Fighting Renal Diseases in Poor Countries: Building a Global Fund with the Help of the Pharmaceutical Industry

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Chronic kidney diseases are emerging as a global threat to human health. More than 1 million people worldwide are alive on renal dialysis or with a functioning graft (1). The incidence of renal failure has doubled during the past 15 yr, a trend that is likely to continue in the next decade. It has been forecast that by 2010 in the United States, >600,000 patients will need renal replacement therapy; the costs will grow to $28 billion (2). In the United States and in many other countries, diabetes is the most common cause of ESRD. Patients who have diabetes and are on renal replacement therapy have a worse outcome, require more hospital admissions, and cost a great deal more as compared with patients who are on dialysis for other diseases (3).

Whereas data on the epidemiology of ESRD are ready available through national dialysis registries and are very reliable, much less is known about the true incidence and prevalence of chronic kidney disease in the predialysis phase. According to the Third National Health and Nutrition Examination Survey, it can be estimated that 800,000 people in the United States have a serum creatinine ≥2 mg/dl and 6.2 million people have serum creatinine ≥1.5 mg/dl (4). Extrapolation from data of the Framingham Study suggests that nearly 20 million people are at risk for chronic renal insufficiency in the United States (5). A sizable proportion of these people could lose their renal function over time and reach ESRD.

Progression of Kidney Diseases Can Be Prevented

Mechanisms of progression have been investigated by many laboratories during the past 20 yr. Laboratory studies have generated hypotheses for therapeutic interventions that have been challenged in several clinical trials during the past decade (6). Clinical studies have actually demonstrated for the first time in nephrology that the once inevitable progressive loss of renal function can be significantly slowed or even arrested in nondiabetic and diabetic renal diseases by effectively lowering BP. Drugs that block the renin-angiotensin system offer additional renoprotection.

The clinical trial Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy was one of the first studies to show with enough patients and statistically robust data that progression of nephropathy in type 1 diabetes could be slowed by captopril and led to the first federally approved treatment for halting progressive nephropathy (7). A number of clinical studies were then designed with the aim to evaluate the renoprotective effect of angiotensin II blockade in other conditions (reviewed in (8)). In the Ramipril Efficacy In Nephropathy (REIN) study, patients with nondiabetic renal disease and proteinuria received either the angiotensin-converting enzyme (ACE) inhibitor ramipril or placebo on top of the conventional antihypertensives. Ramipril lowered by 50% the rate of decline of the GFR and reduced the need for dialysis (9).

The results of other studies were summarized in a meta-analysis of 11 clinical trials done in patients with proteinuric nephropathies. Results showed that ACE inhibitors limit GFR decline and disease progression considerably better than other antihypertensives (10). The African American Study of Kidney Disease and Hypertension (11) found similar renoprotective effect in patients—black individuals with hypertensive nephropathy—generally considered poor responders to ACE inhibitor therapy. Indeed, ramipril as compared with amlodipine decreased GFR decline by 36% and progression to clinical end points by 38%.

The renoprotective effects of the relatively new class of drugs, the angiotensin receptor blockers, have been demonstrated in three large clinical trials in patients with type 2 diabetic nephropathy (12, 13). The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (12) study showed that as compared with conventional treatment alone, losartan combined with conventional treatment decreased the level of proteinuria by 35% and reduced the risk of ESRD by 28%. In the Irbesartan Diabetic Nephropathy Trial (13), the risk of the combined end point of a doubling of the baseline serum creatinine level, the onset of ESRD, or death from any cause was 20% lower in patients who were treated with irbesartan than in those who were treated with conventional therapy and 23% lower than in those who were treated with amlodipine.

