Important Tools in Determining Whether a Signal Warrants Further Investigation

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1

Tools for Signal Assessment

- Published case reports
- Elements of biologic plausibility

2

Published Cases

- **Hazen PG, Carney JF, Walker AE, Stewart JJ: Depression - a side effect of 13-cis-retinoic acid therapy. J Am Acad Dermatol. 1983; 9 (2): 278**
- **Scheinman PL, Peck GL, Rubinow DR, DiGiovanna JJ: Acute depression from isotretinoin. J Am Acad Dermatol 1990; 22 (6): 1112**
- **Duke EE, Guenther L: Psychiatric reactions to the retinoids. Canadian J. Dermatol 1993; 5 (4): 467**
- **Bravard P, Krug M, Rzeznick JC: Isotretinoin et depressoin, soyons vigilantes. Nouv. Dermatol. 1993; 12: 215**
- **Byrne A, Hnatko G: Depression associated with isotretinoin therapy. Can J Psychiatry 1995; 40 (9): 567**
- **Byrne A, Costello M, Greene E, Zibin T. Isotretinoin therapy and depression – evidence for an association. Ir J Psych Med 1998: 15:58**

3

Elements of Biologic Plausibility

- Same adverse event with pharmacologically related substances that bind to the same physiologic receptor
- Dose effect
- Temporal association that is consistent with the pharmacokinetics of the drug
- Retinoids and the central nervous system

4

Biologic Plausibility

Occurrence of psychiatric adverse events with distinct substances that bind the same physiologic receptors:

- High-dose vitamin A (acne)

  RM Restak 1972; EF McCance-Katz and LH Price, 1992

- Etretinate (psoriasis)

  Martinez et al 1987; CA Henderson and AS Highet, 1989

- All-trans-retinoic acid (leukemia)

  Sacchi et al. 1999 Leukemia & Lymphoma

5

All-trans retinoic acid (ATRA)

- Unexpected high incidence of severe toxicities when ATRA added to IFN-alpha and low-dose ara C for leukemia
- Possible synergistic toxicity between IFN and ATRA

  » Sacchi et al. 1999 Leukemia & Lymphoma

6

All-trans retinoic acid (ATRA)

(Sacchi et al. 1999 Leukemia & Lymphoma)

	+ ATRA n = 42	No ATRA n = 134
Depression	31%	13%
Psychosis	5%	0
Headache	62% (36% severe)	0
Pseudotumor	5%	0
Overall CNS	84%	27%

7

Dose Effect

- Dose effect is clear for Vitamin A
- For isotretinoin and etretinate
  - there are isolated case reports that *suggest* a possible dose response
  - a dose threshold *cannot* be ascertained from spontaneous reports

8

Biologic Plausibility: Pharmacokinetics

- The terminal elimination half-life of isotretinoin is 10-20 hours
- The pharmacokinetics of isotretinoin are consistent with observed time to resolution of psychiatric adverse events in many patients upon drug discontinuation

9

Temporal Pattern in Sponsor Analysis of Adverse Events

- A majority of substantive mood disorder cases had off-set within 30 days, most of those within 15 days
- For 25 cases with both on-set and off-set within 15 days:
  - 23 had resolution within 7 days
  - 17 of those had resolution within 4 days

10

Temporal Pattern in Published Cases

- Depression in 7 of 700 patients
  - Symptoms resolved within 1 week of stopping Accutane; one patient had positive re-challenge
    - » Sheinman et al JAAD 1990
- Depression in 6 of 110 patients
  - Five continued drug despite depression, which "rapidly" resolved upon discontinuation of Accutane
    - » Hazen et al JAAD 1983

11

Retinoids and Central Nervous System

- Retinoids enter the central nervous system
- Retinoid receptors are present in adult brain
- Of all organ system categories, the nervous system ranks second only to "psychiatric" in the highest percentage of *serious* adverse events in the HLR post-marketing database for Accutane

12

Overall Assessment

- No mechanism is known for the psychiatric adverse events observed with retinoids
- An association is not biologically implausible
- None of these elements of adverse event assessment, nor their totality, proves that isotretinoin causes psychiatric disease

13

"Thus, be vigilant"

- Isotretinoin and Depression: Care is Needed

» Bravard, Krug, and Rzeznick
Nouv. Dermatol. 12:215 1993

14

Risk Management and Assessment

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15

Labeled Warnings: 21 CFR 201.57

- The labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur
- The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug
- A causal relationship need not have been proved

16

Current Labeled Warning

"Accutane may cause depression, psychosis and rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events".

17

Risk Management and Assessment

- Short-term goal
  - Management of uncertain risk
- Long-term goal
  - Resolution of uncertainty

18

Management of Uncertain Risk

- Information and Education
- Intervention

19

Management of Uncertain Risk: Information and Education

- Information for Health Care Professionals
  - CME programs
  - Professional labeling
- Information for Patients
  - Patient Package Insert (optional)
  - Brochure (optional)
  - Medication Guide (required distribution)
- Informed Consent

20

Management of Uncertain Risk: Intervention

- Monitoring of Patients
- Management of Events
- Drug Distribution

21

Resolution of Uncertainty: Formal Studies

- Basic science research
- Open cohort study
- Retrospective epidemiologic cohort study
- Prospective controlled trial

22

Formal Studies Might Answer Clinically Important Questions

- Is there a dose threshold that is within the minimum effective dose for acne?
- Is there an identifiable subset of patients at increased risk?
- Once symptoms occur, is dose adjustment/ treatment with anti-depressants safe or must Accutane® be discontinued?

23

Options

- Education & Information
  - Information for Health Care Professionals
    - CME programs
    - Professional labeling
  - Information for Patients
    - Patient Package Insert (optional)
    - Brochure (optional)
    - Medication Guide (required distribution)
  - Informed Consent
- Intervention
  - Monitoring of Patients
  - Management of Events
  - Drug Distribution
- Formal Studies
  - Basic science research
  - Open cohort study (survey)
  - Retrospective epidemiologic cohort study
  - Prospective controlled trial

24