Ascertaining the Efficacy of Rare Chronic Disease Therapies

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Clinical Trial Design for Alpha-1 Antitrypsin Deficiency: A Model for Rare Diseases
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“The paradox of the clinical trial is that it is the best way to assess whether an intervention works, but arguably the worst way to assess who will benefit from it.”


“The benefit or harm of most treatments in clinical trials can be misleading and fail to reveal the potentially complex mixture of substantial benefits for some, little benefit for many, and harm for few.”

R Kravitz, Milbank Quarterly, 2004
Augmentation therapy with alpha-1 antitrypsin cannot be recommended in view of the lack of evidence of clinical benefit and the cost of treatment.
### α1AT Augmentation

Other evidence

<table>
<thead>
<tr>
<th>Baseline FEV₁ % Predicted</th>
<th>FEV₁ Slope (mL·y⁻¹)</th>
<th>Slope Difference (CI)</th>
<th>% Wgt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Augmentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>Mean</td>
<td>SE</td>
<td>n</td>
</tr>
<tr>
<td>30-65%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Seersholm et al, 1997 (6)</td>
<td>75</td>
<td>-24.2</td>
<td>2.7</td>
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<tr>
<td>AATD Registry Study Group, 1998 (9)</td>
<td>349</td>
<td>-43.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Wenczer et al, 2001 (12)</td>
<td>25</td>
<td>-19.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Chapman et al, 2005 (26)</td>
<td>5</td>
<td>-57.8</td>
<td>27.1</td>
</tr>
<tr>
<td>Pooled</td>
<td>454</td>
<td>-30.6</td>
<td>12.0</td>
</tr>
<tr>
<td>&gt; 65%</td>
<td></td>
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<tr>
<td>Seersholm et al, 1997 (6)</td>
<td>112</td>
<td>-61.8</td>
<td>2.4</td>
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<tr>
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<td>211</td>
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<td>4.1</td>
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<tr>
<td>Wenczer et al, 2001 (12)</td>
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<td>-37.8</td>
<td>3.2</td>
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<tr>
<td>Chapman et al, 2005 (26)</td>
<td>15</td>
<td>-23.3</td>
<td>13.3</td>
</tr>
<tr>
<td>Pooled</td>
<td>308</td>
<td>-50.8</td>
<td>15.9</td>
</tr>
</tbody>
</table>

Total

| Seersholm et al, 1997 (6)  | 198                  | -53.0                  | 2.7   | 97   | -74.5    | 6.1  | 21.5 (8.5 to 34.5) | 22.0 |
| AATD Registry Study Group, 1998 (9) | 581   | -51.6                  | 2.7   | 317  | -56.0    | 3.6  | 4.2 (-4.9 to 13.3) | 31.2 |
| Dirksen et al, 1999 (11)   | 28                   | -78.9                  | 12.0  | 28   | -59.1    | 11.9 | -19.8 (-52.9 to 13.3) | 8.6  |
| Wenczer et al, 2001 (12)   | 96                   | -34.3                  | 3.0   | 96   | -49.2    | 6.2  | 14.9 (2.6 to 27.2) | 23.3 |
| Chapman et al, 2005 (26)   | 21                   | -26.7                  | 12.1  | 143  | -59.0    | 7.0  | 32.4 (13.1 to 51.7) | 15.0 |
| Pooled                      | 924                 | -48.0                  | 10.7  | 681  | -59.4    | 7.3  | 13.4 (1.5 to 25.3) | 100.0 |
Chapman et al 2013
RAPID Trial Group

Am J Respir Crit Care Med 187;2013:A6069

Loss of lung density Annual rate

Augmentation
Placebo

60 mg/kg over two years

Secondary endpoints
- Spirometry
- KCO
- Shuttle
- adverse events

P=0.017

NS
“Pivotal” Studies

- Trial designed & executed to get statistically significant evidence of efficacy and safety as required by HAs for NDA / sNDA approval.

