The clinical pharmacology of biotechnology products
M M Reidenberg, editor

THE IMPACT OF ECONOMIC ISSUES ON THE THERAPEUTIC USAGE OF BIOTECHNOLOGY PRODUCTS. A VIEW FROM THE HOSPITAL

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BACKGROUND

Biotechnology products at the moment comprise about 1% of the $\$130 \times 10^9$ worldwide drug market (1). According to a recent estimate U.S. sales of biotechnology-derived products are expected to triple from $900 million in 1989 to $3000 million in 1993 (2). Current FDA-approved products which include tissue plasminogen activator (t-PA), Alpha-interferon, human recombinant insulin, growth hormone and erythropoietin and hepatitis B vaccine are expected to achieve a $1950 million U.S. market size by 1993.

TABLE I

FDA-APPROVED BIOTECHNOLOGY PRODUCTS
Expected U.S. market size in 1993

	$ million
t-PA	400
Alpha-Interferon	350
Human Insulin	250
HGH	200
Erythropoietin	600
Hepatitis B Vaccine	150
Total	1,950

(Adapted from ref. 2).

About twenty other products will become available by the mid-nineties. These will include activated protein C and factor VIII-C, Superoxide dismutase, beta and gamma interferon, interleukins, growth and wound-healing factors, colony

stimulating factors, malaria, herpes, hepatitis C and, hopefully, AIDS vaccines and a variety of monoclonal antibodies. More than a hundred products are now undergoing clinical trials. In addition, a colossal market is expected for new biotechnology-derived biosensors, equipment and instrumentation (3).

Turning from these grandiose images and their stock-market counterparts to our present hospital pharmacy budget reveals a surprisingly modest impact of biotechology products. Is it the tip of an iceberg or just flakes before the avalanche? The answer is both.

The Hadassah University Hospital in Jerusalem, Israel, has 876 beds. It serves as both a community hospital for the half-million residents of the city, and as a tertiary-care center and oncological center for the country. It performs kidney, heart and bone-marrow transplantations. Its' annual budget amounts to $110 million and the pharmacy budget to $9 million, out of which $8 million pays for purchase of drugs.

Current Use of Biotechnolgy Products

All FDA-approved biotechnology drugs are registered in Israel and all but t-PA and Alpha Interferon approved for hospital use. However, thus far the only biotechnology product for inpatient use included in the Hadassah Hospital formulary is human insulin, which comprised 2/3 of the $21,000 hospital insulin purchase in 1989. Altogether the price of insulin has remained stable.

Fibrinolytic therapy mainly with streptokinase and urokinase, was administered last year to about 250 patients at a cost of $75,000. Our cardiologists and the P and T Committee follow with great concern the ongoing clinical trials comparing t-PA with streptokinase. Though several such trials have reported more rapid and frequent coronary artery thrombolysis following t-PA (4,5), more recently the results of the GISSI II Study (6) concerning in-hospital mortality (9.2% in those treated with t-PA + heparin vs. 7.9% for SK + heparin) do not warrent a non-reimbursable expenditure to the hospital of $0.75 million per year, to be caused by the introduction of t-PA. Hadassah does not at this time purchase t-pa and routinely supplies only streptokinase

and urokinase (for later follow-through).

The Hospital has approved screening for HBc antibodies and vaccination of its' 4,600 personnel with recombinant hepatitis B virus vaccine. The cost of screening ($10 per person) and vaccination ($16.5 per person) amounts to $107,380. The Hadassah administration has attempted to fund these expenses from various non-budgetary sources (donations, grants). It is predicted by our hepatologist that this program will eventually prevent the development of about 80 cases of cirrhosis and 8 cases of hepatocellular carcinoma (7). Recombinant erythropoietin, growth hormone and alpha-interferon are provided on ambulatory basis directly supplied by the insurers' pharmacy and funds.

In Jerusalem there are about 170 patients with end-stage renal disease, 35 are treated with erythropoietin (rHuEpo) at an average cost of $5,000 per patient per year. The Ministry of Health, has issued vigilant prescribing criteria in line with the guidelines of the American National Kidney Foundation (8). The benefit to the patient appears to be very favourable, including transplantion of patients who were previously considered to be untransplantable. This cost is covered by each patient's insurer (sick-fund).

Human growth hormone is prescribed following approval by experts of the Ministry of Health, to 10 Jerusalem children at an annual cost of about $10,000 each. Natural human growth hormone is no longer used. Hairy-cell leukemia is thus far the only Ministry-approved indication for Alpha-interferon. (1-2 patients annually). About a dozen patients receive the drug on experimental protocols for chronic myeloid leukemia, lymphomas and viral hepatitis. The cost, covered by research grants or by the patients themselves, was estimated at close to $70,000 last year.

