Benefit-risk assessment and communication: A case study of natalizumab and PML.

29th ICPE
26th August 2013
Montreal

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Disclosure

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 Medicines 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.

No relationships to disclose.
IMI- PROTECT Work Package 5
Benefit-risk integration and representation

Objectives:

- To assess and test methodologies for the benefit-risk assessment of medicines
- To develop tools for the visualisation of benefits and risks of medicinal products

⇒ Individual and population-based decision making
⇒ Perspectives of patients, healthcare prescribers, regulatory agencies and drug manufacturers
⇒ From post-approval through lifecycle of products
Disclaimers

“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.”
Recommendation Roadmap

Evidence gathering and data preparation

Analysis

Exploration

Conclusion and dissemination

Planning
**Stage 1: Planning**

- encourages stakeholders to focus on critical issues related to BR assessment
- encourages sufficient thinking and thorough discussions between stakeholders to clearly define the purpose and context of the BR assessment
- ensures clear detailed summary documentation of discussions and results
- allows future analyses and updates to utilise the same foundations
## Planning the Natalizumab Case Study

<table>
<thead>
<tr>
<th>PrOACT-URL</th>
<th>BRAT</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>Define decision context</td>
<td>What is the benefit-risk balance of natalizumab following the occurrence of PML cases?</td>
</tr>
<tr>
<td>Objective</td>
<td>Identify benefit and risk outcomes</td>
<td>Benefits: Reduction in relapse rate, slowdown in disability progression.&lt;br&gt;Risks: PML, reactivation of serious herpes viral infections, seizures, abortion or congenital abnormalities, transaminases elevation, infusion or injection site reactions, hypersensitivity reactions, flu-like reactions</td>
</tr>
<tr>
<td>Alternative</td>
<td>Define the decision context</td>
<td>Interferon beta-1a, glatiramer acetate, placebo. Which option to choose?</td>
</tr>
<tr>
<td>Consequence</td>
<td>Extract source data</td>
<td>Build a data source data table (BRAT) or an effects table (PrOACT-URL)</td>
</tr>
<tr>
<td></td>
<td>Customise framework</td>
<td>If required, repeat step 2 following in regards to available data</td>
</tr>
<tr>
<td>Trade-off</td>
<td>Assess outcome importance</td>
<td></td>
</tr>
<tr>
<td>Uncertainty</td>
<td>Display &amp; interpret key BR metrics</td>
<td>Dealt with in stages 3 and 4</td>
</tr>
<tr>
<td>Risk tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linked decisions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Natalizumab: Value tree

Benefit-risk balance

Benefit
- Reduction in relapse rate
- Slowdown in disability progression

Administration

Severe side effects
- PML
- Reactivation of serious herpes viral infections
- Seizures
- Abortion or congenital abnormalities

Risks
- Transaminases elevation
- Infusion or injection reactions
- Hypersensitivity reactions
- Flu-like reactions

Mild side effects
Recommendation Roadmap

- Planning
- Evidence gathering and data preparation
- Analysis
- Exploration
- Conclusion and dissemination
Stage 2: Evidence gathering and data preparation

- Identifies and extracts evidence relevant to the BR assessment in relation to the set criteria
- Determines what data to be collected from anticipated type of BR analysis
- Aggregating multiple sources of evidence, may require the use of estimation techniques
- Encourages systematic handling of missing data
- Requires engagement of clinical, statistical, epidemiological and database expertise
Natalizumab: Synthesising evidence in ITC

Natalizumab

Direct (Polman 2006, EPAR)

Placebo

Direct (Johnson 1998)

