



Working to benefit all people affected by genetic disorders

Risk Communication Workshop

19th July 2005

London

Report by the Genetic Interest Group

Introduction

Given the pace of recent progress in our understanding of the biological basis of disease, creating an appropriate regulatory framework to ensure quality, safety and efficacy of innovative therapies derived by biological processes is a significant challenge. Too burdensome a framework will stifle innovation and leave potentially treatable diseases uncured. Too light a framework and the risk of serious, unwanted sequelae becomes greater than can reasonably be allowed if patient safety and trust in the system is to be preserved.

The problem is particularly acute in the area of “bio-similars” – copies of original biological medicines containing large molecules derived by novel biological methods rather than through the more traditional technologies employed to create small molecule pharmaceuticals. Large biological molecules for treating a given disorder that are produced by (slightly) different methodologies may be broadly the same, but they may differ in important details in ways that alter their effectiveness or change their potential for initiating a range of reactions, some of which may be significantly adverse.

The key questions for patients for whom a biological molecule is prescribed as a therapy for their disease are around the establishment of safety and effectiveness in two or more “bio-similars”. In other words, how much do two molecules have to diverge in their structure before they become distinct entities, what are the associated risks and how acceptable are these? How can we ensure that the possibility of effective intervention is maximised when facing the challenge of serious (and often intractable diseases) whilst at the time taking steps to contain risk to levels acceptable to patients making choices to take the treatment?

Central to discussion of these issues is the process of communication and information sharing between stakeholders in situations where certainty is not possible, and knowledge necessarily incomplete. GIG recognises the importance of communicating the

patient safety considerations surrounding biosimilars, and equally appreciates the challenge in effectively relaying the associated risks of these new products. A number of GIG members currently rely on biologics, and may therefore be affected by the arrival of these follow-on products. For this reason, GIG hosted a dedicated workshop on Tuesday, 19th July in London to engage patients and patient representatives in a discussion around risk communication in general, as well as looking at the specific case of biosimilars. The day commenced with a short session on biosimilar medicines and the current scientific and regulatory issues surrounding them in Europe. The session then explored the immediate considerations for patients and why it is important and appropriate to understand the implications of biosimilars that might potentially differ from the reference product. The rest of the day was spent on a range of issues relating to patients experiences and expectations of therapy and therapy development gathering direct feedback from all participants.

This workshop was convened on the basis of equal value participation by all delegates. The importance of patient views, knowledge was explicitly stated to be of equal weight to that of professionals participating. Those taking part represented scientific, clinical and regulatory expertise as well as those with direct personal experiences of some of the diseases where therapy using biological molecules is either available or in prospect.

The event was timely because questions about proof of quality, safety and efficacy are on the agenda of major agencies such as EMEA and NICE, and are being addressed by research funders such as the Wellcome Trust and MRC, who are anxious to target their research resources effectively when addressing questions of biological effectiveness and relevance.

Biosimilars: Are they different?

Chemical drugs are well established, and a lot is known about the active ingredients in small molecule compounds and how they exert their effects. When a patent on a branded drug expires then it is open to competitors to produce generic equivalents that count on the same active ingredient as the branded product.

Biotechnological therapeutics are inherently more complicated than traditional small molecules. The first biotechnological drugs to be produced are now approaching or at the end of their patent life, opening up the opportunity for copies to be developed and put on the market. Because of the complex structure of these large biological molecules, producing exact copies is challenging, and there may be small but potentially significant variations between the original and the copy. Hence these copies are referred to as “bio-similars”, not generics.

Traditional regulatory requirements, established to ensure the quality and safety of chemical drugs may not be wholly appropriate for large biological molecules. New criteria may have to be established for determining quality, safety and efficacy of bio-similar products that reflect the specific character of these products. Variations (even if slight) in the processes adopted by different manufacturers can result in changes in the product that are difficult or impossible to detect by laboratory based testing, but which become apparent when bio-similars are trialled in patients. Slight changes can have dramatic physiological effects, and the risk to patient safety (if any) must be established and monitored before bio-similars are adopted for use in clinical practice. Protecting patient safety is important. Appropriate regulatory frameworks need to be developed to secure this if a proper regime for evaluating the relative merits of bio-similars and the original therapeutic molecule is to be established.

