Biosimilars – an update

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Context

• Biologic drugs alter physiological processes as either
  • Antagonists (eg. monoclonal antibodies against interleukins, TNF, CD20), or
  • Agonists (eg. erythropoeitin, growth hormone, G-CSF)

• They are an exciting development in medicine

• Revolutionised the treatment of many conditions:
  • Diabetes
  • Renal anaemia
  • Autoimmune inflammatory disease
  • Oncology and haematology
  • Many others
However, they are costly

Biologics are 6 of the top 10 drugs by cost to government (PBS)
Top 10 drugs by cost to government

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost to government (A$)</th>
<th>DDD/1000 pop/day</th>
<th>Prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ledipasvir and sofosbuvir</td>
<td>570 730 056</td>
<td>†</td>
<td>25 205</td>
</tr>
<tr>
<td>2. sofosbuvir</td>
<td>372 094 623</td>
<td>0.14</td>
<td>18 738</td>
</tr>
<tr>
<td>3. adalimumab</td>
<td>335 857 859</td>
<td>0.62</td>
<td>194 405</td>
</tr>
<tr>
<td>4. ranibizumab</td>
<td>241 256 012</td>
<td>†</td>
<td>163 595</td>
</tr>
<tr>
<td>5. aflibercept</td>
<td>231 194 036</td>
<td>†</td>
<td>155 404</td>
</tr>
<tr>
<td>6. esomeprazole</td>
<td>170 554 177</td>
<td>23.18</td>
<td>6 889 031</td>
</tr>
<tr>
<td>7. etanercept</td>
<td>166 538 773</td>
<td>0.32</td>
<td>97 291</td>
</tr>
<tr>
<td>8. trastuzumab</td>
<td>157 134 211</td>
<td>†</td>
<td>50 217</td>
</tr>
<tr>
<td>9. fluticasone and salmeterol</td>
<td>148 878 399</td>
<td>†</td>
<td>3 003 985</td>
</tr>
<tr>
<td>10. insulin glargine</td>
<td>146 202 125</td>
<td>7.71</td>
<td>367 253</td>
</tr>
</tbody>
</table>

Patient numbers

- Quantifying the number of patients: incident (new) and prevalent (all)
  - For example new and all patients treated with a bDMARD market for psoriatic arthritis over time*

*Source: DUSC report of bDMARDs for psoriatic arthritis, October 2015.
Cost is also a necessary consideration of physicians.
What are biosimilars?

• Biologic drugs

• Produced by a different manufacturer to the originator drug

→ Although amino acid structure is identical, subtle changes in manufacturing processes may induce a significant change in the structure or product.
Structure of biologic drugs

• Biologic drugs have a complex structure
  • Manufactured in cell cultures
  • Partly or fully humanised
  • Amino acid sequence is known, but other modifications during manufacturing
    • Post-translational changes (eg. glycosylation) can changes the structure

• The manufacturing process determines the final product
  • Protein structure (folding) and function
  • Impurities.

• (Conventional drugs: the structure is clearly known)
Manufacture of biologic drugs

• Generally recombinant proteins isolated from & manufactured in living tissue.

Sources of errors in eukaryotic protein synthesis:
Manufacture of biologic drugs

- Generally recombinant proteins isolated from & manufactured in living tissue.

Sources of errors in eukaryotic protein synthesis:
“There are over 250 biosimilars being developed globally and medicines companies are looking locally to determine which countries to introduce them, how they will be introduced and what is the environment they will be entering.”

Mr Wes Cook, Chairman, Medicines Australia, 2016
It is anticipated that a large number of biosimilars will be marketed soon ...

https://en.wikipedia.org/wiki/Biosimilar
What’s all the controversy about biosimilars?

• From a clinical perspective: switching

• Concerns of immunogenicity and the *in vivo* development of antidrug antibodies which may
  • Inactivate the drug and its effect, or
  • Cross-react with the originator biologic drug, or
  • Induce a hypersensitivity response.

