Patient and Public Involvement in Regulatory Decision-Making

Kimberley Hockley
Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium

The overall objective of PROTECT is to strengthen the monitoring of the benefit-risk of medicines.

Work Package 5:
• Develop methods for continuous benefit-risk monitoring of medicines, by integrating data on benefits and risks from clinical trials, observational studies and spontaneous reports
Patient and Public Involvement

Patient and public:
Clinical trial participants, patients and potential patients, disabled people, parents and guardians, people who use health and/or social care services, carers, members of the public, and the organisations who represent the interests of these consumers.

Involvement:
An active partnership between stakeholders in the research process, rather than the use of people as ‘subjects’ of research. Public involvement in research is often defined as doing research ‘with’ or ‘by’ the public, rather than ‘to’, ‘about’ or ‘for’ them.
“EBM is the conscientious explicit, and judicious use of current best evidence in making decisions about the care of individual patients” taking into account “individual patients predicaments, rights and preferences using best evidence from clinically relevant research.”

Sackett et al, 1996
The task of regulators (EMA, FDA etc) is to make good and defensible decisions regarding which medicines should receive a license for specific indications, based on the available evidence of risks and benefits.

It is increasingly important to be able to justify and explain these decisions to patients and other stakeholders.

Can more formal approaches of decision-making help regulators do this better?
Aim

To test and evaluate formal methods of decision-making that can be used to justify and explain regulatory decisions to patients and public.

Descriptive framework:
Pharmaceutical Research and Manufacturers of America (PhRMA) Benefit-Risk Action Team (BRAT) framework

Case study: Raptiva (efalizumab)
Divides decision making process in the following 6 steps:

1. Define decision context
2. Identify outcomes
3. Identify data sources
4. Customise framework
5. Assess outcome importance
6. Display & interpret key B-R metrics

Decision & communication of B-R assessment
## Step 1: Decision Context

<table>
<thead>
<tr>
<th>Indication</th>
<th>Raptiva is indicated in the treatment of “high need” adult patients with moderate to severe chronic plaque psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Raptiva (efalizumab) is a recombinant, humanized IgG1 monoclonal antibody that targets CD11a</td>
</tr>
<tr>
<td>Formulation/Dose</td>
<td>An initial single dose of 0.7 mg/kg body weight is given followed by weekly injections of 1.0 mg/kg body weight, subcutaneously</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
</tr>
<tr>
<td>Population</td>
<td>“High need” adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies</td>
</tr>
<tr>
<td>Time Frame for Outcomes</td>
<td>12 weeks for PASI 75 (efficacy/favourable effects), 3 years for PML</td>
</tr>
<tr>
<td>Perspective</td>
<td>Regulator (at EMA)</td>
</tr>
</tbody>
</table>
Step 2: Identify and select benefit and risk outcomes and associated measures

Benefits
- Favourable effects (i.e. efficacy)
  - PASI75
  - PGA
  - OIS
  - DLQI
  - PASI50

Benefit-Risk Balance

Risks
- Unfavourable effects (i.e. safety)
  - PML
  - ADR1
  - ADR2
  - Meningitis aseptic
  - Severe infections (including pneumonia, sepsis, cellulitis)
  - Severe thrombocytopenia
  - Opportunistic infections (including fungal infections, tuberculosis, herpes virus, EBV, CMV)
  - Immune haemolytic anemia
  - Psoriasis severe forms (i.e. erythrodermic, pustular)
  - Nervous System disorders (including inflammatory, polyarthritis, facial palsy, GBS, Fisher Miller)
  - Interstitial lung diseases (including lung infiltration, pulmonary fibrosis)
  - Serious cases of psoriasis (exacerbation or rebound)
### Step 3: Identify and extract data sources