Assessing & Communicating Risks

Much, if not all, of the advice and information given to patients by clinicians is based on incomplete knowledge. Indeed it is impossible to know everything about a particular disease, the therapeutic interventions available and how these will be perceived by the patient taking them. The complexity and the incomplete nature of knowledge is particularly apparent in clinical genetics, where decisions are often based on patient understanding due to the state of our knowledge. Professionals have therefore had to develop strategies for helping patients appreciate the risks they face in ways that are meaningful to them, and which help them to make properly informed choices in difficult and stressful situations.

Depending on the situation a genetic counsellor can be asked about a Mendelin risk (i.e. there is a 1 in 4 risk of having a baby with A or B condition), an Empirical risk, when the inheritance pattern is not clear and the advice may be derived from statistical analysis, or a Susceptibility where clinical experience may help to put a “framework” road a relatively obscure picture which considers family history, prevalence in the population and other potentially relevant factors.

The language of risk communication is important. Some people want the precision that figures give – but even here a 1 in 4 chance of something happening is a 3 in 4 chance that it won't, and is this perceived as the same thing? Others require description or valued images, metaphors etc to appreciate and internalise the risk they face in order to be able to make an informed decision.

Even apparently straightforward descriptors can be open to misinterpretation. For example, something described as a “very high” risk by a regulator as a doctor may be seen as an event that occurs in between 1 and 10% of cases, whereas a patient hearing the words “very high risk” often takes this to mean a virtual certainty.

Testing assumptions, using a variety of ways to communicate, and checking understanding are all central to discussions about “risk” if patients are to be able to take control of the situation in which they find themselves. This applies whether the discussion is about the genetic risks a family may face or the choice/selection of the appropriate therapeutic to use for a range of bio-similar products developed to treat the condition.

Safety and Regulation

Biosimilar versions of therapeutics have the potential to vary significantly in their effect by virtue of the possibility of differences in the molecular structure arising as a result of variations in the manufacturing process. These changes may result in altered efficacy, toxicity and immunogenicity of biosimilar products. Laboratory based assays are unlikely to reveal the extent of any changes in these parameters, creating a requirement for testing of biosimilars in human subjects before licensing them as safe for use in clinical practice. Although it is possible that biosimilar products will be less effective/have greater potential for adverse reactions than the original product it is not necessarily so – some bio-similar products may be more effective/safer either in general or for particular groups of patients (perhaps due to specific genetic variations or other factors influencing on individual’s ability to utilise/react to one molecular form as opposed to another).

Establishing the clinical impact of bio-similar molecules will be essential if patient safety is not to be compromised and prescribing accuracy is to be maximised. Subtle variations are unlikely to be spotted prior to marketing authorisation being granted by the European Medicines Agency or by the national competent authority unless the clinical trial regime required is substantial and (arguably) disproportionate to the likely hood of risk anticipated. Post marketing surveillance, with traceability of individual biosimilar variations, will therefore be essential if the effectiveness/risk profile of different

biosimilar molecules is to be properly established.

Discussion

It is clear that producing general guidance for patients and professional about biosimilarity will be difficult or impossible, and product by product guidelines will be needed. This is because a small change with relation to one product may be of minor importance with respect to therapeutic impact, immunogenicity or whatever, whilst a change of a similar magnitude in another may substantially affect the characteristics of that substance.

The question of proximity of the “artificial” molecule to the natural one it is replacing in the defective biological system also remains problematic. Even if an exact copy of the human molecule is possible there is still potential for immunogenicity. There is a need for regulatory systems to recognise this and build in appropriate quality checks to test for this. However, regulatory frameworks cannot provide a complete answer. Patient and professional education is also a key part in the process for the successful introduction of biological and biosimilar therapeutics into clinical practice. Unlike conventional (small molecular) therapeutics, where the active ingredient is clinically identical in the original and the generic product, biosimilars require individual follow up and monitoring.

Given the global development and application of these therapies, standardisation and compatibility of testing and monitoring systems to check clinical utility and safety need to be developed. These need to take account not only the variability of biosimilar molecules, but also any known variations between populations (for example as a result of genetic differences) in order to allow patients to be confident that like is being compared with like.

Patients can also make an input to determining what constitutes appropriate/acceptable criteria for establishing risk/safety/acceptability.

They are, for example, able to comment on whether or not monitoring regimes proposed are acceptable or too intrusive. They should not be asked to comment on issues where expert technical views are more relevant (such as the appropriate numbers to include in clinical trials) unless their experience is relevant.

Many diseases that are potentially treatable with biological molecules affect children and adults. Given physiological differences as individuals grow and mature, reasonable steps for this must be incorporated into regulatory procedures. The current Paediatric Medicines Regulations proposals need to be checked to ensure that this is the case.