  →May have a detrimental effect on a patient who had achieved disease control

• Data are currently limited ...
Transitions between drugs

• Patient level analyses can be undertaken, using various methods, to examine switching, adding or ceasing medicines.
  - For example psoriatic arthritis patients issued a first Authority approval for a bDMARD prior to January 2014 were followed to June 2015 to assess patterns of bDMARD use*

<table>
<thead>
<tr>
<th>Adalimumab initiators</th>
<th>Patients (%)</th>
<th>Etanercept initiators</th>
<th>Patients (%)</th>
<th>Infliximab initiators</th>
<th>Patients (%)</th>
<th>Golimumab initiators</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA only</td>
<td>1623 (57%)</td>
<td>ETN only</td>
<td>762 (54%)</td>
<td>INF only</td>
<td>119 (46%)</td>
<td>GOL only</td>
<td>299 (56%)</td>
</tr>
<tr>
<td>ADA -&gt; ETN</td>
<td>480 (17%)</td>
<td>ETN -&gt; ADA</td>
<td>333 (24%)</td>
<td>INF -&gt; ADA</td>
<td>45 (18%)</td>
<td>GOL -&gt; ADA</td>
<td>91 (17%)</td>
</tr>
<tr>
<td>ADA -&gt; INF</td>
<td>73 (3%)</td>
<td>ETN -&gt; INF</td>
<td>26 (2%)</td>
<td>INF -&gt; ETN</td>
<td>17 (7%)</td>
<td>GOL -&gt; ETN</td>
<td>67 (13%)</td>
</tr>
<tr>
<td>ADA -&gt; GOL</td>
<td>187 (7%)</td>
<td>ETN -&gt; GOL</td>
<td>81 (6%)</td>
<td>INF -&gt; GOL</td>
<td>19 (7%)</td>
<td>GOL -&gt; INF</td>
<td>&lt; 5 (1%)</td>
</tr>
<tr>
<td>ADA -&gt; CZP</td>
<td>&lt; 5 (0%)</td>
<td>ETN -&gt; 2 bDMARDs</td>
<td>158 (11%)</td>
<td>INF -&gt; CZP</td>
<td>&lt; 5 (0%)</td>
<td>GOL -&gt; 2 bDMARDs</td>
<td>56 (11%)</td>
</tr>
<tr>
<td>ADA -&gt; 2 bDMARDs</td>
<td>368 (13%)</td>
<td>ETN -&gt; 3 or more bDMARD</td>
<td>43 (3%)</td>
<td>INF -&gt; 2 more bDMARD</td>
<td>38 (15%)</td>
<td>GOL -&gt; 3 or more bDMARD</td>
<td>14 (3%)</td>
</tr>
<tr>
<td>ADA -&gt; 3 or more bDMARDs</td>
<td>96 (3%)</td>
<td>-</td>
<td>-</td>
<td>INF -&gt; 3 or more bDMARD</td>
<td>17 (7%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>2829 Total</td>
<td>1403 Total</td>
<td>256 Total</td>
<td>531</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Transitions (single or multiple) between reference and biosimilars could also be incorporated into these types of analyses.

*Source: DUSC report on bDMARDs in psoriatic arthritis, October 2015.
What clinical data are available for biosimilars?

• Multiple pharmacokinetic studies confirm similarity
  • Publication bias of quality studies and products?

• A handful showing effect of a single one-way switch
  • Efficacy, safety, development of anti-drug antibodies

• Duration of clinical studies generally <2 years, or shorter

• Comparator studies may not have been performed in all indications
  • Is extrapolation reasonable?
There is precedent for concern ... (1)

- Pure red cell aplasia from a particular brand of EPO-alpha
  - Due to anti-EPO antibodies (target endogenous and exogenous EPO)
  - Developed after 1-2 years of treatment

- Occurred after a change in formulation in 1998
  - Removal of albumin, use of alternative stabiliser, change in rubber plug
  - Only following subcutaneous administration
  - Possible impact of storage and handling

- Mainly affected countries outside of US
  - Europe, including ANZ

- Mechanism?
  - Reason for the break in B-cell tolerance still uncertain
But there is precedent ... (2)

- Similar issues with a bio-copy EPO in Thailand 2011
  - Regulatory standards considered very different to those elsewhere for biosimilars

(Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies)

(Kidney International (2011) 80, 88–92; doi:10.1038/ki.2011.68)
Regulatory perspective on biosimilars

Multiple regulatory agencies (FDA, EMA, TGA) have considered the implications of these concerns and developed guidance documents.
Any lessons learnt from the originator products?

BRIEF REPORT

**Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents**

Balázs Vezér, Zsuzsanna Buzás, Miklós Sebeszta and Zsombor Zrubka
Apples and pears?

“Entries for 29 mAbs with publicly available EPAR reports ... contained details of 404 manufacturing changes authorized by the EMA: 22 were categorized as high risk, 286 as moderate risk and 96 as low risk manufacturing changes. A limitation of this analysis is that it only summarizes publicly available data from EPAR documents.”


Perhaps the current “originator” products are effectively biosimilars of the actual originators?
Seemingly minor differences can lead to products with different characteristics.

