Safety of Biologic Therapies:
What’s the Real Story?
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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY
Mark Ling, MD, PhD
Focus U097
Safety of Biologic Therapies

Financial relationships
Current clinical research grants
   Amgen
   Abbott
   Centocor
   CollaGenix/Galderma
   Novartis
No other financial ties in last year
   No speakers’ bureau, consultancies, etc

Disclosure Statement
All drugs discussed are “on-label” for the treatment of psoriasis
   Stelara (ustekinumab) now approved
Per AAD policy, information presented is in the public domain and has been published
   Single exception will be clearly labeled as to source

Handouts
Available on our website for download
   www.NewnanDermatology.com
   Under Your Health > Resources

Safety of Biologic Therapies

What’s the real story?
Safety is a critical element in the choice of treatments for moderate to severe psoriasis
Failure to understand safety issues puts both patient and doctor at risk
Goal of this lecture is to look in depth at recent data on safety of the three most popular biologics for psoriasis
   Etanercept (ETN)
   Infliximab (IFX)
   Adalimumab (ADA)
And a brief look at the newest biologic for psoriasis, ustekinumab (UST)

Biologic Therapy for Psoriasis
And then there were three (then four…)
   Why ETN, IFX, and ADA?
      TNF inhibitors are the vast majority of biologics for psoriasis in 2009
      Alefacept has never achieved more than a percent or two of market share
      Efalizumab off market
Therefore, TNF inhibitors dominate the current market
   Impact of UST to be seen
Only TNF inhibitors have sufficient postmarketing experience to allow reliable analysis

Biologic Therapy for Psoriasis
Biologic drugs for psoriasis are a revolution in our approach to this disease
Since Amevive was approved in January 2003, there has been a wholesale shift in how dermatologists treat moderate to severe psoriasis
For those dermatologists who choose to treat patients with moderate to severe psoriasis, they represent a true paradigm shift

Trends in Biologic Use
Still, many pts who are candidates for biologic therapy do not use them
Pts do not want them or
Dermatologists do not offer them
Main concerns are cost and safety for both parties
Copays and deductibles for pts
Prescribing profiles, “P4P” for derms
Systems that label dermatologists who prescribe expensive therapies as “substandard” physicians
Safety concerns for both

Trends in Biologic Use
Issues of cost are beyond scope of this talk, and my expertise
Safety however is an issue that can be addressed
We have the ability to analyze safety to a degree never seen with older agents such as MTX
While we will never know all the answers, these are some of the most closely studied drugs in history

Biologics and Safety
Drug toxicity takes many forms
Understanding risk depends on knowing how to look for it
Toxicity comes in many forms
Early vs late
Common vs rare
Mild vs severe

Biologics and Safety
Analysis often confounded by risks associated with:
Underlying disease state
i.e. increased lymphoma rate in RA pts
Other concomitant therapies
IFX and MTX for RA
Confounding factors
e.g. women taking antidepressants are more likely to consume large amounts of alcohol
Thus, increases in cirrhosis may not be due to antidepressants themselves

Biologics and Safety
The type of toxicity being considered determines where the proper source of data should be
Three main sources of data
Randomized, placebo-controlled clinical studies
Standard Incidence Ratios
Long term observational studies based on
Registries
Spontaneous post marketing reports

Evaluating Safety Data
Relative Risk Analysis (RR)
Comparison between treatment arm and placebo control arm of randomized, controlled clinical trials (RCTs)
Randomized placebo group represents best biological comparator
Best able to compensate for issues relating to underlying disease state and disease-associated confounders

Evaluating Safety Data
Limitation of Relative Risk Analysis
Duration of studies too short to permit analysis of long term drug use
i.e. induction of malignancy
Studies too small to detect rare events
Patients in randomized clinical trials may not be representative of the general population

Evaluating Safety Data
Standardized Incidence Ratio (SIR)
Comparison of rates from RCTs and open label phases of controlled clinical trials to general population reference
Limitation of SIR
The general reference population may have different levels of risk compared to patients treated in randomized clinical trials
Like RR analysis, may be underpowered to identify rare AE’s and too brief to detect long term events

Long term data collection
Third alternative for data acquisition
   Only way to gather information on events that are rare and may take extended time to develop

Two sources of data
   Registries: large pools of patients on therapy who are followed over extended time frames
   Post marketing reporting
      Spontaneous reports to manufacturer or FDA

**Post marketing Reporting**

Limitations
   Registries have no formal control group, relying on general population incidences as comparator
   Intensity of monitoring much lower
   Post marketing reporting heavily underreports events
      Rely upon clinicians going “out of their way” to voluntarily report experiences

**Short Term Safety**

Safety events elucidated by Randomized Clinical Trials data
   Typical length of pivotal study for psoriasis drug approval is 12 weeks
      Often with subsequent open label long term studies for safety and efficacy information
      Much of what is in package insert is based on these data

**Short Term Safety**

Toxicities likely to be identified during short term RCT’s
   Early in onset
   Frequent enough to be detected by relatively small trials populations
   Usually less severe
      Severe, early and frequent toxicities usually mean an unapprovable drug

**Infliximab Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>3 mg/kg</th>
<th>5 mg/kg</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated</td>
<td>51</td>
<td>98</td>
<td>99</td>
<td>197</td>
</tr>
<tr>
<td>Average weeks of follow up</td>
<td>20</td>
<td>29.6</td>
<td>30.7</td>
<td>30.2</td>
</tr>
<tr>
<td>Patients with 1 or more adverse events</td>
<td>63%</td>
<td>78%</td>
<td>79%</td>
<td>78%</td>
</tr>
</tbody>
</table>

**IFX Adverse Events in ≥ 5% of Patients**

**Reasonably Related Serious Adverse Events Through Week 30**

4 reasonably related SAE’s
   3 mg/kg
      Squamous cell carcinoma
      Cholecystitis and cholelithiasis
   5 mg/kg
      Diverticulitis
      Sepsis and pylonephritis

**Incidences of IFX Infusion Reactions Through Week 26**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>3 mg/kg</th>
<th>5 mg/kg</th>
<th>Combined</th>
</tr>
</thead>
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<tr>
<td>Patients treated</td>
<td>51</td>
<td>98</td>
<td>99</td>
<td>197</td>
</tr>
<tr>
<td>Total number of infusions</td>
<td>147</td>
<td>341</td>
<td>343</td>
<td>684</td>
</tr>
<tr>
<td>Infusions with infusion reaction</td>
<td>1 (0.7%)</td>
<td>19 (5.6%)</td>
<td>26 (7.6%)</td>
<td>45 (6.6%)</td>
</tr>
</tbody>
</table>
   Mild | 1 (0.7%) | 11 (3.2%) | 18 (5.2%) | 29 (4.2%) |
   Moderate | 0 (0.0%) | 8 (2.3%) | 6 (1.7%) | 14 (2.0%) |
   Severe | 0 (0.0%) | 0 (0.0%) | 2 (0.6%) | 2 (0.3%) |

**Antibodies to Infliximab**

Overall incidence of antibodies
23.3% (38/163)
  3 mg/kg - 27.6%
  5 mg/kg - 19.5%

Low titers
  37/38 are ≤ 1:40
  1 subject - 1:80
13 inconclusive patients
  4 in 3 mg/kg
  9 in 5 mg/kg

Percent of patients with antibodies is comparable to similar patient populations in other infliximab studies

Laboratories

Few markedly abnormal values
  Generally equal across treatment groups
24% of infliximab treated patients newly positive for ANA during study
  13.5% positive at final visit
  1 placebo patient newly positive for anti-dsDNA
No patients with signs of connective tissue disease

Most Frequent Infectious Adverse Events

percent of patients

Injection Site Reactions

Injection site reaction (ISR): all events at the injection site including erythema and/or itching, hemorrhage, pain or swelling

Incidence rates of ISRs in pivotal trials
  20% of patients treated with Adalimumab™
  14% of patients treated with placebo

Study withdrawals due to ISR-related events
  0.3% of patients treated with either Adalimumab or placebo

Biologic Safety Issues

Based on the RCT’s done for drug approval, these drugs look remarkably well-tolerated
These data however, while used in the marketing of drugs and in the FDA’s analysis of risk/benefit issues, are incapable of answering the most important questions

Biologic Safety Issues

Toxicities can be
  Common vs rare
  Serious versus non-serious
  Early or late in treatment course

The most worrisome toxicities are rare, serious, and delayed in onset
  Common and serious: detected by RCT
  Rare, serious, and early in course: rapidly detected as clinical experience gained
  Rare, serious and late are the most difficult to identify

Biologics and Safety

Perhaps the wisest place to start when thinking about toxicity is based on our theoretical understanding of the side effects that would be predicted by the drugs’ mechanisms of action
These are fundamentally drugs that suppress an arm of the immune system
Immunosuppression-associated toxicities should be the greatest concern

Biologics and Safety

Immunosuppression is predicted to create issues in two main areas
  Infection
  Malignancy via suppression of immune surveillance
Infection certainly most logical concern
  Black box warnings
    Adalimumab: “Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens”
Etanercept and infliximab: “Patients treated with [ETN/IFX] are at increased risk for developing serious infections that may lead to hospitalization or death”

**Biologics and Infection**

Role of TNF in immunity
- Part of a highly complex network of inflammatory mediators
- Produced primarily by activated monocytes/macrophages as response to many stimuli
- LPS and other components of gram positive and negative bacteria, viral infections
- Can also be expressed by activated T cells, B lymphocytes, NK cells

**TNF Biology**

Effects of TNF are broad
- Anti-tumor activity
- Antiviral activity
- Mechanisms of shock

Released early by innate and adaptive immune system as response to injury
- “Sentinel” cytokine initiating defense response

**TNF Biology**

TNF plays particularly important role in immunity against granulomatous diseases
- Histoplasmosis, fungal, and particularly mycobacterial infections

Effects are multiple
- Increases ability of macrophages to phagocytose and kill mycobacteria
- Essential to production of chemokines and leucocyte chemotaxis needed to form granulomas
- Maintenance of granulomas essential when invading mycobacteria are not successfully killed
- TNF continuously sustains continuous recruitment and activation of cells that maintain granulomas

Based on roles of TNF, blockade would be predicted to increase risk of infections, particularly granulomatous

Confirmed in multiple animal models including TNF-deficient mice

Theoretical models are however, no substitute for real-world experience

What do the clinical data tell us about infection risk with TNF inhibitors (TNFi)?

