Hospital pharmacists taking the lead

More than 3500 people from 73 countries gathered in Vienna for the 21st EAHP Congress. Key topics included advanced therapy medicinal products, interchangeability of biosimilars and new roles for pharmacy staff

Laurence Goldberg
Editorial Consultant, HPE

Christine Clark
Editor, HPE

At present, few pharmacists have experience of handling advanced therapy medicinal products (ATMPs), such as tissue-engineered products, but the field is likely to grow and it presents special challenges for pharmacists, according to Lenka Taylor (Head of Clinical Trials, Pharmacy Department, University Hospital, Heidelberg).

ATMPs comprise a diverse collection of products. An ATMP can be:

- A gene therapy medicinal product. An example is a virus-derived protein vector for treatment for lipoprotein lipase deficiency.
- A somatic cell therapy medicinal product. An example is autologous peripheral blood mononuclear cells for treatment of prostate cancer. (This product was approved by the EMA but later withdrawn for commercial reasons)
- A tissue engineered product (TEP). An example is a limbal stem cell transplant using cells collected from the patient's good cornea, for the treatment of limbal stem cell deficiency, a condition that can cause blindness.

ATMPs are governed not only by medicines' regulations but also by a number of other EU instruments covering tissue cells and viability, blood products and genetically-modified organisms, explained Dr Taylor.

Two products are currently approved and marketed in Europe but some 650 trials of advanced therapy investigational products (ATIMPs) have been registered in Europe. Of these, 187 involve TEPs, 160 gene therapy products and 307 somatic cell products.

Pharmacists are most likely to encounter ATMPs in the clinical trial setting. Some unlicensed products will also be used for patients with special needs, according to Anne Black (Assistant Director of Pharmacy – QA, Newcastle-on-Tyne Hospitals NHS Foundation Trust, UK). "It is a largely uncomfortable area for pharmacists, at first sight, however, ATMPs are often injectable and they are medicines and so pharmacists need to understand how to handle them safely", she said.

When ATIMPs are made off-site, they are often stored in liquid nitrogen or a –150° freezer and have to be defrosted before administration. These products commonly have to be prepared in clinical areas for immediate administration and there is no time to prepare them in an aseptic facility. It is quite possible that the whole process – manufacture, release, transportation and administration – takes place within 24 hours and so hospital procedures need to be established to make this possible, explained Mrs Black. "ATMPs are medicines but because they have not necessarily come through the conventional medicines route pharmacists might not know about them", she emphasised.

> "It is a largely uncomfortable area for pharmacists; however, ATMPs are often injectable and they are medicines, and so pharmacists need to understand how to handle them safely"

Interchangeability of biosimilars

Monoclonal antibodies are huge molecules made by cell culture techniques – they are always heterogeneous mixtures and, theoretically, there could be more than 100 million variants of the same molecule in the final product, Paul Declerk (Professor of Pharmaceutical Biotechnology, University of Leuven, Belgium) told the audience. The final mix depends on the processes for synthesis and purification but can often contain 10–20 different variants, he continued. Different mixes can have differences in biological activity and immunogenicity.

A biosimilar is a version of the original, authorised product. It is similar in quality, biological activity, safety and efficacy. There can be differences that do not affect clinical activity or safety and these are all described in the European public assessment report (EPAR) that is published at the time of approval. Thus, authorisation does not imply interchangeability and, furthermore, there can be divergence of products over time, said Professor Declerk. Another important point is that two or more

biosimilars for the same reference product have not been compared to each other and are not interchangeable.

Norwegian experience

Against this technical background, hospital pharmacists need to look for the best market opportunities when selecting products for local formularies, explained Arnold Vulto (Professor of Hospital Pharmacy and Practical Therapeutics, Erasmus University Medical Centre, Rotterdam, The Netherlands). So far, the uptake of biosimilar products varies widely across Europe. In Norway, infliximab was introduced in 2014 with 39% discount, increasing to 69% in 2016. Uptake is now 80% and savings are now estimated to amount to €6000 per patient, per year. Several factors contributed to this success. An advisory board helped with the pre-tender conditions and the drug was only given to new patients. In addition, the savings resulting from use of the biosimilar were re-invested in trials to answer key questions in this field and were not just lost in the system, he said.

