The GPs role with biologics for immune-mediated inflammatory diseases

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Overview

- What are biologics?
- When and why are they used?
- The care of patient starting and using biologics
- Questions you may be asked by patients
What are biologics?

- Specific cell signalling pathways targeted
- Manufactured in a living system such as a microorganism, or plant or animal cells
- Very large, complex molecules or mixtures of molecules
- Produced using recombinant DNA technology

- Traditional drugs are small molecules and generally have well-defined chemical structures
Chemists can make exact generic copies of conventional pills. But, scientists making 'biosimilar' drugs are copying much more complex biotech drugs. A Rituxan molecule is about 120 times larger—in terms of molar mass—than the basic chemical unit of Lipitor, below.

A Lipitor molecule has a definite structure with 160 atoms.

A Rituxan molecule has a complex structure with thousands of atoms.

Images not to scale.

### Lipitor (Atorvastatin) vs. Rituxan (Rituximab)

<table>
<thead>
<tr>
<th>High cholesterol</th>
<th>Indications</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A handful of atoms, mostly carbon and hydrogen, combined in specific, replicable formula</td>
<td>Cancer, arthritis</td>
<td>Hundreds of amino acids bound together in a complex structure that scientists can't fully document</td>
</tr>
</tbody>
</table>

### Cost to Copy

<table>
<thead>
<tr>
<th>Less than $10 million</th>
<th>How It's Made</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemicals are mixed at subzero temperatures</td>
<td>Living cells with altered DNA produce the injectable drug</td>
</tr>
</tbody>
</table>

### A Biosimilar Recipe

1. Scientists copy key DNA sequences used to make branded drugs.
2. The strands are inserted into living cells.
3. The cells replicate and secrete antibodies in a bioreactor.
4. Antibodies to use in treatments are filtered out.

Sources: FDA; National Comprehensive Cancer Network; WSJ reporting

Graphic by Alberto Cervantes/The Wall Street Journal
Biologics in practice

- Most are monoclonal antibodies
- Directed against selected targets – TNF, IL-1, IL-6, IL-20, B and T cell surface markers
When are they used?

- Failure of standard DMARD therapy
- Side effects of traditional DMARDs
- Dermatology – psoriasis
- Gastroenterology – IBD
- Ophthalmology – uveitis/iritis
- Rheumatology – RA, psoriatic arthritis, ankylosing spondylitis, JIA
Who can start them?

- Initiated by specialist
- PHARMAC special authority criteria
- Review of special authority every 6 months
- Can be prescribed by any practitioner
Why are they used?

- Improve symptom burden
- Improve QOL
- Reduce long term effects of condition
- Reduce use of corticosteroids

Does having RA impact your ability to work?

- 66.1% Yes
- 26.7% No
- 7.2% No answer
How has your severe RA impacted your ability to work?

- I am tired at work. 90.5%
- Pain affects my ability to work. 85.7%
- Physical limitations affect my ability to work. 61.9%
- My family doesn’t understand. 17.5%
- Job-related travel is too difficult for me. 12.7%
- My colleagues are not understanding. 11.1%
- My direct supervisor is not understanding. 6.3%
- I am taking too many sick days. 25.4%
- It is difficult to get to/from work. 12.7%
- Other 9.5%

RA RheumatoidArthritis.net
What is your employment status?
(Participants with severe RA)

- Retired early or on disability: 36.7%
- Employed full time: 18.3%
- Other: 10.3%
- Full retirement: 7.8%
- Homemaker: 7.5%
- Unemployed (not looking): 6.4%
- Employed part time: 5.3%
- Self employed: 3.1%
- Unemployed (looking): 2.8%
- Full time student: 1.1%
- All other responses: 0.8%

RA RheumatoidArthritis.net
## PREMIER study

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Biologic</th>
<th>DMARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of job</td>
<td></td>
<td>13%</td>
<td>30%</td>
</tr>
<tr>
<td>Unable to work</td>
<td>45%</td>
<td>11%</td>
<td>17%</td>
</tr>
<tr>
<td>Difficulty at work</td>
<td>88%</td>
<td>15%</td>
<td>34%</td>
</tr>
<tr>
<td>Limitation climbing stairs</td>
<td>67%</td>
<td>12%</td>
<td>21%</td>
</tr>
<tr>
<td>Can not walk 1 block</td>
<td>45%</td>
<td>7%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Patient story

