The clinical pharmacology of biotechnology products
M M Reidenberg, editor

BIOTECHNOLOGICAL PRODUCTS, CAN THIS COMMODITY BE AFFORDED?

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INTRODUCTION

There is an important gap between basic biotechnological research and the subsequent product application in clinical practice. Thanks to this basic research it is possible to obtain products such as Growth Hormone, Interleukin, Interferon, Somatostatin or Erythropoietin. As soon as they are obtained a long searching process for clinical indications starts. In this process a conflict between four agents is generated:

- The developing Pharmaceutical Company, that would like to quickly extend the authorized clinical indications .
- The potencial prescribing physicians, who would like to use the new product in indications that are still waiting for the clinical trials' results.
- The Regulatory Authority, that tries to be quite sure before approving new indications.
- The National Health Services (NHS), that don't have funds enough to finance these new and very expensive products.

This clash of interests arise from curious situations that would be interesting to analize.

THE CASE OF GROWTH HORMONE

Short stature was treated with Growth Hormone (GH) obtained from human pituitary gland in 1958 for the first time (1). In 1985 the original biosynthetical GH was introduced after several young men who were treated in their childhood with GH died of Creutzfeldt-Jakob illness (2). This new GH has allowed not only a more extensive use, but also the exploration of potentially new indications. The current approved indications are: defficiency of GH secretion, neurosecretory dysfunction, inactive GH and Turner syndrome (3).

Other pathologies that could be new indications for GH treatment in the future are: constitutional short stature, intrauterine growth retardation, renal insufficiency, osteochondrodysplasias and Prader-Willi syndrome. GH could also be used as a simply aesthetic factor in men over 60 years old. This

new perspective arises from a recently published study showing that the disminished secretion of GH is partially responsible for the decrease of lean body mass, the expansion of adipose-tissue mass, and the thining of the skin that occurs in old age (4).

This situation envisages a new GH expansion in the market and its limits are impossible to predict. In Spain 65.300 vials of GH were prescribed during 1986, 367.000 vials in 1987, 885.000 vials in 1988 and 1.387.784 vials in 1989 (5). This represents a $138 million expenditure in 1989 for the Spanish NHS in spite of the fact that this drug is "hospitalary diagnostic" (a category that forces the prescription of this drug to be made under a medical report that has to be checked by a Health Inspector). To evaluate this magnitude, it's interesting to know that the total drug expenditure on primary health care financed for the Spanish NHS was $4000 millions during 1989 (6).

Bearing in mind these data, the affordability of this commodity has been possible so far but probably won't be in the very near future. Perhaps it should be taken into consideration if it must be afforded. In a society where resources are limited, these must be used in an efficient way. What is expended in GH is to the detriment of other health resources. Deciding what clinical indications must be approved, or the economical limits on GH financing is very difficult, because physicians and health planners don't usually agree on these matters.

In any case, we have to admit that the current situation is not good and reveals the lack of adjustment between the quick development of biologically obtained products and established drug evaluation systems. It is curious to observe how the GH consumption in Spain presents great disagreements when compared with consumption data from other European countries. Regarding the 1988 data, there were 152 patients per million Spanish inhabitants treated with GH , whereas there were 38 in Germany , 37 in the United Kingdom, 67 in Holland, 100 in France and 88 in Italy (7). Even admitting that achieving this reckoning is difficult and that involves some error, there appears to be differences between European Countries that are hardly justifiable. The same occurs when the data from the seventeen Spanish Autonomous Regions are analized. When adjusted per population, results indicate that some Regions consume GH eight times more than others.

THE CASE OF INTERFERON

Currently there are three Interferons in Europe developed by three different Laboratories. The obtaining mechanism changes from one to another but, at least theoretically, we could not expect high differences concerning their clinical efficacy. In spite of this, the indications that each laboratory applies for are not coincidental. Particularly we will analyze Interferon alfa 2b. Table I shows that the Company has applied for up to 10 different clinical indications along the 12 EEC countries, that the 12 different Regulatory Authorities have accepted in 12 different ways, that is to say that there are not even two countries accepting the same conditions. There seems to be a relative accord on Hairy cell leukemia and AIDS-related Kaposi's Sarcome, but for the indications left, it seems difficult to find a laudable explanation.

Another remark deserves the Hepatitis case, because the frequency of this illness could represent a hardly bearable economical charge in countries where the appropiate indication is approved. In November 1989 the use of Interferon alfa 2b, was approved for Hepatitis B and C in four countries (Greece, Ireland, Italy and Portugal). The eight countries left are still deciding. In this situation two conjectures can be made:

a) The four countries that approved this indication have a slightly less strict regulation system.
b) The four countries that approved this indications have an efficient regulatory system that response quickly to scientific evidence.

Which of the two conjectures is true, if any?. In case of doubt, we leave it to the reader's criterium. It is curious to know that in November 1989, two clinical trials were published in the same issue of The New England Journal of Medicine, and both of them conclude that a 24 week course of Interferon alfa 2b therapy is effective in controlling disease activity in many patients with Hepatitis C, although relapse after the cessation of treatment is common (8) and that Interferon alfa 2b therapy is beneficial in reducing disease activity in chronic hepatitis C, however the beneficial responses are often transient (9).