**Infection risks**

TNF inhibitors are as a group some of the most closely studied drugs in history
- Enormous efforts from all parties involved: FDA, manufacturers, and the academic medical community
- Have resulted in more knowledge about these drugs than ever seen before
- Greatly facilitated by the creation of numerous large, well-organized registries

**TNF inhibitors and TB**

The greatest concern based on mechanism of action

Also the most significant infection risk from the earliest days of TNFi use
- Remains a critical concern
- In the Black Box warnings for all three TNFi’s in the U.S.
- PPD’s mandated before therapy for all, with treatment for latent TB prior to initiation of therapy mandatory

**Tuberculosis**

Two most valuable sources of information
- Published data from large registries
- Unpublished data collected by manufacturers and submitted annually to the FDA
  - Includes spontaneous reports and survey data
  - Latter is not sanctioned by the AAD for discussion at this meeting

Date cited here are all in public domain
- Publications
- Meeting abstracts subsequently published

**Tuberculosis**

Most recent data from large registries
- Askling, EULAR 2007, Abst THU0125
  - Swedish national registry
  - 6304 RA pts treated with TNFi between 1998 and 2006 compared to 67,581 biologic-naïve RA pts and 470,361 from the general population
  - Groups compared via Relative Risk ratios (i.e. incidence in treated group divided by incidence in control group)
Askling 2007 results
  RR of TB in TNFi treated group was 31 (95% CI 18 – 51) versus general population
  RR compared to biologic-naïve RA pts was 9.0 (4.9 – 16)
  RR in first year was 12, in second year 7.7, and in third year 7.8
  Earlier cases presumed to contain reactivation TB, later years new onset infections
  Concludes that TB is increased in RA, and further increased by TNFi treatment

Tuberculosis

  BIOBADASER Spanish registry
  5,198 RA pts treated with TNFi, most treated after 2003
  PPD screening recommendation promulgated in 2002 (PPD x 2 if first negative)
  RR of active TB vs general population was 1.8 (.28 – 7.1) when protocol followed
  RR was 13 (6 – 25) when not followed

Tuberculosis

Gomez-Reino
  Incidence per 100,000 for active TB was 383 for infliximab, 176 for adalimumab, and 114 for etanercept
  Not statistically significant
  Conclusion: lack of compliance with screening/ treatment protocol was a significant risk factor

Tuberculosis

  Older data
  U.S. NDB registry
  Based on surveys and medical record reviews
  Data on IFX treated pts only
  Incidence rate of TB prior to introduction of IFX was 6.2 cases/100,000 (1.6 – 34.4)
  In pts on IFX IRR was 61.9/100,000

Tuberculosis

Tubach, Arth Rheum 2009, 60:1884
  French RATIO registry
  Survey of all TB cases 2004 - 2007
  Patients prescreened with PPD
  69 cases of TB noted
  SIR vs general population:
    All TNFi: 12.2 (9.7, 15.5)
    IFX 18.0 (13.4, 25.8)
    ADA 29.3 (20.3, 42.4)
    ETN 1.8 (0.7, 4.3)

Tuberculosis

Tuback
  Odds ratio
    IFX versus ETN 13.3 (2.6, 69.0)
    ADA versus ETN 17.1 (3.6, 80.6)
  Other risk factors identified
    Age
    First year of TNFi treatment
    Pt born in endemic TB area

Tuberculosis

Dixon et al, Ann Rheum Dis online 22 Oct 2009
  British BSRBR registry
  10,712 TNFi pts vs 3232 on DMARDs
  40 cases of TB in TNFi, none in DMARD cohorts
  Rates of TB/100,000 pt-yrs
    ADA 144, IFX 136, ETN 39
  Incidence rate ratio versus ETN
    ADA 3.1 (1.0, 9.5)
    IFX 4.2 (1.4, 12.4)
  Time to event 5.5 mo IFX, 13 mo ADA, 18.5 mo ETN
  1/3 of cases after discontinuation of treatment
62% were extrapulmonary

**Tuberculosis**

**Conclusions**
- Risk of TB clearly elevated with TNFi therapy
- Risk reflects local endemic TB rates
- Screening markedly reduces but does not eliminate risk
  - Double screening (second PPD if first negative) appears superior

**Tuberculosis**

Risk strongly dependent on type of TNFi
- ETN appears to induce at most modest added risk, and in some studies, no increase in risk of TB
  - Aggarwal J Rheum 2009, 36:914
  - 80 PPD-positive pts, 74 treated for LTBI
  - All treated with ETN
  - No cases of active TB noted
- IFN and ADA appear to increase risk substantially
  - Increased risk up to 17-fold vs ETN in some studies

**Non-TB Serious infections**

Concerns here are more generally related to immunosuppression
- TNF plays a diverse range of roles in the immune response and thus would be expected to have some impact on immunity to non-granulomatous infection as well
- Again, registry data are abundant and important to review

**Non-TB Serious infections**

- British BSRBR registry
- 8,659 RA pts on TNFi, and 2,170 on DMARD only
- Total of 1089 serious infections (those resulting in hospitalization or death, or requiring i.v. antibiotics)

**Non-TB Serious infections**

Dixon
- Rate of serious infection was 39.2/100,000 pt-years with DMARDs, and 63.2/100,000 with TNFi’s
  - ETN 61.7
  - IFX 68.9
  - ADA 54.2
- Risk peaked at 6 months and declined over time
  - Possible selection bias

**Non-TB Serious infections**

Curtis, ACR 2007, Abst 1024
- North American CLAIMS database
  - 937 pts on MAb-based TNFi
  - 1201 pts on non-MAb based TNFi
  - 2933 pts on MTX
- Incidence rates for serious infection
  - Within 6 months of initiation of Rx:
    - 4.5 (2.7 – 7.1) for IFX/ADA
    - 1.9 (0.9 – 3.5) for ETN
    - 1.7 (1.0 – 2.6) for MTX
  - After 6 months:
    - 1.1 (0.4 – 2.4)
    - 1.2 (0.7 – 2.0)
    - 1.5 (1.1 – 2.1)

**Non-TB Serious infections**

Listing, Arthritis Rheum 2005: 52: 3403
- German RABBIT registry
  - 1529 RA pts
- Risk ratio for non-serious infections
  - 2.31 (1.4 – 3.9) for ETN
  - 3.01 (1.8 – 5.1) for IFX
- Risk ratio for serious infections
  - 2.82 (1.4 – 5.9) for ETN
Non-TB Serious Infections

Greenberg et al, 2009, Ann Rheum Dis online 8 April 2009
CORRONA N. American registry
7971 pts
Incidence rate ratios for overall infections
MTX 1.30 (1.12, 1.50)
TNFi 1.52 (1.30, 1.78)
Prednisone > 10 mg daily 1.30 (1.11, 1.53)
For opportunistic infections
TNFi 1.67 (.095, 2.94)
Prednisone 1.63 (1.20, 2.21)

Conclusions
TNFi appear to significantly increase risk of serious infections
Risk highest early after initiation of treatment
Unlike TB, risks appear roughly equal independent of whether TNFi was MAb based (IFX, ADA) or non-antibody based (ETN)
Concomitant use of steroids, poor overall status at treatment initiation add additional risk

Fungal Infection
Recent change to labeling to emphasize risk of invasive fungal infections
Histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, pneumocystosis
May be disseminated
Consider empiric therapy with severe systemic illness

Surveyed all published reports of fungal infection associated with TNFi use
281 cases found
226 assoc with IFX
44 with ETN
11 with ADA (duration effect?)
Commonest: histo, Candida, aspergillosis
Pneumonia most common pattern
32% of cases fatal

Smith and Kauffman, Drugs 2009, 69:1403
Review article
“these agents…associated with increased risk of infection with the endemic fungi, particularly H. capsulatum and Coccidioides spp. The greatest risk appears to be with IFX, followed by ADA and then ETN.”
TNFi pts should be monitored
“Anorexia, weight loss, malaise, fever, chills, sweats, cough and dyspnoea should be promptly evaluated”
“Early empirical therapy is vital because delay…is associated with poor outcomes”

Herpes Zoster
Perez-Zafrilla, EULAR 2008 Abst FRI0129
BIOBADASER database
11,636 pt-years of exposure
75 cases of zoster seen giving incidence of 6.44/1000 pt-yrs
Compared with EMECAR non-biologic exposed pts, incidence of HZ 2.64/1000 pt-yrs
Global hazard ratio 2.44

Herpes Zoster
Strangfeld, et al, JAMA 2009, 301:737
German RABBIT registry
Rate of zoster in pts on TNFi vs conventional DMARDs
Incidence rates/1000 pt-years
11.1 (7.9, 15.1) MAbs
Differentiating TNF Inhibitors

Is there a reason to explain why etanercept might have a different toxicity profile versus infliximab and adalimumab?

