UPDATE ON BIOSMILAR MEDICINES

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What is a
biosimilar medicine?

- ***A biosimilar medicine*** (biosimilar) is a biological medicine that is developed to be *highly similar* to an approved (reference) biological medicine

- A ***biological medicine*** (biologic) is one that contains one or more active substances made by, or derived from, a biological source*. Therefore “biologics” include the following:
  - vaccines
  - blood and blood components
  - recombinant therapeutic proteins
  - somatic cells, gene therapy products, tissues
  - Monoclonal antibodies

*animal-derived, human / blood-derived, recombinant proteins, monoclonal antibodies

Question..

Why do we need the term “biosimilar medicine”?

Is it not just a generic version of a biological medicine?

Answer..

It’s complicated….

Why?

Biologics are *large complex molecules*, with *inherent variability in their structure*, unlike classical small molecule (i.e. chemically-based) medicines

Differences between biologics and small molecule medicines

Parameter	Biologics	Small Molecule Medicines
Properties: • Size • Structure • Degradation • Variability	• Large • Complex • Complex mechanism(s) • Heterogeneous product	• Small • Simple • Precise and known • Single, defined structure
Manufacturing	Unique bank of living cells (unlikely to achieve identical copy) →	Predictable chemical and reagent reaction (identical copy can be made)
Characterisation	Difficult to fully characterise	Easy to fully characterise
Stability	More sensitive to storage and handling conditions	Less sensitive to storage and handling conditions
Immunogenicity	Higher potential	Lower potential

Therefore

In the manufacturing of a biological agent

- Usually many complex steps
- For the more complex biologics, the 3-D structure is vital for their activity
- Micro-heterogeneity / batch-to-batch variation

It is said of biologics that "***the process is the product***"

Back to Biosimilars..

- A biosimilar is not assumed to be identical to the reference biologic due to
  - the inherent variability in the manufacturing of biologics
  - the complexity of making an exact copy

- A biosimilar is required to show *comparative quality, safety and efficacy* (with respect to the reference biologic). In particular, a candidate biosimilar
  - must establish similarity to the *key characteristics of the molecular and biological activity of the reference product* and
  - will be expected to have *similar clinical outcomes* in terms of safety and efficacy (extrapolation of indications on a case-by-case basis)
  - [the immunogenic potential of each candidate biosimilar must be evaluated]

Post-approval, all biosimilars are subject to ▼ safety monitoring in EU

What are the practical implications of using biosimilars?

Questions include

1. How many biosimilars are available for use?

2. Why use a biosimilar?

3. How can / may they be used in practice?

List of biologics for which biosimilar(s) have been approved for use in the EU

Active Ingredient [Reference Biologic]	Therapeutic area	Biosimilar available in Ireland*
Somatropin** [Genotropin®]	**Growth hormone deficiency conditions**	**Yes**
Epoetin** [Eprex®]	**Symptomatic anaemia associated with specified medical conditions**	**Yes**
Filgrastim** [Neupogen®]	**Neutropenia associated with cancer therapy / specified medical conditions**	**Yes**
Follitropin alfa** [Gonal-F®]	**Infertility conditions**	**Yes**
Infliximab** [Remicade®]	**Arthritides, inflammatory bowel disease, psoriasis**	**Yes** [Remsima®; Inflectra®]
Etanercept** [Enbrel®]	**Arthritides, psoriasis**	**Authorised on 14th January 2016** [Benepali®]
Insulin glargine [Lantus®]	**Diabetes Mellitus**	**Yes** [Abasaglar®]

*more than one biosimilar may be available; **under specialist physician prescription and monitoring.
Exact indications approved for each individual medicine are listed in its Summary of Product Characteristics

2. Why use a biosimilar?

Possible advantages of using biosimilars?

They have shown *comparable quality, efficacy and safety* with respect to the reference biologic (*always* check the relevant SmPCs for approved indications)

They should be *less costly* than the reference biologic (but manufacturing costs may still be high)

How can / may biosimilars be used in practice?