Glatiramer acetate

Indirect

Interferon beta-1a

Indirect

Indirect

Indirect

Indirect
## Natalizumab: evidence synthesis summary

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Outcome</th>
<th>Natalizumab Risk / 1000 pts</th>
<th>Comparator Risk / 1000 pts</th>
<th>Risk Difference (95% CI)/1000 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convenience Benefits</td>
<td>Convenience (weight 0.6%)</td>
<td>-</td>
<td>-</td>
<td>- (-, -)</td>
</tr>
<tr>
<td>Medical Benefits</td>
<td>Relapse (weight 3.9%)</td>
<td>280</td>
<td>450</td>
<td>-170 (-350, -60)</td>
</tr>
<tr>
<td></td>
<td>Disability Progression (weight 5.6%)</td>
<td>110</td>
<td>140</td>
<td>-30 (-50, -10)</td>
</tr>
<tr>
<td>Infection</td>
<td>Reactivation of serious herpes viral infections (weight 6.7%)</td>
<td>80</td>
<td>70</td>
<td>10 (-26, 45)</td>
</tr>
<tr>
<td></td>
<td>PML (weight 55.9%)</td>
<td>2</td>
<td>0</td>
<td>2 (-16, -3)</td>
</tr>
<tr>
<td>Liver Toxicity</td>
<td>Transaminases elevation (weight 11.2%)</td>
<td>50</td>
<td>40</td>
<td>10 (-16, 38)</td>
</tr>
<tr>
<td>Reproductive Toxicity</td>
<td>Congenital abnormalities (weight 5.6%)</td>
<td>-</td>
<td>-</td>
<td>- (-, -)</td>
</tr>
<tr>
<td>Neurological Disorders</td>
<td>Seizures (weight 5.6%)</td>
<td>0</td>
<td>11</td>
<td>-11 (-23, 0)</td>
</tr>
<tr>
<td>Other</td>
<td>Infusion/Injection reactions (weight 2.8%)</td>
<td>236</td>
<td>312</td>
<td>-76 (-150, -5)</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity reactions (weight 1.1%)</td>
<td>90</td>
<td>40</td>
<td>50 (20, 82)</td>
</tr>
<tr>
<td></td>
<td>Flu-like reactions (weight 1.1%)</td>
<td>399</td>
<td>608</td>
<td>-209 (-320, -98)</td>
</tr>
</tbody>
</table>

**Diagram:**

- **Higher for Drug A**
- **Higher for Comparator**

**Risk Difference (per 1000 patients):**

- Convenience (weight 0.6%)
- Relapse (weight 3.9%)
- Disability Progression (weight 5.6%)
- Reactivation of serious herpes viral infections (weight 6.7%)
- PML (weight 55.9%)
- Transaminases elevation (weight 11.2%)
- Congenital abnormalities (weight 5.6%)
- Seizures (weight 5.6%)
- Infusion/Injection reactions (weight 2.8%)
- Hypersensitivity reactions (weight 1.1%)
- Flu-like reactions (weight 1.1%)
Recommendation Roadmap

1. Evidence gathering and data preparation
2. Planning
3. Analysis
4. Exploration
5. Conclusion and dissemination
Stage 3: Analysis

- Evaluates data collected at previous stage in a BR assessment
- Quantifies the magnitudes of benefits and risks
- Weighs or integrates quantitative measures of the BR balance depending on the type of analysis
MCDA: a tool for BR assessment of natalizumab

MCDA has 3 ingredients:

- Value functions
- Preference weights
- B-R evidence data

Overall benefit-risk balance
The Benefit-risk is the product of the weight and the value.

Most of the Benefit-risk contribution is coming from prevention of relapses.

Infusion site reactions are the worst risk.
Natalizumab: Criteria contribution
Waterfall plot for Natalizumab vs. placebo

- Like a horizontal bar chart, except that the end of the previous bar determines the start of the next bar
- End of the last bar gives the overall benefit-risk.
- Brown = positive BR; Orange = negative BR; Purple = overall

http://public.tableausoftware.com/views/T_Waterfall/WaterfallRisk
Recommendation Roadmap

- Evidence gathering and data preparation
- Analysis
- Exploration
- Conclusion and dissemination
- Planning
Stage 4: Exploration

- Assesses the robustness and sensitivity of the main results to various assumptions and sources of uncertainties
- Assesses further consequences of a decision
- Considers any impact or added value to the RMPs
- Requires both statistical and clinical input
The base case value of the weight for each outcome is shown under each bar.

- The **low values** and **high values** of ±20% change in weight are shown at the ends of the bars.
- The incremental benefit-risk at the base case is the x-axis value at the middle.
- How this changes with each weight is shown by the position of the bar ends.
- From this plot we see that changes in the weight of relapse has the most influence on the benefit-risk score.

Recommendation Roadmap

1. Planning
2. Evidence gathering and data preparation
3. Exploration
4. Analysis
5. Conclusion and dissemination
Stage 5: Conclusion and dissemination

- The point at which a conclusion is reached
- The results and consensus from the BR assessment are communicated to a wider audience
- Explicitly states findings and conclusions that could influence future actions
- Emphasises a transparent audit trail of the whole assessment process i.e. brings everything together and sets the course of action
- Ensures the "big picture" overview is not lost
Final remarks

- Benefit-risk assessment methodologies support decision-making and are not intended to replace medical expertise.

- Patient and public involvement studies are currently being planned in a sample of MS patients:
  - to evaluate the feasibility and compare different methods of eliciting patient preferences on the benefits and risks of treatments for RRMS
  - to evaluate the benefit-risk balance of three treatments (natalizumab, interferon beta-1a, glatiramer acetate) for RRMS using the patient preference data.