

# Current concepts and controversies in the safety of dermatologic therapeutics

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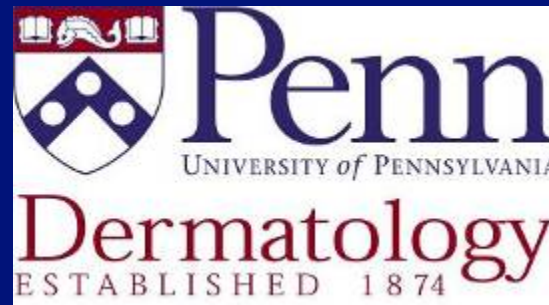
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# Disclosure statement

- I have been an investigator and/or consultant for Amgen, Abbott, Centocor, Pfizer, Celgene, Novartis, and Genentech
- I have no significant COI's as defined by the American Association of Medical Colleges (<http://www.aamc.org/research/coi/start.htm>)
- This presentation is the sole work of Dr. Gelfand

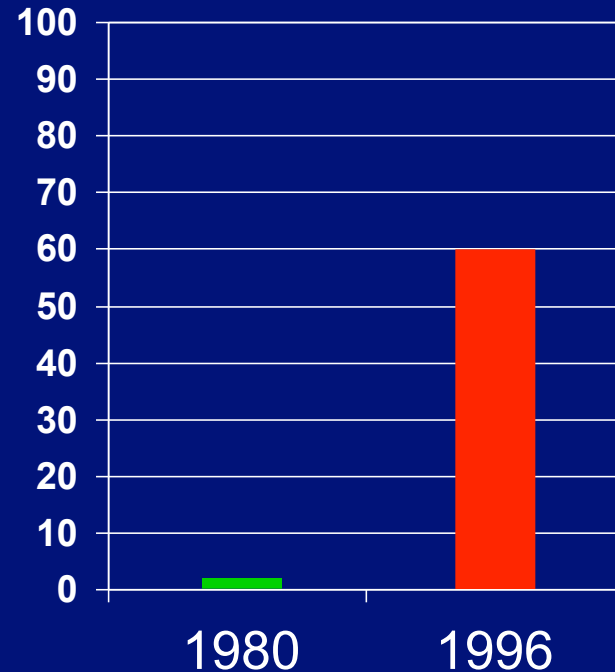
# Lecture Goals

- Recognize the strengths and limitations of the drug approval process for assessing safety
- Develop an advanced understanding of current serious safety issues affecting dermatological therapeutics

# Drug Safety: Increasing Concern

- Prescription medications are widely used.
  - 3.1 billion prescriptions in 2004
  - 60% increase from previous decade
- Public health consequences:
  - 1.5 million US hospitalizations annually for ADRs
  - 100,000 Americans die each year from ADRs

% of new drugs first released in US



# Limitations of the approval process

1. Clinical trials study “healthy” subjects
2. Exposure to medication in a clinical trial is only short term
3. Clinical trials lack statistical power
  - 3000 patients = Can only detect adverse events of  $> 1/1000$
  - Drug approval process designed to test short term safety of common (1% rate) adverse events in “healthy” treatment population

# “Rare” events unlikely to be detected prior to approval

*Most serious medical events are rare*

| <u>Outcome</u>      | <u>Rate/1000/year</u> |
|---------------------|-----------------------|
| Heart dz            | 2.58                  |
| Cancer              | 2.0                   |
| Influenza/pneumonia | 0.2                   |
| <b>Lymphoma</b>     | <b>0.2</b>            |
| Suicide             | 0.1                   |
| <b>IBD</b>          | <b>0.1</b>            |
| MS                  | 0.03                  |
| <b>PML</b>          | <b>0.00025</b>        |

# Who cares about rare side effects?

- Patients
- Regulators
- Lawyers
- Media

Front page, New York Times 5/8/03

# New Risks Routinely Identified After FDA Approval

- 51% of approved drugs have serious adverse effects not detected before approval
- 7.5% of drugs have BLACK BOX warning added after approval
- 2.7% withdrawn for safety reasons