- It may relate to the monomeric, non-crosslinking nature of the receptor fragment, versus the divalent, crosslinking binding of the monoclonal antibodies

Differentiating TNF Inhibitors

There are clear biological differences

- Etanercept ineffective in granulomatous diseases like Crohn’s
- Not surprising then that you might see a higher risk of granulomatous infectious diseases with monoclonals

This is what the data show

Mechanism

Zou et al* have shown in vitro differences in monocytes from pts with ankylosing spondylitis treated with infliximab and etanercept

- Etanercept led to up-regulation of T cell production of both TNF alpha and interferon gamma, and an increase in the number of TNF and IFN-positive CD8+ T cells after antigen challenge
- Infliximab produced opposite effect, with significant reduction in TNF and interferon production, and a reduction in TNF/IFN+ T cells, possibly due to induction of apoptosis of TNF+ T cells

Differentiating TNF Inhibitors

Saliu, et al, JID 194: 486

- Infliximab and adalimumab decreases TB-responsive CD4 cells and interferon gamma production 70%, etanercept had no effect

Shen, et al, Aliment Pharm Ther 21:251

- Adalimumab and infliximab, but not etanercept, induces apoptosis of cultured monocytes and reduces IL-10 and -12 production

Differentiating TNF Inhibitors

These differences would predict differences seen in clinical effects

- Infliximab and adalimumab effective in granulomatous diseases like Crohn's
- Etanercept not effective

May see greater degree of immunosuppression with monoclonals, with increases in risk of granulomatous infection in particular

Infection and TNFi

Conclusions

- TNFi therapy does lead to significant increase in risk of infection
  - Particularly with granulomatous infections, especially TB
  - TB risk reduced but not eliminated with pre-treatment screening and treatment of latent TB
  - Double screening appears useful
  - Risks particularly high early in treatment

Infection and TNFi

Conclusions

- High awareness and early initiation of therapy including empiric coverage for opportunistic pathogens appropriate
- Risks are dependent upon geographic factors
  - i.e. TB in Eastern Europe, coccidio in SW U.S.
- Risks for granulomatous infections higher with MAb TNFi (IFX and ADA) vs soluble receptor TNFi (ETN)

Infection presents significant concern

- From risk-benefit perspective, appears still to be an appropriate choice
  - For example, Curtis data suggest that MTX, generally recognized as first line alternative to TNFi for RA, may present similar infection risks as ETN, and for IFX and ADA after first six months of therapy
Counterbalanced by lower incidence of non-infectious complications

**PML and Biologic Therapy**

“Hot off the presses”
A topic of intense interest for any dermatologist using biologics
By February 2009, multiple reports of PML in pts on efalizumab
Drug pulled off market in Canada, Europe and then U.S. by April 2009

**PML**

Demyelinating disease of the CNS
Predominantly among severely immunocompromised
Caused by activation of the JC polyomavirus
Normally dormant in kidney and lymphoid tissue
65% are seropositive by age 17
If activated, causes destruction of myelin-producing oligodendrocytes
Results in loss of coordination, weakness, visual deficits, speech disturbances, seizures, mental impairment and memory loss

**PML**

Found typically with profound immunosuppression
HIV/AIDS
Now 55%-85% of PML HIV-associated
Up to 3.8% of AIDS pts will develop PML
Lympho- and myeloproliferative disease—HD, CLL
Autoimmune and granulomatous disease
Transplant anti-rejection therapy and cancer chemotherapy

**PML**

Therapy
Currently no proven treatment
Early suggestions that cytosine arabinoside and interferon might be useful have been disproved
Most cases fatal
Only proven therapy is anti-retroviral therapy in AIDS-associated cases
Especially in less advanced cases
CD4 > 100, low JC viral load

**PML and Biologics**

FDA had reports of 3 confirmed, and 1 possible case of PML in pts treated with efalizumab
Initial report of one proven and one suspected case in October 2008
Proven case in 70 y.o. on therapy for 4 years
Suspected case 62 y.o. on for over 3 years
Second proven case in November
73 y.o. on for 3.75 years
Initial suggestion was that risk factors were age as well as duration of therapy

**PML and Biologics**

Latest case suggested otherwise
German male, only 47 y.o., but on therapy for 3.2 years
Only common risk factor duration of therapy
Very troubling: Craig Leonardi quoted at 2009 Hawaii Derm meeting:
“Efalizumab exposure is often estimated at 46,000 [patients] worldwide, but … the number treated for three years is about 1,100.”
"If you are talking about three out of 1,100 that is a very different number than three out of 46,000”
Efalizumab withdrawn off market as of April 9, 2009

**PML and ETN**

Data for TNFi are much more reassuring
ETN: 3 possible cases reported
1 pt with Wegener’s, on ETN and cyclophosphamide within one year of PML diagnosis
This combination of therapies is contraindicated due to lymphoma risk
2nd case 74 y.o. RA pt with multiple Rx including prednisolone, gold, penicillamine, MTX, leflunomide, and cyclophosphamide
Developed progressive encephalomenigitis
PCR for JC virus negative x 2

**PML and ETN**
Third case
60 y.o. RA pt
Prior MTX, penicillamine, azulfidine
Within two months of starting ETN 25 mg BIW, developed symptoms of leukoencephalopathy
ETN d/c’d and pt treated with high dose steroids
After 4 days symptoms resolved and at 3 months pt was fully well
Highly unlikely to be PML

PML and ADA, IFX
No reports of PML associated with ADA use
Either in clinical trials or subsequent reporting
IFX
Durez 2005, Rheumatol 44:465
Evaluated efficacy and safety of dose adjustment of IFX in RA pts on MTX
511 pts
Single death reported, considered by Centocor to be probably PML

PML and IFX
Van Assche 2005, NEJM 353:271
60 y.o. pt with CD
Treated with natalizumab (Tysabri)
Presented with CNS symptoms, died three months later
Diagnosed with PML
Had taken IFX but last dose was 20 months before hospitalization
natalizumab well established as risk factor for PML
IFX unlikely to have played a role

PML and IFX
Retrospective chart review of severe adverse reactions to IFX in pediatric pts with CD/UC
One report of 16 y.o. with extremely severe CD on IFX and azathioprine
Developed septicemia with subsequent deterioration and MRI findings that were called PML
Unlikely to be PML
Onset was acute
MRI findings not typical for PML
CSF negative for papovavirus (highly cross-reactive for polyomavirus)
Histopathology nonspecific
MRI lesions resolved rapidly and pt fully recovered within six weeks

PML and TNFi
Conclusions
PML rare with TNFi use
Only two cases with adequate data to confirm PML diagnosis
One in pt on ETN and CTX
Single case in pt on IFX and MTX
All other cases do not appear to meet reasonable clinical criteria for Dx
Given enormously larger cumulative exposure to TNFi versus efalizumab, these data are reassuring
However, any pt on TNFi presenting with neurological symptoms should be carefully evaluated with
PML as one consideration

Malignancy and TNFi
The other rare, serious, and delayed toxicity of great concern
Immunosuppressive drugs may in theory interfere with immune surveillance
Certain malignancies (B cell lymphoma) may be directly triggered by infectious agents
Drugs such as TNFi raise concerns over malignancy

Malignancy and TNFi
Three distinct areas of concern
Lymphomas
Particularly virally-induced, e.g. Epstein Barr-induced B cell lymphoma
Other visceral malignancies
Skin cancers

Malignancy and TNFi
Cancer is an infrequent occurrence with a significant latency period
Drug-induced malignancies would be predicted to be rare, and to develop relatively late after initiation of
therapy
RCT’s are underpowered and too short in duration to detect drug-related malignancies
Fortunately, current TNFi have been in use for extended time
Development of registries facilitates analysis

**Lymphoma and TNFi**

A heterogeneous group of relatively rare lymphatic cancers
Annual incidence in U.S. estimated at 20/100,000
Dramatic increase over last few decades
Much felt secondary to increased use of immunosuppressive medications

**Lymphoma and RA**

Majority of data on use of TNFi derived from RA patients
Leads to important confounder in analysis
RA patients are at increased risk for lymphoma based on disease itself
Multiple studies dating back to 1970’s consistently show a 2- to 4-fold increase in lymphoma compared to general population