It has also emerged that the care of patients with chronic nephropathies requires a multitask approach, which should include treatment of dyslipidemia, tight glycemic control in
diabetics, control of other metabolic abnormalities (e.g., metabolic acidosis, calcium homeostasis), and lifestyle modification (exercise, banning of smoking, body weight reduction) (6). Demonstration that the application of these measures on a population-wide basis may reduce the incidence of renal failure is not yet available, because these therapies have not been sufficiently widely applied for a long enough time to show the effect. It is interesting to mention a report, which appeared in abstract form, that in Japan there are regional differences in the incidence of ESRD that were negatively correlated with the amount of expenses spent on ACE inhibitors in the different regions. The authors hinted that the increasing use of ACE inhibitors is associated with a decreased incidence of ESRD (14). Thus, we now can affirm with confidence that interventions that may delay progression of renal diseases are possible and that these interventions may result in substantial amelioration of both quantity and quality of life and in reduction of costs for the public health.

On the basis of the results of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study, it has been estimated that the expanded use of an angiotensin receptor antagonist in patients with type 2 diabetes in the European Union could reduce health care expenditure by $2.8 billion in 3.5 yr (15).

This all is true for those who live in rich countries. Indeed, of the 1 million people on dialysis, >80% live in high-income countries. It is hardly surprising: 1 yr of dialysis costs $50,000 per patient, a cost that is unattainable for all low-income and for almost all medium-income countries. Indeed, there is a relationship between the number of patients on renal replacement therapy and the gross national product, as demonstrated by comparing the data from the European Union with the Eastern European Countries (16, 17).

Inequalities in the Care of Kidney Diseases

In low-income countries, facilities for dialysis are extremely scarce or altogether nonexistent. Kidney patients in those countries could only hope in a global effort to extend to them the achievements of clinical studies. The application of measures that prevent or retard progression of renal diseases is a lifesaving treatment (18).

It has been shown in limited although extremely important experiences that programs aimed to reduce the burden of chronic kidney disease are feasible also in poor countries and among underprivileged communities (19–21). As an example, the Kidney Help Trust rural project in India was able to screen 25,000 people with the help of six health social workers at a cost of <$6000 per year, a mere $0.25 per capita. Excellent BP control was achieved among hypertensive patients, and blood glucose control in individuals with diabetes was considered good (19).

The obstacles in providing adequate health care to millions of people in poor countries are widely known. Poor infrastructure such as roads and sanitation, famine and malnutrition, cultural attitudes and practices, ignorance, and inadequate public health systems all are important factors in determining the failure of poor countries to cope with many infectious diseases, such as AIDS, malaria, and tuberculosis. However, the lack of access to essential drugs is one of most striking aspects: it underlines dramatically the existence of two different worlds.

A number of strategies have been devised to increase the access to essential medicine where they are most needed: discounted pricing of patented drugs, manufacturing of generic drugs in poor countries, and waivers of patent protection through renegotiation of trade-related aspects of intellectual property rights in the World Trade Organization (22). Pharmaceutical companies have also maintained excellent philanthropic programs, mostly based on drug donations to poor countries (23). However, drug donation programs have been questioned by several parties as costly and ineffective.

For many tropical diseases that affect the poor of the world, the problem is that there are no new drugs, and the industry is reluctant to invest in research and development, because the prospect of profit is scarce because the potential buyers have no money to purchase medicines. For the treatment of progressive chronic kidney diseases, there is not really the problem of developing new drugs. As we have said before, potent renoprotective agents are already available, and effective strategies for preventing progression are well developed. The problem, then, is how to make these drugs and strategies available in developing countries to the largest number of patients. The problem is not different from that posed by AIDS in poor countries. By analogy with AIDS, a Global Fund for Kidney Disease could be established with the aim to export to developing countries the know-how on combating progressive renal diseases.

A Global Fund for Kidney Diseases

Who should contribute to such a fund? Governments of developed countries, of course, and charities, just as they are doing for the Global Fund for AIDS, Tuberculosis and Malaria, are called to contribute, but we believe that also pharmaceutical industries should be involved.

The pharmaceutical industry nowadays is a very profitable enterprise, and its returns are on the average greater than those of other industries. It benefits from publicly funded research, government-granted patents, and tax breaks (24). Many innovative drugs are developed by the industry on the basis of the results of experimental work supported by public funding agencies (24). It is extremely difficult to say how much the government-supported research in the development of new drugs is worth, but it is not unlikely that the preclinical research could account for as much as 20 to 25% of a company’s research budget (25).