- Agent vs placebo/comparator

- Also includes studies with the aim to include claims into the label as well as Post-marketing commitments.
Conventional Statistical Reasoning

1. Starting hypothesis (Null hypothesis - H0):
   - new treatment = standard one

2. To demonstrate: new treatment >> standard
   - reject null hypothesis (p<0.05)

3. To reject null Hypothesis:
   - Large Sample Size

4. Only information collected within the experiment can be used in interpretation of study results
Example
Diseases X & Y – treatment A

Mortality

X (N=12000)  Nil vs A  15% vs 12.5%

P = 0.0007  $H_0$ Rejected: A is effective in X

Y (N=240)  Nil vs A  15% vs 7.5%

P=0.066  $H_0$ not rejected: A not shown effective in Y
The statistical burden

- A study **must** have an adequate size
- Required Size, based on:
  - **Significance level** (usually 5%)
  - **Minimal clinically worthwhile difference**
  - **Power** (usually 80-90%)
- Results: Test of significance
  - P<0.05 = Positive Study
  - P>0.05 = Negative Study

<table>
<thead>
<tr>
<th>Relative reduction in event rate %</th>
<th>Needed number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>71</td>
</tr>
<tr>
<td>40</td>
<td>125</td>
</tr>
<tr>
<td>30</td>
<td>252</td>
</tr>
<tr>
<td>20</td>
<td>635</td>
</tr>
<tr>
<td>10</td>
<td>2830</td>
</tr>
</tbody>
</table>

A = 0.05  
**power = 80%**
Disorder frequency

1 : 50 000

➢ Demonstration of a 50% reduction in the occurrence of an endpoint with 95% confidence
Regulators are reasonable
Rare plasma protein deficiencies

- FDA approval of Baxter Protein C
  - Pivotal study n=18 patients with deficiency

- FDA approval of CSL fibrinogen
  - Pivotal study n=15 patients with afibrinogenemia

- EMEA approval for Novoseven in FVII deficiency
  - Data on 32 patients with FVII deficiency treated in 28 different sites in 6 countries 1988 - 1999.
RCTs have focused on identifying interventions that are effective, on average, across a broad patient population. However,

- Interventions that yield a statistically significant treatment effect across a study population may not necessarily work for all treated patients; they may be ineffective for some patients and harmful for others.

- Interventions that do not yield a statistically significant treatment effect across a study population—and that may be dismissed as ineffective—may work for certain subsets of the population.
Distribution of individual treatment effects in the population (large unshaded curve) and in three hypothetical samples (shaded curves).

**Sample 1** is centered but fails to reflect the diversity of the population in terms of net treatment benefit. **Sample 2** is composed of individuals who happen to derive much more net benefit from the treatment than does the average member of the population. Only **sample 3** is broadly representative of the population in terms of risk, responsiveness, and vulnerability.

What is Personalized Medicine?

Personalized medicine (PM) is the tailoring of medical care to the particular traits (or circumstances or other characteristics) of a patient that influence response to a health care intervention. These may include genetic, sociodemographic, clinical, behavioral, environmental, and other personal traits, as well as personal preferences. PM does not refer to the creation of interventions that are unique to a patient, but the ability to classify patients into subpopulations that differ in their responses to particular interventions.
What Is Patient-Centered Care?

“The term ‘patient-centered medicine’ was introduced by Balint and colleagues (Balint et al., 1970), who contrasted it with ‘illness-centered medicine’. An understanding of the patient’s complaints, based on patient-centered thinking, was called ‘overall diagnosis’, and an understanding based on disease-centered thinking was called ‘traditional diagnosis’.”
Evolution of Personalized Medicine

1950
- DNA Structure Described (1953)
- 1st RCT (1948)

1960
- Genetic Code Cracked (1967)
- “Pharmacogenetics” (1959)

1970
- CYP450 Metabolic Enzymes Identified (1977)
- HTA (1974)