Reason for increased risk unclear
Little evidence to support genetic predisposition
No clear association with “shared environmental factor”
i.e. occupation, alcohol use, obesity, etc.
Leading hypothesis is that persistent immune activation predisposes to both RA and lymphoma
Speculates that chronic activation of B-cells by exposure to foreign or auto-antigens leads to mutations and malignant transformation

**Lymphoma and RA**

Immune activation theory consistent with observation that risk of lymphoma correlates with severity of RA
Case control study showing that moderate RA pts had 5-fold increase in lymphoma while severe RA pts had over 20-fold increase
This further increases potential for erroneous bias, as TNFi would be predicted to be used more frequently in pts with more severe RA: “channeling bias”

**Lymphoma and Psoriasis**

This phenomenon is not confined to RA
Gelfand 2006: J Invest Dermatol 126: 2194
Risk of lymphoma in mild and severe (on systemic rx) psoriasis pts
Relative risks:
Lymphoma 1.34 (1.16 – 1.54) and 1.59 (0.88 – 2.89)
Hodgkin’s 1.42 (1.00 – 2.02) and 3.18 (1.01 – 9.97)
CTCL 4.10 (2.70 – 6.23) and 10.75 (3.89 – 29.76)
NS for NHL
Appears increased but as authors note “risk…is low given that lymphoma is a rare disease and the magnitude of association is modest”

**Lymphoma and TNFi**

Concerns raised early in experience
26 cases of lymphoma reported to FDA in pts on TNFi
Onset was early: median time 6-8 weeks
Raised concern of “latent lymphoma”

What are the data?

Package inserts raise concerns
All three state “In controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients”
ETN 3/4509 vs 0/2040
ADA 2/3853 vs 1/2183
IFX 5/5707 vs 0/1600
Does this confirm an increased risk?

**Lymphoma and TNFi**
Is increase in lymphoma seen in actively treated pts in RCT’s indicative of TNFi-induced risk? Interestingly, with all three TNFi, this appears to reflect not an increased risk of lymphoma in treated patients compared to general population, but a lower risk of lymphoma in placebo-treated pts versus general population.

Unclear what the significance of this is.

Other analyses of RCT data

Gottlieb 2008: Eur Coll Rheum Abst FRI0113
- Safety data of all pts treated with ETN during controlled portions of RCT’s sponsored by Amgen/Wyeth across all approved indications
- Control groups treated either with placebo or DMARD
- 13,926 pts with 17,656 pt-years of ETN exposure

Lymphoma and ETN

Increase in RA may be explainable based on intrinsic risk associated with disease.

Lymphoma and ADA

Burmeister 2009: ARD Online First: 10.1136/ard.2008.102103
- Data from 36 global trials across 6 indications
- RCT, open-label, and long-term extension studies through April 2007
- Total of 19,041 pts, 25,731 pt-years of exposure

Lymphoma and TNFi
- Lymphoma and TNFi
- Lymphoma and IFX

Burmeister
- Only significant increase in lymphoma was in RA trials (SIR 2.98, 1.89 – 4.47)
- While trend is towards higher rates in other indications, none show statistically significant increase

Centocor data
- ALERT: data I am presenting is not published in the public domain
- Data for ETN and ADA are in public domain
- To ensure balanced presentation, similar data on IFX were essential
- Data is on file at Centocor and CAN be accessed by any dermatologist by placing a request to Centocor Medical Information at 1-800-457-6399
- Request for information on Occurrence of Malignancies relating to IFX

IFX clinical trials data
- Total of 4990 pt-years of f/u in IFX-treated pts
- Incidence in controlled and open-label portion of RA trials 0.08 cases/100 pt-yrs
- Relative risk versus SEER database (general population) approximately 3
- Would appear roughly comparable to expected rate in RA population
- No equivalent data across all indications was discoverable to me

Hepatosplenic T-Cell Lymphomas
- An important side note
- May be unique to IFX and IBD
- Approx 100 cases reported worldwide
- Extremely rare aggressive lymphoma
- Fatal outcome within 2 years in most cases
- As of Oct 2006, the FDA AERS system had received 10 reports of HSTL in young pts
- Most cases fatal
- All cases in pts on concomitant azathioprine or 6-MP

Clinical trial data give conflicting data
- Rates of lymphoma are higher when compared to placebo-treated pts
- But that is based mainly on lower than expected rate of lymphoma in placebo groups
- Rates of lymphoma do not appear increased when compared to general population (non-RA trials), or to a comparable population of RA pts not treated with TNFi
- What’s the answer?

Other approach is to utilize registry data
As with infection, multiple registries now exist that may help address this question. A brief summary of some of the most relevant registries sheds additional light.

**Asking 2007 EULAR Abst THUD0124**
- **ARTIS Swedish registry**
  - 6304 RA pts on TNFi vs 67,338 RA pts not on TNFi
  - RR lymphoma vs RA: 0.95 (0.55 – 1.67)
  - Vs general population 2.08 (1.16 – 3.43)

**Lymphoma and TNFi**

**Callegan 2007 ACR Abst 989**
- **N. American CORRONA database**
  - 10,453 RA pts
  - SIR for lymphoma for all pts 1.92 (0.96 – 3.44)
  - IFX-exposed: 1.85 (0.38 – 5.41)
  - Any TNFi: 2.08 (0.76 – 4.53)
  - No TNFi exposure: 1.76 (0.57 – 4.11)
  - No statistically significant difference between RA pts with/without TNFi exposure

**Lymphoma and TNFi**

**Wolfe 2007 Arthritis Rheum: 56: 1433**
- **U.S. National Data Base**
  - 19,591 RA pts
  - Lymphoma SIR for all pts 1.8 (1.5 – 2.2)
  - Odds ratio for TNFi therapy 1.0 (0.6 – 1.8)
  - IFX: 1.2 (0.6 – 2.2)
  - ETN 0.7 (0.3 – 1.6)
  - ADA 1.2 (0.3 – 5.1)

**Lymphoma and TNFi**

**Mariette 2008 EULAR Abst FRI0116**
- **RATIO French registry**
  - All lymphomas reported to 490 clinical departments over three years
  - Case control study
  - Risk of NHL roughly 2-fold increased and of HL 5-fold increased vs general population--similar to RA population as a whole
  - Trend towards higher risk with IFX and ADA vs ETN

**Lymphoma and TNFi**

**Mariette et al, Ann Rheum Dis online 14 Oct 2009**
- **French RATIO registry 2004 – 2006**
  - 38 lymphomas reported in TNFi users
  - Overall SIR lymphoma 2.4 (1.7, 3.2)
  - Significant increase risk for MAbs vs receptor
    - SIR for ADA 4.1 (2.3, 7.1)
    - IFX 3.6 (2.3, 5.6)
    - ETN 0.9 (0.4, 1.8)
  - Statistically significant increase in MAb risk vs ETN
    - ADA odds ratio versus ETN 4.7 (1.3, 17.7)
    - IFX vs ETN 4.1 (1.4, 12.5)
  - Increase in lymphoma rates in TNFi users may reflect disease state, but a drug effect cannot be excluded, esp for MAbs

**Lymphoma and TNFi**

**Conclusions**
- Lymphoma risk issue not answered at this time
- In some settings, increased risk is seen
  - Most reflects intrinsic disease-associated risks
- Some cases there is still additional risk seen with TNFi
  - Suggestion that MAbs may increase risk more than receptor fragments
- Registry data are in general reassuring
  - Risks, if at all, appear modest

**Malignancy and TNFi**
Similar questions can be asked about non-lymphoma malignancies
While less directly related to immunosuppression than lymphomas, interference in immune surveillance theoretically may predispose to malignancies of all types
Package inserts for all three TNFi address this concern

**Malignancy and TNFi**

**ETN:** “Sixty-seven malignancies, other than lymphoma, were observed….similar in type and number to what would be expected in the general population. Rates at 6 month intervals suggest constant rates over five years of observation.”

**Malignancy and TNFi**

Of note, one RCT of ETN for Wegener’s granulomatosis did show significant increase in malignancy versus placebo-treated pts
6 solid tumors in ETN-treated vs none on placebo
All six were on concomitant cyclophosphamide therapy
Combined ETN-cyclophosphamide therapy contraindicated

**Malignancy and TNFi**

**ADA:** During the controlled portions of HUMIRA trials … malignancies, other than lymphoma and non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.6 (0.3, 1.0)/100 patient-years among 3853 HUMIRA-treated patients versus a rate of 0.4 (0.2, 1.0)/100 patient-years among 2183 control patients

**Malignancy and TNFi**

**IFX:** During the controlled portions of REMICADE trials…14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years among control patients),
The rate of malignancies among REMICADE-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

**Malignancy and TNFi**

Raw numbers from RCT are difficult to analyze
Numbers too small
Duration too short
Confounding factors inadequately controlled for
i.e. placebo groups with lower than expected malignancy rates
Are there other ways to utilize RCT data to better analyze these questions?