Eleven more biosimilars are now in development but there are many uncertainties for prescribers. Third-generation therapeutic proteins, such as the biological drug, trastuzumab, exert effects over periods of years rather than hours. Trastuzumab treatment is associated with a 20% chance of improved survival (from breast cancer) over five years. “So we need a lot more trust in the similarity principle before we can accept a product”, said Professor Vulto. Biosimilars offer no clear advantage for doctors but only for the healthcare system and so there is an information gap. Although all the information is available in the EPAR at the time of authorisation, these documents are not easy to read or interpret, he added. However, biologicals appear to be remarkably safe – the assessment system has worked well – over ten years there has not been one serious untoward incident, he emphasised.

Some biologicals are highly immunogenic (for example, infliximab and rituximab) and biosimilar versions could be more immunogenic than the innovator products. This may be less of a problem with drugs of low immunogenicity (for example, etanercept).

> "Once a biosimilar is licensed, it is interchangeable at a population level.This means it can be given to new patients – switching existing patients is a different matter"

Once a biosimilar is licensed, it is interchangeable at a population level. In practice, this means it can be given to new patients – switching existing patients is a different matter, said Professor Vulto. “Be cautious about switching in the first year of treatment – and measure anti-drug antibodies before switching, otherwise, if the patient already has antibodies and suffers a reaction, the biosimilar and the tendering process will be blamed”, he cautioned.

Responsible use of biosimilars involves keeping a registry of use, something that has been an EU requirement since 2010, although not always observed. All stakeholders need more education in this field – including doctors, pharmacists, policy-makers, governments, and especially patients. Hospital pharmacists should play a key role in this process, he concluded.

Biosimilars improve access

The use of biosimilars can make available treatments otherwise thought to be unaffordable, Paul Cornes (Consultant Oncologist, Bristol Haematology & Oncology Centre, UK) told the audience. On occasions, the introduction of biosimilars can even and reverse negative funding decisions, he continued.

Prescribers need to be confident that switching from an originator product to a biosimilar does not lead to disproportionate risks. The most likely problem is differences in immunogenicity and this is closely regulated both when biosimilars are launched and when manufacturing changes are made. Theoretically, therefore, the risk of this is low, said Dr Cornes. In practice, there have been millions of patient-years of experience with biosimilar HGH, EPO and GCSF and “enhanced immunogenicity has yet to be seen”, he said. The critical question is whether the theoretical risks [with biosimilar monoclonal antibodies] are proportional to the risks that are already accepted with these products. Moreover, in spite of numerous manufacturing changes, only one problem has occurred – red cell aplasia with EPO. From the payers’ perspective, the risk of switching to

biosimilars is acceptable and less than the risk of not providing treatment. However, doctors still struggle to understand biosimilars and Dr Cornes called on pharmacists to use their expertise to provide education and information in this area.

CSTD leads to savings

Degradation of monoclonal antibodies can involve denaturation, fragmentation or aggregation of the proteins resulting in loss of effect or increased immunogenicity Rigorous testing of the physico-chemical, biological and microbiological stability of reconstituted trastuzumab in a closed system transfer device (CSTD) (Tevadaptor) has shown that the product retains its integrity for 28 days. This could reduce the need to discard reconstituted drug and allow for more economical use, according to Alan Wilkinson (Director, Biopharma Stability Testing Laboratory Ltd, Nottingham, UK). These data are not transferable to other CSTDs because of potential differences in leachable components.

