Realities and future prospects of precision medicine.
Type 2 diabetes and hypercholesterolaemia

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INTRODUCTION

Cardiovascular diseases are still the leading cause of morbidity and mortality in industrialised countries. The main risk factors, excluding smoking, include type 2 diabetes and dyslipidaemia, primarily hypercholesterolaemia predominantly due to low-density lipoprotein (LDL). In both situations, the metabolic abnormality occurs usually as a result of the combination of a genetic predisposition and an adverse environment, which is characteristic of what is commonly called the complex diseases \[^1\]. In addition, the role of epigenetics in type 2 diabetes and cardiovascular diseases is attracting increasing interest \[^2\, 3\]. While better lifestyle forms the basis of the treatment strategy, the use of various pharmacological interventions is very often essential to improve prognosis in terms of quality of life and life expectancy.

Personalised medicine is designed to target pharmacotherapy better depending on individual patient characteristics in order to optimise the benefits and minimise risks. Patients suffering from a disease such as type 2 diabetes are characterised by extreme heterogeneity both in terms of pathophysiology and in terms of response to treatment. The current pragmatic strategy involves giving the same drug to all patients, which inevitably include a mixture of good responders and poor responders, and therefore only a relatively modest average final response. Conversely, personalised or precision medicine involves initially identifying patients most likely to benefit from a drug judiciously selected using biomarkers, and not giving the same drug to other patients who do not have predictive factors for a good response (Figure 1). This treatment optimisation strategy helps to avoid the ‘trial and error’ approach which is seen too often in clinical practice. Personalised medicine must be complementary to conventional medicine and evidence-based medicine \[^4\]. Its practice, however, represents a new challenge for clinicians \[^5\]. We describe a few recent advances in personalised or precision medicine for the treatment of type 2 diabetes and hypercholesterolaemia.
TYPE 2 DIABETES AND PRECISION MEDICINE

Type 2 diabetes is the most common form of diabetes mellitus and affects approximately 5% of the population, although it affects over 10% of people over 65 years old. It carries a high morbidity and mortality, with microangiopathic (retinopathy, nephropathy) and macroangiopathic damage (myocardial infarction, stroke). Approximately two-thirds of patients suffering from type 2 diabetes die from a cardiovascular disease.

Type 2 diabetes is a heterogeneous disease involving several dysfunctions, primarily including a relative deficiency in insulin secretory function and insulin resistance. Other abnormalities have, however, been reported, targeting various organs, the pancreas (oversecretion of glucagon), the liver, adipose tissue, intestine and the kidney. Type 2 diabetes is therefore a very heterogeneous disease. Experience gained from single gene MODY (maturity-onset diabetes of the young) diabetes should help to break down the common type 2 diabetes affecting adults in the future and contribute to the introduction of precision medicine. The most spectacular treatment success has been the ability to replace daily insulin injections simply by the prescription of a blood glucose-lowering sulphonylurea tablet, at the same time improving glycaemic control. This affects a minority of patients who have developed diabetes from childhood as a result of a mutation in the potassium channel Kir6.2 subunit, which is sensitive to adenosine triphosphate (ATP) in pancreatic islets of Langerhans B cells.

In addition to lifestyle and dietetic measures, an increasing number of pharmacological approaches targeting different mechanisms of action in one or other organs are available to treat common type 2 diabetes (Figure 2). In view of the heterogeneous nature of the disease, the treatment responses to a given pharmacological class may vary depending on the person, and a personalised patient-centred approach is recommended.

Currently, in clinical practice, the personalised approach to type 2 diabetes is a phenotypic approach, taking account of the patient’s clinical features and those of the disease (Figure 3). While this pragmatic approach is useful in guiding treatment choices, it does, however, have serious limitations, with the result that some patients remain ‘resistant’ to the treatment prescribed.
In recent years, major efforts have been made to identify genetic markers which can influence the pharmacokinetics, pharmacodynamics and ultimately, the effectiveness of treatment of some antidiabetic drugs \[13\]. Metformin is currently recognised as the first line choice of drug in the treatment of type 2 diabetes. Recent studies have demonstrated the existence of ‘variants’ in some transporters or promoters which influence both the anti-hyperglycaemic effectiveness and the gastrointestinal tolerability of this drug \[14\]. ‘Variants’ have also been reported which influence responses to blood glucose-lowering sulphonylureas and the glitazones \[13\]. Other more recent work has examined the heterogeneity of response to new oral antidiabetic agents, the dipeptidyl peptidase-4 (DPP-4) inhibitors, also known as the gliptins \[15\]. These findings also open the way to precision medicine for this new treatment class which is increasingly being used in clinical practice \[10\].

The contribution of pharmacogenetics and pharmacogenomics to personalised medicine remains, however, limited and major advances are expected before being able to implement a genotypic approach in addition to the phenotypic approach in routine clinical practice \[9\]. There can hardly be any doubt, however, that precision
medicine will sooner or later conquer the field of type 2 diabetes and this new paradigm will undoubtedly better individualise and optimise the pharmacological treatment of this complex disease \[16\]. The input of the ‘big data’ approach should also contribute to a better understanding of the heterogeneity of type 2 diabetes and reclassify the phenotypes more appropriately, in particular making use of new better performing biomarkers \[17,18\].

