

Biologic Therapy for Psoriasis

A Clinician's Perspective

Mark Ling, MD, PhD

Medical Director, MedaPhase, Inc.

Atlanta, Ga.

DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Mark Ling, MD, PhD

- Financial relationships
 - Current clinical research grants
 - Amgen
 - Abbott
 - Celgene
 - Centocor
 - CollaGenix/Galderma
 - Eli Lilly
 - Novartis
 - Pfizer
 - Stiefel
 - Speaker's bureau: Amgen, Pfizer
- Disclosure Statement
- All drugs discussed are “on-label” for the treatment of psoriasis
 - Information presented is in the public domain and has been published
 - Single exception will be clearly labeled as to source
- Biologic Therapy for Psoriasis
- Introduction of biologic therapy (2003 in U.S.) has dramatically altered how moderate to severe psoriasis is treated
 - Biologics have rapidly replaced other systemic therapies in the U.S.
 - Management of psoriasis is now often seen as a question of “which biologic?” rather than “biologic versus systemic?”
- Biologic Therapy for Psoriasis
- Questions of when to choose a biologic versus systemic agent, phototherapy, or topical therapy beyond scope of this lecture
 - Focus here is choosing optimal biologic for given patient

- Choice can be simplified into three criteria
 - Efficacy
 - Safety
 - Cost
- Other factors may enter decision, but are generally less important
 - Ease of administration
 - Dosing regimen
 - Availability

Biologic Therapy for Psoriasis

- Scope of this lecture will mainly encompass safety issues
 - Efficacy will be addressed in passing, but in my opinion, is a relatively straightforward issue to address
 - Safety on the other hand, is a highly complex subject, with much opinion and often too little fact cited
 - Cost is a country-specific issue also beyond the scope of this talk

Safety of Biologic Therapies

- 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), and Adalimumab (ADA)
- And an update on the newest biologic for psoriasis, ustekinumab (UST)

Biologic Therapy for Psoriasis

- And then there were four, then three, then four
- Why ETN, IFX, and ADA?
 - TNF inhibitors are the vast majority of biologics for psoriasis in 2010
 - Alefacept has never achieved more than a percent or two of market share
 - Efalizumab off market
 - Ustekinumab market share growing but drug remains relatively new (2 years)
- Therefore, TNF inhibitors dominate the current market
 - Impact of UST to be seen

- *Only TNF inhibitors have sufficient postmarketing experience to allow valid analysis*

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: relative risk analysis
 - Standard Incidence Ratios
 - Long term observational studies based on
 - Registries
 - Spontaneous post marketing reports

Evaluating Safety Data

- Relative Risk Analysis (RR)
 - Comparison between patients treated with drug versus placebo in randomized, controlled clinical trials (RCTs)
 - Strengths:
 - 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

■ Weaknesses

- Study duration too short to permit analysis of long term side effects
 - 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

■ Second approach: Standardized Incidence Ratio (SIR)

- Compares the rate of an adverse event seen in an RCT versus the rate of that event in the general population
 - i.e.—the rate of cancer in treated study patients, versus the rate of cancer in the general population

Evaluating Safety Data

■ Strengths of SIR

- “Half” of the equation is broad-based, reliable

■ Limitation of SIR

- The general population may not reflect the study population in specific ways
 - i.e. patients in lung cancer study have higher rate of COPD versus general population, but that is due to tobacco exposure, not the drug
- Like RR analysis, may be underpowered to identify rare AE's and too brief to detect long term events since still relying on RCTs for data

Evaluating Safety Data

■ 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 intentionally followed for extended time
 - Post marketing reporting

- Spontaneous reports to manufacturer or regulatory agency
- Post marketing Reporting

■ Limitations

- Registries have no formal control group, relying on large population incidences as comparator
- Intensity of monitoring much lower
- Selection of patients in registry may be biased
 - i.e. patients willing to participate in registry may be more health conscious and thus more compliant than “average” patient
- Post marketing reporting heavily underreports events
 - Rely upon clinicians going “out of their way” to voluntarily report experiences

Safety of Biologic Therapies

■ The heart of this lecture

- Will attempt to analyze a broad range of available data relating to use of TNFi
- Goal is to elucidate a deeper understanding of safety issues, backed by actual data, beyond what is often held by clinicians
 - Based on package inserts or drug rep claims

Safety of Biologic Therapies

■ Short term toxicities are the starting point

- These are 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 or considered acceptable (chemo)
 - Why? Any severe unexpected toxicity which is common enough to be detected during a brief RCT often leads to discontinuation of drug development