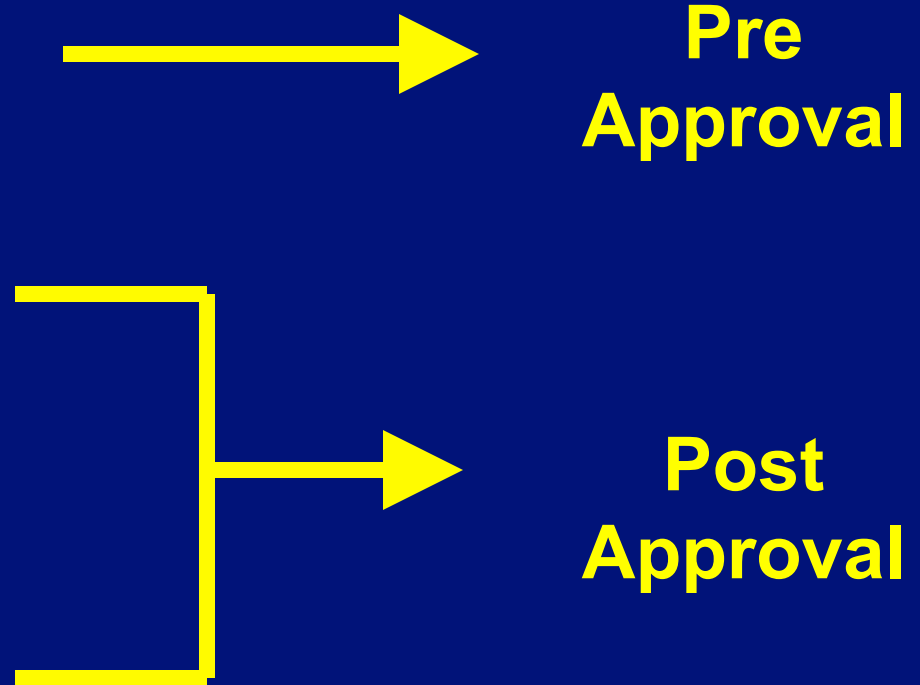
Strom BL ed. Pharmacoepidemiology, 3rd Edition. West Sussex, England. 2000

