Imagination, skills and organisation

More than 3,500 attendees from 35 countries gathered in Barcelona for the 19th congress of the European Association of Hospital Pharmacists in March 2014. The main theme was the innovative hospital pharmacist

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Research and development (R&D)

in medicines in Europe has lost momentum. We have become totally risk averse and have created a climate in which the ladder and the wheel would not be allowed if invented today, according to Daan Crommelin (Emeritus Professor of Biopharmaceutics, Utrecht University, The Netherlands). The proportion of its gross domestic product (GDP) that a country spends on R&D gives a good guide to its success in innovation. World leaders in this field are Israel and South Korea, countries that spend 4.2% and 3.7% of GDP, respectively, on R&D. In Europe, Germany and the Scandinavian countries lead the way, but other European countries probably spend less than 1% of GDP on R&D. In general, European countries tend to be good at research but not as good at development, he added. Globally, R&D expenditure is increasing but the output of new molecular entities is falling. For example, at present, millions of euros are spent on excellence in research in The Netherlands but there is insufficient emphasis on innovation and development, he said.

One factor that could help to increase the focus on development would be strong leadership from 'innovators' and 'early adopters' of new technologies. Another important factor would be non-competitive, collaborative research initiatives in which regulators, academia and industry work together.

Daan Crommelin

New oral anticoagulants

In a Synergy satellite session (see box) devoted to the effective use of new anticoagulants Sabine Eichinger (Associate Professor, Head of Anticoagulation Clinic, Medical University of Vienna, Austria) reminded the audience that the vitamin K antagonists have numerous disadvantages. They act by interfering with the production of factors II, VII, IX and X and therefore have a slow onset of action, which means that 'heparin bridging' is required to ensure immediate anticoagulation. They have an unpredictable dose–response relationship and show marked inter- and intra-individual variability. As a result, clotting status has to be monitored and the international normalised ratio (INR) must be kept between 2 and 3 to avoid bleeding or thrombotic complications. There are also rare complications, such as coumarin necrosis and hair loss, during the first month of treatment for 5–10% of patients.

The disadvantages of the vitamin K antagonists drove the search for alternatives – the new oral anticoagulants (NOACs) – also known as direct oral anticoagulants (DOACs), explained Dr Eichinger. Rivaroxaban, apixaban and edoxaban are all direct inhibitors of activated factor X and dabigatran targets activated factor II (thrombin). As a group, the NOACs all have short half-lives, are cleared by the kidneys and require no monitoring. Dabigatran is a

Synergy satellites

Synergy satellite sessions are a new feature of the European Association of Hospital Pharmacists (EAHP) congress. They are high-level sessions developed and managed by the EAHP Scientific Committee and supported by industry grants. The contents of the Synergy programme are selected and compiled by well-respected professionals within the hospital pharmacy field to ensure the highest level content and with the intention of helping hospital pharmacists prepare for and deliver cutting-edge innovation in service delivery and patient care. Synergy satellite sessions are accredited by the Accreditation Council for Pharmacy Education (ACPE) and attending participants may obtain continuing education points.

prodrug that has to be hydrolysed to its active form.

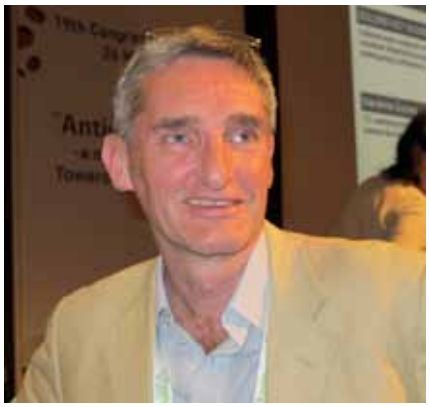
Potentially important interactions are those with inducers or inhibitors of P-glycoprotein (P-gp) – a substance found in the wall of the gut that prevents the drug from entering the system. Thus, concurrent administration of a P-gp inhibitor, such as amiodarone, could increase anticoagulant effects. Monitoring of renal function is mandatory – Dr Eichinger pointed out that a small, elderly, female patient could already be at the cut-off point of creatinine clearance of 30 ml/minute. CYP3A4 inhibitors and inducers affect the actions of rivaroxaban and apixaban but not the others.