Short Term Safety

■ Etanercept

- In placebo-controlled studies on psoriasis
 - No differences in any infectious or non-infectious adverse event vs placebo except for
 - Injection site reactions (15% vs 6%)
 - Mild to moderate, none requiring drug discontinuation

- Trend towards increased rate of non serious infections in treated RA pts

- No difference in serious infections

Short Term Safety

■ ADA

- Similar to ETN

- No significant increases in AEs, Serious AE's, infections, serious infections
- Only significant increase in non infectious AEs were rash and injection site reaction

Short Term Safety

■ IFX

- Significant increases in headache, pruritus, pain, arthralgis, pharyngitis, rhinitis, flushing, etc

- All typical symptoms of infusion reactions (seen overall in 6.6% of treated vs 0.7% of placebo pts)
- Trend towards more infections (36% vs 25%)

Short Term Safety

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

Biologic Safety Issues

■ Toxicities can be

- Common or rare
 - Common are easily detected in RCTs
- Serious or non-serious
 - Non-serious are of minimal importance
- Early or late in treatment course
 - Early are more likely to be detected during short-term studies

Biologic Safety Issues

- The most worrisome toxicities are rare, serious, and delayed in onset
 - They are also the most difficult to detect
 - Rare events require large numbers of subjects to detect
 - Long induction times of late toxicities make it impossible to study using short term clinical trials

- Yet these serious toxicities are extremely important
 - MUST have long term data to have adequate length of follow up and adequate numbers of participants to detect these rare events

Biologic Safety Issues

- Fortunately, we do have a tremendous body of clinical data on safety with TNFi
- This is mainly due to the widespread use of TNFi for the treatment of RA
 - Huge population of RA pts worldwide means in depth analysis possible
 - However, a leap of faith needed to assume these data can be extrapolated to psoriasis pts
 - Pneumonitis from MTX in RA, not in psoriasis
 - Higher incidence of liver toxicity with MTX in psoriasis vs RA
 - Still, a valuable insight into the effects of TNFi therapy

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
- 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
 - Increases ability of macrophages to phagocytose and kill mycobacteria
 - Essential to formation and maintenance of granulomas

TNF biology

- 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

- How significant a risk does TB present in patients on TNFi?
 - Classic example of a question that cannot be answered based on controlled clinical trials
 - Incidence too low to allow statistically significant comparison
 - This is a question that can only be addressed using long term registry data

Tuberculosis

- Most registries are national in origin
 - Typically they allow comparison between TNFi-treated patients vs the general population, and in many cases, vs patients with same disease not treated with TNFi
 - Data presented as Relative Risk ratios ("RR"--i.e. the incidence in treated group divided by incidence in the control group, usually the general population or non-TNFi treated patients with same disease)

Tuberculosis

- Summary of major registries
 - Askling, EULAR 2007 abst THU0125
 - Swedish national registry¹
 - RR of TB in TNFi treated RA patients = 31 (18-51) vs general population
 - RR vs biologic-naïve RA pts = 9.0 (4.9-16)
 - Highest risk in year one

Tuberculosis

- BIOBADASER (Spain)¹

- Gomez-Reino, Arthritis Care Res 2007:57:756
- RR = 13 vs general population
- RR fell to 1.8 after institution of protocol to check PPD x 2 before instituting Rx
- Raw incidence per 100,000
 - IFX 383
 - ADA 176
 - ETN 114
 - Not statistically significant

Tuberculosis

- RATIO (France)¹
 - Tubach, Arth Rheum 2009: 60:1884
 - SIR vs general population
 - All TNFi: 12.2
 - IFX 18.0
 - ADA 29.3
 - ETN 1.8
 - Odds ratios
 - IFX vs ETN 13.3
 - ADA vs ETN 17.1

Tuberculosis

- BSRBR (Great Britain)¹
 - Dixon, Ann Rheum Dis online 22 Oct 2009
 - Rates of TB vs RA pts on DMARDS
 - DMARD rate = 0
 - Crude incidence
 - ADA 144
 - IFX 136
 - ETN 39
 - Incidence rate ratio vs ETN
 - ADA 3.1 (1.0 – 9.5)
 - IFX 4.2 (1.4, 12.4)

Tuberculosis

- Conclusions
 - Findings across all registries consistent
 - Risk of TB clearly elevated with TNFi therapy

- 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
 - IFX and ADA clearly increase risk
 - ETN appears to induce at most modest added risk, and in some studies, no increase in risk at all
 - Aggarwal¹ treated 80 PPD-positive pts with ETN, **no** cases of active TB noted
 - J Rheum 2009, 36:914

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 registry¹
 - Dixon, Arthritis Rheum 2007: 56: 2896
 - 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 (more severe pts given TNFi?)