Drug Safety 2004;27:509-17

Lasser, KE JAMA 2002;287:2215-20

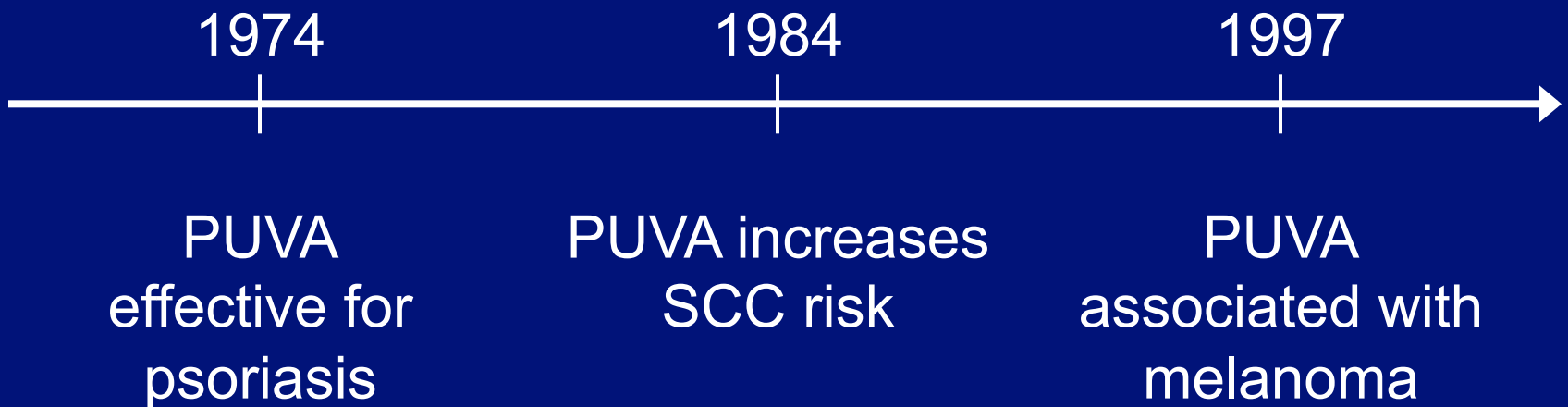
# Drug Safety: Types of side effects

- Type A: Pharmacologic
  - Common, dose-dependent
  - Example: Isotretinoin induced cheilitis
- Type B: Idiosyncratic or Allergic
  - Rare <1:1000, occur in close proximity to exposure
  - Example: Dapsone induced agranulocytosis
- Type C: New Morbidities
  - Delayed, uncommon
  - Example: PUVA and SCC



# Type C effects: Cancer example

## *PUVA Follow-up Study*



# Safety of dermatological therapeutics– a brief history

- Terfenadine and astemizole: Fatal arrhythmias
- Isotretinoin - ? Suicide risk
- Biologics: lymphoma?
- Topical calcineurin inhibitors – Black Box warning regarding malignancy
- Efalizumab: withdrawn due to PML risk

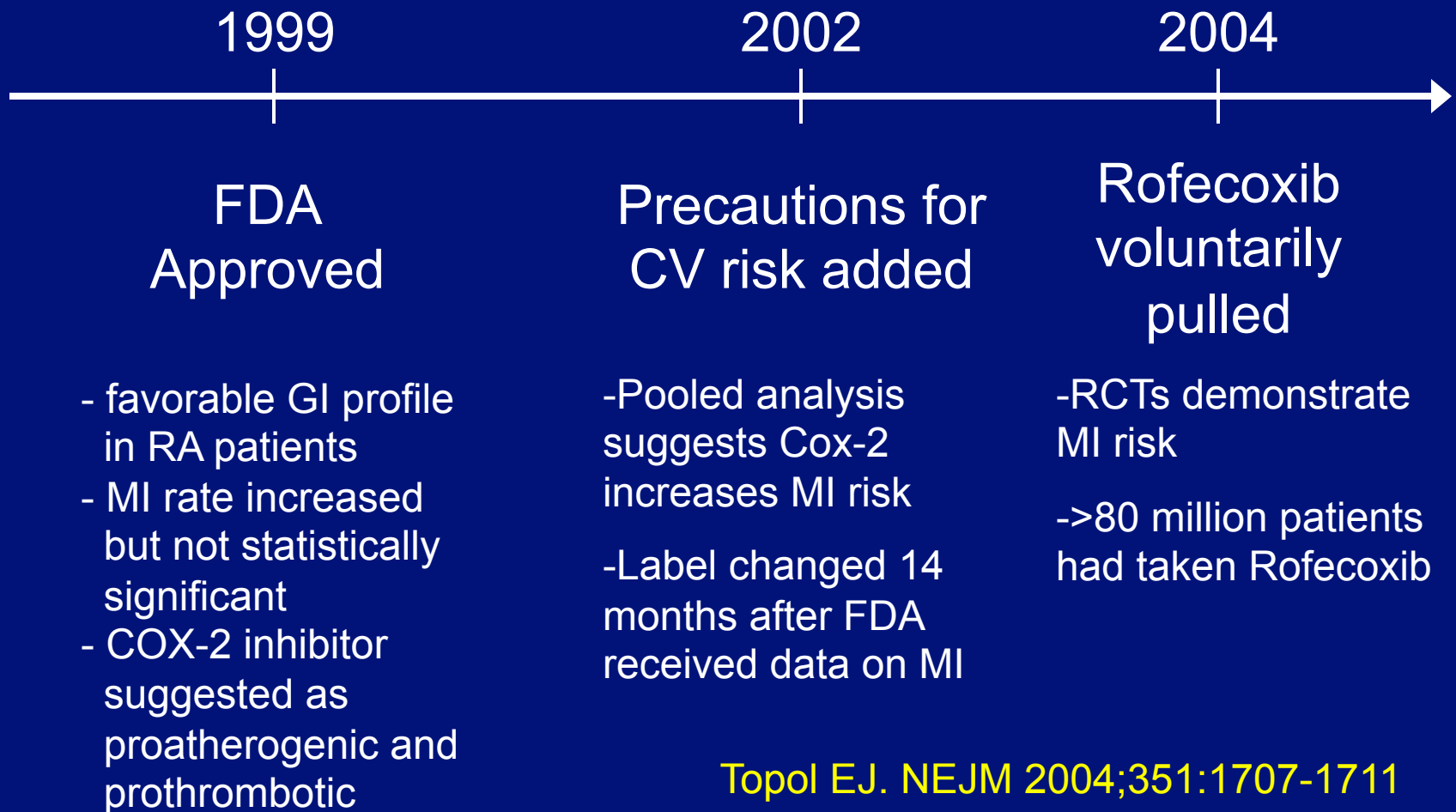
# Thiazolidinediones: Risks of off label use for psoriasis