Turning to therapeutic use of the NOACs, Dr Eichinger said that they are all at least as effective and safe as warfarin for venous thromboembolism treatment but only rivaroxaban is licensed for this indication at present. The trials of NOACs in atrial fibrillation (AF) cannot be compared head to head because of differing trial designs and the use of different patient groups. The ROCKET AF trial recruited only high-risk patients whereas the patients in the RE-LY and ARISTOTLE trials were evenly distributed across risk groups, she said. However, they all decrease the risk of intracranial bleeding significantly. The most important point is to use the drugs as licensed, adjust the dose if necessary and to know the contraindications. In summary, Dr Eichinger said there were many advantages to using the NOACs but the fact that no monitoring is required means that there is no way to check adherence and there can be reduced awareness (among healthcare professionals) that the patient is taking a potentially life-threatening drug.

Adherence and new oral anticoagulants

Between a third and a half of medicines for long-term conditions are not used as intended by the prescriber, said Duncan McRobbie (Associate Chief Pharmacist, Clinical Services, Guy's and St Thomas' NHS Foundation Trust, London, UK). Adherence is often dismissed as "too difficult to measure" and yet non-adherence can have a significant economic impact, he continued. One study showed 30% of patients discontinued their medication in the first 10 days of treatment. Another study showed that about a third of patients did not persist with clopidogrel after acute myocardial infarction (MI) and these were twice as likely to suffer a non-fatal MI as those who persisted with treatment.

Sabine Eichinger



Duncan McRobbie

Intentional and unintentional non-adherence can be dynamic and occur in the same patient. Pharmacists tackle unintentional non-adherence with measures such as legible labels and reminder charts. However, they struggle with intentional non-adherence and either threaten patients with possible consequences or beg them to take their medicines, but neither strategy works, explained Mr McRobbie. In order to tackle intentional non-adherence effectively it is necessary to understand patients' knowledge, beliefs and concerns about their disease and medicines. He noted that discontinuation rates with NOACs vary from 15–25% in published studies and 'time in the therapeutic range' (TTR) was about 60% in major trials. "Even in the highly-controlled environment of clinical trials people are dropping out of treatment," he said.

Studies show that low satisfaction with medicines information correlates with non-adherence. Mr McRobbie emphasised that patient satisfaction hinges on having concerns acknowledged and addressed rather than the quality of the information given. Work at his hospital had shown that doctors and nurses did not discuss matters such as the risk of side effects and potential effects on patients' sex lives and these were areas where patients commonly expressed dissatisfaction. A reminder leaflet listing the types of questions the patients might wish to ask was distributed and when satisfaction was retested improvements were seen in the satisfaction scores in all domains.

A UK multicentre study showed that patients were more satisfied with the information they received about warfarin than for NOACs. For further guidance on supporting anticoagulated patients, Mr McRobbie recommended the European Heart Rhythm Association (EHRA) practical guide to the use of NOACs in patients with AF. In conclusion, he said that NOACs brought significant benefits for patients but also posed challenges regarding adherence. Pharmacists need to listen to patients and understand their concerns but they also need the skills and time to deliver appropriate care.

Economics of new oral anticoagulants

An economic analysis of the relative costeffectiveness of warfarin, dabigatran, rivaroxaban and apixaban in a Norwegian setting showed that sequential dabigatran (150 mg up to age 80, thereafter 110 mg as recommended by the European Medicines Agency [EMA]) was the most cost-effective option, followed by apixaban, according to Marianne Klemp (Research Director, Norwegian Knowledge Centre for Health Services (NOKC), Oslo, Norway). In order to perform the study a decision-analytic model was constructed to include all the critical events (e.g. acute MI, intracranial bleed) and health states (e.g. AF, heart failure). It was then populated with probabilities of events derived from randomised trials for two different risk levels defined according to the CHA_2DS_2-VASc and HAS-BLED scoring algorithms. The medium-risk patients were defined as those with no clinical risk factors other than age, i.e. a CHA_2DS_2-VASc score of 2 and HAS-BLED score of 1. The high-risk group was patients with a CHA_2DS_2-VASc score of 4 and a HAS-BLED score of 2.

The cost data for the study are Norwegian; the efficacy data were derived from the intention-to-treat analyses of three major trials comparing NOACs with warfarin in AF and the quality-adjusted life years (QALYs) were based on the EQ5D instrument.

The conclusions depend on the amount that a health system is willing to pay for a gain of one QALY, explained Professor Klemp. In the UK, the National Institute for Health and Care Excellence (NICE) uses a threshold of £20,000 to £40,000 whereas in Norway the threshold is

€80,000. If the threshold is less than €20,000 then warfarin is the most cost-effective option. For thresholds up to €80,000, sequential dabigatran was most cost-effective and above this value apixaban became the most cost-effective option. Sequential dabigatran was always the most cost-effective option for high-risk patients, she added.