Complex communications about biosimilars in therapy can easily be misinterpreted. ("What you think you heard is not what I think I said") so research is needed to establish the parameters of a successful encounter between clinician and patient, such that the patient is able to acquire necessary information on an appropriate, accessible and user friendly way.

A key element in successful communication is trust in the source of the information, and in the robustness of the system/personnel delivering it. For this, transparency and completeness are essential. Honesty about what is not known, and what the nature of any risk might be will help to build and maintain trust, making it more likely that the introduction of new therapies will be managed properly, and reach those in need who are likely to benefit.

Safety information is of major importance. This is not because patients may have unrealistic expectations about the possibility of risk-free interventions, but because they need to understand the nature and extent of the chances they may be taking (insofar as this can be known).

Risk communication needs to be checked in the clinical encounter as the words used to quantify risk may be interpreted differently (sometimes dramatically so) by patients and

professionals.

Discussion of the risks associated with a particular intervention needs to be offset against the risks and consequences of the condition it is intended to treat. A lethal condition often brings with it a greater tolerance of risk and an acceptance of a smaller benefit among patients, although not necessarily among regulators or other professionals.

Patients need and are able to assimilate information to different degrees. Some are more prepared to accept their doctor's advice, whilst others want to study things in great detail. Fostering access to robust information that is user friendly, and which has been tested out for its comprehensibility on those for whom it is intended, will facilitate this and boost confidence and trust.

Unlike generic copies of branded small molecule drugs biosimilars are not necessarily chemically identical. For effective post marketing surveillance it will be essential for biosimilars to be prescribed in an identifiable way – use of the trade name rather than the generic descriptor would probably be the easiest way of doing this. Given the complex interaction possible by the combination of variation between biosimilars and variation between people taking them this is necessary for effective tracing and evaluation. Any temptation to treat follow-on products as less desirable should also be strongly resisted. Biosimilar molecules may show improved therapeutic effectiveness and/or fewer side effects in some people because they reflect the complex nature of the variation between the drugs and the people taking them. It will only be possible to determine this if adequate trace-ability is ensured. In many cases it will be the family doctor who needs to understand the complexities associated with biosimilars as it will be at the level of primary care that decisions may have to be made about whether to use a branded product or a bio-similar. The family doctor will also have to be involved in post marketing surveillance procedures, especially if individual varieties of a biosimilar product have to

be separately tracked to detention in their relative effectiveness/risk profile. Information to patients and families about these products and the securing of concordance with the therapeutic regimes required for them to work to best effect will also demand effective communication between the primary care team members and the patient and his or her family. This will demand that consideration be given to developing training and support materials to ensure that this happens to a uniformly acceptable standard wherever these products are brought into use.

Patients should be actively engaged in monitoring the effectiveness and impact of the treatments prescribed for them, and encouraged to report this systematically alongside other established mechanisms for pharmacovigilance. Mechanisms for this should include the recording of positive as well as adverse responses. Also biosimilars should have a unique name as to allow for tracking mechanisms to work and patients to know which product they are taking. Clearly there is a role for patient organisations to work alongside other stakeholder groups as partners in developing way to make this happen quickly and efficiently.

Recommendations

- It is clear that producing general guidance for patients and professional about biosimilarity will be difficult or impossible, and product by product guidelines will be needed.

- Patient and professional education is also a key part in the process for the successful introduction of biological and biosimilar therapeutics into clinical practice.

- Given the global development and application of these therapies, standardisation and compatibility of testing and monitoring systems to check clinical utility and safety need to be developed.

- Patients can also make an input to determining what constitutes appropriate/acceptable criteria for establishing risk/safety/acceptability.

- Many diseases potentially treatable with biological molecules

affect children and adults. Given physiological differences as individuals grow and mature reasonable steps for this must be incorporated into regulatory procedures.

- (“What you think you heard is not what I think I said”) so research is needed to establish the parameters of a successful encounter between clinician and patient, such that the patient is able to acquire necessary information on an appropriate, accessible and user friendly way.

- Risk communication needs to be checked in the clinical encounter as the words used to quantify risk may be interpreted differently (sometimes dramatically so) by patients and professionals.

- For effective post marketing surveillance it will be essential for biosimilars to be prescribed in an identifiable way – use of the trade name rather than the generic descriptor would probably be the easiest way of doing this.

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