Moreover, most clinical trials are carried on in collaboration with the academic research infrastructures and personnel. Even though the industry provides support with conspicuous grants the research, the infrastructures and the expertise of the physicians, nurses, and other professional are the result of the investments of public institutions. Also, clinical development is possible thanks to the availability of the most precious public commodities: The free, voluntary participation of patients in clinical studies. Helping patients of a less developed country is
a way to thank the contribution of so many volunteers for the success of a new drug and is a demonstration of solidarity toward the most unfortunate people.

Antihypertensive medications that have been used in clinical studies and have shown to be renoprotective are now recommended by all guidelines and used extensively by general practitioners worldwide. That the results of clinical trials translate to an increase in sales has recently been documented for an ACE inhibitor in Canada (26). There is little doubt that these drugs have guaranteed substantial revenues, and their development costs have been largely paid off, because their commercial effect is on the order of billions of dollars worldwide. Also, cholesterol reducers and oral antidiabetic drugs (two other important elements of the multidrug treatment of chronic nephropathies) are with ACE inhibitors among the 10 leading therapy classes in pharmaceutical sales (27).

The manufacturers of drugs with renoprotective effects (ACE inhibitors and angiotensin receptor antagonists, but in a broad sense also other antihypertensive drugs, lipid-lowering agents, oral antidiabetics, etc., should be included) could contribute with donations that represent 1% of the sales of these drugs in rich countries to help people in poor countries. The contribution to a fund for the advancement of the global health, with a sum that is a small proportion of the profit but is a substantial amount of money, can be considered a sort of refunding for the provisions obtained.

Of course at this stage, it is premature to formulate a detailed proposal for practical implementation of such a fund. The most important question is how to determine the dimension of the burden of kidney disease in a given country of the developing world and how to deliver care. The issues already have been raised in another context: the Global Fund to Fight AIDS, Tuberculosis and Malaria. A recent article by Tan et al. (28) examined the benefits and pitfalls of two traditional approaches to disease control: “Vertical” disease-specific programs, which are relatively independent of the rest of the health care system, and “horizontal” approaches aimed to improve health care systems across the board. In other words, it is important that effective drugs and other medicines are made available to all those who need them, through specific disease-centered programs, but it is at least as important (if not more) that the health care infrastructures meet minimal standards to secure the delivery of care.

There are several examples of the results of each of these approaches, and the conclusion is that, predictably, an ideal solution is still to be found and is likely to be a combination of both. Regarding the program to prevent the progression of renal diseases, its implementation could follow different paths in different parts of the world. There are countries that are providing renal dialysis at least to a part of their population (we have previously mentioned the Eastern European Countries). They therefore have sufficiently efficient health care systems, but budget constraints may limit availability of renal replacement therapy for all those in need. In these countries, a renal progression prevention program is highly feasible and should be reinforced and supported by adequate funding.

In other countries, the health care infrastructures are much less developed. In these countries, not only is dialysis not available, but also the real burden of renal diseases is not known. Here, of course, the international concourse of funding bodies, global agencies, nongovernmental organization, and national governments is required to afford more basic needs, starting from epidemiologic evaluation of the impact of renal diseases. The examples of India, Bolivia, and Australia that we have mentioned showed that there are starting strategies that may be tried with success.

An important role could be played by professional associations. For example, the International Society of Nephrology is committed to promote the global development of nephrology, with educational and training programs, and is already collaborating with the World Health Organization to design strategies to improve the renal care in developing countries. The International Society of Nephrology can offer its collaboration to local governments at several levels: It can provide advice for the training of health professionals, for conduction of epidemiologic surveys to evaluate the impact of kidney diseases on population health, and for implementation of preventive and curative strategies.

It is becoming increasingly intolerable to know that innumerable lives are lost in poor countries only because relatively simple measures are not available because of their cost. The contribution of the pharmaceutical industry, in a joint effort with the public authority and academia, is fundamental to starting a new era of hope.

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References