Non-TB Serious infections

- North American CLAIMS database
 - Curtis, ACR 2007, Abst 1024
 - 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

■ German RABBIT registry

- Listing, Arthritis Rheum 2005; 52: 3403
- 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
 - 2.70 (1.3 – 5.9) for IFX

Non-TB Serious Infections

■ CORRONA N. American registry

- Greenberg et al, 2009, Ann Rheum Dis online 8 April 2009
- 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)

Non-TB Serious infections

■ 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)

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

Fungal Infection

■ Tsiodras 2008, May Clin Proc 83: 181

- 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

Fungal Infection

- 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

- BIOBADASER database¹
 - TNFi treated RA pts
 - Compared with EMECAR non-biologic exposed pts
 - Global hazard ratio 2.44
- RABBIT registry²
 - Rate in TNFi vs DMARD treated RA pts
 - Incidence rates/1000 pt-years
 - 11.1 (7.9, 15.1) MAbs
 - 8.9 (5.6, 13.3) ETN
 - 5.6 (3.6, 8.3) DMARDs
 - Hazard Ratios
 - MAbs 1.82 (1.05, 3.15)
 - ETN 1.36 (0.73, 2.55)
 - ¹Perez-Zafrilla, EULAR 2008 Abst FRI0129
 - ²Strangfeld JAMA 2009, 301:737

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

Differentiating TNF Inhibitors

- Mechanism
 - Zou et al* have shown that ETN led to
 - up-regulation of T cell production of both TNF alpha and interferon gamma
 - increase in the number of TNF and IFN-positive CD8+ T cells after antigen challenge-
 - IFX produced opposite effect
 - significant reduction in TNF and interferon production
 - 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 and TNFi

■ 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

■ “Last year’s news”

- 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 CNS¹
 - 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
 - Eng 2006, Neurology 67: 884

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
 - Pt with Wegener's, on ETN and cyclophosphamide
 - contraindicated regimen due to lymphoma risk
 - RA pt on prednisolone, gold, penicillamine, MTX, leflunomide, and cyclophosphamide
 - PCR for JC virus negative x 2
 - 60 y.o. RA pt with symptoms of leukoencephalopathy
 - Symptoms resolved rapidly, highly unlikely to be PML
 - Eng 2006, Neurology 67:884; Yamamoto 2007, Mod Rheumatol 17: 72; Kashup 2008, J Neurol 255:452

PML

- ADA
 - No reports of PML

PML

- IFX
 - Three reports
 - Single death reported, considered by Centocor to be probably PML, in a study of IFX use in pts on MTX¹
 - Pt treated with natalizumab (Tysabri) with prior IFX use (20 months preceding PML)²
 - Natalizumab strongly correlated with PML

- Doubtful that IFX played role
- 16 y.o. with CD on IFX and azathioprine
 - Dx of PML very questionable: MRI atypical, CSF seronegative, pt fully recovered in six weeks³
 - ¹Durez Rheumatol 2005, 44:465 ²Van Assche 2005, NEJM 353:271 ³Kolho 2007, Acta Paediatrica 96:128

PML and IFX

- Kolho 2007, Acta Paediatrica 96:128
 - 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 efilizumab, 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

Lymphoma and RA

- 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
 - Baecklund 1998: Br. Med. J. 318: 181
 - 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

- Lymphoma risk 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
 - Brown 2002: Arth Rheum: 46: 3151
 - 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?

Lymphoma and TNFi

- 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
 - Lymphoma and ETN
- 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
- 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

Lymphoma and IFX

■ Centocor data

- There are the only 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

Lymphoma and TNFi

■ 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

Lymphoma and TNFi

■ 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
Lymphoma and TNFi

- 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?