- Approved by FDA for type II diabetes based on glucose control in late 1990's
- 2000 – case reports of psoriasis responding to troglitazone; withdrawn from market for liver toxicity
- 2007- rosiglitazone fails to show efficacy for psoriasis in large pivotal trials
- 2007 – rosiglitazone linked to excess risk of MI

Ellis, CN. Arch Derm 2000;136:609-616

Nissen, SE NEJM 2007;356:2457-71

# Case study: Rofecoxib



Topol EJ. NEJM 2004;351:1707-1711  
FitzGerald GA NEJM 2004;351:1709-1711

# Safety evaluation post FDA approval: Key Points

- Pharmacovigilance is the activities involved in the detection, assessment, understanding, and prevention of adverse effects or any other drug related problems (WHO definition)
- Relies primarily on epidemiologic studies
  - Descriptive: Generate Hypotheses
    - Case reports, Cross sectional, Ecological
  - Analytic: Test Hypotheses
    - Case control, Cohort, Clinical Trial

# Safety evaluation post FDA approval: Key Points

- FDA sponsored MEDWATCH program
- Relies on spontaneous reporting
- Advantages:
  - Cheap, covers “entire” population, generates safety “signals”
- Disadvantages:
  - Under-reporting, hard to attribute causality, can't determine “incidence”

# Case Report and Case Series: Signal Detection

- “A set of data constituting a *hypothesis* that is relevant to the rational and safe use of a drug in humans”
- They are the major source of information that drives labeling changes
- <5% of published case reports of adverse drug reactions are investigated with controlled studies
- They are not uniformly adopted into the prescribing information

Loke, YK, et al. BMJ 2006; 332(7537):335-9  
Drug Safety 1997;16:355-65

# Efalizumab and PML: Signal Detection in Action

- 2003 FDA approved Efalizumab
  - 2764 patients treated
  - 218 treated > 1 year
- 2008
  - 46,000 patients treated
  - 3000 treated for  $\geq 2$  years
  - 3 confirmed and one suspected case of PML spontaneously reported
- PML is an untreatable CNS infection that leads to death or serious disability
- PML occurs primarily with immunosuppression

# Efalizumab

- Estimated risk of PML in efalizumab treated patients:
  - Overall: 1 in 15,000 per year
  - Patients treated > 2 years: 1 in 1000
  - Likely an underestimate due to incomplete reporting
- Relationship likely causal
  - PML only occurs with immunosuppression
  - Odds reports were coincidental: <1 in 10,000
- Drug withdrawn in 2009

# Efalizumab and PML: Key points

- Spontaneous reports can be useful for very rare diseases such as PML, SJS, etc
- Absolute risk likely low but not well characterized.
- Risk judged unacceptable given treatment alternatives and disease indication
- Certain infections may require prolonged exposure to identify

**Do TNF inhibitors cause  
lymphoma?**

# What would you tell this patient?

I have been using Enbrel for three years and developed aggressive lymphoma. I can't help but suspect the Enbrel at least contributed to the disease. The Enbrel helped my arthritis, but I will never ever take another new wonder drug — it just isn't worth it!

