Prescribing by ethnicity: (Im)precision medicine?

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The right drug, for the right patient, at the right time. Who wouldn't want this? For diabetologists, after decades of domination by biguanides and suphonylureas , only briefly punctuated by thiazolidinediones, the choice of early stage glucose lowering agents has recently more than doubled, now including GLP1 receptor agonists, and DPP4 and SGLT2 inhibitors. Armed with this greater choice, can we now fulfil the promise of precision medicine?

Half of the 500 million people in the world with diabetes live in either China or the Indian subcontinent(1). Aside from simple demographics, these huge numbers are largely due to the greater diabetes susceptibility experienced by both populations. In this issue, Gan and colleagues(2) hypothesise that pathophysiological differences contributing to this greater susceptibility may be associated with different glycaemic responses to diabetes medication. This is not unreasonable; 20% of new drug approvals show differences in exposure or response by ethnicity(3). They performed a systematic review and meta-analysis of published randomised clinical trials comparing absolute change in HbA_{1c} from baseline to either 24 or 52 weeks, in studies which recruited predominantly (>70%) Asians, with studies which recruited predominantly (>70%) Whites. They report that SGLT2 and, possibly, DPP4 inhibitors are more effective in lowering HbA_{1c} in Asians than in Whites. There was no ethnic difference in efficacy of GLP1 receptor agonists.

Their findings are somewhat at odds with previous work. The most striking observation, of an ~0.3% lower HbA_{1c} in Asians than Whites in response to SGLT2 inhibitors, contrasts with a previous meta-analysis, reporting no ethnic difference(4), though an agent specific analysis did show modest superiority of Dapagliflozin (0.16%) in Asians versus non-Asians. Gan and colleagues do not offer an explanation for the greater efficacy of SGLT2 inhibitors in Asians. They do however report that effects are greater in studies of leaner participants. Median body mass index (BMI) of participants in predominantly Asian studies was ~ 6 kg/m2 lower than that of participants in predominantly White studies. The marked BMI difference between ethnicities may simply mean that, in this analysis, BMI is acting as a proxy for ethnicity (or vice versa). Notably though, Cai et al, while also finding a marked ethnic difference in recruitment BMI, do not report an association between BMI and glycaemic effectiveness(4), in keeping with previous work(5; 6).

The greater effect of DPP4 inhibitors in Asians reported here confirms previous observations(7), though in this analysis, the ethnic difference was only strongly apparent in a sensitivity analysis that opened inclusion to studies of >12 weeks duration. Ethnic differences in pharmacodynamic responses (demonstrated in a comparison of Japanese versus non-Japanese participant studies), are invoked as the explanation. The lack of an ethnic differential in response to GLP1 receptor agonists contradicts a previous meta-analysis, reporting greater efficacy in Asians(8). Authors speculated that greater efficacy may be due to lower BMI in Asians. However, in the current meta-analysis, recruitment BMI was not associated with efficacy of either incretin based therapy.

This is a careful meta-analysis conducted to the highest standard, yet it is hard to draw firm conclusions. Data limitations frustrate this and previous attempts to determine ethnic group specific drug efficacy. No individual trial has sufficient numbers of each ethnic group to perform a sufficiently powered within trial analysis. Comparing efficacy in one trial with another is clearly sub-optimal, as differences in trial design, conduct and analysis cannot wholly be accounted for. Numbers of trials including Asians, and numbers of Asians in these trials, were limited. To ensure adequate numbers for analysis, authors defined an Asian trial as that which contained at least 70% Asian participants (previous meta-analyses set a lower threshold of 50%). The term 'Asian' here encompasses hugely different populations, Chinese, Japanese, Korean and people from the Indian subcontinent. Numbers were too small to report results by more specific ethnic categories. Thus, this heterogeneity, lumping disparate ethnic groups as Asian, and mixing of Asian and non-Asian in studies classified as Asian, seriously undermines attempts to identify true ethnic specific effects.

The authors of this paper conclude that, if individual patient data analysis confirm their findings, 'ethnicity should be incorporated into the treatment guidelines'. Is this a reasonable conclusion? The presumption here is that ethnicity proxies for biology sufficiently reliably to be used as a therapeutic stratifier. This already occurs. Guidelines for treatment with Rosuvastatin recommend halving the initiation dose in Asians to achieve equivalent drug exposure, reflecting differences in drug metabolism(9). Low renin hypertension appears more prevalent in people of Black African descent(10). This difference in disease pathophysiology, coupled with data

from clinical trials designed to test effects of different classes of anti-hypertensive agents by ethnicity, informed guidelines recommending preference of calcium channel blockers over ACE inhibitors for this population(10; 11).

Thus ethnicity, acting both as a proxy for drug responsiveness, and/or disease phenotype, appears a valid and simple tool for therapeutic stratification, even precision medication. However recent experience of the latter suggests this should be approached with caution. BiDil, a combination of hydralazine and isosorbide dinitrate, is marketed specifically to the African American population as a treatment for heart failure. Adequacy of supporting trial data, motives of key investigators, and of industry, and the role of the Federal Drug Administration all attracted criticism(12).

What could determine ethnic variation in glycaemic response? Ethnicity is a complex construct, combining ancestry, geography and sociocultural factors, which can flux with age and time. Available categories combine markedly different groups, as this meta-analysis demonstrates, where drug metabolism and disease pathophysiology is not homogenous. Genetically assigned ancestry may provide answers, as this is a potentially more precise measure, but this also poorly differentiates groups with differing drug metabolising propensities(13). Ethnic group comparisons have been valuable in highlighting important metabolic pathways in diabetes aetiology, for example the role of hepatic insulin resistance, and of early beta cell failure. Yet, like drug metabolism, group average pathophysiological phenotype masks considerable inter-individual heterogeneity. Diabetes is a consequence of multiple intersecting processes with no single pathway overwhelmingly predominant.

So ethnicity appears an imprecise proxy for biology. And if biology drives therapeutic response or disease pathophysiology, should we not perform detailed molecular characterisation and phenotypic profiling for each individual that better enables targeted therapy? Such profiling is enormously expensive and time consuming, and likely even if effective, out of reach for the majority of the global population with or at risk of diabetes. Yet that is the promise of precision medicine.

This doesn't mean that we should abandon exploration of ethnic differences or other subgroup differences in drug response, as these often provide initial indications of important underlying metabolic pathways. In-depth characterisation of individual

patient data offers a scalable approach, both in trial and real world settings. Gan et al were able to examine the roles of sex, baseline HbA$_{1c}$, BMI and diabetes duration in the ethnicity-drug response relationship. But many factors remain understudied, e.g. concomitant medications, medication adherence, comorbidity, central obesity, diet, physical activity, smoking, alcohol consumption, deprivation, and healthcare access. Importantly we should look beyond glycaemic effectiveness to endpoints such as vascular complications, which truly impact lives, health care consumption and the economy, and which, given the pleiotropic effects of many drugs, cannot be assumed from understanding glycaemic effectiveness alone. Finer grained ethnic group characterisation, and enhanced access to individual trial and electronic health record data, to allow such detailed characterisation, is a vital next step. This would both enable further stratification of treatment response by sub-population and highlight potential explanations for ethnic differences in treatment response. If these remain once sociodemographic, phenotypic and lifestyle variables have been accounted for, and if we can demonstrate that ethnicity is a valid proxy for therapeutic response, claims that treatment decisions can be governed by ethnicity will be far more robust.

Acknowledgements

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