Lymphoma and TNFi

- Other approach is to utilize registry data

- As with infection, registry data valuable

- ARTIS Swedish registry

- Askling 2007 EULAR Abst THUD0124
- 6304 RA pts on TNFi vs 67,338 RA pts not on TNFi
- RR for lymphoma vs general population 2.08 (1.16 – 3.43)
- RR lymphoma vs RA: 0.95 (0.55 – 1.67)

Lymphoma and TNFi

- N. American CORRONA database

- Callegan 2007 ACR Abst 989
- SIR for lymphoma for all RA pts vs general population 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

- U.S. National Data Base¹

- Wolfe 2007 Arthritis Rheum: 56: 1433
- 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

- **RATIO French registry¹**
 - Mariette et al, Ann Rheum Dis online 14 Oct 2009
 - 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)

Lymphoma and TNFi

- **Conclusions**
 - Three of four registries cited here show no increased risk
 - One study shows increased risk with MABs, but not ETN
 - Lymphoma risk issue not conclusively answered at this time
 - 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

Malignancy and TNFi

- **Only 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

- **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 FRI0113
 - 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
 - Bongartz 2006: JAMA: 295: 2275
 - 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 RA trials were pooled
 - To increase power of meta-analysis
 - Out of 144 studies identified as possibly relevant, 135 excluded for variety of design, duration issues

- Final total 9 studies, 5014 pts, variety of comparators
 - Placebo, MTX plus placebo, DMARD plus placebo
- Bongartz Meta-analysis

■ Results

- 29 malignancies seen among the 3493 patients who received at least one dose of anti-TNF drug
- 3 seen among 1512 control patients
- 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

■ Dose response

- Often seen as evidence of drug-related effect
- 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

■ Reactions to study

- Since publication, many criticisms leveled at study, and conclusions questioned
- Also, subsequent analysis extended to ETN

Bongartz Meta-analysis

■ Drug exposure not addressed

- Actively-treated patients typically stay in studies longer than placebo-treated patients since they are getting treatment
- Results in longer duration of treatment exposure for actively treated patients, increasing likelihood of detecting infection, malignancy

Bongartz Meta-analysis

■ Questionable dose relationship

- 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

■ Inadequate duration

- Analysis based on trials all of which lasted one year or less
 - But cancer typically is a disease process that takes years to evolve
 - Likely that many cancers seen had their induction well before study began
 - Optimal observation period would be much longer than one year

Bongartz Meta-analysis

■ Inadequate sample size

- Even after meta-analysis pooling, total number of malignancies identified (29 in TNF inhibitor-treated patients) was very small
 - Almost 1/3 of these cancers (10) were non –melanoma skin cancers
 - Much less potential risk, easier to manage
 - Thus total number of visceral cancers was 19

Bongartz Meta-analysis

■ Outlier conclusions

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

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 ratios of 1.0 and 0.97 respectively
- ETN data showed no increase even versus placebo

Bongartz ETN Analysis

- Most recently, Bongartz has used the same statistical techniques with ETN
 - Meta-analysis of 9 RCT with ETN and RA
 - 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

- So is Bongartz correct?
 - 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

- ARTIS database¹
 - Raaschou ACR 2007, Abst 1344
 - Risk of death from cancer not changed by TNFi exposure
 - RR of death in TNFi-exposed pts was 0.78 (0.50 – 1.26)
- BSRBR British registry¹
 - Watson EULAR 2006, Abst SAT0202
 - TNFi-treated vs biologic-naïve DMARD-treated RA 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

- CORRONA U.S. registry¹

- Greenberg ACR 2007, Abst 282
- RA pts treated with TNFi vs 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

■ NDB U.S. data bank

- Wolfe Arthritis Rheum 2007: 56:2886
- 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

■ Swedish RA registry¹

- Askling, Arth Rheum 2009, 60:3180
- 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

Malignancy and TNFi

■ RABBIT German registry¹

- Strangfield Arth Res Ther 2010, 12:R5
- 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

■ All six cited registries *do not show* an 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
 - Askling 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. “

Pediatric Malignancy

- 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 (etanercept) 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

Pediatric Malignancy

- My (personal and 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 purported statement of fact

Other Issues of Interest

- Data are also available on a number of interesting aspects relating to use of TNFi
 - I will review a few select topics (there are many more)
 - Use with concomitant Hepatitis
 - Effects on vaccination
 - Use in pregnancy
 - Update on demyelinating disorders
 - Effects on CHF

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

- Ferri, et al, J Rheum 2008, 35:10
 - 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)
 - MTX alone had significant reduction in response vs controls (roughly 25% vs 55%)

Vaccination

- Gelnick Ann Rheum Dis 2008:67:713
 - Response to influenza vaccination 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
 - Data on Zoster also argue for zoster vaccine before initiation of TNFi therapy