# Let's Play the FDA

- Discussion of evidence
- Vote to decide:
  - Pull from market
  - BLACK BOX Warning
  - Warning
  - No action

# Let's Play the FDA

## (e) Warnings

The TPI should include a description of serious adverse reactions and potential safety hazards and limitations of use imposed by them, as these become known through the drug development program. *A causal relationship need not be demonstrated. Reasonable evidence should drive the listing.* FDA may require a BOXED warning if the risk may lead to death or serious injury - this is derived from clinical data usually, but can be from animal toxicology.

# Psoriasis and Lymphoma: Is this important

*Have you ever seen a patient with psoriasis and lymphoma?*

*With rare events individual practitioners are unlikely to observe an adverse reaction*

“Who you gonna believe  
– me or your own eyes”

Chico Marx –Duck Soup

# Psoriasis and Lymphoma

- Do psoriasis patients have an increased risk of lymphoma?
- Is the increased risk of lymphoma related to the disease or its treatment?

# Does psoriasis itself increase the risk of lymphoma?

- Conflicting results
- Unclear degree to which psoriasis and/or its treatment increases lymphoma risk
- Strong association of psoriasis with CTCL

| Study                | All Lymphoma | T-Cell Lymphoma | Hodgkin's Lymphoma | Non-Hodgkin's Lymphoma |
|----------------------|--------------|-----------------|--------------------|------------------------|
| Positive Association | 6 +          | 5 +             | 2+                 | 4+                     |
| Not associated       | 2 -          |                 | 5-                 | 5 -                    |

# Clinical Implications: Psoriasis and Lymphoma

Consider biopsy in severe disease, treatment failures

*CTCL may progress rapidly with immuno-suppression*

# Psoriasis and Lymphoma: Is this important

- Lymphoma is the 5<sup>th</sup> most common form of cancer and 5<sup>th</sup> most common cause of death from cancer
- Incidence is about 20/100,000 per year
- About 50,000 new cases per year, 20,000 deaths per year
- Lifetime risk is 1:50
- An estimated 2000 patients develop lymphoma related to psoriasis per year.

# Psoriasis and lymphoma: Safety of traditional therapies

- Several case reports of lymphoma associated with methotrexate treatment of psoriasis
- No adequate data from epidemiologic studies to determine the risk of lymphoma associated with methotrexate in psoriasis
- Several case reports of lymphoma associated with cyclosporine treatment of psoriasis

# Psoriasis and lymphoma: Safety of traditional therapies

- Observational cohort study in 11 European countries involving 277 centers
- Exposed Population – Psoriasis patients treated with cyclosporine for at least 1 month
- 1252 patients followed for 4440 person years
- 781 at most 2 yrs of CsyA; 471 2+ yrs
- Control Population – rates of cancer from registries of respective countries yields a *Standardized Incidence Ratio*

# Psoriasis and lymphoma: Safety of traditional therapies

|                     | Overall SIR   | <2 yrs SIR    | 2+ yrs SIR      |
|---------------------|---------------|---------------|-----------------|
| Any Cancer          | 2.1 (1.6-2.9) | 1.8 (1.2-2.6) | 3.3 (1.9-5.3)   |
| Any Skin Cancer     | 6.1 (3.8-9.1) | 4.8 (2.6-8.1) | 10.1 (4.6-19.2) |
| Any non-skin cancer | 1.3 (0.8-1.9) | 1.2 (0.7-1.9) | 1.7 (0.7-3.5)   |
| Lymphoma            | 2.0 (0.2-7.2) | 1.3 (0.0-7.2) | 4.3 (0.1-23.9)  |