1980
- Effectiveness Research (1988)
- Pharmacoeconomics (1989)

1990
- Outcomes Research (1986)
- EBM (1990)
- CED (2006)

2000
- Human Genome Sequenced (2003)
- CER (2003, 2009)

2010

Source: C. Goodman © 2009 The Lewin Group
Evolution of PCOR

Source: C. Goodman © 2011 The Lewin Group

www.pptaglobal.org
An example of a rare, chronic disorder

Hemophilia A
Personalizing Prophylaxis
Effect of variability of FVIII $t_{1/2}$

[Diagram showing the logarithm of FVIII concentration over time (hours).]
Observed FVIII levels (n = 2035) plotted against time after the infusion.

The log-normal distribution of individually estimated clearance (mL/h per kg) in the 100 adolescent/adult patients.
Thoughts on Alpha One Anti-Trypsin Deficiency
Simulations for different dosage regimes
Effect on protective A1PI level

- 250 mg/kg/28 days
- 180 mg/kg/21 days
- 120 mg/kg/14 days
- 60 mg/kg/7 days

Malmö Sweden (Eur J Clin Pharmacol 2003; 59: 151–156)
  • N=7 to generate model
    ➢ 1-2 g twice weekly

Barcelona Spain (Ann Pharmacother 2008;42:640-6)
  • MC simulation, results tested in N=6
    ➢ 10 g /two weeks (one); 11-14 g/three weeks (five)

Barcelona Spain (Thorax 2006;61:1059–1064)
  • Single compartment model, through PK of N=seven
    ➢ 123.1 mg/kg/two weeks
Differences between products

<table>
<thead>
<tr>
<th>Function t1/2 (mL/day/kg)</th>
<th>Vd (g/L·h /dose)</th>
<th>AUC</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>9.7</td>
<td>158.5</td>
<td>32.2</td>
</tr>
<tr>
<td>B</td>
<td>7.5</td>
<td>92.6</td>
<td>42.2</td>
</tr>
</tbody>
</table>


Chest 2002;122 (1) :66-74
On behalf of individuals and their family members who suffer from Alpha-1 Antitrypsin Deficiency, commonly known as Alpha-1, we write to alert you to a bad policy decision in your 2014 Prescription Drug Guide. The Alpha-1 Foundation and Alpha-1 Association strongly oppose Humana’s decision to implement a strict, single agent formulary for alpha-1 antitrypsin augmentation, a critical therapeutic available in four formulations that, as biologics, are not considered generically equivalent. Our opposition is based on medical practice, patient tolerance and scientific literature which indicates that products for the augmentation of Alpha-1 Antitrypsin Deficiency are not clinically equivalent or interchangeable. Instituting a single source formulary will endanger your beneficiaries who have Alpha-1 Antitrypsin Deficiency and require this life saving and medically effective treatment.

November 26, 2013

Mr. John Walsh
Alpha-1 Foundation
3300 Ponce de Leon Blvd
Coral Gables, FL 33134


Dear Mr. Walsh:

Thank you for reaching out to us regarding our coverage of biologic agents used to treat Alpha-1 Antitrypsin Deficiency.

Humana’s Pharmacy & Therapeutics Committee evaluates pharmaceutical products utilizing an evidence-based medicine (EBM) approach. This results in the development of an outcomes-based formulary that is structured to deliver the right outcome at the right cost. Items considered include but are not limited to, clinical trial data, updated FDA prescribing information, United States Pharmacopeia (USP) Standards, current therapeutic guidelines, outcomes research, cost-effectiveness analyses (CEAs), and comparative effectiveness research (CER).