**Malignancy and TNFi**

Same analyses just presented on lymphoma data also give overall malignancy data
Gottlieb Eur Coll Rheum 2008, Abst FRIO113
Burmeister ARD Online Jan 2009, 10.1136/ard.2008.102103
FOI data from Centocor

**Gottlieb ETN**
**Burmeister ADA**
**Centocor IFX**

Malignancy incidence in controlled portion of RCT
0.52/100 pt-yr IFX
0.11/100 pt-yr in control
All malignancies excluding lymphoma and NMSC
Malignancy incidence in all RCT and long-term f/u studies
SIR versus SEER database IFX 1.04 (0.80 – 1.33)
Placebo 0.84 (0.38 – 1.59)

**Malignancy and TNFi**

RCT data
Other attempts to analyze these data
Meta-analysis: results from multiple independent studies are pooled to increase ability to detect rare events
Typically has been used to assess drug efficacy
Use to study harmful effects less common, somewhat controversial
Bongartz searched all published studies, plus unpublished trials presented at meetings, and data
provided by manufacturers

**Bongartz Meta-analysis**

Study investigated infliximab and adalimumab (the two monoclonal antibodies)
Etanercept was excluded: different mechanism of action
Data from infliximab and adalimumab trials were pooled
Presumably to increase power of meta-analysis
Out of 144 studies identified as possibly relevant, 135 excluded for variety of design, duration issues

Total of 9 trials analyzed
Total of 5014 patients
All randomized controlled studies
Unlike psoriasis studies, control groups were usually not placebo
6 studies used MTX plus placebo
1 used DMARD plus placebo
2 used placebo only

**Bongartz Meta-analysis**

Malignancies
29 seen among the 3493 patients who received at least one dose of anti-TNF drug
3 seen among 1512 control patients
Data excluded NMSC (7), and lymphomas seen during follow-up, after actual trial period ended (6)
Pooled odds ratio for malignancy in RA patients using anti-TNF therapy versus control was 3.3 (95% CI 1.2 – 9.1)

**Bongartz Meta-analysis**

Malignancies
A significant difference in the malignancy rate was seen between high- and low-dose treated patients
Odds ratio between high- and low-dose patients was 3.4 (95% CI 1.4 – 8.2)

**Bongartz Meta-analysis**

Confounding influences
Both in the article’s discussion, and in a series of letters published in JAMA November 8, 2006, a number of potentially confounding factors are explored
New data also provided in letter regarding analysis of patients on etanercept

Authors
Note that due to earlier drop-outs of patients in control groups, anti-TNF treated patients had greater exposure to MTX
However, they note that there are no data showing an increased risk of malignancy due to MTX in RA patients

**Bongartz Meta-analysis**

Confounders
Others have pointed out that while discussed by Bongartz, the issue of duration of exposure is not addressed
Actively-treated patients typically stay in studies longer than placebo-treated patients
Results in longer duration of treatment exposure for actively treated patients, increasing risk of infection, malignancy

**Bongartz Meta-analysis**

Confounders
Authors claim that dose-related risk of malignancy supports causal effect
However they labeled 20 mg of adalimumab weekly, and 40 mg every other week, as low-dose and high-dose groups respectively, despite the identical dose and similar pharmacokinetics of the two regimens

**Bongartz Meta-analysis**

Confounders
Analysis based on trials lasting one year or less
But cancer typically is a disease process that takes years to evolve
Optimal observation period would be much longer than one year

**Bongartz Meta-analysis**

Confounders
Total number of malignancies identified (29 in TNF inhibitor-treated patients) is very small. Almost 1/3 of these cancers (10) were non-melanoma skin cancers. Much less potential risk, easier to manage.

**Bongartz Meta-analysis**

Confounders
- Data on solid tumors conflicts with other published studies.
  - Registry data in particular are important and will be reviewed subsequently in this lecture.

Letters
- **Costenbader et al**
  - Added data from PREMIER adalimumab trial not available to Bongartz.
  - Deceased OR for malignancy from 3.29 to 2.02 (95% CI 0.95 to 4.29).
  - Authors added the START infliximab and the PREMIER data and showed OR for malignancy still elevated at 2.4 (95% CI 1.2 – 4.8).

**Bongartz Meta-analysis**

**Okada and Siegel letter**
- From CDER at the FDA.
  - Reported two prior meta-analyses done at the request of the FDA.
  - Differ in several important ways.
    - Analyses adjusted for duration of drug exposure.
    - Included analysis of all three TNF inhibitors, including etanercept.
    - Compared malignancy rates to age/race/sex controlled data from the SEER database.

**Okada Siegel letter**
- **Results**
  - Infliximab showed malignancy rate of 0.65 per 100 patient-years, versus 0.13 for controls (5x increase).
  - Adalimumab 0.7 per 100 PY, vs. 0.4 (1.75x increase).
  - However, when compared to SEER database, neither drug showed increased risk.
    - Odds rations of 1.0 and 0.97 respectively.

**Okada Siegel letter**
- Thus, anti-TNF antibodies appeared to increase cancer risk versus matched controls, but not compared to the general population rate.

**Okada Siegel letter**
- Etanercept data were significantly different.
  - No increase in malignancy risk compared with control group.
  - Data also did not exclude lymphoma and NMSC.
  - No SEER data but would presume that malignancy risk with etanercept would be equal or lower than SEER rates.
- The most conservative assumption would be that control groups are better comparators.
  - To the extent that inclusion criteria differentiates them from the general population.

**Bongartz ETN Analysis**
- Most recently, Bongartz has used the same statistical techniques with ETN.
  - Meta-analysis of 9 RCT with ETN and RA.
  - 3316 pts, 2484 on TEN, 1072 control.
  - 26 malignancies in ETN, 7 in control.
  - Hazard ratio 1.84 (0.79 – 4.28) non-significant.
  - No comparisons to general population incidence.

**Malignancy and TNFi**
- Registry data are the other key tool for analyzing risks.
  - Many of the same registries described in the lymphoma section also report overall malignancy rates.
  - Brief summary of most recent published data provides more insights.

**Malignancy and TNFi**
- **Raaschou ACR 2007, Abst 1344**
  - ARTIS database.
    - Risk of death from cancer not changed by TNFi exposure.
    - RR of death in TNFi-exposed pts was 0.78 (0.50 – 1.26).
Malignancy and TNFi

Watson EULAR 2006, Abst SAT0202
BSRBR British registry
9998 first-exposure TNFi RA pts vs 1877 biologic-naïve DMARD-treated pts
Adjusted RR with TNFi use 0.7 (0.4 – 1.2)
RR in pts with Hx of cancer prior to TNFi use had increased risk of subsequent cancer RR 2.5 (1.2 – 5.8)
But only 6 pts in this group

Malignancy and TNFi

Greenberg ACR 2007, Abst 282
CORRONA U.S. registry
4651 RA pts with TNFi exposure vs 4153 biologic-naïve DMARD treated
IRR for overall and specific cancers not significantly increased
Only exception skin cancer 2.10 (1.00 – 4.43)

Malignancy and TNFi

Wolfe Arthritis Rheum 2007: 56:2886
NDB U.S. data bank
13,001 RA pts
Biologic use IFX 4277, ETN 3011, ADA 763
No increase in overall cancer risk OR 1.0 (0.8 – 1.2)
Increases noted for melanoma 1.5 (1.2 – 1.8) and NMSC 2.3 (0.9 – 5.4)
Only agent-specific significant association was IFX and NMSC 1.7 (1.3 – 2.2)

Malignancy and TNFi

Askling, Arth Rheum 2009, 60:3180
Swedish RA registry
6366 pts on TNFi
240 cancers found
Risk Ratio vs non-biologic RA pts 1.0 (0.86 - 1.15)
Similar lack of significance vs DMARD pts, and general population
No overall increase in risk with increasing time on TNFi
In 1st year of treatment, statistically significantly lower risk of cancer with ETN, and higher with IFX
No differences from year 2 on

Malignancy and TNFi

Strangfield Arth Res Ther 2010, 12:R5
RABBIT German registry
5000 RA pts in registry, reviewed 2001 - 2006
74 new cancers found
Incidence rate 6.0/1000 pt-yrs, 5.1/1000 for TNFi users
Rate was non-significantly lower than general population
15 recurrent cancers
Incidence rates 45.5 for TNFi, 31.4 for DMARDs
IRR TNFi vs DMARDs 1.4 (0.5, 5.5)

Malignancy and TNFi

Registry data appear to support lack of association of TNFi use and malignancy, excluding lymphoma and skin cancer
Reassuring but absolutely not the final word: caution still needed

Leukemia and TNFi

Another recent FDA red flag raised
Added new section to Prescribing Information for TNFi
“FDA concludes there is a possible association between treatment with TNF blockers and the development of leukemia in all patients treated with these drugs “
“FDA is requiring the incorporation of information on post-marketing reports of leukemia into the prescribing information for TNF blockers “

Leukemia and TNFi

Basis for amendment
147 postmarketing reports of leukemia
AML (44 cases), CLL (31 cases), and CML (23 cases)
No incidence rates directly cited, but quotes rate in Enbrel clinical trials of 30/100,000 pt yrs
SEER rate 12.2/100,000
But, data show that rate of leukemia is increased in pts with RA
Asking Ann Rheum Dis 2005, 64:1414
Risk of lymphoma and leukemia equally increased, roughly two-fold vs general population
I am unaware of any data proving an increased risk of leukemia in TNFi users

**Pediatric Malignancy**

New black box warning!
Issued August 4, 2009 for all TNFi
“Lymphoma and other malignancies, some fatal, have been reported in children and adolescent
patients treated with TNF blockers”
“An analysis of U.S. reports of cancer in children and adolescents treated with TNF-blockers
showed an increased risk of cancer, occurring after 30 months of treatment on average. About
half of the cancers were lymphomas, a type of cancer involving cells of the immune system.
Some of the reported cancers were fatal. “

What are the data?
All postmarketing-based
48 total malignancies noted
“U.S. reporting rates for cases of malignancy with Remicade (infliximab) were consistently higher
compared to expected background rates for lymphomas and all malignancies. The malignancy
reporting rates for Enbrel (etancercept) were also higher than background rates for
lymphomas, but were similar to background rates for all malignancies.”