Are there guidelines / rules relating to their usage?

In Ireland….

- *The Health (Pricing and Supply of Medical Goods) Act 2013* in Ireland specifically excludes biological medicines (including biosimilars) from being added to the "*list of interchangeable medicinal products*"

- [All biosimilars are subject to a review by the National Centre for Pharmacoeconomics, in order to evaluate its potential cost-effectiveness within the Irish healthcare setting].

Other guidance documents?

"The decision on whether to substitute a biological medicinal product lies outside the remit of the EMA/CHMP and is the responsibility of the relevant competent authorities within each EU Member State…

Differences across EU wrt national healthcare systems, structures and processes impact biosimilar medicines' uptake. Such differences may be any or all of the following:

- Physician perception of biosimilar medicines
- Patient acceptance of biosimilar medicines
- Local pricing and reimbursement regulation
- Procurement policies and terms"

What you need to know about Biosimilar Medicinal Products
Consensus Information Paper, European Commission, 2013

Potential Uses in Clinical Practice

Scenario 1:

Previously untreated patient…

Patient is suitable for biosimilar therapy (in agreement with prescriber and patient)

Note:

Prescribing by "*brand*" name is recommended to prevent future inadvertent switching to another "*brand*" (and for safety monitoring)

Potential Uses in Clinical Practice

Scenario 2:

Patient is already receiving treatment with reference biologic / specific branded biosimilar

Recommendation is that patient remains on his/her current “brand” as switching back and forth between “brands” is not recommended

Note:

Prescribing by “brand” name is recommended to prevent future inadvertent switching to another “brand” (and for safety monitoring)

Potential Uses in Clinical Practice

Scenario 3:

Ongoing treatment with reference biologic where patient requests change / physician considers change to use of biosimilar

Final decision rests with the prescribing physician and patient, following full evaluation of the individual case and all available information

Note:

If a decision is made to change the prescribed brand, *the dispensing pharmacist should be alerted to this change* to prevent future inadvertent switching to another brand* (and for safety monitoring)

Summary

- It is likely that increasing numbers of biosimilars will be available over the next few years, for the management of diseases such as certain cancers, autoimmune diseases e.g.
  - recombinant proteins
  - monoclonal antibodies

- The availability of *less-costly* biosimilar medicines enhances competition, with the potential to improve patient access to biological medicines

- Usage of biosimilars is under review by expert groups….

Summary

[There is] “a real potential for biosimilars to revolutionize biologic therapy by increasing access to a wider patient population across disciplines, but only with appropriate implementation of post-marketing strategies to monitor risk-benefit profiles over the long term”

Brown J et al, Biosimilars: A Multidisciplinary Perspective.
Clinical Therapeutics, 2016 *in press*

Summary of clinical use scenarios

Clinical Scenario	Suitability for biosimilar	Comments
Previously untreated patient	Patient is suitable for biosimilar therapy (in agreement with prescriber and patient)	Prescribing by brand name is recommended to prevent future inadvertent switching to another brand* (and for safety monitoring)
Ongoing treatment with reference biologic / specific branded biosimilar	It is recommended that patient remains on his/her current brand* as switching back and forth between brands* is not recommended	Prescribing by brand name is recommended to prevent inadvertent switching to another brand* (and for safety monitoring)
Ongoing treatment with reference biologic where patient requests change / physician considers change to use of biosimilar	Final decision rests with the prescribing physician and patient, following full evaluation of the individual case and all available information	If a decision is made to change the prescribed brand, the dispensing pharmacist should be alerted to this change to prevent future inadvertent switching to another brand* (and for safety monitoring)

Useful References

Guide to Biosimilars for Healthcare Professionals and Patients. Health Products Regulatory Authority. 14 October 2015 (AUT-GO141-1). Available online at www.hpra.ie

What you need to know about biosimilar medicinal products (consensus information document) EU Commission. Available online at: http://ec.europa.eu/DocsRoom/documents/8242. (Accessed 5th May 2016)

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