# Biologics Adverse Events

| Biologic           | Common<br>>5%   | Uncommon<br>0.1%-5%  | Rare<br><0.1%  | Black Box  |
|--------------------|---|--|--|--|
| <b>Adalimumab</b>  | Injection site reaction<br>+ ANA<br>Elevated Alk phos, cholesterol    | Neutralizing antibodies<br>Serious Infections<br>Allergic reactions<br><b>Malignancy</b> | Tuberculosis,<br>Lupus like syndrome,<br>Hypersensitivity , Hep B reactivation. Demylenization,<br>Congestive heart failure,<br>Pancytopenia                     | Infection (bacterial sepsis, Legionella, Listeria, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens)<br>Lymphoma and other malignancies in children<br>hepatosplenic T-cell lymphoma (HSTCL) |
| <b>Etanercept</b>  | Injection site reaction<br>+ANA                                       | Serious infection<br><b>Malignancy</b>   | Tuberculosis,<br>Lupus like syndrome,<br>Hypersensitivity , Hep B reactivation. Demylenization,<br>Congestive heart failure,<br>Pancytopenia                     | Infection (bacterial sepsis, Legionella, Listeria, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens)<br>Lymphoma and other malignancies in children  |
| <b>Infliximab</b>  | Infusion reactions<br>+ANA<br>Elevated LFT<br>Neutralizing antibodies | Hypersensitivity<br>Serious infection<br><b>Malignancy</b>                               | Severe hepatic injury,<br>Tuberculosis, Lupus like syndrome, Hypersensitivity , Hep B reactivation. Demylenization,<br>Congestive heart failure,<br>Pancytopenia | Infection (bacterial sepsis, Legionella, Listeria, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens)<br>Lymphoma and other malignancies in children<br>hepatosplenic T-cell lymphoma (HSTCL) |
| <b>Alefacept</b>   | Lymphopenia   | Lft elevation<br>Serious infection<br><b>Malignancy</b>                                  | Hypersensitivity   | None   |
| <b>Ustekinumab</b> | None  | Serious infection<br><b>Malignancy</b>   | Reversible posterior leukoencephalopathy   | None   |

# Biologics and lymphoma: data from case reports

- Alefacept and efalizumab: Limited experience with (lymphomas observed in clinical trials and published case reports)
- TNF alpha inhibitors (for IBD, RA): By 2002, >80 reports of lymphoma to FDA (2-52 weeks into therapy).
- 12 psoriasis patients reported in literature to have developed lymphoma associated with biologics – 2 confirmed deaths, 4 cases of CTCL

# TNF inhibitors and Lymphoma: Meta-analysis Clinical Trials Data

| Study   | Group                                      | N lymphoma | Person years |
|---|--|------------|--------------|
| Bongartz et al<br>Ann Rheum Dis<br>2009;68:1177-83<br>RA                                | Placebo                                    | 0          | 1072         |
|   | Etanercept                                 | 2          | 2484         |
| Bongartz, et al<br>JAMA<br>2006;295:2275-85<br>RA                                       | Placebo                                    | 0          | 1512         |
|   | Adalimumab or<br>Infliximab                | 10         | 3493         |
| Askling et al.<br>Pharmacoepid and<br>Drug Safety<br>2011;20:119-130<br>All indications | Placebo                                    | 2          | 7486         |
|   | Etanercept,<br>Adalimumab or<br>Infliximab | 12         | 15418        |

# TNF inhibitors and Lymphoma: All Clinical Trials Data

| Drug       | N patients | N person years | N lymphoma | SIR (SEER)           |
|------------|------------|----------------|------------|----------------------|
| Etanercept | 3389       | 7364           | 6          | 2.31<br>(0.85-5.03)  |
| Infliximab | 2421       | 4116           | 6          | 6.98<br>(2.56-15.19) |
| Adalimumab | 2400       | 5760           | 10         | 5.42<br>(2.6-10.0)   |

