Apotex-Olivieri Affair: a Case Study in BioEthics

Dr. James A. Smith, PEng

BME 100 class; Feb. 2012
After Viewing The Video…

What struck you most about it?
Questions? Concerns?

http://www.youtube.com/watch?v=yxIaQXSWs6E
Let’s go over the facts

• Add details that were not mentioned in Dr. Olivieri’s address
Thalassaema

• Inherited blood disorder
• Abnormal haemoglobin
  – Does not bind & release oxygen
  – Chronic fatigue, bone deformities, death
• Treatment
  – Blood transfusions (3-6 weeks)
• Iron Overload Side Effect
  – Hepatic fibrosis, cirrhosis & death
Treating Iron Overload

• Chelation
  – Agent binds with iron & expels it
  – Experts: Weatherall & Olivieri
  – Deferoxamine: standard in 1980s
    • Subcutaneous injection
      – Daily with pump
      – 10 - 12 hours
      – Demanding
  • Need for oral alternative!
Nancy Olivieri

- Hematologist
- Professor of Medicine
- Head of Hemoglobinopathy Research Program at Sick Kids (Toronto)
- 1989: begins works on deferiprone (L1)
- 1993: Contract with Apotex
  - 50% sponsorship

Photo: University Health Network
Apotex

- Largest producer of generic drugs in Canada
  - e.g. ASA (generic “Aspirin”)
  - $1B in sales per year
- CEO & Chair: Bernard Sherman
  - Worth $3.3B
  - Forbes List: #334
Where are they?

- Apotex
- Sick Kids
- Ryerson
The Contract

• 1995
  – Olivieri & colleagues receive LA-02 contract
  – Confidentiality provision (3 years after trial)
  – NEJM: “favorable effect of deferiprone on iron balance”
  – LA-03 trial displays undesirable iron conc.
Changing the Trials

• Olivieri wants consent forms changed
• Why?
  – Inform patients of negative results
• Apotex requests HSC REB not be informed
• Olivieri submits to REB
• Apotex submits differently to REB
• REB: change the consent forms
Action

• May ‘96
  – Olivieri attempts to tell patients
  – Apotex cancels sponsorship
  – Apotex remind O. & colleagues of secrecy
    • Legal action threatened
    • VP reminds of nondisclosure agreement
Outside Help…

• June ‘96
  – Olivieri contacts U of T Dean of Medicine
    • Many Toronto hospitals are “teaching hospitals” for U of Toronto
    • Mediate dispute?
  – Apotex review board finds Olivieri wrong
    • Errors in drug administration
    • Errors blamed on Apotex ending trials early
  – Apotex denies consent for O.’s pubs
Conference Publication

• Olivieri presents LA-03 in Florida
• Liver biopsies done to examine toxicity
  – Accelerated progression of fibrosis
• Colleague Koren stops working with O.
  – Publishes positive deferiprone results
  – (see Naimark report)
End of L1 Prescription

• Feb 1997
  – New biopsies requested
  – Patients informed of results
  – Olivieri stops L1 (deferiprone) prescriptions
  – REB informed
  – Apotex states L1 is safe
    • Informs admin & patients
Admin Doesn’t Agree & Olivieri Publishes

• Sept. ‘97:
  – Olivieri not satisfied with Dean
  – U of T admin can’t find enough specifics
  – (Naimark Report)

• Nov. ‘97:
  – Olivieri publishes abstract
  – “L1 was discontinued in all patients because of safety concerns”
Dismissal & Report #1

• April ‘98
  – Olivieri complains of working conditions
  – HSC interprets as resignation; dismissal

• Summer
  – Olivieri refuses to share data with Apotex
  – Publishes liver toxicity in NEJM

• Dec. ‘98
  – Naimark Report (HSC Board of Trustees)
    • says HSC did not act improperly
Firing & Rehiring & Lobbying

• Jan ‘99:
  – O. fired from head of Hemoglobinopathy
  – Rehired & told HSC will support her

• U of T President writes to P.M. (Canada)
  – Lobbies for Apotex
  – Later apologizes
Colleagues turn on each other

- 1999-2000
  - Dr. Koren found to be anon. source of letters against Olivieri
  - He’s source for Naimark Report
  - Suspended & Chair revoked
2000 - 2003

- College of Physicians and Surgeons of Ontario
  - Dismisses case of HSC vs. Olivieri
  - O. acted in “best interest of patients”
- Can. Assoc. of Uni. Teachers Report
  - U of T didn’t protect Olivieri
- High personal cost
  - $300,000 in defending herself
Further Reading

• “The Drug Trial” by Miriam Shuchman
  – Based on Olivieri’s case
  – Wife of Donald Redelmeier (CMAJ editorial board)
  – Letter by Dr. Olivieri is response to CMAJ review of “The Drug Trial” (2006)
    • http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1389830/
• Apotex Webpage: www.apotex.com
• Uni. Health Network Webpage
  – http://www.uhnres.utoronto.ca/researchers/profile.php?lookup=4539
• http://post.queensu.ca/~forsdyke/peerrev5.htm
• http://www.hemoglobal.org/
• http://www.rottentomatoes.com/m/constant_gardener/
• http://meds.queensu.ca/medicine/histm/oilivieri/BaylisJM.pdf
• http://jme.bmj.com/content/30/1/8.full
References


Solutions?

- Sponsorship?
- Regulation?
- Whistleblower Acts?
- Conflicts of interest
  - Financial (paid by…)
  - Personal (family members, friends)
- How would you have acted?
  - As the sponsor
  - As the researcher