Debates in Evidence-Based Medicine

In answer to the question "Diabetes Drugs: Are we getting value for money?" Orville G. Kolterman, MD, Amylin Pharmaceuticals, San Diego, California, United States offered a resounding "yes," while Edwin Gale, MD, University of Bristol, United Kingdom, countered with a firm "no, not yet."

Dr. Kolterman began by pointing out that, as several important diabetes medications go off patent within the next 4-6 years, generic substitutions will add to the value received by patients. He further added that a consideration of drug costs must take into account the arduous FDA path that new drugs must traverse to pass through three clinical trial phases. The average process takes 8.5 years, and new estimates place the total cost of drug development and introduction to the market in excess of $1.5 billion (up from $802 million in 2000). Furthermore, the price of pharmaceuticals is determined by the marketplace and reflects not only the development expense, but a reward for the cumulative risks sustained by drug developers and manufacturers. Citing the pharma-biotech symbiosis, combining biotech's high-risk drug innovation with pharma's development and marketing prowess, he asked "What would be the incentive to invest in a high-risk 14-year undertaking if the rewards were determined other than by the marketplace?"

The value of "me too" drugs, an industry focus also often criticized, derives not only from prices restrained by increased competition, but also because agents do differ in terms of routes of metabolism and side-effects and tolerance profiles. Also, the lower risk for a company developing a "me too" drug helps fund riskier pioneering programs for that company as well. Finally, the value of improved lives enters the equation.

Prof. Gale opened with a depiction of a pharmaceutical industry characterized by the face of a "Mr. Nice," who brings the new drugs that have the potential to truly change society and wants to make the world a better place, and the face of a "Mr. Nasty," who believes only in the bottom line, complains about any government restrictions, and sues anyone who enters the market with a cheaper product. In the final analysis, Mr. Nasty's truth is: "Drug companies are machines for making money."

That machine has been a successful one, consuming, for example, proportions of the US economy that have grown geometrically since 1990 (+573%) versus the arithmetic growth progression of the overall economy (+57%). During the last decade, drug costs have increased faster than other components of diabetes care. But at the same time that newer, more expensive drugs have been emerging, clinical evidence is not showing them to be more efficacious than traditional agents, or their benefits are marginal or relegated to second-line use.

"There is no evidence that increased drug costs have paid for themselves," Prof. Gale said. Furthermore, the focus on newer agents has diverted attention from lifestyle change, a known means to prevent or treat diabetes. "The attempt to substitute pharmacotherapy for lifestyle change is a recipe for failure," he stated.

Prof. Gale offered the ironic concept of the NNNT (the number needed *not* to treat), pointing out that the savings from treating 80 diabetes patients with metformin instead of rosiglitazone would fund one diabetes nurse educator. He concluded, "Far from paying for themselves, more expensive therapies for diabetes have important negative costs." In addition, he pointed to excessive profit-taking in the industry, as witnessed

by the fact that the profit margin of the top 10 American drug companies (18.5% of sales), far exceeded the Fortune 500 median of 3.3%.

Prof. Gale noted the emerging demand for evidence-based medicine and appropriate government regulation which should lead to drug costs that are linked to evidence-based value. He closed with a plea for collaboration between industry and the medical profession.

The second debate in this evidence-based medicine session centered around the question of whether GLP-1-based therapies will substitute for sulfonylureas. Jens Juul Holst, MD, University of Copenhagen, Denmark, took the affirmative position (although he noted that GLP-1 based therapies were still in their "neonatal period"), listing the therapeutic virtues of GLP-1 in type 2 diabetes. These include improvements in insulin secretion and biosynthesis, improved β-cell function, proliferation, and differentiation reductions in β-cell apoptosis favorable effects on gastric emptying, satiety, appetite, food intake, and weight plus beneficial cardiovascular effects.

Turning to GLP-1 receptor activators, he noted favorable incretin mimetic (eg, with exanatide) effects on HbA1c, body weight, cardiovascular risk factors, insulin dose, and health-related quality of life.

Similarly, he reviewed liraglutide as added to glimepiride or metformin, and the DDP-IV inhibitors (vildagliptin, sitagliptin) alone and in combination with metformin, finding a wide range of benefits. Comparing the benefits of DPP-4 inhibitors/GLP-1 receptor agonists benefits with those of sulfonylureas, Prof. Holst pointed to issues of weight gain, hypoglycemia, durability of effect, effects on β-cell health and cardiovascular risk factors all to favor the former. One study [Maedler K et al. *J Clin Metab Endocrinol* 2005] demonstrated sulfonylurea-induced β-cell apoptosis in cultured human islets. "These little facts," he concluded, "talk for themselves."

David R Matthews, MD, The Oxford Centre for Diabetes, Endocrinology and Metabolsim, Oxford, United Kingdom, said "no" to substituting GLP-1 based therapies for sulfonylureas. He suggested that the idea of substitution is the wrong concept given that polypharmacy has proven to be necessary in contemporary treatment of hypertension, cancer, heart failure, pain relief and rheumatic illnesses. Pointing to studies of exenatide added to metformin, sulfonylureas or a combination of the two that demonstrated the benefit of polypharmacy on HbA1c levels and weight gain, Prof. Matthews suggested that the treatment benefits of the newer agents over sulfonylureas are marginal (less than 0.3% at 5 years for rosiglitazone, for example).

Prof. Matthews urged caution with the DPP-IV inhibitors and GLP-1 analogs because of the paucity of long-term trials and of cardiovascular disease outcome trials, and noted potential pleiotrophic effects of DPP-IV inhibition as well. Even the long-term effects of GLP-1 agonist- and homolog-induced weight loss need to be evaluated. On the other hand, there is an evidence base for significant heart attack reductions with metformin and reduced diabetes-related endpoints and microvascular disease with sulfonylureas. He added that while β-cells do fail faster on sulfonylureas, the effect is comparatively small.

At the same time, the cost differences are enormous, Prof. Matthews said, with exanatide about 15 times more expensive than gliclazide or glibenclamide. The developing world cannot afford these new injectable therapies, and in the developed world expensive therapies divert a large proportion of resources.

Matthews concluded that sulfonylureas are low-cost and highly efficacious drugs for type 2 diabetes. "Therefore," he said, "we should not abandon sulfonylureas that are tried and tested in favor of the new and sexy."