Beta-interferon, IL-2 and CSFs are being used in the hospital as part of experimental protocols approved by the IRB and the Ministry of Health. For the time being the drugs are provided by the manufacturers, free of charge. OKT 3 was used on two patients who received the drug from abroad (cost $10,000). In addition, monoclonal antibodies and molecular probes are used for diagnostics. The annual expenditure

amounts to $280,000 Thus, although the direct hospital expenditure on biotechnology drugs is only a modest $15,000 (or less than 0.2% of the pharmacy budget), the real cost at present of biotechnology products for our in-patients and out-patients treated in our hospital is close to 700,000 dollars annually (8% of the pharmacy budget).

TABLE 2

EXPENDITURE ON BIOTECHNOLOGY PRODUCTS
Hadassah's Patients and Personnel (1990)

	$
Human Interferon	15,000
Alpha Interferon	70,000
HGH	100,000
Erythropoietin	140,000
Hepatitis B Vaccine	107,000
t-PA	*none*
Experimental products	gratis
Antibodies & probes	280,000

Another consideration is of course the money-saving properties of biotechnology products. Cure, prolongation and better quality of life, productivity and decreased need for medical services are all of paramount importance from the general medical point of view. For the hospital budgetary system, financial gains appear to be modest and relate to the operating reimbursment systems. To give one example, according to our DRG system the hospital is being paid $15,000 for a bone-marrow transplant. It is expected that the use of CSFs will shorten the length of hospitalization and decrease the cost to the hospital by 20%.

Future use of biotechnology products

The present situation does not forecast the future economic impact of biotechnology products. Many of the drugs currently undergoing clinical trials will, unlike the competitive price of human insulin or the rareness of indication for HGH, enjoy the expensive combination of being

both unique and of relatively wide applicability. Moreover, biotechnology products are expected to reach the market much faster than conventional drugs (i.e. < 15 years) (3). Herfindal (9) has recently described the "beachhead" strategy of the industry, namely registration of the product for a narrow indication, followed by unlabeled drug use, allerting the general and medical public and creating pressure on the P and T committees. (A good example is the use of interferon). Unlabled use is of particular concern to hospitals as third-party payers tend not to reimburse such use.

Strategies for dealing with biotechnological innovation

Herfindal (9) suggested the following strategies:

* Implement prescribing protocols and guidelines
* Analyze impact on other treatments
* Analyze economic impact
* Implement monitoring and surveillance programs

As for analysis of economic impacts, his experience at the University of California, San Francisco, is being cited. Requests for high-cost drugs are handled by the hospital administration as major capital purchases, similar to the opening of new clinical services, or the implementation of a heart transplantation program. Complete economic, clinical and strategic justification are required in such a process, including cost, reimbursement, impact on other services and personnel requirement. He concluded that for a pharmacy department it is impossible to absorb the cost of high-cost drugs without shift of resources and that the ability to pay for the new therapeutic modalities will quickly be outpaced by the industry's ability to produce them. We agree with these forecasts and would like to expand on the application of hospital strategies.

The informed public is demanding a rational and consistent program for the appropriate use of the limited health resources. Priorities must be selected in medical care and a scale of "reasonable requirements" established (10). In seeking a scale of "reasonable requirements" in the hospital setting, health-care providers, clinically and administratively involved with hospitalized patients must formulate a flow-chart of averaged, relative, weighted,

multiple parameters bearing on the main aspects of the patients' health to replace those of arbitrary triage by financial resources, age of patient and delay. All parameters should comprise measurable elements of technology: equipment, devices, drugs, procedures and capital and human investments. Each parameter along the scale must be regularly assessed for its efficacy, safety and relevance in the provision of hospital care - both in specific situations and in the wider social and ethical spheres. Nine parameters compose the suggested scale. They are: 1) the net therapeutic contribution of the procedure - the degree to which it will preserve life, limb or function; 2) the reduction of physical and/or mental suffering; 3) improvement of the quality of public health - both in prevention of disease or injury, and in promoting the effectiveness of health services and community health practices; 4) the balancing of therapeutic against diagnostic procedure; 5) diagnostics - perfecting its positive predictive value; 6) therapeutics - achieving objectives, which include: elimination of pain, easing and speeding maximal recovery and rehabilitation; 7) costs - direct, indirect and capitalization; 8) development program, its potential contribution in the future; 9)hazards of medications both nonspecific and unidentified.

These complex parameters, together with further potential facets, are naturally subject to periodic variations, to overlap and merging, and to changing trends of science, morbidity, utilization and economics. They therefore have to be correctly weighted in the particular algorithm relevant to each case.

They are proposed as the basis on which to build a systematic methodology for the provision of hospital biotechnology innovations. The target of any such methodology should be an objective weighting algorithm for regulating the decision-making process - one that is capable of accomodating both anticipated and unforeseen problems.

Parameters for the evaluation of the economic impact of biotechnology products in the hospital setting.

