the various gene mutations that have been identified to be involved in diabetes and their function in the context of SU therapy.

Conclusion

Precision medicine is likely to become a major area in the therapy of diabetes mellitus. Given the insufficiency of conventional antidiabetic therapies, along with the added complexity of their side-effects, precision medicine appears to be the ideal therapy for patients with diabetes. Sulfonylureas including glimepiride have been found to be efficient as precision medicine in the treatment of different types of diabetes.
diabetes mellitus. Identification of genetic polymorphisms in such patients has aided the appropriate choice or inappropriateness of SUs in the therapy of patients with diabetes. With more clinical studies in the coming years, SUs are likely to be prominent members of precision medicine in the treatment of diabetes.

Conflict of Interest

SA is an employee of Sanofi India. All other authors report no conflicts of interest.

Funding

This initiative was supported by Sanofi India. All authors had full access to the chapters of the supplement and take complete responsibility for the integrity and accuracy of the content presented herein.

Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, reviewed and have given their approval for the final version to be published.

Acknowledgements

We thank Dr. Shalini Menon from Sanofi India for her constructive inputs, critique and periodic review on the supplement. Medical writing and editorial support were provided by Dr. Rajshri Mallabadi and Dr. Kavitha Ganesha of BioQuest Solutions Pvt. Ltd. which was paid for by Sanofi, India. Editorial support was also provided by Ms. Anahita Gouri and Dr. Rohan Mitra from Sanofi India.

References