An epidemiologist’s view

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EHC Round Table on concentrate-related risk of inhibitor formation in haemophilia A

Brussels, 2 March 2015
Conflicts of interest

• financial relations with pharmaceutical companies
  none

• royalties from patents
  listed as inventor on patents on prothrombotic genetic variants
Topics

- side-effects of medicines in general
- the side-effect of inhibitors with certain concentrates
- the future
Three main aspects

- experimental versus observational studies
  - why and when are randomised studies needed?
  - when is adjustment needed and sufficient?

- Occam’s razor
  - William of Ockham (1287–1347)
  - explanation with fewest assumptions is preferred

- in dubio abstine
  - what is best for patients?
Side-effects in general

- unintended, often unexpected and unpredictable
  - different risk factors than intended effect

- often low incidence
  - high incidence: detected pre-marketing
  - low incidence: detected post-marketing

- often not a class effect

- difficult to detect when rare and quantitative
A few examples

• unintended, often unexpected and unpredictable
  • hormones and venous thrombosis
  • statins and rhabdomyelysis

• often low incidence
  • high incidence: hair loss with chemotherapy
  • low incidence: rofexoxib (Vioxx) and myocardial infarction

• often not a class effect
  • ximegalatran and liver damage

• difficult to detect when rare and quantitative
  • antidepressants and suicide in adolescents
  • 3rd vs 2nd generation oral contraceptives and thrombosis
Experimentation vs observation

- doctors tailor treatment to prognosis
- link between prognosis and treatment
- observational studies confounded (‘by indication’)

Examples
- higher cancer death rate with chemotherapy than surgery
- cardioprotective effect of postmenopausal hormones

Solution
- randomise
- state-of-the-art in therapeutic studies
How about side-effects?

- if wholly unpredictable, no link of drug with prognosis
  - prescription is random in respect of side-effect
  - no need to randomise

- if some risk factors known
  - prescription usually still random
  - full adjustment feasible

Bottom line
- randomisation not required for side-effects
- adjustment for confounding or accidental skewness
How about inhibitors?

• different risk factors than bleeding (in severe haemophilia)

• limited number of known risk factors

• no prior information on immunogenicity of rFVIII types

Therefore
• doctors could not tailor type of rFVIII on risk profile
• no randomisation required

• but if they did: few risk factors that are known
• adjustment feasible and sufficient
Side-effects in general

- often detected post-marketing
- major (financial) stakes
- ‘good doctor bias’
  - prescribed to many patients
  - benefit more common than side effect
- unnecessary complex discussions
Standard discussion process

• flat denial
• authoritative denial
• it is unexpected and unproven
• it might also be ... (something wildly implausible)
• there is no complete understanding of mechanisms
• we need more studies
Counterarguments

• side-effects are by definition unexpected

• apply Occam’s razor: simplest solution
  • is it impossible that the drug causes the side-effect?
  • are the alternative explanations really more likely?

• proof is not necessary
  • for effect we need proof
  • for harm suspicion suffices: in dubio abstine

• knowledge of mechanism is not necessary
  • lots of mechanisms unknown, also for therapies
  • we never found out why FVIII CPS-P caused inhibitors
  • if it works, it works, and if it damages, it damages
It has happened before

A higher than expected incidence of factor VIII inhibitors in multitransfused haemophilia A patients treated with an intermediate purity pasteurized factor VIII concentrate.

Peerlinck K¹, Arnout J, Gilles JG, Saint-Remy JM, Vermylen J.


A Sudden Increase in Factor VIII Inhibitor Development in Multitransfused Hemophilia A Patients in The Netherlands


Blood, Vol 81, No 8 (April 15), 1993: pp 2180-2186
The four studies
The four studies

<table>
<thead>
<tr>
<th>Design</th>
<th>Period</th>
<th>Countries</th>
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<tr>
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<td>FCN cohort</td>
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<td>UKHCDO cohort</td>
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<td>EUHASS case-series</td>
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*: number of previously untreated patients (PUPs) reported

The four studies

<table>
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<th>Study</th>
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<th>Inhibitors</th>
<th>Adjustments</th>
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<tr>
<td></td>
<td></td>
<td>all</td>
<td>high</td>
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<tr>
<td>RODIN</td>
<td>486</td>
<td>145 (30%)</td>
<td>92</td>
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<tr>
<td>FCN</td>
<td>303</td>
<td>114 (38%)</td>
<td>63</td>
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<tr>
<td>UKHCDO</td>
<td>319</td>
<td>85 (27%)</td>
<td>43</td>
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<tr>
<td>EUHASS</td>
<td>259</td>
<td>62 (24%)</td>
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*: number of PUPs using rFVIII, non-overlapping

The four studies

all inhibitors

<table>
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<tr>
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<th>CI95</th>
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<tbody>
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<td>1.60**</td>
<td>(1.08 - 2.37)</td>
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<tr>
<td>FCN</td>
<td>1.55**</td>
<td>(0.97 - 2.49)</td>
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<tr>
<td>UKHCDO</td>
<td>1.64**</td>
<td>(0.94 - 2.87)</td>
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<tr>
<td>EUHASS</td>
<td>0.99</td>
<td>(0.62 - 1.61)</td>
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*: 2nd vs 3rd generation
**: adjusted for major confounding variables

The four studies

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<th>high-titre inhibitors</th>
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<td>(1.09 - 2.94)</td>
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<td>1.56**</td>
<td>(0.82 - 2.98)</td>
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<tr>
<td>UKHCDO</td>
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<td>(0.93 – 4.34)</td>
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<td>EUHASS</td>
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*: 2nd vs 3rd generation  
**: adjusted for major confounding variables

## Adjustment for confounding

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Meta-analysis: all inhibitors

RR=1.42
CI95 1.13-1.80
Meta-analysis: high-titre inhibitors

RR = 1.76
CI95 1.23-2.49
Meta-analysis: high-titre inhibitors

RR = 1.54
CI95 = 1.13-2.10
Conclusion

• is it proven?
  • no

• is it likely?
  • yes

• does this matter?
  • no! In dubio abstine
The future

• positive side: this side-effect was discovered

• question: could it have been seen earlier?
  • will always require some years of use
  • re-analysis by calendar time of the studies

• what is needed
  • properly designed international cohort studies
  • identification and replication cohorts
  • availability of all information on registration trials
  • open mind: side-effects occur more often than we like

• remaining questions
  • how about previously treated patients?
  • how many instances of increased risk have we missed?