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MEETING PROCEEDINGS

Insulin Analogues: A Critical View on Their Future

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Abstract

Insulin analogues represent a class of insulin formulations with improved pharmacokinetic and pharmacodynamic properties. The introduction of rapid-acting and long-acting insulin analogues into the market in the last decade has helped optimize metabolic control in patients with diabetes. Unfortunately, the number of good randomized controlled clinical trials (RCTs) that fulfill rigid criteria brought up by evidence-based medicine is low. The consequence is that reimbursement has become an issue, at least in some European countries. In addition to some principal questions about the validity of RCTs to provide the best possible evidence for each and every clinically relevant question, one wonders about the end points of such studies. Other end points, may they be long-term end points such as morbidity and mortality or other short-term end points such as variability in blood glucose levels, are probably more relevant for patients with diabetes. The question is who will fund new clinical studies? From my point of view we will have to start over again on this topic, employing a fresh look on this story. Discussing old data and strategies over and over again will not provide us with the answers needed for the (critical!) evaluation of new diagnostic and therapeutic development.

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Introduction

We have come a long way in the treatment of diabetes mellitus (DM)—from impure insulin formulations made from bovine or pork insulin to a variety of highly purified human insulin formulations and insulin analogues. For many years only a limited number of insulin formulations were available. In view of their distinct disadvantages, the call for action by famous diabetologists to develop new insulin formulations with improved time-action profiles was taken up by the pharmaceutical industry. Considerable progress in this direction has been made in the last two decades by developing insulin analogues with distinct differences in their pharmacological properties in comparison to the respective human insulin formulations; today three rapid-acting insulin analogues and two long-acting insulin analogues are on the market. These insulin analogues are widely used worldwide nowadays, with interesting differences among the countries; however, there are a number of black clouds accumulating over the future of these novel insulin formulations.

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Abbreviations: (DM) diabetes mellitus, (HbA1c) hemoglobin A1c, (RCTs) randomized clinical trials

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A large number of clinical trials investigating the properties of these insulin analogues and their clinical relevance have been performed during the clinical development process of these analogues and also in the years after their approval. Nevertheless, (very) critical analysis of these studies by institutes—established, for example, in Germany to review the evidence of such studies—came to a negative evaluation of these new insulin formulations in comparison to the respective human insulin formulations with respect to their benefit. According to these evaluations, no additional benefit was detectable when summarizing data from the studies that fulfill the inclusion and exclusion criteria applied by such institutes. These studies were only a subset of all studies that were published. Subsequently, the higher prices for such insulin analogues are not reimbursed any more, for example, in Germany. Interestingly, there is not a European institute performing such an evaluation for all countries in this union, but the countries act independently and differently. The view of such institutes on new insulin analogues (and many other developments in diabetes technology) is that these are nice new "toys" without addressing a clear medical need. Therefore, their position is that only drugs that allow a real reduction of (long-term) costs for our health care systems will get reimbursement.

The aim of this short commentary is to highlight different aspects of this story and not to go into details with this or that clinical trial. Some of the statements might be disregarded as coming from someone that was brainwashed by the pharmaceutical industry. However, my position is that it is necessary to understand the views of all sides involved in such developments in order to able to work together in a constructive manner. Simply by disregarding the pharmaceutical industry and the people working in those companies (which from my point of view do an excellent job in practically all cases) is not helpful at this time. We need to take a look at the different aspects of insulin analogues that are of importance to the different players to help us understand the differences in their reactions.

- Patients: quality of life, no injection meal interval, no need for snacks
- Treating physician: optimize metabolic control
- Scientist: clear differences in pharmacokinetics/pharmacodyamics properties, but does significance mean clinical relevance?
- Pharmaceutical industry: market approval, a lot of investment, no or limited reimbursement, the system does not work any more
- Health care insurance: where shall we invest our limited amount of money?
- Politician: reduction of costs spent for the health care system, keep your voters happy

As long as we have no data from good new randomized clinical trials (RCTs) in our hands, this would mean opening a battle that has no meaning and constructive outcome. The performance of RCTs focusing on hard end points would—these would be the ideal studies—require the inclusion of many patients and a long study duration with many patient visits. The costs of such studies are tremendous. These costs, in turn, drastically decrease the probability that such long-term studies will ever be performed in view of all critical aspects combined with them (see later).

The development of new insulin analogues (and of other new types of insulin formulations/forms of insulin application) depends critically on the reimbursement provided for those already on the market (some of them for several years) and those just entering the market or in clinical development. It is fully understandable that health insurance companies request demonstration of a positive cost–benefit ratio for each new diagnostic or therapeutic option; however, it can also be used to block the introduction of such options more or less completely. This in turn would stifle the development of all new insulin analogues (as an example) rapidly. The suspicion is that health care providers try to turn down the introduction of new diagnostic/therapeutic concepts in order to stop the ever-increasing costs for the health sector in general. In that sense the "scientific evaluation" of the evidence of insulin analogues can also be used as a fig leaf. The trouble with such evaluations is that when it comes to detail, there is also a lot of room for personal opinions, which have an impact on the outcome. Such a statement can be clearly disregarded again as coming from a biased view from someone who works closely with the pharmaceutical industry. However, this is a double-sided sword!

