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FDA Hearing on mipomersen for treatment of Homozygous Familial Hypercholesterolemia (HoFH)

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* We do not have any financial conflicts of interest.

Unethical Clinical Trials on mipomersen: I

As we discussed yesterday, the agreed-upon standard for treatment of HoFH is apheresis to get rid of excessive amounts of LDL:

"LDL apheresis is currently the best treatment option to bring these [HoFH] patients closer to target LDL levels, and has been shown to reduce the risk of CVD along with LDL-C levels."

"Before the availability of apheresis, homozygotes rarely survived the third decade of life; however, based upon clinical observation, the present-day life expectancy of homozygotes treated with different combinations of available treatment modalities can reach at least to the fourth and fifth decades."

Thompson, et al. Current Opinion in Lipidology 2010, 21:492–498

Unethical Clinical Trials on mipomersen: II

Despite this standard, in Isis human trials apparently allowed by the FDA, “Mipomersen has not been studied in individuals that have had LDL-apheresis in the last three months nor has it been studied in conjunction with LDL-apheresis.” (FDA briefing document, page 6)

In one such trial, involving 58 patients with HoFH randomized to get the mipomersen or a placebo, FDA acknowledged that “This represents a patient population that is considered to have the same or higher risk for cardiovascular events as patients in whom LDL-C apheresis is indicated in the US.” but that “Individuals on apheresis were excluded.” (FDA Briefing document, page 34).

Unethical Clinical Trials on mipomersen: III

In Isis' zeal to demonstrate mipomersen to be effective, the trials involved the use of a placebo (nothing) as a comparator (in addition to standard cholesterol lowering drugs) but excluded the use of a known effective treatment, LDL apheresis.

In contrast, the Phase III trial with lomitapide involved 29 HoFH patients, but the 18 who were already getting LDL apheresis were allowed to stay on their previous treatment during the trial.

It will be interesting to find out why the IRBs overseeing the mipomersen trials (or the FDA) allowed these highly unethical trials to go forward.

Prolonged half-life and adverse events

- Terminal elimination half-life of approximately 1 to 2 months (= 5-10 months to complete clearance). (p. 78)

- Thus, on-treatment AE rates may underestimate true difference in AE occurrence between mipomersen and placebo because of lasting AEs.

- Given the high discontinuation rate due to AEs (18.0% [47/261] of mipomersen-treated individuals vs. 2.3% [3/130] of placebo-treated individuals, patients may continue to suffer long after stopping the drug. (p. 6)

- “In general, when mipomersen therapy was stopped, ALT levels [in those with significant elevations] trended back to baseline values over a period of months.” (p. 78)

Hepatic Toxicity

- The incidence of at least one elevation in ALT ≥ 3x ULN was higher with mipomersen than placebo in both HoFH subjects only (4/34 [12%] vs. 0/17 [0%]) and the overall treated population in the pooled Phase III trials (43/261 [17%] vs. 1/129 [1%]). (p. 12)

- Hepatic steatosis in ISIS 301012-CS7 and ISIS 301012-CS12 (mipomersen vs. placebo): (p. 12)

  – 9.6% vs. 0.02% median increase in hepatic fat fraction (CS7)

  – 62% vs. 8% with a ≥ 5 percentage point change from baseline hepatic fat content (CS12)

Monitoring for Hepatic Steatosis

- Inadequacy of transaminase screening to identify steatosis: 84% of mipomersen-treated patients with hepatic fat accumulation ≥ 5% had no (>3X ULN) ALT elevation (p. 89).

- "If mipomersen is approved, consideration should be given to monitoring all patients with an ultrasound or MRI at baseline and every 6 months to assess for liver fat accumulation." (FDA clinical reviewer, p. 97).

Carcinogenicity

- Animal data suggestive of carcinogenicity at close to recommended human dose (statistically significant at small multiples of human exposure):
  - Fibroma + fibrosarcoma + fibrous histiocytic tumors (<1x human dose), female rats)
  - Fibrosarcoma (2x, male mice)
  - Hemangiosarcoma (2x, female mice)
  - Hepatic adenoma and carcinoma (2x, female mice)

- Both malignant (1.2% [9/749] vs. 0.5% [1/221]) and benign and malignant combined (3.2% [24/749] vs. 0.9% [2/221]) neoplasms were higher in mipomersen-treated individuals than placebo-treated individuals. (p.136-138)

High Discontinuation Rate in HoFH Patients

- 58% of HoFH patients discontinued the treatment by the end of the open-label extension trial, due to adverse events or withdrawal of consent (p. 7)

- Most HoFH patients would thus incur all the short-term risks without any long-term cardiovascular benefit

- The high discontinuation rate in HoFH patients may also increase the potential for widespread off-label use in non-HoFH patients; inadequately addressed in the proposed REMS: (p.4, REMS)
  - No genetic test required
  - No patient enrollment or monitoring