## Lymphoma rates in RA population treated with anti-TNF therapy: cohort studies

| Author          | N TNF                | SIR                  | RR   |
|-----------------|----------------------|----------------------|--|
| Wolfe           | 8,614                | 2.9 (1.7-4.9)        |  |
| Wolfe           | 10,815               | 1.8 (1.5-2.2)        | 1.0 (0.6-1.8)                                |
| Wolfe           | 2,221                |                      | 1.0 (0.5-2.)                                 |
| Askling         | 6,604                | 2.0 (1.0-3.5)        | 1.35 (0.8-2.11)                              |
| Askling         | 4,160                | 2.9 (1.3-5.5)        | 1.1 (0.6-2.1)                                |
| Geborek         | 7,57                 | 11.5 (3.7-27)        | 5.0 (0.9-26)                                 |
| Setoguchi       | 1,152                | 2.2 (1.7-2.9)        | 1.1 (0.5-2.4)                                |
| Mariette        | 19,037*              | 2.3 (1.6-3.3)        | ADA 4.7 (1.3-17.7)**<br>INF 4.1 (1.4-12.5)** |
| <b>Mariette</b> | <b>Meta-analysis</b> | <b>2.5 (1.9-3.2)</b> | <b>1.11 (0.7-1.5)</b>                        |

Association → Causation

# Criteria for Causation: TNF inhibitors and Lymphoma

|                                  |  |
|----------------------------------|--|
| Time sequence                    | Yes, in case reports, clinical trials  |
| Biologic credibility             | Yes  |
| Dose response                    | Not well established   |
| Strength of study design         | Case reports and cohort studies  |
| Strength of association (OR, RR) | Modest to strong association depending on drug and study design                    |
| Consistency with other studies   | Studies controlling for channeling bias generally negative but may be underpowered |

# Let's Play the FDA

- Discussion of evidence
- Vote to decide:
  - Pull from market
  - BLACK BOX Warning
  - Warning
  - No action

# *Risk of lymphoma in TNF inhibitors*

- Risk well defined for 3-4 years of TNF exposure in RA population
- Some data suggest small excess risk of TNF antibodies compared to etanercept
- Absolute risk estimated to be small:
  - NNH 2000\*
- Expect to see 1 extra case of lymphoma for every 200 patients treated for 10 years\*

\*Dharamsi JW et al. Brit J of Dermatol. 2009; 161:605-16

**Does Isotretinoin Cause IBD?**

# Does isotretinoin cause inflammatory bowel disease?

1. *Is the association between isotretinoin and IBD due to chance (statistical error)*
2. *Are there third factors associated with isotretinoin that are independent risk factors for IBD (confounding)*
3. *Does the indication (severe acne) increase the risk of inflammatory bowel disease (channeling bias)*

# Isotretinoin and inflammatory bowel disease

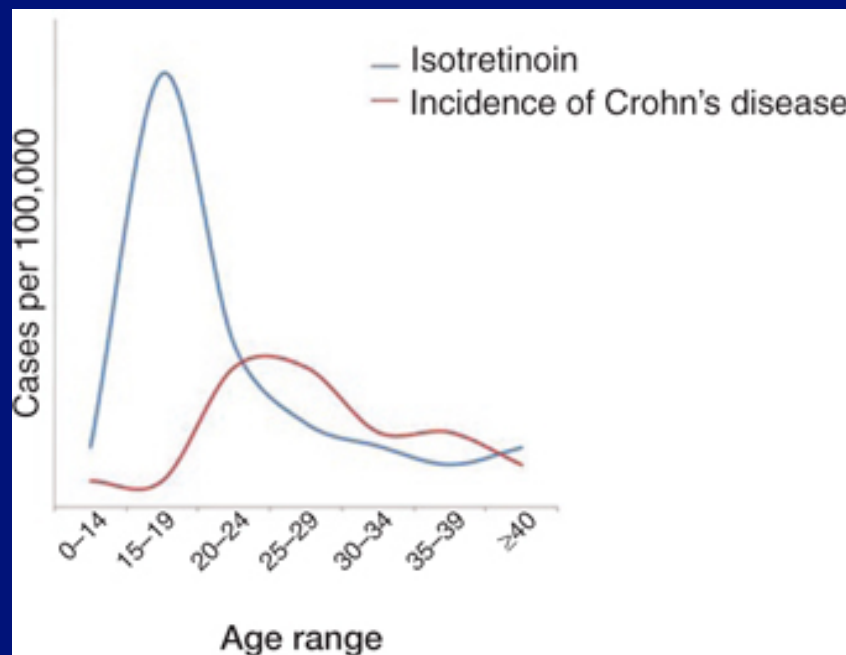
- 1982: Approved for severe nodular acne
- 1986 first report of a case of UC in patient treated with isotretinoin
- 1998: warning added to PI
- 2003 first lawsuit for IBD
- 2008 NJ woman awarded \$11 million
- 2009 Roche stops making Accutane (isotretinoin)