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

- I have relied on Vinet's comprehensive review of literature
 - Vinet 2009, Expert Rev Clin Immunol 5:27
 - IFX
 - Katz: Series of 96 pregnancies: 68 live births, 14 miscarriages, 18 ther abortions: 2 congenital malformations
 - 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 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
 - 6 miscarriages, 3 ther abortions, 13 live births
 - No birth defects

Pregnancy

- Joven, BIOBADASER registry
 - 14 pregnancies in TNFi-exposed RA pts
 - 7 live births with no complications, 3 ther abortions, one miscarriage, 3 unknown, no malformations

Pregnancy

- 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

- 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

- Study has been criticized heavily
 - No reliable comparison group
 - Carter chose to use “general population” as comparator
 - Huge selection bias in cases reported to FDA
 - 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
 - However, many diagnosed by Carter with “incomplete VACTERL” had abnormalities found in 3-5% of the general population

Pregnancy

- Editorial conclusions from same issue of journal
 - “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

- 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
 - Particularly for MAb, which pass placenta extensively
 - ETN appears to be transferred much less
 - 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

Pregnancy

- Conclusions
 - 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

Demyelinating Diseases and TNFi

- 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 also raised concerns
 - Dimeric protein comprised of two TNF receptors fused to fragment of IgG
 - Tested as treatment for MS
 - 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

- Mohan 2001, Arthritis Rheum 44:2862
 - AERS FDA database
 - 19 cases reported, 17 after ETN administration, 2 after IFX
 - All temporally related to TNFi therapy
 - All partially or completely resolved after discontinuation of TNFi
 - One positive rechallenge

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

Demyelinating Diseases and TNFi

- 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

Demyelinating Diseases and TNFi

■ Long term clinical trial data

• 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

Demyelinating Diseases and TNFi

■ Long term data

• 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

Demyelinating Diseases and TNFi

■ 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

Demyelinating Diseases and TNFi

■ 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

Demyelinating Diseases and TNFi

- 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 ration 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
- Still a cautious approach is wise

Demyelinating Diseases and TNFi

- Conclusion: any prior suggestion of demyelinating disease is at least a relative contraindication to TNFi therapy
- As all three package inserts note, “exercise caution in considering the use of [TNFi] in patients with preexisting or recent-onset central nervous system demyelinating disorders”
- Monitor patients carefully and discontinue therapy and refer for neurological consultation 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

- 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**

Infliximab in CHF: FDA Stance

CHF and TNFi

■ Other analyses

- Wolfe 2004, Am J Med 116:305
 - NDB analysis
 - 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

CHF and TNFi

■ 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
 - 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

Hypoglycemia and ETN

- Series of case reports of hypoglycemia in pts with DM after initiation of ETN therapy

- Wambier et al: 51 y.o. psoriasis pt
 - Pustular psoriasis flare. DM requiring insulin. ETN administered
 - Within 7 hrs, hypoglycemia developed with seizure and serum glucoses near 0
 - Eventually stabilized, off insulin, but developed cellulitis, sepsis and died.

Hypoglycemia and ETN

- Cheung & Bryer-Ash

- 72 y.o. psoriasis pt, Type II DM, stable on regular and NPH insulin.
- ETN started and pt began experiencing frequent episodes of hypoglycemia.
- Over 16 months, pt's insulin doses progressively reduced and eventually discontinued, with DM stable on oral hypoglycemic agents alone

Hypoglycemia and ETN

- Mechanism unclear

- No clear evidence of increased insulin production or insulin sensitivity with ETN
- Relatively rare event
- However does argue that pts with DM, especially those on insulin, should be monitored more intensively during the period after initiation of ETN

TNFi: 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_H1-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
 - CRP from 1 to 3 intermediate, and >3, high risk for CVD
 - From 2.7 to 1.4 in Pso, and 5.5 to 1.8 in PsA
 - Abramovits EADV 2008, Abst FP1307
 - CRP similarly reduced
 - Ps 6.5 to 5.2, PsA from 11.6 to 5.3

Cardiovascular Risk

- Dixon 2007, Arthritis Rheum 56: 2905
 - BSRBR British registry
 - 8670 pts on TNFi vs 2170 on DMARDs
 - No reduction in rate of MI in TNFi cohort vs DMARD
 - However, analysis of TNFi pts who responded in first six

months vs non-responders, rates of MI reduced dramatically

- IRR 0.36 (0.19 – 0.69)
- “supports the notion that inflammation plays a pivotal role in MI”

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

Cardiovascular Risk

■ Lennart 2005, J Rheum 32:7

- Swedish local registry
 - 983 pts, 531 with TNFi therapy
 - Incidence of first Cardiovascular Event
 - Controlled for other risks, adjusted risk ratio 0.46 (0.25 – 0.85) in TNFi vs DMARD treated pts