Until now pharmaceutical companies performed RCTs to demonstrate efficacy and safety to get approval for their new substance. Interestingly, it is sufficient for these studies to demonstrate noninferiority to already

approved substances. These studies are not necessarily studies that evaluate and demonstrate the full medical benefits of a given new insulin analogue. The design and performance of such a study might differ from that for an approval study. It would probably be a good idea to alter the design of phase III studies (which can costs hundreds of millions of dollars) required for approval. In order to achieve data for relevant end points for innovative products, such phase III trials should directly focus also on these.

The design and performance of RCTs, which are absolutely mandatory when studying the benefits of new developments, clearly can be improved (and in this respect critical reflection is helpful); however, we should also acknowledge the limitations of such studies (see later). For example, the question is whether patients seen in daily practice are comparable to those patients who are included in RCTs. Patients with comorbidities and/or taking concomitant medications often are not included in such trials, but these are the majority of the patients a treating physician actually sees. In addition, patients in daily practice may have a more severe degree of disease and potentially would benefit further from the new drugs or application than patients included in the RCTs. Other approaches (e.g., epidemiologic studies) also have limitations (e.g., no randomization), but they could provide a better evaluation of a patient's actual daily experience (= the unperturbed reality without the profound study effect seen in most RCTs) and add relevant information to the discussion.

Reason for the Development of Insulin Analogues

As indicated earlier, there are many ways to improve insulin absorption and thereby insulin action. However, such measures have one disadvantage from the perspective of the pharmaceutical industry: they are more difficult to patent than distinct changes in the primary structure of a peptide. When a company cannot protect its intellectual properties (= investment) there is a high risk that another company can come along with a very similar product for a lower price and the first company does not get a return on their investment.

A careful look into the history of the development of insulin analogues shows that Novo Nordisk was the front runner for quite a while in the development of insulin analogues and still today owns many of the respective patents. Other companies pay royalties for the use of these analogues. However, in the not too distant future these patents will expire and most probably generic insulin analogues will be available in the market immediately after this date.

Evidence for Benefits of Insulin Analogues

When the first data from animal experiments and clinical–experimental studies with rapid-acting insulin analogues were presented, the impression was that huge improvements in their pharmacological properties were achieved, i.e., the much more rapid onset of action and the shorter duration of action would allow a much better coverage of the prandial insulin requirements. Having such data in mind, Eli Lilly (and subsequently Novo) initiated a number of phase II and III trials in which regular human insulin was replaced by insulin lispro on a 1:1 basis, without changes in basal insulin therapy. The assumption was that the successful outcome of these studies was granted.

The "negative" outcome of these studies was frustrating for the company in view of the investment of a lot of money: only a moderate benefit with respect to metabolic control, reduction of hypoglycemic events, and so on could be demonstrated. It turned out that the therapeutic schemata (= optimization of basal insulin therapy) has to be adjusted to make full use of the advantages of rapid-acting insulin analogues. As a result, the invention of insulin analogues did not induce a "revolution" in insulin therapy. Improvements in the pharmacological properties were not that profound that they overruled all other aspects that have an impact on metabolic control in daily life. This in turn also means that there is still a need for insulin formulations with even further improved pharmacological properties; these must not necessarily be novel insulin analogues.

Insulin Analogues and RCTs

In view of the high level of metabolic control that can be achieved with the currently available diagnostic and therapeutic options in well-trained patients, for example, it is not an easy task to show a further improvement in metabolic control by a new insulin formulation. Clearly, for physicians, the aim of treatment for patients with DM is to optimize their metabolic control; therefore, he or she must educate patients about the importance of intensified insulin therapy. We should keep in mind, however, that the goal is quite different for patients. Their goal is simply to live their life as normal as possible, so discretion and ease of use with regard to insulin administration and glucose monitoring are of paramount relevance for them.

Therefore, a regimen that is easy to follow and avoids acute metabolic deterioration is very attractive. Although not all improvements in diagnostic and therapeutic tools result in a decline in glycosylated hemoglobin values, they may lead to a better quality of life for the patients.

The current focus of health care and health insurance, however, is very much on improved metabolic control, the major outcome measure in RCTs. If no improvement with respect to this parameter can be shown, results may indicate that an intervention has no proven benefit. However, from a patient's point of view, an intervention might offer considerable advantages, but such "soft" parameters receive little attention. For example, what is the benefit of a patient's reduced need for snacks between meals when taking a rapid-acting insulin rather than regular insulin?