An economic analysis conducted in Hungary has estimated that a saving of €26,600 over a period of three months was possible when residual biological drugs, reconstituted using a Tevadaptor, were used over 14 days instead of being discarded.

New and emerging roles

New roles for pharmacy staff are already having a considerable impact on effectiveness and efficiency in healthcare. 'Doctor-light' discharge is the latest in a long line of groundbreaking initiatives in Northern Ireland, according to Michael Scott (Director, Medicines Optimisation Innovation Centre, Antrim, Northern Ireland). "Pharmacists always write the discharge medication prescription but we are now piloting a scheme in which pharmacists write the two-line clinical summary as well", he explained. This initiative is strongly supported by the Chief Executive, who is a doctor, he added.

Over the past 15 years, a range of new roles for pharmacy staff has been developed in Northern Ireland on the basis of systematic research and development initiatives. One example is a consultant pharmacist post in intermediate care, primarily for care of the elderly. This has improved medicines management and reduced the hospital admission rate as a result. The estimated return on investment is a factor of 2.35–4, said Professor Scott. This has been so successful that it is to be rolled out across Northern Ireland. A consultant pharmacist post in nursing homes has been similarly successful, delivering a return on investment factor of about 3.

Other developments include a medicines management clinic, led by a specialist pharmacist, to which patients with medication problems are referred by consultants and a post-discharge medicines follow-up service that has reduced readmissions from 70% to 19%.

Future plans include case management in domiciliary care and acute care at home – initiatives designed to replicate the benefits seen in intermediate and nursing home care, said Professor Scott.

The developments make extensive use of technology; for example, medicines reconciliation is now carried out seven days a week and is supported by software that enables a discharge summary to go directly to GPs and be imported into their computer systems. However, the achievements are attributable to "90% system, 10% technology" according to Professor Scott.

> "Teamwork, human factors and situational awareness were key ingredients for success. Staff now use a checklist and emphasise the importance of preparation in advance"

EasyJet example for IV dosing technicians

Pharmacy technicians are now involved in preparation and administration of IV doses at ward level (at Birmingham Children's Hospital), according to Marie Slimm (Chief Pharmacy Technician, Birmingham Children's Hospital, UK). Nurses always administer the drugs but technicians check calculations and allergy status, prepare drugs, check pump rate, etc. Technicians go to the ward to cover the busiest rounds. Four technicians have now been trained for this role.

Teamwork, human factors and situational awareness were key ingredients for success. Two staff spent a day at EasyJet to see how these things are put into operation in commercial aviation. They now use a checklist and emphasise the importance of preparation in advance. As a result of the scheme there has been a significant reduction in the number of safety incidents reported and IV doses are given on time.

Information technology

A plethora of new gadgetry is already transforming healthcare, according to Katarzyna Wac (Associate Professor, University of Copenhagen and University of Geneva). Up until now we have practised "imprecision medicine" using population data rather than personalised data to determine treatment, she said. In future, precision medicine will be personalised, preventive, proactive and participatory. Key developments include rapid identification of genetic diseases, which account for 30% of premature deaths, and the use of a 'molecular stethoscope' for DNA profiling to identify likely responders to drug treatment and those at risk of adverse effects. Other developments will include wearable, point-of-care devices to monitor physiological functions. A device like a large wrist watch that can monitor blood gases and ECG is already available. The use of 'sticker-based' diagnostics is likely to increase, relying on devices that are "wearable, wireless, waterproof", she predicted.

Another development is the use of miniaturised in-body gadgets that will reduce the need for invasive tests. Examples include a miniature camera in a capsule that can be swallowed to perform a non-invasive colonoscopy. Other capsules have been developed that can perform intestinal gas measurements, ECGs and vital signs. In addition, greater use will be made of smart phones to monitor patients and transmit information. One innovative approach is the use of a smartphone to measure lung function by analysing breath patterns on the microphone. ●

The 21st European Association of Hospital Pharmacists Meeting was held in Vienna, Austria, in March 2016