Biosimilars

European law regarding biosimilars is short, simple, flexible and pragmatic. By contrast, US law is complex and detailed and has probably delayed approvals of biosimilar medicines there, explained Sandy Eisen (Chief Medical Officer, Frontline Consulting, UK) speaking at a satellite meeting sponsored by Sandoz.

The first biosimilars were recombinant growth hormones and these were approved in 2006. A steady stream of products has followed, culminating in the recent approval of the biosimilar infliximab. Some products have been marketed under several names, for example, biosimilar filgrastim was marketed by four different companies but there was only one underlying product, he noted. More recently, two biosimilar infliximab products have followed parallel marketing pathways. Dr Eisen also pointed out that two products that are technically biosimilars – a prolonged release growth hormone and a long-acting filgrastim – have not been approved as such because the manufacturers legitimately chose a different regulatory pathway. However, there are also many biosimilar products that have failed to reach the market – either because they received negative opinions from the EMA or were withdrawn. The failure rate is similar to that for new chemical entities, he added.

The extrapolation of indications (from the originator product to biosimilar) has major indications for product marketing. For biosimilar products it is possible to gain approval for all the indications of the innovator product without performing studies in all of them. Clearly, this depends on a proper understanding of the mechanism of action of the drug and it assumes that the same mechanism operates in all indications. Extrapolation can be more challenging for monoclonal antibodies, especially if, for example, a product is licensed for immune disease and cancer treatment, there may be less certainty that the same mechanism of action applies in both indications, acknowledged Dr Eisen. Looking forward,

Marianne Klemp

Sandy Eisen

it cannot be assumed that all biosimilars will always have all indications extrapolated, he added.

Dr Eisen concluded that the current EU biosimilars guideline is a sensible, thorough process that works well. In fact, the EU system has set a standard that is increasingly being adopted worldwide.

"Many doctors think they know about biosimilars but often they have no clue," said Arnold Vulto (Professor of Hospital Pharmacy and Practical Therapeutics, Erasmus University, Rotterdam, The Netherlands). Pharmacists have to educate doctors about biosimilars, he continued

The pharmaceutical industry is working on five main drugs, namely adalimumab, etanercept, infliximab, rituximab and trastuzumab. Professor Vulto predicted that there would be fierce competition in this field and that it would fall to pharmacists to guide decisions on which products to use. In the process they will have to educate doctors about biosimilarity. This will be challenging because doctors do not like uncertainty and the world of biosimilars is full of uncertainty. When a new (chemical) drug product is launched the innovator always promises doctors a solution to a problem and therefore prescribers are willing to accept more risk. The situation is different with biosimilars because they can only promise to do the same as the innovator products, providing little incentive to alter prescribing. Moreover, some companies have sown the seeds of doubt in doctors' minds about the safety of biosimilar products. There is a need to build trust in biosimilar drugs and reduce the information gap, said Professor Vulto. He criticised the regulators for remaining silent on this topic until recently – they could have said publicly that over the past six years there has not been a single serious incident with biosimilars – and this would have done much to allay fears, he argued. He praised the EMA booklet published in April 2013 that sets out balanced information including the fact that reduced costs mean that more patients can be treated.

In order to educate doctors it is necessary to understand how they think. In general they use five basic criteria but these do not always play well with biosimilars, he explained. The first is 'relative advantage' or the extent to which the new drug is better than its predecessors; however, biosimilars are, by definition, 'more of the same'.

'Compatibility' is the extent to which an innovation is seen as being consistent with the company's existing values, past experiences and needs of potential adopters.

'Complexity' is the extent to which a drug is perceived to be difficult to use. If a drug appears to be complex to understand and use there may be little incentive to use it. 'Trialability' is critical: "for 50 years we have been telling doctors that the double-blind, randomised, controlled trial is the gold standard," but the issue here is not to demonstrate superiority but similarity and such trials are "absolutely useless to show similarity," said Professor Vulto. The final criterion is 'observability,' that is, the extent to which the results can be seen in practice. For biosimilars this is limited because there is relatively little experience of their use so far. Thus, the problem with biosimilars is that the knowledge base appears small to doctors because they do not understand the huge laboratory task that has been undertaken in establishing similarity.