- **SEBs are similar...**
  - "Burgundian" Earthy

- **But not identical...**
  - "Californian" Fruity

**Pinot Noir**

- Burgundy, France
  - Temperate climate
  - Frequent rainfall
  - Intermittent sunshine

- Santa Ynez, California
  - Hot
  - Rare rainfall
  - Constant sunshine

Karin A Burke, AMGEN, 2015
Relevance to ANZ

• This discussion gained momentum in Australia and New Zealand with the availability of biosimilar infliximab.
  
  • New Zealand: following a tender process the originator product retained its role following a price reduction.

• Australia, PBS:
  • biosimilar infliximab introduced Dec 2015 and classified as an ‘a-flag’ drug – it is interchangeable with the originator product
  • Biosimilar etanercept introduced Feb 2017
  • (insulin glargine approved 2015 – not marketed)
Who are the decision-makers?
Who is interested?

- Health departments
  - Australian government – PBAC
  - State Health Departments
  - NZ

- Hospital drug and therapeutic committees
  - CATAG document to support decision-making

- Prescribers

- Patients

- Pharmacists
Concerns raised

8 September 2015
The Hon Sussan Ley, MP
Minister for Health
PO Box 6022
House of Representatives
Parliament House
Canberra ACT 2600

Dear Minister

We are writing to express our ongoing concerns regarding ‘a’ flagging of biosimilars following the PBAC’s recommendation to ‘a’ flag the Inflectra and Remicade brands of infliximab (an anti-TNF inhibitor) on
Australian Government broadened consultation

And established the Biosimilar Awareness Initiative
Core themes

- Improving the evidence base
- Optimising data capture
- Pharmacovigilance and naming conventions
- Building stakeholder confidence and shared decision-making through high quality information

- Forum held in Sydney on 23 June 2016
- 80 attendees
- RACP was on the organising committee
What data are required to inform switching?

| What information/support is needed                | - Details on previous use and whether switching has occurred previously  
|                                               | - Data on multiple switching – is it an issue?  
|                                               | - Data on one-way switching  
|                                               | - Data on staying with the same product – biologic, biosimilar  
|                                               | - Real world data on switching – prescriber, pharmacy  
|                                               | - Inadvertent v deliberate  
| What already exists?                            | - CATAG Guiding principles (currently under revision)*
|                                               | - Current international studies*  
| Where are the gaps?                            | - Clinician acceptable outcome data – numbers vs quality of life  
|                                               | - Patient understanding about switching  
|                                               | - Understanding patient outcomes from switching  
|                                               |   - How easy it is to measure outcomes  
|                                               |   - What is the disease variability  
|                                               |   - What patient characteristics can be quantified  
|                                               | - Methods to assess whether switching has happened  

Q2: What are the gaps and what can be improved?

Specific information required to help guide shared decision making

- Prospective data
- Retrospective data
- Real world data
- Is it safe and effective?
- Immunogenicity
- Duration
- Interchangability (multiple switching)

- Ability to link data between multiple groups
- Nationally consistent system at point of care
- Systematic approach, united with pharmacy
- Utilising eHealth records/software
- Registries (incl. funding for these)

Evidence base

Data collection & linking

- Paediatric regulatory standards/evaluation
- Hospitals
- No nationally consistent framework for hospital medicines decision making
- Management of off-label use

- Visibility and understanding of risk management plans
- PV should be monitoring and evaluating outcomes
- Follow-up and continuity of care for patients

Other settings

Patient outcomes

Better awareness and understanding of the unique nature of biologics and biosimilars, taking into consideration the health literacy of the audience, to better inform decision making
### Data sources, insights gained & role of clinicians

<table>
<thead>
<tr>
<th>First steps</th>
<th>Stakeholders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Randomised controlled trials (pre-market authorisation)</strong></td>
<td>Industry, clinicians, researchers</td>
</tr>
<tr>
<td>- Interchangeability</td>
<td></td>
</tr>
<tr>
<td>- How many switches</td>
<td></td>
</tr>
<tr>
<td>- Immunogenicity</td>
<td></td>
</tr>
<tr>
<td><strong>2. Naturalistic design studies</strong></td>
<td>Clinicians, researchers, professional bodies</td>
</tr>
<tr>
<td>- To provide a guide for use in practice</td>
<td></td>
</tr>
<tr>
<td>- Case definition – clinical, interventional</td>
<td></td>
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<tr>
<td><strong>3. Retrospective</strong></td>
<td>Government, pharmacy, clinicians</td>
</tr>
<tr>
<td>- Analysis of PBS use, dispensing frequency and switching (AE incidence)</td>
<td></td>
</tr>
<tr>
<td>- Laboratory to explore case definition</td>
<td></td>
</tr>
<tr>
<td>- Database of Adverse Event Notifications – clarify clinical options</td>
<td></td>
</tr>
</tbody>
</table>