**Pediatric Malignancy**

FDA clarifications
Type of malignancy
10 cases of Hepatosplenic T-cell lymphoma
Well recognized complication of treatment using IFX in combination with mercaptopurine: 13 IBD
pts were on 6-MP
7 NHL, 6 HD, 6 leukemia, 3 melanoma, 3 thyroid, and 1 each of 13 other types
Disease treated
25 pts with IBD, 15 with JIA, 3 AS, 2 in utero exposure, 1 each PsA, sarcoid, unknown

**Pediatric Malignancy**

FDA clarifications
Method of calculating reporting rates
Denominator of estimated total pediatric use of ETN and IFX
Versus general population
FDA unable to provide confidence intervals for cancer rates with ETN and IFX: “because of the
limitations of AERS…we believe that calculating confidence intervals would convey a degree
of precision which we believe to be lacking”
Did not account in any way for underlying disease
FDA comments “the background incidence of malignancy in children with JIA is not well defined.”
FDA notes no dose association with malignancy

My (purely unscientific) comments
If we don’t know the underlying intrinsic rate of cancer, how can we state it’s increased?
If our data are too unreliable to provide confidence intervals, then isn’t the actual value also useless?
If we exclude HSTCL, we are looking at 38 cancers out of roughly 50,000 pt-years of exposure
Hopefully additional clarification will be forthcoming: for better or worse, though, we all now operate
under this black box and its apparent statement of fact

**Other Issues of Interest**

Data are also available on a number of interesting aspects relating to use of TNFi
Use with concomitant Hepatitis
Effects on vaccination
Effects on liver function
Use in pregnancy
Update on demyelinating disorders
Effects on CHF
Use in pediatric populations
Other Issues of Interest

Not a comprehensive review but a survey of some interesting information in the public domain
All present data that are much less substantial than infection and malignancy data
Not to mention the dozens of case reports published every year of unknown clinical significance

Hepatitis

Seemingly TNFi would present risks
However data do not appear to support this
Notion that much of the damage done by chronic hepatitis is inflammatory rather than infectious in nature

Roux Rheumatology 2006:45: 1294
6 RA pts with chronic Hep B and 3 with Hep C
No changes in viral load or transaminases after addition of TNFi (5 ETN, 1 IFX, 2 ADA)

Hepatitis

Peterson Ann Rheum Dis 2003;62:1078
16 HCV-infected RA pts who received ETN or IFX analyzed retrospectively
8 HCV-infected RA pts prospectively treated with ETN
No significant changes in LFT’s or in HCV levels

Hepatitis

31 pts with chronic Hep C
With TNFi treatment there was no elevation in mean ALT or viral loads for group as a whole
4 pts did show a significant individual increase in Hep C load
1 pt was taken off TNFi due to an increase in ALT, but it was not accompanied by increase in viral load and may have been unrelated

Hepatitis

Li et al, 2009 Clin Rheumatol online, 17 March 2009
3 pts with chronic Hep B, 8 with chronic Hep C
One Hep B pt with transient elevation AST
One Hep C pt with permanent increase of AST and 4-fold increase in viral load
All others showed no increase in viral load or transaminases

Hepatitis

Zein J Hepatol 2005; 42:315
Placebo-controlled trial of ETN as adjuvant to IFN and Ribavarin in chronic HCV pts
Significantly higher numbers of pts on ETN had absence of HCV RNA than on placebo at
Week 24 67% vs 32%, p=0.040
Week 48 56% vs 32%, p=0.046
Suggestion of decrease in fibrosis
55% of ETN vs 33% of placebo-treated pts who underwent liver biopsy improved at least one grade

Hepatitis

Conclusion
TNFi treatment, while immunosuppressive, is often well-tolerated in pts with chronic Hepatitis
More data for Hep C
Even some suggestion of therapeutic benefit in chronic Hep C pts
Anti-inflammatory effects protecting liver?

Vaccination

Standard protocol is to avoid live virus vaccinations in pts on TNFi
No clear guidelines exist for length of time pt should be taken off TNFi before essential live vaccination can safely be given
Opposite issue with non-live vaccines
Does immunosuppression from TNFi prevent adequate protective response to killed vaccines?

Vaccination

Kepetanovic Rheumatology 2006:45:106
Measured response to pneumococcal vaccine
Healthy controls and RA pts vaccinated
TNFi users had response equal to controls (approx 70% vs 55% achieved 2-fold increase)
TNFi plus MTX uses had lower response than TNFi alone, but not different than control
MTX alone had significant reduction in response vs controls (roughly 25% vs 55%)
Response to influenza vaccination in 112 pts with autoimmune disease treated with or without TNFi vs 18 healthy controls. Mean increase in titers was significantly lower in TNFi-treated vs non-TNFi-treated or control groups. However, proportion achieving protective titers was high and not significantly different in all groups.

**Vaccination**

**Conclusions**

Live virus vaccines ideally should be administered before initiation of TNFi therapy. If not possible, suggestion is that TNFi therapy be discontinued before and after vaccine, but length of time needed unclear. Killed vaccine responses may be attenuated but not to a degree that prevents them from working. TNFi pts should receive influenza, pneumonia vaccines as appropriate for age, medical status.

**Liver Effects**

Generally we do not worry much about end-organ toxicity with TNFi’s. Much diminished need for monitoring of liver, renal fct, lipids, BP, etc vs oral agents. However, there are reports of hepatotoxicity with TNFi use.

Strand ACR 2008, Abst 1657

CORRONA database
RA pts using TNFi or DMARDS
6861 pts with LFT’s recorded

**Liver Effects**

**Liver Effects**

**Liver Effects**

Conclusions
Elevations 1xULN were uncommon and 2.ULN were rare. Most common with IFX, less frequent with ADA, and not seen with ETN. Most transient, did not require d/c of Rx. Monitoring, and dose reducing or discontinuing, as with DMARDs, may be appropriate.

**Pregnancy**

Treatment of psoriasis during pregnancy presents significant challenges. Even high potency topical steroids are teratogenic in animal models. Systemic agents traditionally viewed as contraindicated:

MTX strong abortifacient
CyA coupled to LBW births but otherwise appears relatively non toxic
Acetretin obviously contraindicated

What are the data with TNFi?

**Pregnancy**


Comprehensive review of literature

IFX
Katz: Series of 96 pregnancies: 68 live births, 14 miscarriages, 18 ther abortions: 2 congenital malformations
Other drug exposure in some
Lichtenstein, TREAT registry (Crohn’s) 66 pregnancies, 36 with IFX exposure
No birth defects, no increase in miscarriage
Mahadevan, series of 10 women treated with IFX during pregnancy for CD
All resulted in live births, no malformations

**Pregnancy**

ETN
Cush, 417 pregnancies in RA pts exposed to TNFi, 81% with ETN
387 normal deliveries, 25 miscarriages, 5 ther abortions, 9 preterm births
Rates comparable to general population
No malformations

Hyrich, BSRBR registry
22 pregnancies in RA pts exposed to TNFi
9 on MTX, 2 on leflunomide
All stopped in first trimester except two who continued ETN throughout
Pregnancy

Vinet review

Joven, BIOBADASER registry

14 pregnancies in TNFi-exposed RA pts

7 live births with no complications, 3 therapeutic abortions, one miscarriage, 3 unknown no malformations

Pregnancy

Vinet review

Conclusions

Data do not support large excess risk of adverse pregnancy or fetal outcomes

Limited by small number of reported cases, concomitant drug exposure, variable TNFi exposure (esp lack of 2nd/3rd trimester exposure)

Carter data a concern, but as with all spontaneous reporting, no denominator makes analysis impossible

Pregnancy

Conclusions

Must evaluate each case individually

TNFi use in 1st trimester may be a consideration

Late 2nd and 3rd trimester use more uncertain given evidence of placental transfer and therapeutic levels in fetus

Superior to most DMARDs for use during possibly prolonged period while conception attempted

Toxicity during lactation likely minimal as drug likely to be digested in GI tract

However, cautionary note sounded in 2008

Carter J Rheum 2009: 36, 635

Review of FDA database: all children with anomalies reported to FDA after in utero exposure to TNF inhibitors

41 children with congenital anomalies born to women on TNFi reported to FDA

22 ETN, 19 IFX

"24 of 41 children had one or more anomalies part of the VACTERL association"

VACTERL: non-random association of defects: vertebral, anal, cardiac, tracheal, esophageal, renal

Pregnancy

Carter 2009

Of 13 children with more than one anomaly, 7 had at least two defects associated with VACTERL

1 child formally diagnosed with VACTERL

Conclusion: "Congenital anomalies that are part of VACTERL...are occurring at a rate higher then historical controls...raises concerns of a possible causative effect of the TNF antagonists"

Pregnancy

Carter study was immediately criticized heavily

Koren and Inoue, editorial in same issue of J Rheum note multiple serious flaws

Spontaneous reporting system has no reliable comparison group

Carter chose to use "general population" as comparator

Huge selection bias in cases reported to FDA

Pregnancy

Selection bias

Example: VSD

Many close spontaneously in first year of life and go undetected

Women taking TNFi much more likely to have fetal ultrasounds

Therefore, VSD much more likely to be detected purely due to more intensive screening

Furthermore, finding of a VSD much more likely to be reported to FDA if occurring after TNFi exposure than if simply a spontaneous VSD

Pregnancy

Additional flaws

Carter assumed any defect affecting any of the VACTERL organ systems was "part of" the VACTERL association
Many of the anomalies are frequently found independently and unassociated with VACTERL. Carter argued that because they shared some features of VACTERL, they should be considered VACTERL.