<table>
<thead>
<tr>
<th>Measure</th>
<th>Source</th>
<th>Inclusion</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI75</td>
<td>Clinical trials</td>
<td>Yes</td>
<td>Complete data</td>
</tr>
<tr>
<td>PGA</td>
<td>Clinical trials</td>
<td>Yes</td>
<td>Complete data</td>
</tr>
<tr>
<td>OLS</td>
<td>Clinical trials</td>
<td>Yes</td>
<td>Complete data</td>
</tr>
<tr>
<td>DLQI</td>
<td>Clinical trials</td>
<td>No</td>
<td>Average and standard deviation missing</td>
</tr>
<tr>
<td>PASI 50</td>
<td>Clinical trials</td>
<td>Yes</td>
<td>Complete data</td>
</tr>
<tr>
<td>ADR1</td>
<td>ISS</td>
<td>Yes</td>
<td>Complete data</td>
</tr>
<tr>
<td>ADR2</td>
<td>ISS</td>
<td>No</td>
<td>Percentage of events in placebo group not given; percentage of events for Raptiva not precise (range given)</td>
</tr>
<tr>
<td>Meningitis aseptic</td>
<td>PSUR10</td>
<td>No</td>
<td>Background epidemiology not known</td>
</tr>
<tr>
<td>Serious infections including pneumonia, sepsis, cellulitis</td>
<td>ISS</td>
<td>Yes</td>
<td>Complete data</td>
</tr>
<tr>
<td>Opportunistic infections including fungal infections, tuberculosis, herpes virus infections, EBV, CMV</td>
<td>PSUR10</td>
<td>No</td>
<td>RMP only states background epidemiology of tuberculosis; background epidemiology of other conditions not known</td>
</tr>
</tbody>
</table>
Step 4: Customise framework

- Benefits
- Benefit-Risk Balance
- Risks

- Efficacy
  - PASI75
  - PASI 50
  - PGA
  - OLS

- Safety
  - PML
  - ADR1
  - Psoriasis severe forms
Step 5: Assess outcome importance

Outcomes are assessed for their importance to decision-makers and other stakeholders, and the subsequent rankings and weightings are applied to the tree.

BRAT framework does not advocate a specific method to weigh the preferences of outcomes in the value tree.

Use of multi-criteria decision analysis (MCDA)
### Key benefit-risk summary table

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Outcome</th>
<th>RAPTIVA Risk /1000 pts</th>
<th>Placebo Risk /1000 pts</th>
<th>Risk Difference (95% CI)/1000 pts</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>PASI75</td>
<td>280</td>
<td>36</td>
<td>244 (151, 362)</td>
<td>7.819 (4.999, 12.380)</td>
</tr>
<tr>
<td></td>
<td>PASI 50</td>
<td>567</td>
<td>200</td>
<td>360 (303, 431)</td>
<td>2.800 (2.210, 3.650)</td>
</tr>
<tr>
<td></td>
<td>PGA</td>
<td>305</td>
<td>52</td>
<td>251 (141, 396)</td>
<td>5.778 (3.602, 9.337)</td>
</tr>
<tr>
<td></td>
<td>OLS</td>
<td>292</td>
<td>37</td>
<td>254 (145, 392)</td>
<td>7.813 (4.731, 13.270)</td>
</tr>
</tbody>
</table>

| Risks    | PML           | 0                      | 0                      | 0 (0, 0)                          | 18.400 (5.400, 45.960) |
|          | ADR1          | 410                    | 240                    | 170 (130, 210)                    | 1.710 (1.510, 1.940)   |
|          | Psoriasis severe forms | 33  | 15        | 17 (6, 29) | 2.170 (1.270, 3.970) |

**Psoriasis severe forms**

Step 6: Display and interpret key benefit-risk metrics
Step 6: Display and interpret key benefit-risk metrics

Forest plot: Risk difference for key favorable and unfavorable effects (Raptiva compared to placebo)
Step 6: Display and interpret key benefit-risk metrics

Forest plot: Relative Risk for key favorable and unfavorable effects (Raptiva compared to placebo)
Discussion

• Easily communicable, highly transparent
  • Provides insight by providing a strong context to decision-making

• Framework can apply to any stage of a product lifecycle
  • I.e. early development to post-marketing
Discussion

- Various data sources of differing quality
  - Clinical trials
  - Epidemiological studies
  - Spontaneous reports

- Framework is only possible when data for a comparator such as placebo, background epidemiological rates, or active comparator is available
Further Work

From an ethical and moral perspective, the values and preferences of patients should be included in regulatory decision-making:

» Who can be involved?
» How can they be involved?

Methods of preference elicitation:

• Multi-criteria decision analysis
• Nominal group techniques
• Discrete choice experiments
Acknowledgements

Collaborators:
Diana Hughes (Pfizer), Alain Micaleff (MerckSerono) and the Raptiva Taskforce

Supervisors:
Prof. Deborah Ashby (Imperial), Sarah Meredith (MRC CTU), Prof. Peter Smith (Imperial)

PhD funding: MRC CTU

‘The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines. This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency.’

The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency.

The PROTECT project has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.
Questions