Another issue is the relevance of hemoglobin A1c (HbA1c) values in terms of long-term outcomes. Metabolic control is monitored by measuring HbA1c because there is no other viable parameter. However, this parameter, as an integrated blood glucose memory, tells us nothing about the swings in glycemia that may occur nor do capillary blood glucose measurements, performed by patients to make appropriate decisions about the use of intensified insulin therapy. Patients with identical HbA1c levels might differ considerably with respect to these variations.

However, if continuous monitoring systems become available, how will we study the potential benefits of new insulin formulations or insulin application techniques in the future? When patients can see their current blood glucose levels displayed on the system at any time and then immediately counteract any swing in glycemia, there probably will be no chance of seeing a difference in HbA1c levels at the end of the study because differences in the metabolic activity of the study drugs will be balanced by the patients. However, patients may be able to provide information on the need to counteract glycemic excursions with one drug versus another, which, until now, was not an accepted study outcome.

One can also foresee that, with regular use of continuous glucose monitoring systems, interpretation of the outcome of RCTs may become difficult, and we need a paradigm shift at this end. If such techniques are available, would it be ethical to treat patients in clinical trials over prolonged periods (i.e., if one blinds the display of the device to prevent immediate counteracting by the patients to determine the "unperturbed" effect of the study drug and its comparator) without providing them at least a safety net in the form of an early warning system at hypo- or hyperglycemic values?

Who Will Fund New Clinical Trials?

If we want high-quality studies with clear-cut outcomes that allow for an exact statement about the cost–benefit ratio of a new diagnostic or therapeutic option, we must agree on how to finance such studies. Typically, new studies are expected to be paid by the pharmaceutical industry. Yet when a study is paid by a pharmaceutical company and there is a positive outcome, the results are treated with suspicion. Studies performed by academic institutions are regarded as being of higher value than studies performed by organizations that are funded by the pharmaceutical industry. However, in reality one has to acknowledge that at least the data quality of studies performed by academic institutions is often quite lower than those of professional organizations.

The performance of clinical trials is highly formalized and controlled. Once a study design is approved and the study is completed, there is no room for influencing the study outcome. This is clearly an improvement compared with the situation before Good Clinical Practice guidelines were implemented. However, in the choice of study design and in the analysis and interpretation of study data, there is room for shifting the study results in a certain direction.

Pharmaceutical companies have a clear strategy: they invest in the preclinical and clinical development of a new insulin formulation to get market approval. Then they invest even more money into marketing in order to get a sufficient uptake by physicians/patients to earn money, which in turn covers the investment for this drug and for several other nonsuccessful substances. Their interest in investing in studies that prove the benefits of a new insulin formulation after the approval is very limited.

Such companies are now faced with the situation that the reimbursement for insulin analogues is banned several years after their approval. For them the enthronement of new institutions evaluating the benefits of already approved substances acts as a second approval. In a sense, the rules of the game were changed after the game had started. In hindsight it is always easy to say that these studies are missing and this and that are not proven, but we cannot change the past. One also has to acknowledge that companies have been ignorant for quite

a while about the necessity of running adequate studies. They have believed that their economical and political power would prevent them from any harm. However, it turned out, at least in Germany, that David has won against Goliath.

Before we demand better clinical trials (which should be paid by the companies), we must acknowledge the fear of pharmaceutical companies that if they agree to support such expensive studies, the outcome might not be accepted anymore (independent from being a positive or negative outcome) once the studies are finished because the rules have been changed during the years that are necessary to run these studies again.

Another question is at which point in time should such studies be performed, before or after market approval? Until now, companies have had to perform a rather well-described set of studies showing safety and efficacy of a new drug and then apply for drug approval. If more clinical trials with much longer study durations are required to be able to make statement on better end points than HbA1c, this would also prolong the time period before the drug can get approval. This in turn would reduce the time before the patent for this drug expires. This would force the company to increase the price of the drug to get the necessary return on investment. If data from studies on hard end points are required before new drugs become available, it would mean that patients have to wait longer before they have access to such new drugs as well. Whether this is a disadvantage or advantage depends on the point of view.

Conclusions

In summary, the future of newly developed insulin analogues depends very much on the performance of adequate clinical trials to prove the benefits of such innovations in good clinical studies. In view of the logistics and costs of such studies it is doubtful that they can be performed by academic sites without cooperating with professional organizations and the pharmaceutical industry. This requires an open discussion involving all relevant parties (including patients) about which clinical studies are required and how they should be performed and financed. This in turn also requires that if a benefit can be clearly demonstrated, we (= payers) have to accept that the costs for such developments have to be paid for. Such sounding boards should be established by academic experts in a given area of research. They should invite all people/groups with an interest in this topic. Clearly it is mandatory to provide a full transparency of all financial aspects involved to avoid any skepticism about the activities of such working groups. The aim of such groups can be to provide more general statements or suggestions for clinical studies. They can also probably organize appropriate studies. In view of the still suboptimal metabolic control of many patients with diabetes, there is still a huge potential for new technological/pharmacological concepts to support improvement in metabolic control.

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