**Pregnancy**

Editorial conclusions
- Notes the "very feeble nature of these data"
- "Carter’s data are far away from establishing an association, let alone causation"
- "On a grid of 0 to 10 for proving causality….we believe that the present report scores 1."
- Editors decry the negative impact of report
  - Patient and physician anxiety (and legal liability—my comment)
  - Unnecessary abortions
  - Harmful discontinuation of needed treatments
  - Increased risk to unborn child due to untreated maternal conditions

**Pregnancy**

Similar criticism from Ostensen, Nature Reviews, April 2009
- Criteria for Dx VACTERL are stringent
  - At least three anomalies, exclusion of chromosomal anomalies
  - Only one of Carter’s purported cases met these criteria
  - Many anomalies cited by Carter as VACTERL associated are common in the general population
  - Only 3 children had abnormalities specific for VACTERL
  - Other children labeled with "incomplete VACTERL" had abnormalities found in 3-5% of the general population
- Carter argues that TNF inhibition is cause of defects “similar to thalidomide,” ignoring fact that glucocorticoids are powerful TNF inhibitors

**Conclusions**
- Data on exposure during first trimester appear reassuring
- 2nd and 3rd trimester use does lead to significant fetal exposure, impact unclear
  - Particularly for MAbs, which pass placenta extensively
  - ETN appears to be transferred much less
- In general, TNFi should be discontinued as soon as pregnancy recognized
  - Therapeutic abortion not mandated
- However in cases where substantial maternal morbidity would result, continued therapy can be considered with appropriate informed consent
- However, bar is higher with psoriasis than with more crippling illnesses like RA

**Demyelinating Diseases and TNFi**

Use of all TNFi has been associated with rare cases of new onset or exacerbation of CNS demyelinating disorders
- Role of TNF in demyelination controversial
  - Some models suggest it promotes, while others suggest it protects nerves from demyelination
  - TNF has been found in CSF and MS plaques of pts with MS

**CNS demyelinating disease reported in all clinical trials programs of TNFi**
- IFX
  - 2 cases in 2427 pts over 5443 pt-yrs as of 2003
- ETN
  - 2 cases in 3839 pts over 8336 pt-yrs
- ADA
  - 4 cases in 2468 pts over 4870 pt-yrs

**Demyelinating Diseases and TNFi**

Lenercept trial
- Dimeric protein comprised of two TNF receptors fused to fragment of IgG
  - Neurology 1999, 53:457
  - No differences overall between lenercept and placebo
  - Significant increase in number of exacerbations, and earlier onset of exacerbations, in lenercept group
  - Non-significant trend towards more severe deficits with lenercept

**Demyelinating Diseases and TNFi**
Demyelinating Diseases and TNFi

Compared to infection or malignancy, analysis of data hampered by extremely small number of reported cases

Even in large registries number of events small
Underlying incidence of disease also poorly understood
Especially in special populations like RA and other autoimmune diseases which may be predisposed to demyelination

**Long term clinical trial data**

**ETN**

Klareskog EULAR 2008, Abst THU0124
10 year cumulative data all N.A. and European controlled and open-label studies
7863 cumulative pt-yrs exposure
2 cases of MS reported

**ADA**

Burmeister 2009, ARD Online First
10 year cumulative experience across all indications
RA, PsA, AS, CD, Ps, JIA
19,041 pts
13 total cases in RA
6 MS, 2 GBS, 2 optic neuritis, 2 non-specific, 1 optic nerve disorder
3 cases of ON and 1 of MS in CD
None in JIA, PsA, Ps

**IFX**

6273 adult CD patients from community and academic practices have been enrolled in TREAT (July 1999 – February 2008)
3396 patients (14,184 pt-yrs) have received infliximab
2877 patients (10,391 pt-yrs) have not received infliximab
1 infliximab patient and 1 patient who received only other treatments developed multiple sclerosis
IFX was given 11 months prior to the onset of MS

**Van Oosten 1996, Neurology 47: 1531**

Two pts with rapidly progressive MS intentionally treated with IFX 10 mg/kg
No clinical deterioration noted but
Increase in gadolinium enhanced brain lesions on MRI
Increase in CSF IgG index
Increase in number of lymphocytes in CSF were all noted

**Fromont et al, 2009, 45: 55**

Three pts reported who developed inflammatory demyelinating disease after TNFi exposure
All had TNFi therapy discontinued:
One pt had total regression of neurological Sx
Second had stabilization of symptoms
Third went on to develop full-blown MS with exacerbations even after TNFi discontinued

**Bernatsky et al, Ann Rheum Dis, online 23 Jul 2009**

Case control study using 105,000 pt RA cohort
Initial raw data showed higher risk of CNS event in pts on anakinra compared to TNFi
Adjusted risk ratio of 0.56 for TNFi vs 2.23 for anakinra. However, this is "channeling bias"—pts with preexisting symptom suggestive of demyelination were preferentially prescribed anakinra, rather than TNFi.

**Demyelinating Diseases and TNFi**

After excluding high risk patients, trend reversed.
- Adjusted rate ratio for CNS event in pts on TNFi was 1.31 (0.68, 2.50) versus anakinra 0.80 (0.29, 2.29)
- Not statistically significant but a reversal of trend.

**Demyelinating Diseases and TNFi**

Multiple case reports of development of demyelinating diseases after initiation of therapy with TNFi.
- As with all anecdotal reports, difficult to assess given lack of "denominator".
- Studies may suggest trend but inadequate to show statistical reliability.
- Conclusion: any prior suggestion of demyelinating disease is at least a relative contraindication to TNFi therapy.
- Ongoing attention to any symptoms suggestive of demyelination mandatory in all TNFi users.

**Demyelinating Diseases and TNFi**

Conclusions
- Difficult to draw any definitive conclusions.
- Numbers of cases are small and appear to be remaining stable over time.
- Reassuring as there is no sign of a cumulative increase as more pts are exposed for longer time periods to TNFi.
- However, lenercept data, temporal associations, and particularly, improvement upon withdrawal and positive rechallenges raise legitimate concerns.
- As all three package inserts note, at the very least "exercise caution in considering the use of [TNFi] in patients with preexisting or recent-onset central nervous system demyelinating disorders".
- Discontinuation appropriate if CNS symptoms do develop.

**Congestive Heart Failure and TNFi**

TNFi are commonly thought to be contraindicated, or at least used with caution, in the presence of CHF.
- Package inserts reflect this.
  - "Remicade has been associated with adverse outcomes in patients with heart failure".
  - "Exercise caution when using Enbrel in patients who also have heart failure".
  - "Exercise caution when using HUMIRA in patients who have heart failure".

**CHF and TNFi**

What are the actual data for CHF and TNFi?
- Differ from what many assume.
- Appear to be agent-specific differences in effects on CHF.
- Overall data are reassuring.

**CHF and TNFi**

Interest in using TNFi as treatment for CHF.
- Studies done with both ETN and IFX.
- In both cases, trials were ended prematurely due to preliminary analysis of data.
- Results led to recommendations on package inserts.
- Significantly different implications for the studies.

**CHF and ETN**

ETN studies
- **RENAISSANCE**
  - 925 pts, NYHC class 2-4.
  - Placebo vs 25 mg ETN BIW vs TIW.
  - Death rates: 14.2%, 17.9%, 19.8%.
- **RECOVER**
  - 1123 pts class 2-4.
  - Placebo vs 25 mg ETN QW vs BIW.
  - Death rates 8.8%, 5.9%, 7.2%.
- **RENEWAL**
  - Combined data from both trials with covariate analysis.

**CHF and ETN**

Conclusions
Trend (NS) towards higher mortality in RENAISSANCE was not duplicated in RECOVER. When data pooled and other risk factors accounted for, no trend towards higher mortality emerged (RR = 0.96, p = 0.79). Trial was terminated for lack of efficacy, not higher mortality.