Cardiovascular Risk

■ Carmona 2006 ACR poster 501

- BIOBADASER Spanish registry
 - Compared to EMECAR registry excluding TNFi pts
 - SMR for CV events 0.610 (0.361 – 0.963) in men, and 0.427 (0.0195 – 0,811) in women

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

- There are solid data indicating risks of therapy
 - TB, other infection
 - Lymphoma esp with MABs
 - Hepatotoxicity with IFX, ADA
- And other areas where there are at least concerns
 - Thrombocytopenia?
 - Demyelinating diseases?
 - Malignancies esp with MABs?

TNFi Safety Summary

- Clearly regular clinical evaluation and laboratory screening are appropriate

- Some users have fallen into belief that these are “totally safe drugs”
 - “That’s what the reps tell us!”
- They are arguably safer than alternatives
- But that does not mean they are *risk-free*

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

Update 2011: Stelara

- ustekinumab (Stelara, 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
 - Available data are only from clinical trials
 - 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

- Latest safety information
 - (Gordon, poster P560, EADV 2010)

- 3 year pooled safety data from all trials¹
 - 3117 pts, 4782 pt-years exposure
 - 1247 pts with > 2 yrs exposure
- Adverse Events
 - AE, SAE, infections, serious infections, serious cardiovascular events, malignancies, and AE leading to d/c, were all stable or declined over time
 - No increase in AE in 90 mg vs 45 mg dose groups
 - Suggests lack of drug-related toxicity

Ustekinumab

- Common AE's
 - Nasopharyngitis, URI, headache, arthralgia, back pain, influenza, sinusitis
- Serious infections
 - Rates 1.70/100 PY for placebo, 0.49/100 for 45 mg, and 1.97/100 for 90 mg dose groups
 - Rates observed consistent with rates expected in general population
 - Expected rate 1.19/100 PY
 - Observed rate 1.19/100
 - SIR 1.01 (0.76 – 1.30)

Ustekinumab

- Malignancy
 - Rates of NMSC and other malignancies no higher than placebo in controlled portions of studies
 - Over 3 years, rates of NMSC and other malignancies remained stable with increasing duration of exposure
 - Rates for malignancies other than NMSC over 3 years consistent with rate in general population based on SEER database
 - SIR 1.05 (0.69 – 1.53)

Ustekinumab

- Cardiovascular events
 - Major adverse cardiovascular events (MACE)
 - CV death, MI, stroke
 - Controlled portions of studies
 - 0 MACE in placebo group, 5 in all UST-treated

- 1 MI 3 days after controlled portion of study ended in placebo patient
- Over 3 year exposure, rates of MACE low and stable, no dose effects
- Rates of MI and stroke consistent with
 - General population (Framingham) SIR 0.52 (0.31 – 0.84)
 - Psoriasis population (GPRD) SIR 0.34 (0.20 – 0.55)
 - Protective effect? Too soon to say

Ustekinumab

- Safety
 - Encouraging to date but
 - Data not yet adequate to make firm conclusions
 - Efalizumab safety appeared good on similar analyses
 - Poulin et al, J Cutan Med Surg 2005 9:313
 - “A favourable benefit/risk ratio with efalizumab: A review of the clinical evidence “
 - “results from 12-week, six-month, and three-year trials, focusing on the drug’s safety, efficacy, and therapeutic response time ... Efalizumab emerges as an important addition to the dermatological pharmacopeia for the long-term treatment of psoriasis”
 - 2009--drug withdrawn from market

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

Choices

- How does this affect the choice of biologics?
 - There are clear differences in efficacy between these agents but
 - Individual responses are still unpredictable, with no biomarkers yet identified which would predict success

Choices

- Equation: “Efficacy+Safety/Cost”
 - We have just reviewed some safety data
 - Efficacy?
 - Opinion/experience, not substantiated here with data
 - IFX> or =UST
 - IFX > ADA
 - ADA > ETN
 - But, unpredictable on patient by patient basis
- Cost, in US, roughly equivalent
 - Insurance coverage more a factor than raw costs
 - Some still require documentation of failure of phototherapy, systemic agent
 - Prohibitive without insurance
 - Unless income levels very low
 - Problematic with Medicare, Medicaid
- Each will prioritize these factors differently
- Your opinion?

Handouts

Available on our website:

www.newnandermatology.com/health/resources.html