The net therapeutic contribution of the product is of

course of paramount importance; so is the reduction of suffering in any medical setting. The third parameter is the improvement in the quality of public health which relates perhaps most to the post-hospitalization state and should not be underestimated. Hospital staff should not take the narrow view of the patient in a time-limited stay. The fourth parameter will exhibit itself forcefully with the increased introduction of biotechnology products. The fifth point relates particularly to the use of monoclonal antibodies and molecular probes for diagnosis, while the sixth point is obvious in any case. The seventh parameter, cost, will be discussed separately.

As to the eighth parameter, hospital biotechnology drug development schemes should be evaluated on the basis of their anticipated duration and estimates as to their final contribution. Lastly, the hazards of drugs - particularly by biotechnology methods, have to be taken into account

The Assessment of Cost

When facing costs, hospital administrators tend to look at an issue differently if its costs are met through the regular operating budget as against any other "non-budgetary" source (i.e. donations, grants, contracts, patents etc.). If the utilization of particular new biotechnology products are considered budgetary - the hospital administration will institute a terrific battle to recover the outlay from regular budgetary sources (i.e. insurers, third party carriers, governmental subsidy or the patients themselves). To this end, the administration will use various pressure techniques to force the payers to pay. This could be by insinuating to the patients that the specific product was absolutely essential or at least far better for their particular need, and then use a phalanx of fearful and agitated patients and their families to force an agreement from a payer. The beachhead technique described by Herfindal (9) is well known to hospital administrations; get the payer to agree that interferon is the drug of choice and to be paid for hairy cell leukemia and thus introduce it to the hospital formulary and then use the salami technique extending its use slice by slice - indication by indication.

Obviously in parallel with the battle which the hospital administration, allied with its' clinicians, wages against the payer - it wages an internal front against its own clinicians. The attempts by the clinicans to introduce new biotechnology products are, except in a few extraordinary uses which can boast of exemplary scores on each of the nine parameters, resisted by the administration ferociously. Before agreeing to a budgetary acceptance management will try to insist that the new drug be paid for from the clinicans' research funds (being "his own baby" and not an accepted drug) or from a grant if the clinican is in anyway at all connected to a manufacturer or other large research institute. In most Western countries the official certification of drugs, initiated of course primarily for safety reasons, hands management an oportunity for delaying and procrastinating for the introduction of biotechnology products: the process is long and even after formally completed a lot of small details remain to be completed. These multiple steps enable a determined management to resist an increase in its drug purchasing line in the budget, mainly by delaying through officiousness.

CONCLUSIONS

The introduction of biotechnology products involves the same boons and banes of all new high tech. The blessings are extremely powerful effects, never thought of even a few years ago. The curse lies in the cost: similarly to other high tech developments, these products are, initially, with rare exceptions, each individually expensive. In the climate where cost containment is the overlying grand motto of todays' medicine and when a letter to the New England Journal of Medicine suggests that the contemporary physician's Oath will contain "I will always use generic drugs" (11), expensive medications suffer the same travail of being approved, accepted and made available as other expensive medical products. A certificate-of-need legislation pertaining to drugs has not yet been suggested, to the best of our knowledge, but administrative reluctance leading to administrative obstruction is widespread and perhaps natural.

How does one overcome all this? We suggested the

application of the scale of "reasonable requirements" using the check list of nine parameters in an atmosphere cognizant of there being limits to available resources and that it is the duty of clinicians, researchers, administrators and manufacturers to priorize with moral responsibility.

ACKNOWLEDGMENTS

Drs. Gotsman, Jacobs, Livshits, Rubinger, Shouval and Slavin provided helpful data and advice.

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Discussion -THE IMPACT OF ECONOMIC ISSUES ON THE THERAPEUTIC USAGE OF BIOTECHNOLOGY PRODUCTS. A VIEW FROM THE HOSPITAL

M.M. Reidenberg

Do you think that the improvement of quality of public health is an issue that should be dealt with by a formulary committee on whether to include a product, or do you feel that an individual physician treating an individual patient should weigh the value for the particular patient against what it does to society as a whole?

M. Levy

I think that for the hospital committee it is a general issue. I should not refer to the individual patient.

B.R. Meyer

As a chairman of pharmacy and therapeutics committee I think you have summarized very well the problems that we face. The numbers in our hospital are very similar to yours. We however have spent considerably more on erythropoietin where we spend about $400,000-500,000 a year. We have an extensive renal dialysis programme and we get about 75-80% of that back by third party payers. We also spent an awful lot of money on something you didn't mention which is i.v. gamma globulins

L. Gauci

I would like to refer to your list of reasonable requirements. I cannot agree with the notion that biotechnology products should be considered in a separate category because they are the most expensive drugs. This is not true, there are other drugs which are very expensive. I think that in the case of modern drugs, which are expensive to develop, pricing considerations should be included in the phase III studies.

M. Levy

I agree. As a group the most expensive drugs known to hospitals are antibiotics. We spend between to $2-3 million a year on sophisticated last-generation antibiotics.