HYPERCHOLESTEROLAEMIA AND PRECISION MEDICINE

The dyslipidaemias are also very heterogeneous metabolic disorders which need to be clearly subdivided in order to offer a personalised approach (Figure 4) \[19\]. We will limit the subject to the best studied lipid risk factor: raised LDL cholesterol. This abnormality is seen in familial hypercholesterolaemia (the homozygous form, and more commonly the heterozygous form), which is the most typical form of the disease. Since the work of Goldstein and Brown, which attracted the Nobel Prize in medicine, this genetic abnormality has been attributed to a deficit (complete in the rare homozygous forms and 50% in the heterozygous forms) in liver LDL receptors. There is also a more common form of hypercholesterolaemia: polygenic hypercholesterolaemia. In addition to dietetic measures designed to reduce saturated fat and cholesterol intake, two pharmacological means are available to reduce blood cholesterol levels. The first is to reduce intestinal absorption of dietary cholesterol, previously with a resin and now using a Niemann Pick protein inhibitor, ezetimibe. The second, which is more effective, is to block hepatic synthesis of cholesterol by inhibiting the enzyme HMG-CoA-reductase using drugs belonging to the statin class, which substantially increase the number of LDL receptors on the surface of the hepatocytes. ‘Good absorber’ patients are believed to benefit more from an absorption inhibitor whereas ‘good synthesiser’ patients are understood to respond particularly well to a cholesterol synthesis inhibitor \[20\]. Different blood biomarkers have been proposed to separate these two categories of patients, although these have never become incorporated into clinical practice \[20\]. In practice, both approaches are additive or even synergistic, with the effect that the patients with the most severe hypercholesterolaemia should benefit from dual pharmacological intervention.

Figure 4: Schematic illustration of individualised management of hypercholesterolaemia.

<table>
<thead>
<tr>
<th>VERY HIGH</th>
</tr>
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<tbody>
<tr>
<td>Positive family enquiry</td>
</tr>
<tr>
<td>Investigation for mutations - Screening of relatives</td>
</tr>
<tr>
<td>Statin (potent, high dose) + ezetimibe</td>
</tr>
<tr>
<td>+ PCSK9 inhibitor</td>
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</tbody>
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<table>
<thead>
<tr>
<th>MODERATELY HIGH</th>
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</thead>
<tbody>
<tr>
<td>CV risk score</td>
</tr>
<tr>
<td>Diet + other corrections in cardiovascular risk factors</td>
</tr>
<tr>
<td>Statin (choice and titration depending on target)</td>
</tr>
<tr>
<td>+ Ezetimibe if LDL remains high</td>
</tr>
<tr>
<td>+ Fenofibrate if Tg raised and HDL low</td>
</tr>
</tbody>
</table>

CV: cardiovascular, CVRF: cardiovascular risk factors, Tg: triglycerides, LDL: low-density lipoproteins, HDL: high-density lipoproteins

While the statins are remarkable cholesterol-lowering drugs which have widely been shown to be able to reduce cardiovascular events in high-risk patients, they also have adverse effects, particularly myopathy, which may be severe in some patients. They may also vary in efficacy between patients. Research has been carried out to investigate genetic ‘variants’ (particularly SLC01B1 genotypes), which may contribute to this diversity in response to and tolerance of statins. This approach should help to select candidate patients for statin treatment more precisely in a personalised approach \[21\].
The recent revolution in the field of treatment of hypercholesterolaemia deals with the emergence of the PCSK9 (proprotein convertase subtilisin/kexin type 9) protein inhibitors \(^{[22]}\). This protein plays an inhibitory role in hepatocyte LDL receptor recycling. The development of these drugs was started following the discovery of an inhibitory mutation for this protein which was associated with a lower level of LDL cholesterol and a reduced risk of cardiovascular disease. Following this finding, monoclonal antibodies which specifically inhibit this protein were developed, two of which have already been marketed (evolocumab and alirocumab). These drugs can reduce LDL cholesterol levels by half in patients with familial hypercholesterolaemia, including those already treated with a statin, through a synergism between the two approaches and for a large variety of gene mutations responsible \(^{[23]}\). The PCSK9 inhibitors have recently been shown to be able to reduce cardiovascular events in patients with familial hypercholesterolaemia and/or those at very high cardiovascular risk \(^{[24]}\). These results open the way to increasingly targeted and effective precision treatments. The problem remains as to the cost of these new treatment approaches, the use of which needs to be incorporated into a rational reasonable pharmacoeconomic perspective targeting as a priority those patients at highest cardiovascular risk \(^{[25]}\).

CONCLUSION

Precision medicine had a remarkable impact on the treatment approach for some cancers, leading to the emergence of targeted therapies. We are still far from being advanced to the same extent in the management of cardiovascular diseases. Nevertheless, advances have been made in recent years in the treatment of type 2 diabetes and hypercholesterolaemia. A so-called patient-centred approach is advanced in the most recent international guidelines and personalised or precision medicine needs to form part of this dynamic and contribute extensively to it.

TAKE HOME POINTS

• Many chronic disorders are complex diseases which combine a genetic with an environmental component. They exhibit considerable heterogeneity which needs to be broken down in order to target the individualised treatment approach better.
• Personalised or precision medicine is designed to select patients liable to achieve the most effective and safest response to treatment through predictive biomarkers: the right drug for the right patient at the right dosage and at the right time.
• Advances have been made recently in the management of type 2 diabetes and hypercholesterolaemia, with research into genetic markers or genotypes which can contribute to improve the purely phenotypic approach currently used in clinical practice.
• There still seems to be a long way to go, however, in order to be able genuinely to apply true personalised or precision medicine in type 2 diabetes and the dyslipidaemias.

Conflicts of interest: The author declares that he has no conflicts of interest with this article.
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BIBLIOGRAPHIE (Underlined references are linked to PubMed abstracts)