In determining our coverage of alpha-1 proteinase inhibitors, we reviewed guidelines set forth by the American Thoracic Society (ATS) as well as available primary literature applicable to alpha-1 replacement therapy. The ATS guidelines provide equal recommendation for all available alpha-1 replacement therapies.”
Hierarchy of strength of evidence of therapeutic efficacy

1. “N of 1” randomized controlled trial
2. Systematic reviews of randomized controlled trials
3. Single randomized controlled trial
4. Systematic reviews of observational studies
5. Single observational study
6. Physiological studies
7. Unsystematic clinical observations

N of 1 trails
Trial of therapy

- Randomized clinical trial used in just one patient
- Patient undergoes pairs of treatment periods
  - one period is the experimental treatment
  - other period is the comparator (placebo or alternative treatment)
- N of 1 trials are considered to provide the strongest level of evidence about the existence of a causal relationship between a treatment and an outcome.
- Do not permit any generalization of the findings on the individual patient to any patient population.
N of 1 trails
Trial of therapy

• BUT - may be combined
  – through meta-analysis
  – through a Bayesian random effects model

• Combination provides a population estimate for treatment effectiveness while retaining the capacity to provide a distinct effectiveness estimate for each individual patient
Typical N-of-1 trial.

The order of treatment and placebo are randomly assigned for each cycle.
Example of N of 1 trial
Children with attention deficit hyperactivity disorder

Example of a responder and a nonresponder to dexamphetamine

Bayesian combination of 23 N-of-I trial results
Amitriptyline vs placebo for fibromyalgia.

Based on this distribution
- 50% chance that the treatment effect $\gg 0.44$
- 99.9% chance that the difference in the disease status score with amitriptyline compared with placebo was greater than 0.
- The 95% Bayesian confidence interval constructed about the posterior mean yielded a 95% chance that the treatment effect was between 0.18 and 0.71.
Therapies suitable for N-of-1 trial

- Condition for which the medication is being prescribed is chronic and relatively stable
- Half-life of the medication being tested is short
- Rapid onset/offset of biological action of the medication
  - (NA for Alpha 1?)
  - (Trial for bioequivalence?)
- Effect of the medication can be measured using a validated outcome measure
- Medication does not alter the underlying condition
  - (ie does not cure – NA for GT)
Trials for augmentation therapy

• RAPID indicates that a placebo arm is now to be considered unethical

• Propose N of 1 versus an established comparator

• Propose personalizing through PK

• Post market follow up for agreed endpoint – years

• Conditional approval – needed for this landscape?
“EUnetHTA strongly supports improved publication and access to clinical trial data as described in EMA’s draft policy. HTA needs other independent and high quality data sources. **Data submitted to regulatory agencies are therefore essential for HTA agencies.** A key aim of HTA is to estimate relative or comparative effectiveness. Methods used by HTA require full information about study methods.

EUnetHTA strongly supports the statement that clinical trial data (indeed for all trials, involving medicines, devices or other healthcare interventions) cannot be considered commercially confidential information (CCI), and that the interests of public health outweigh consideration of CCI for clinical trial data.”

Draft agenda of the European Medicines Agency / Health-Technology-Assessment-body workshop on parallel scientific advice in drug development

8 October 2013
EMA/620552/2013
• Found that $\alpha_1$AT Augmentation is not cost-effective (costs/QALY too high)

• But
  – Only used small part of evidence (one patient registry)
  – Used 3% discounting of the QALY
  – Estimated QALYs without asking patients (asked doctors)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost</th>
<th>Effectiveness (QALYs)</th>
<th>Incremental Cost-effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO Treatment</td>
<td>$92,091</td>
<td>4.62</td>
<td></td>
</tr>
<tr>
<td>Treatment for Life</td>
<td>$895,243</td>
<td>7.19</td>
<td>$696,933</td>
</tr>
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</table>
Summary

• Rare chronic disease difficult to fit into current EBM paradigm
• Regulatory agencies are flexible but other areas eg CC are giving payers an excuse for restricting reimbursement
• Personalized medicine is challenging EBM
• Especially relevant for rare disease but needs optimizing
• Patient input in trial design, including QoL measurements, is crucial
• All solutions are possible if THE PATIENT COMES FIRST