The question

Has mifepristone 200mg the same efficacy as mifepristone 600mg for termination of pregnancy in combination with a prostaglandin administered 36 to 48 hours later?

Interpretation of a difference in an active-control trial

Risk difference

Test better | Reference better
---|---
$P < 0.05$ | ns
ns | ns
ns

Conclusion: identity of the groups is impossible to demonstrate:

*Absence of evidence is not evidence of absence*

Non-inferiority trials

Non-inferiority not shown

$\Delta = \text{non-inferiority limit} = \text{what is consented to be lost}$
Comparison of mifepristone 200 mg vs 600 mg in TOP

- No non-inferiority trial comparing 200mg with 600mg

Method
- Choose a relevant end point
- Determine the non-inferiority limit independently of the results of trials comparing 200 with 600mg
- Perform a meta-analysis of the trials comparing 200 with 600mg
- Interpret the results as a non-inferiority trial

Choice of the end point

- Success (complete abortion) is the most commonly used end point (available in all trials)
- Among failures, ongoing pregnancy is the worst situation
- It would be possible to use 200mg instead of 600mg if it was possible to conclude to non-inferiority for both success and ongoing pregnancy

Choice of the non-inferiority limit

- Background: what has been accepted by regulators to grant a marketing authorization to mifepristone
- The mean success rate varied from 92% to 96%, the mean ongoing pregnancy rate from 1% to 1.5%
- Non-inferiority limits = variation of effect accepted by the regulatory authorities
  - Success (complete abortion): -4% (absolute)
  - Ongoing pregnancy: +0.5% (absolute)
  - Same results when considering trials with misoprostol 400 mg per os (up to 49 DA) or with gemeprost 1 mg vaginally

Available studies comparing 200 with 600mg mifepristone

<table>
<thead>
<tr>
<th>Study</th>
<th>Days amenorrhea</th>
<th>Mifepristone (mg)</th>
<th>Prostaglandin</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO 1993</td>
<td>35-56</td>
<td>200 / 400 / 600</td>
<td>Gemeprost 1 mg vaginally</td>
</tr>
<tr>
<td>McKinley 1993</td>
<td>≤63</td>
<td>200 / 600</td>
<td>Misoprostol 600 μg per os</td>
</tr>
<tr>
<td>WHO 2000</td>
<td>≤63</td>
<td>200 / 600</td>
<td>Misoprostol 400 μg per os</td>
</tr>
<tr>
<td>WHO 2001</td>
<td>57-63</td>
<td>200 / 600</td>
<td>Gemeprost 1 mg vaginally</td>
</tr>
</tbody>
</table>
Available studies comparing 200 with 600mg mifepristone

<table>
<thead>
<tr>
<th>Dose, number of subjects</th>
<th>Success</th>
<th>Ongoing pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCKinley 1993</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg 110</td>
<td>103</td>
<td>1</td>
</tr>
<tr>
<td>600 mg 110</td>
<td>103</td>
<td>0</td>
</tr>
<tr>
<td>WHO 1993</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg 388</td>
<td>364</td>
<td>2</td>
</tr>
<tr>
<td>600 mg 389</td>
<td>367</td>
<td>1</td>
</tr>
<tr>
<td>WHO 2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg 792</td>
<td>707</td>
<td>22</td>
</tr>
<tr>
<td>600 mg 797</td>
<td>702</td>
<td>15</td>
</tr>
<tr>
<td>WHO 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg 449</td>
<td>415</td>
<td>6</td>
</tr>
<tr>
<td>600 mg 447</td>
<td>410</td>
<td>7</td>
</tr>
</tbody>
</table>

Main analysis (success)

Meta-analysis

- Rate difference, fixed effect model
- Main analysis: all studies, data as published (ITT)
- Sensitivity analyses
  - Per protocol population (reconstructed from limited published information)
  - Exclusion of the McKinley study (misoprostol 600mg)
  - Restriction to subgroups with <50 DA (at the request of EMEA)

Main analysis (ongoing pregnancy)

Non-inferiority limit = 0.005 (0.5%)

Upper CI limit = increase in additional pregnancies by 1% means 1000 additional ongoing pregnancies each year in France if 200 mg was used instead of 600 mg
Sensitivity analysis (<50 DA, ongoing pregnancy)

Conclusion

- Non-inferiority of mifepristone 200 mg is demonstrated compared with 600 mg for “success”
- Non-inferiority of mifepristone 200 mg is not demonstrated compared with 600 mg for “ongoing pregnancy”
- Final conclusion: depends on the relative importance of “success” and “ongoing pregnancy”

I would like to thank Gilda Piaggio Pareja and Helena Von Hertzen (WHO), for having provided sub-group data of the WHO studies in women with <50 DA