# Isotretinoin and IBD: Case Reports

- Review of FDA spontaneous reports 1997-2002 for “the cause of IBD”
  - Highly probable: 4 (5%)
  - Probable 58 (68%)
  - Possible 23 (27%)
- 3 cases with + dechallenge/rechallenge

# Isotretinoin and IBD: Causal or Coincidental?

- Expect 59 cases per year
- Only 14 cases per year reported
- Association could be due to CHANCE



# Isotretinoin and IBD: Case-Control Study

- Population based study using the Manitoba Health Administrative Database
- N= 2008 cases of IBD and 19, 814 controls
- No association with IBD, Crohn's or Ulcerative colitis
- Limitation: prolonged exposure window may produce bias towards the null

| Timing of Isotretinoin use | OR (95% CI)    | Median years |
|----------------------------|----------------|--------------|
| Prior to IBD               | 1.2 (0.7-1.77) | 2.5          |
| After IBD                  | 1.3 (0.8-1.9)  | 2.9          |

# Isotretinoin and IBD: Case-Control Study

- Large administrative claims database over 55 million patients from >70 health plans in the US
- N=8189 cases of IBD and 21,832 controls
- Exposure measured within 12 months of IBD
- Controlled for age, sex, geographic region

# Results

| Analysis           | OR (95% CI)    |
|--------------------|----------------|
| IBD                | 1.7 (0.98-2.9) |
| Crohn's disease    | 0.7 (0.3-1.7)  |
| Ulcerative colitis | 4.4 (2.0-9.7)  |

# Dose-response only seen for UC

| Dose Response      | Odds Ratio for UC |
|--------------------|-------------------|
| 10 mg increase     | 1.2               |
| 20 mg increase     | 1.5               |
| No dose escalation | 2.0 (NS)          |
| +Dose escalation   | 15                |
| Duration < 60 days | 2.5 (NS)          |
| Duration > 60 days | 5.6               |

# Isotretinoin and UC: Explained by Chance, Confounding, and Channeling Bias?

| Source of Error                            | Present?   |
|--|--|
| Is the association due to chance?          | NO   |
| Is the association due to confounding?     | Maybe: Unmeasured confounders include antibiotics, smoking, and OCPs |
| Is the association due to channeling bias? | Maybe: Not investigated  |

# Criteria for Causation: Isotretinoin and IBD

|                                |   |
|--------------------------------|---|
| Time sequence                  | Yes, in case reports, case control study for UC           |
| Biologic credibility           | Unknown   |
| Dose response                  | Yes for UC  |
| Strength of study design       | + study lacks control for confounders and channeling bias |
| Strength of association (OR)   | Crohn's: None<br>UC: Modest, wide 95% CI                  |
| Consistency with other studies | Only 2 studies with conflicting results                   |

# Mock FDA Advisory Committee

- Does isotretinoin cause inflammatory bowel disease?
- Vote to recommend:
  - Pull from market
  - BLACK BOX Warning
  - Warning
  - No action

# Isotretinoin and IBD: Summary

- Causal association not established
- Enterocolitis may go away with isotretinoin withdrawal and recur if isotretinoin is restarted
- Data suggest a specific association with UC, but data are conflicting, and channeling bias and confounding has not been addressed
- Risk if real is small (NNH =3,000)
- Physicians and patients need to carefully weigh risks vs benefits of isotretinoin treatment

# Conclusions

- The benefits of treatment are well characterized relative to the long-term safety and the risk of rare but serious medical events
- There is a need for ongoing risk assessment throughout the lifecycle of a drug
- For clinicians
  - Use the science of medicine in judging safety
  - Use the art of medicine communicating risk of therapies to patients

# Practical Advice

*Do not be the first to prescribe a new treatment ...and do not be the last to stop prescribing an old one.*

The Lectures of Sir  
William Osler

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