Regarding Hepatitis B, more recently another clinical trial has been published and the author concludes that treatment with

TABLE I

REGISTRATION STATUS OF INTERFERON ALFA 2b FOR THE DIFFERENT INDICATIONS IN THE EEC (NOVEMBER 1989).

Approval date for following indication	BE	DK	GE	GR	SP	FR	IRL	IT	LUX	NL	PO	UK
Hairy cell leukemia	85	86	87	87	88	88	85	87	86	86	86	86
AIDS-related Kaposi's Sarcoma	85	86	-	87	-	86	85	87	86	-	86	87
Multiple Mieloma	85	-	-	-	-	-	85	87	86	-	86	-
Laryngeal Papillomatosis	85	-	-	-	-	-	-	-	-	-	-	-
Basal cell carcinoma	89	-	-	-	-	-	-	-	-	-	89	-
Non-Hodkin's Lymphoma	89	-	-	-	-	-	-	89	-	-	-	-
Cutaneous T-cell Lymphoma	89	-	-	-	-	-	-	89	-	89	-	-
Chronic mielogenicus leukemia	-	-	-	-	-	88	88	89	-	-	89	87
Bladder Cancer	-	-	-	-	-	-	-	-	-	-	-	-
Condyloma Acuminata	-	86	-	-	-	-	85	89	-	-	86	87

Interferon alfa 2b (5 million units per day for 16 weeks) was effective in inducing a sustained loss of viral replication and achieving remission, assessed biochemically and histologically, in over a third of patients. Moreover, in about 10 per cent of the patients treated with Interferon, hepatitis B surface antigen disappeared from serum (10).

This three studies are a good sample of state of the art Hepatitis treatment with Interferon. Its seems very clear that there is a therapeutic benefit but with important restrictions. In the Hepatitis C case, relapse is produced after the end of the treatment. And in the Hepatitis B case, the biochemical and histological remission is only obtained in a third of patients. Is this obtained therapeutic benefit enough to justify the approval of Interferon in the Hepatitis treatment?. This question is intrinsically linked to the next one: Are there funds enough to afford this commodity?. Or even more precisely: Is Interferon, from the National Health Service's perspective, an efficient investment?.

Trying to solve this difficult problem, the Committee for Propietary Medicinal Products (CPMP) is looking for a generally accepted Summary of Products Characteristics (SPC) for the European Community before the end of 1990. This can partially answer the issue but several problems will still remain:

1) The indications demanded by the laboratories owners of the three Interferons are different. This means that, in the best case, we will have three different SPCs in Europe.
2) CPMP decisions are not binding at this moment.
3) In any case, each country needs to solve its financial problems through its NHS.

THE CASE OF ERYTHROPOIETIN

The introduction of recombinant human Erythropoietin has substantially improved the treatment of chronic anemias. It has been sucessfully used to correct the anemia of chronic renal failure in patients mantained by chronic hemodyalisis (11). Also this was the first indication that was approved throughout Europe using the Concertation Procedure that was established in the 87/22 EEC Directive. Afterwards, in July 1990 another indication was approved by the CPMP: "Treatment of severe anemia of renal origin

accompanied by clinical symptoms in patients with renal insufficiency not yet undergoing dialysis". The approval of this indication, and the fact that there are new ones being studied such as the anemia of rheumatoid arthritis (12), anemic AIDS patients on zidovudine (13,) anemia associated with multiple myeloma (14) and even in patients with anemia of cancer (15), make a new therapeutic expectative, but once again limitation of resources to finance it must be recognized.

COST-EFFECTIVENESS STUDIES AND BIOTECHNOLOGICAL PRODUCTS

The expenses associated with Biotechnological Agents have a major impact on health-care economy. A global understanding of the overall impact of these drugs require a complete analysis not only about the cost of drugs but also about the associated changes relating medical-care cost and the resulting health benefits (16). The aforementioned problems with GH, Interferon and Erythropoietin, only could be undertaken from a global prespective if a cost-effectivenes evaluation is added to the classical regulatory evaluation.

It's not enough to decide what indications should be approved. But also economic evaluation must be carried out in order to assess if these therapies are good enough to be financed with public funds. The cost of Erythropoietin, for example, will not be offset simply by savings in transfusion costs. It is important, however, to consider all of the outcome changes that this drug will provide to the patient. These include changes in the cost of treating adverse effects and an improved quality of life (17).

Unfortunately, the methodology of these sort of studies still presents some difficulties and can't be systematically applied to every drug; although it is obvious that biotechnological products should be one of the first targets. It is probably premature to require it by the Regulatory Agencies, but seems judicious that health planners will keep it in their minds when economic resources are distributed.

CONCLUSION

This work started indicating that the quick development of products derivated from biotechnology has generated a conflict

between four agents. By trying to find some advisable solutions, it is possible to suggest one for each.