Ultimately, the incentive for a physician to prescribe a new drug is the result of a balance between his or her affinity with the existing drug and the attractiveness of the alternative, but without a strong incentive doctors will not change their current

practice, said Professor Vulto. All stakeholders need to be convinced about the value of biosimilars, including doctors, policy makers, insurance companies and the general public, he concluded.

Problems in practice

Martin Hug (Director of Pharmacy, University Hospital, Freiburg, Germany) highlighted a number of problems that beset the use of biosimilars in hospital practice.

Although at first sight the prescribing of monoclonal antibodies is straightforward, it turns out to be somewhat problematic in practice. Dr Hug noted that the Association of the British Pharmaceutical Industry (ABPI) recommends that all biological products should be prescribed by brand name to avoid confusion. This is in line with the EU Directive that requires authorities to ensure that all biological products prescribed or supplied should be clearly identified, he added. In his own hospital, prescriptions were written by hand until recently and doctors used brand names. When electronic prescribing was introduced he was dismayed to discover that all prescribing was by INN. In order to find out which product the pharmacy should supply the software will need to be modified, he said.

Some 55,000 individual doses of injectable medicines are prepared each year in Dr Hug's pharmacy and the number of monoclonal antibodies is steadily increasing. This could reflect the expansion in the numbers of monoclonal antibodies on the market but over the period that products have increased fivefold, there has been a 15-fold increase in the hospital usage. This prompted questions about how the products were being used.

Two biosimilar infliximab products were recently launched in Europe and so it was logical to discuss with prescribers the possibility of using them. The discussions revealed that the most common indication for infliximab was sarcoidosis, which is not a licensed indication. Dr Hug had expected to have discussions with rheumatologists and gastroenterologists (in line with the approved indications for the infliximab), but now finds himself having to ask pneumonologists if they would consider the off-label use of a biosimilar product. This is still an open question, he said.

Third-generation biosimilars are not so far away. A South Korean company has launched a biosimilar trastuzumab, which immediately precipitated a 30% fall in the price of the originator product.

Arnold Vulto

Martin Hug

Joaquin Borrás

"There is an immediate payback", commented Dr Hug.

The situation could become much more complicated when biosimilar rituximab is launched, predicted Dr Hug. One company is planning to launch a product that will be licensed for non-Hodgkins lymphoma and rheumatoid arthritis (RA). At the University Hospital of Freiburg, rituximab has already been used for more than 100 indications. Although licensed indications predominate, the others cannot be dismissed and the result is that many prescribers need to be involved in discussions about monoclonal antibodies, he emphasised.

Another matter is the conflicting data concerning stability of products. The big question for many pharmacists was whether stability data obtained on the reference product can be extrapolated to biosimilars. There are difficulties in performing stability studies with biosimilars, he noted.

Drug shortages have a significant impact on patient care. So far there have been no shortages with monoclonal antibodies but such a situation might arise in future with a biosimilar product and it raises many questions. Options could include switching to another biosimilar or discontinuing treatment, both of which carry risks.

Expenditure on monoclonal antibodies is rising rapidly. At the University Hospital of Freiburg it has nearly doubled in the past five years and now accounts for 25% of total drug budget. In Germany, hospitals have tackled the problem by increasing outpatient use because the costs of drugs are fully reimbursed in the outpatient setting but not in the inpatient situation. As this is paid for by the insurance companies, ultimately, they will decide what is used and where. For example, they may tackle this by implementing quotas, by saying that 30% of monoclonal antibodies must be biosimilars, he suggested. Ideally there should be a harmonised, Europe-wide approach to this difficult issue, he said.

Real-world costs

The real-world costs of biological drugs in clinical practice vastly differ from the theoretical or labelled costs. Joaquin Borrás (Pharmacy Services, Sagunto Hospital, Valencia, Spain) told the audience at a satellite session devoted to innovation and the hospital pharmacist, sponsored by Pfizer. Although on paper infliximab has the lowest annual cost for treatment for RA, because dose escalation is often required, a thorough analysis shows that etanercept is associated with the lowest treatment costs. In a further development, a protocol for rational use of biologic therapies has been developed. As all the biologic therapies are effective in RA it is important to have a prioritisation protocol to ensure that they are used in the most economical way, explained Dr Borrás. The protocol calls for etanercept as first-line treatment for all patients except those who have previously failed to respond to etanercept. Thereafter, the protocol defines a logical sequence of second- and third-line treatments. Implementation of the prioritisation protocol has resulted in savings of €200,000 over two years, said Dr Borrás. ●