**IFX and CHF**

Initially studied as treatment for CHF
ATTACH trial
Phase II study
150 subjects randomized to 5 or 10 mg/kg of infliximab or placebo at weeks 1, 2, and 6
ATTACH: Clinical Status at Week 28
ATTACH: All-Cause Mortality
Through One Year

**CHF and TNFi**

Other analyses
NDB analysis
13,171 RA pts 2000 – 2002
Rate of CHF higher with RA versus OA
3.9% vs 2.3%
CHF significantly less common in pts treated with TNFi than others (3.1% vs 3.8%, P<0.05)
Conclusion: RA increases the risk of CHF, which can be ameliorated by anti-TNF therapies

Cole 2006, Rheumatol Int 27:369
Retrospective analysis
TNFi treated (103 pts) vs RA control (100 pts) and control group without RA (100 pts)
No difference in admissions for CHF
6.7% vs 8% vs 7%
No differences in mortality
3.8% vs 7% vs 11%

**CHF and TNFi**

Listing 2008, Arthritis Rheum 58: 637
German RABBIT registry
2757 RA pts treated with ETN, IFX, or ADA vs 1491 RA pts on conventional DMARDs
CHF increased with worsening RA
At baseline, TNFi users had significantly worse RA
After adjusting for risk factors and RA disease activity, there was a residual, non-significant increase in CHF in TNFi population (hazard ratio 1.66, 0.67 – 4.1)
Authors conclude that any residual risk balanced by superior efficacy and reduction in inflammatory effects on other areas including joints, vessels

**CHF and TNFi**

Conclusions
Suggestion of dose-related risk with IFX, but subsequent data are reassuring in lack of significant association of TNFi use and CHF
Use of TNFi in mild stable CHF reasonable with appropriate cardiac monitoring
Use in more severe or unstable CHF should be approached with caution, especially with high-dose IFX

**Thrombocytopenia and TNFi**

Prompted by Brunasso report JAAD 2009, 60:781
Reported surprisingly high rate of thrombocytopenia in psoriasis pts on TNFi
4.30% (0 – 6.2%)
Three pts on IFX, one on etanercept
Not commonly recognized
Mentioned in IFX patient instructions
Seen in 0.9% of clinical trials pts vs 0.4% placebo
Pathare Rheum 2005, 45:1313
Describes two cases with IFX
Second pt switched successfully to ETN
Thrombocytopenia and TNFi
No clear association with ETN previously reported to my knowledge
And no matter what, the incidence of TCP seen in this Italian cohort is extraordinarily high versus any prior observation
Higher than I, or anyone I know who uses biologics has seen
Interestingly, 3 out of the 4 reported cases showed high titer ANA’s of 1:640 or greater
Could this be related to drug-induced lupus?

TNFi: More Good News?
Effects of TNFi on cardiovascular risk and overall mortality
Remember the “big picture” when evaluating a drug for safety
A drug may significantly increase the risk of one specific toxicity, while still lowering overall risk of morbidity or mortality
Early suggestions that benefits of TNFi may indeed outweigh risks of infection, cancer, etc

Emerging Safety Data
Cardiovascular disease
Gelfand et al JAMA 2006
Pts with psoriasis have inherently increased risk of MI
Incidence of MI by group:
  Control 3.58 (CI 3.53 – 3.65)
  Mild psoriasis 4.04 (CI 3.88 – 4.21)
  Severe psoriasis 5.13 (4.22 – 6.17)
Relative risk also dependent on age
  Highest risk in young patients with severe psoriasis (RR 3.10 CI 1.98 – 4.86)

Cardiovascular Risk
Consistent with newer concepts of atherosclerotic vascular disease as an inflammatory, T\textsubscript{h}1-driven process, like psoriasis
Correlation with CRP and systemic inflammation
Increased risk seen in RA as well
Raises question: if psoriasis therapy lowers inflammation, could it have beneficial effect on cardiovascular risk as well?

TNFi and CRP
Evidence suggests that TNFi therapy significantly reduces CRP levels
Strober AAD 2007, Abst P2623
  CRP levels in Ps and PsA pts reduced substantially by ETN therapy
    From 2.7 to 1.4 in Pso, and 5.5 to 1.8 in PsA
  CRP from 1 to 3 intermediate, and >3, high risk for CVD
Abramovits EADV 2008, Abst FP1307
  CRP similarly reduced
    Ps 6.5 to 5.2, PsA from 11.6 to 5.3

Cardiovascular Risk
Kremer et al
EULAR 2006 poster
Analyzed effects of treatment with etanercept on cardiovascular disease (CAD, MI, CHF, stroke)
  Relative risk of CVD in pts taking etanercept was 0.56 (CI 0.36 – 0.872)
  RR of prednisone 1.62, MTX .90, COX2 0.86
  RR of DM 2.00, Female sex 0.55
  Dose dependent: pts on etanercept for 1.5 – 5 years had RR of 0.374—a 62% reduction in risk

TNFi and Overall Mortality
There are even early suggestions that TNFi therapy reduces death from all causes
Gordon AAD 2008, Abst 2610
  SMR (standardized mortality ratio) calculated for all pts in ETN clinical trials across all approved indications
  SMR 0.46 (0.36 – 0.59)
Burmeister ARD Online
  Similar cumulative ADA clinical trials data across all six indications
    SMR significantly reduced for RA and Ps pts
0.64 (0.52 – 0.79) for RA
Roughly 0.2 for Ps

**TNFi Safety Summary**

These represent an enormous advance in the treatment of inflammatory TNF-mediated diseases

Efficacy as good or better than any prior therapy

Safety profiles that are

More carefully documented

Clearly superior

Than any earlier generation therapy

**TNFi Safety Summary**

They are not drugs to be taken lightly

Infection is a real risk

Malignancy may be a risk in at least certain settings

Other risks are as of yet undefined (i.e. demyelinating disease, use in pregnancy, etc) and thus demand careful and thoughtful analysis on a patient by patient basis

**TNFi Safety Summary**

Sending the message that these drugs are to be regarded as no more risky or demanding of great care than tetracycline does neither patient nor physician any favors

“Community standards” among experienced prescribers include regular monitoring visits and periodic labwork

**TNFi Safety Summary**

Even if evidence-based data do not yet exist to guide us with frequency of follow-up and lab monitoring, requiring regular evaluation protects both patient and physician, sending the message that these are indeed drugs to be taken seriously

Knowledge, as always, is our best defense, and our best weapon in offering the best care to our patients

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**Update 2010: Stelara**

Stelara (ustekinumab, FKA CNTO1275) approved in U.S. Sept. 25, 2009

Was available for use by end of 2009

Approved in Canada 12/08, Europe 1/09

Novel mechanism of action

MAb to p40 subset shared by IL-12 and IL-23

Highly effective

PASI 75 rates range between 65 – 75%

Unusual dosing regimen

45 or 90 mg SQ at weeks 0 and 4, followed by one dose q3months

**Ustekinumab**

Limited data!

Clinical trials data are only available to me

T04 Phase II study

Phoenix 1 and 2 Phase III studies

ACCEPT Phase III trial comparing Ustekinumab (UST) to ETN

No substantive postmarketing or registry data yet

Informed consent essential

**Ustekinumab**

Phoenix 1 (Stelara current prescribing information)

In general, adverse eventes mild and did not affect treatment

Most common URI, nasopharyngitis, headache, arthralgia

Infections and AE’s leading to treatment discontinuation were similar across dose groups including placebo

SAE’s rare: 2 placebo, 2 45 mg, and 4 90 mg groups

No malignancies

No dose response for any AE’s noted

No laboratory abnormality increases in treated groups

ISR rates low, no anaphylactic or serum sickness reactions

Similar results reported for Phoenix 2

**Ustekinumab**

ACCEPT (Griffiths 2010, NEFM 362: 118)
Randomized to UST 45 or 90 mg or ETN 50 mg BIW
PASI 75 at week 12
67% and 74% for UST
57% for ETN
ETN non-responders crossed over to UST 90 mg
49% achieved PASI 75

**Ustekinumab**

Safety
AE rates
1.9% of UST 45mg
1.2% of UST 90mg
1.2% of ETN pts
Infection rates
30.6% UST 45mg
29.7% UST 90mg
29.1% ETN
Serious infections
2 UST 45mg
10 UST 90mg
4 ETN
Non-significant differences
5 malignancies noted
Rates of common AE’s equivalent across groups

**Ustekinumab**

Pooled data (Gordon, poster, EADV 2009)
Phase II, PHOENIX, and ACCEPT trials
Rates of serious infection 0.82 and 1.50/100 pt-yrs for 45mg and 90mg groups (difference NS)
Placebo rate over 12 weeks 1.70
Rate of malignancy other than NMSC 0.69 and 0.46/100 pt-yrs
Placebo rate 0.57
Major cardiovascular events 0.41 and 0.35 for 45mg and 90 mg UST
Placebo rate 0.55
NMSC rates 0.64 and 0.77/100 pt-yr
Placebo rate1.13
AE rates remained stable over three years in all major categories without evidence of cumulative toxicity

**Ustekinumab**

Highly efficacious
Unique and attractive dosing regimen
Costs high but comparable to other biologics
Efficacy for PsA unknown, Phase III trial ongoing
Safety: preliminary data encouraging but until additional indications lead to greater use, will not have the body of data to analyze comparable to that with TNFi