### Priority 2 – Improved data collection and linking

<table>
<thead>
<tr>
<th>First steps</th>
<th>Stakeholders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Routinely collected data – “big data” including:</strong></td>
<td>Government, clinicians, professional bodies</td>
</tr>
<tr>
<td>- Individual patient level data</td>
<td></td>
</tr>
<tr>
<td>- Better collated /organised at national level</td>
<td></td>
</tr>
<tr>
<td>- Used to inform future clinical decisions</td>
<td></td>
</tr>
<tr>
<td><strong>Improving approach to detection, recording and analysis of</strong></td>
<td>Government, clinicians, professional bodies</td>
</tr>
<tr>
<td>suspected adverse drug reactions from the front line</td>
<td></td>
</tr>
<tr>
<td><strong>Medicine-focused outcome data (rather than disease-focused)</strong></td>
<td>Government, clinicians, professional bodies</td>
</tr>
<tr>
<td>- Links to PBS funding (initial and ongoing)</td>
<td></td>
</tr>
<tr>
<td>- Potential for eHealth record to address, if well designed</td>
<td></td>
</tr>
</tbody>
</table>
### Priority 3 – Improved patient outcomes

<table>
<thead>
<tr>
<th>First steps</th>
<th>Stakeholders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine what is a valuable response and what is an unacceptable adverse drug reaction</td>
<td>Government, universities, clinicians, community incl. patients, pharmaceutical companies with an interest</td>
</tr>
<tr>
<td>Early conditional registration/reimbursement based on QSE</td>
<td>Government, clinicians, community incl. patients, pharmaceutical companies</td>
</tr>
</tbody>
</table>
| Post-marketing, statistically reliable monitoring of efficacy and safety     | Pharmaceutical companies, government                                         

### Priority 4 – Improved health literacy

<table>
<thead>
<tr>
<th>First steps</th>
<th>Stakeholders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumer centered information about biosimilars</td>
<td>Patient groups, professional bodies</td>
</tr>
<tr>
<td>- Tailored to the information needs of the individual, their condition, the delivery route and mechanism of action</td>
<td></td>
</tr>
<tr>
<td>Empower clinicians to confidently have discussions with their patients about biosimilars</td>
<td>Professional bodies, clinicians, patient organisations and government</td>
</tr>
<tr>
<td>- Creation of a reliable source of information online</td>
<td></td>
</tr>
<tr>
<td>- Develop discussion tools to support the conversation (e.g. pack of cards with key issues – what’s of concern to me)</td>
<td></td>
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</tbody>
</table>

*NB: Given the unique requirements necessary to address the current gaps and improvements required for the use of biologics and biosimilars in other settings/patient populations and in light of time restrictions for the workshop, this aspect was not addressed by the group.*
This discussion is well-timed ...

- Black Triangle Scheme for new and other medicines for which ADR data are needed
- Improvements to PI
- Enhanced pharmacovigilance
  - Patients
  - Health professionals
  - Industry
  - Other
Adverse reactions

- All very well to say that we need to improve pharmacovigilance, but this is a complex area ...

- Case ascertainment of treatment failure or other adverse reactions due to immunogenicity is complex. For example
  - Some diseases have a fluctuating course,
  - Intra- and inter-observer variability in assessing disease activity,
  - Relevance of anti-drug antibodies: Neutralising? Persistent?
  - Varying intra-patient pharmacokinetics,
  - Concomitant diseases and/or medications,
  - Batch-to-batch variation (?), and
  - Drug levels are not widely used or perhaps available.
Other experiences that may be relevant?

• The current definition of biosimilar limits other comparisons

• Other drugs have relatively small changes in structure
  • Insulins
  • Heparins
  • G-CSF
  • EPOs
  • (these are all much smaller in size cf than mAbs)

• Multiple switches not uncommon and immune responses not problematic
What seems to be true?

• This is a complex area with more questions than answers
  • Current experience somewhat reassuring?

• More data are needed. Activities:
  • Existing drug safety processes must be expanded
  • Case definition requires further discussion and debate
  • Role of expanded use of therapeutic drug monitoring (services and skills)

• Doctors who prescribe these medicines should be informed. They should communicate with their patients

• Implications for all health professionals, the industry and the government
What is the role of physicians?

- Ongoing recognition of our role in improving patient care
  - Optimising clinical outcomes
  - Supporting patients
  - Reducing overall drug costs

- Understand the issues, discuss them

- Contribute to evidence
  - Engage in discussions regarding case definition
  - Engage in therapeutic drug monitoring
  - Report suspected events

- Be alert, not alarmed
Thank you