- The developing Pharmaceutical Company. It will facilitate the resolution of the conflict if companies would not try to induce doctors to prescribe these products in indications that have not been approved yet. And also if they avoid conducting "seeding clinical trials" in this area, inducing the prescription of these products under the false appearance of a clinical research work.
- The potencial prescribing physicians. It would be useful if they refuse to participate in these trials, and they understand the fact that the publication of a clinical trial in a worthy journal does not always means that they must reproduce the proposed therapy in their daily practice until it is sanctioned by the Regulatory Authority.
- The Regulatory Authority. It would be useful a much faster reply to the discoveries obtained by clinical trials and if decisions taken would be detached from possible financing of these drugs by the NHS.
- The National Health Services. Their decisions about financing new therapies, especially expensive products like the ones derived from biotechnology, should be based as much as possible, on cost-effectiveness and quality of life studies.

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Discussion -BIOTECHNOLOGICAL PRODUCTS, CAN THIS COMMODITY BE AFFORDED?

P. Juul

I would like to ask you whether you would find it reasonable to combine the registration authorities with the reimbursement authorities? I think that in most of our countries these are two separate authorities which in many ways is an enormous advantage for the authorities granting the marketing authorization. But with some very expensive drugs the problem will evidently be that if the marketing authorization agency accepts a new indication the reimbursement authority may be in a problem.

F. García Alonso

I believe this is the key question. The separation between the regulation and the reimbursement. From a scientific point of view, the best way is to separate, absolutely. But in the real practice this separation may not be evident. In the case of Spain, every drug that we approve automatically is paid by the National Health Service and we cannot resist the situation. We cannot pay for all the new drugs that have been approved.

P. du Souich

One very partial solution in Quebec is to approve the drug but with restrictions. Then, in fact, only some specialists are allowed to prescribe the drug.

F. García Alonso

Of course this is a good solution but you need to deal with the legal peculiarities in every country.

M.M. Reidenberg

In our hospital, and probably in many others, we have some reserved antibiotics that require special permission to use, and then only for specific indications. The staff has accepted this because of the issues of both cost and trying not to develop resistance. We do have a model, probably all over the world, of restricting approved drugs only to approved uses and indications, and I think this could be built on for other expensive drugs if there was the will to do it.

F. García Alonso

This is a model that we can follow but, in real terms, at least in Spanish hospitals,

we have difficulties to follow this system because of the resistance of the physicians. For example, we have restrictions on antibiotics but this approach often creates problems to the Commission on Infectious Diseases in the hospital. Biotechnology products are expensive drugs, and they are often overprescribed for indications that are not approved.

A. Ganser

I would like to say something from the viewpoint from a clinician. I see the limited resources that we can spend for drugs. But what I cannot accept actually is that we should not look into the journals and see whether new applications of drugs have become available. And if there is a publication, even in one of the major journals, I think we have a responsibility as clinicians to see whether this actually holds true. What we should do, I think, is to limit the use of these biotechnology products to certain doctors, as it is done in Quebec.

F. García Alonso

But the question remains: who is the authority in charge to say who are the physicians that can prescribe and who are not? This is really very difficult because every physician mainly working in the hospital, believes that he is a very important researcher.

J. Bigorra

I believe that in general terms therapeutic advances should be made available to society. The question is who will pay for it? I think that, in principle, in a private relationship between a physician and a patient, the patient could pay and there would be no problem. However I also understand that if a new principle needs an experience of more than 20.000 patients to establish what would only be a very minor advancement, the National Health Service can decide that this is not of interest for full reimbursement.

B.R. Meyer

In regard to Dr. Reidenberg's suggestion. We have such a policy where we have very strict restrictions on erythropoietin, intravenous gamma globulin and interferon. And while those are very effective in ensuring that the drugs are only used in appropriate situations it does not ensure that they are cheap. For instance, we only approve erythropoietin for renal insufficiency or renal failure with anemia and intravenous gamma globulin is approved for ITP, congenital agammaglobulinemia or AIDS patients with severe hypogammaglobulinemia. Despite that and being sure that 98% of usage is appropriate, we still have very extensive costs. I do have a hesitation about restrictions

because I do think that therapeutic experimentation of physicians who have a unique case and a unique problem and who attempt to develop a unique solution has been a source of consistent innovation in therapy. So that I also think there is a problem, aside from the obvious ones, which is that restriction tends to rigidify our attempts at therapy and the person who is trying to come up with a novel solution to a difficult novel problem is appropriately angry and frustrated and I think in the long run this may hurt us.

W.M. Wardell

What we are dealing with are systems for controlling drug utilization. Such systems exist and have existed in various forms in many countries for years and are inexorably, for better of worse, encroaching on the use of pharmaceuticals in most countries. The systems can be tuned through computer diagnostic criteria and computer reimbursement lists to just about any degree of constraint that the payor desires. The central question still is once the drug expenditures of a country have been drastically cut by such mechanism, who is going to fund the R&D for new drugs? It is a real dilemma. I come back to the thought that the only way to ameliorate the situation, looking ahead, is to reduce the costs of development and lower the barriers to approval. Once you take the incentives away, new drugs won't be developed.

F. García Alonso

But of course, there is no evidence that reducing the development costs would automatically reduce prices.

W. Wardell

But increasingly, the prices are in the hands of the managers of utilization control systems.