- 38 year old fireman
- Psoriatic arthritis
- Back pain, plantar fasciitis, metatarsalgia
- Failed methotrexate, leflunomide, salazopyrin as well as NSAID and prednisone
- On verge of losing his job
- Started anti-TNF
- No symptoms, working and playing sport
GP’s role

- Advocate for access to effective treatment
- Understand role of new agents
- Counsel patients on benefits and risks
- Facilitate safe initiation of treatment
- Reduce risk of complications once on new therapy
Contraindications

- Chronic or active infection
- Moderate to severe heart failure
- Malignancy in the past 5 years
- Personal or family history of demyelinating disease

Screening before starting biologics

- TB – QuantiFeron Gold +/- CXR
- HIV
- Hepatitis B and C

- Update immunisations – influenza, pneumovax, hep B
- Consider zoster vaccine
- Live vaccines contraindicated once on immune suppression

Injection site reactions

- Warm the pen
- Change the site regularly
- Ice pack to site after injection
- Topical steroid
- Antihistamine
- Avoid alcohol swab pre-injection
- Review injection technique
- Change to syringe rather than pen
Infection risk in immune diseases

- Relative risk approximately 2x general population
- Inherent risk from immune disease
- Affected by comorbidities
- Corticosteroids worst
- Infection rates increased in first 6 months of biologic therapy – especially respiratory


What to do when an infection occurs

- Withhold biologic
  - Lower threshold for investigation and treatment with antibiotics
  - Lack of signs and symptoms common
  - Increased rate of zoster and atypical infections
  - Contact specialist team
Other complications

- Psoriasis
- Drug induced lupus
- Non-melanoma skin cancers
- Treatment failure

BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies

http://rheumatology.oxfordjournals.org/content/suppl/2010/09/14/keq249a.DC1/keq249b.pdf
Blood tests

- Most patients still on traditional DMARDs e.g. methotrexate
- Monitor FBC, LFTs and CRP every 3 months
- Creatinine in patients with CKD or >60 years old
Perioperative care

- No consensus
- Withhold treatment 1-2 dose intervals before surgery
- Restart once wounds healed and no sign of infection
Pregnancy

- Plan pregnancy!
- Increasing evidence of safety
- No increased risk of birth defects
- Underlying condition and steroids can lead to premature labour

Anti-TNF-α therapies are safe during pregnancy in patients with inflammatory bowel disease: a meta-analysis

(See respective Data Sheets for more information)

HUMIRA (Category C)
There are no data from clinical trials for pregnant women being treated with Humira. Because animal studies are not always predictive of human responses, the use of Humira during pregnancy is not recommended. Women of child bearing potential should be advised to use adequate contraception during Humira therapy. The long half-life of Humira should also be considered when discontinuing therapy.

ENBREL (Category B2)
The safe use of etanercept during pregnancy has not been established. Therefore, ENBREL should be used during pregnancy only if clearly needed...There are, however, no studies in pregnant women.

REMICADE (Category C)
It is not known whether REMICADE can affect reproductive capacity or can cause foetal harm when administered to a pregnant woman. REMICADE should be given to a pregnant woman only if clearly needed...It is recommended that adequate contraceptive measures should be taken for at least 6 months after the last REMICADE treatment.
Storage/Travel

- Ideally keep at 2-8 °C
- Can be stored at room temperature for 14 days
- Do not recool
Summary

- Biologics are very effective treatments for immune mediated inflammatory conditions
- Injection site reactions and infection are most common side effects
- Plan immunisations prior to starting new treatment
- Withhold if serious infection present or surgery planned
- Increasing safety data in pregnancy and on travelling with medication
Resources

- **Biologic medicines for the treatment of inflammatory conditions: What does primary care need to know?**
  

- **Disease and Medication Information**
  

- **Arthritis New Zealand**
  
Questions