Practical considerations in the use of biologics

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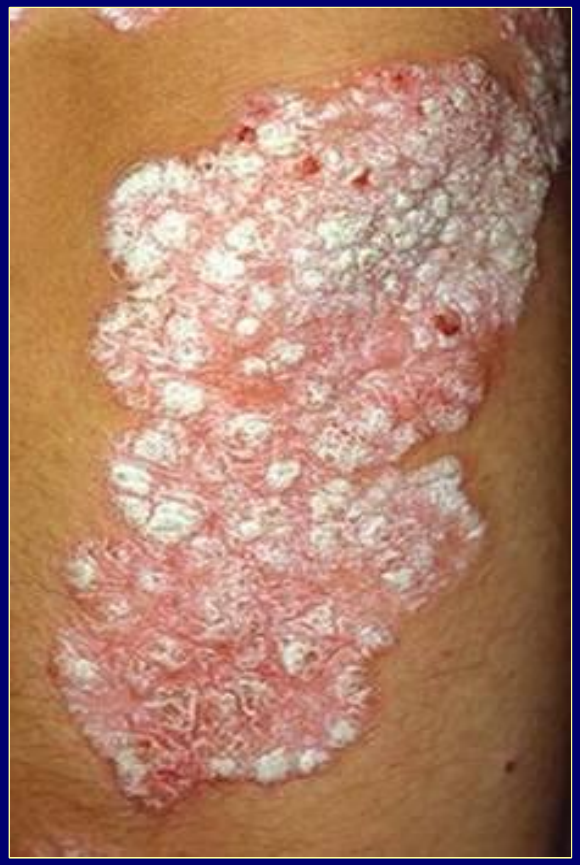
Progress and Promise **A Decade of Scientific Innovation**
15 – 17 March 2007 – Munich, Germany

Practical Considerations in the Use of Biologicals



Alan Menter, MD

Baylor Research Institute &
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Dallas, Texas

Munich
16 & 17 March, 2007

Practical Considerations in the Use of Biologicals

DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Research support and/or consultant and/or lecturer for Abbott Laboratories, Amgen, Astellas, Centocor, Genentech, Wyeth.

IPC INTERNATIONAL PSORIASIS COUNCIL

Data presented during this meeting

- Please note that the individual opinions expressed during this meeting are those of the speakers and do not necessarily reflect those of Wyeth Pharmaceuticals

- During this meeting you will see pivotal clinical trial data related to the licence submission for etanercept

Please note that etanercept is approved for:

- The treatment of active and progressive psoriatic arthritis in adults when response to a previous disease-modifying antirheumatic drug therapy has been inadequate
- The treatment of adults with moderate-to-severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA

Etanercept summary of product characteristics

www.EMEA.europa.eu (Accessed March 2007)

Posology and method of administration of etanercept

- Psoriatic arthritis
  - 25mg etanercept administered twice weekly, or 50mg once weekly, is the recommended dose
- Plaque psoriasis
  - The recommended dose of etanercept is 25mg administered twice weekly
  - Alternatively, 50mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25mg twice weekly
  - Treatment with etanercept should continue until remission is achieved, for up to 24 weeks
  - Treatment should be discontinued in patients who show no response after 12 weeks
  - If re-treatment with etanercept is indicated, the above guidance on treatment durations should be followed. The dose should be 25mg twice weekly

Etanercept summary of product characteristics

www.EMEA.europa.eu (Accessed March 2007)

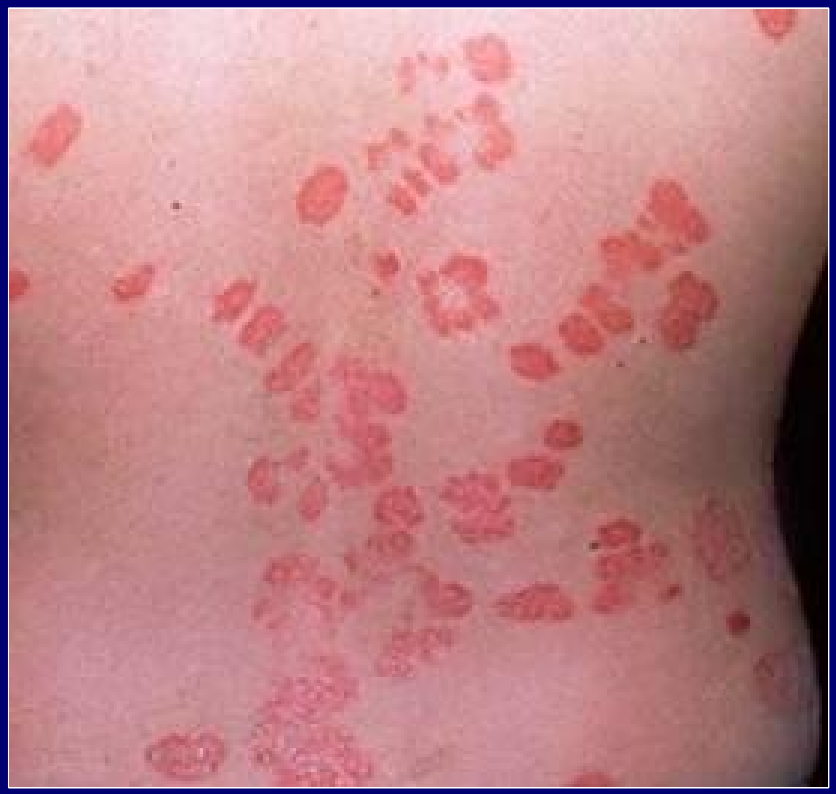
2007 Update on Biological Therapy for Psoriasis

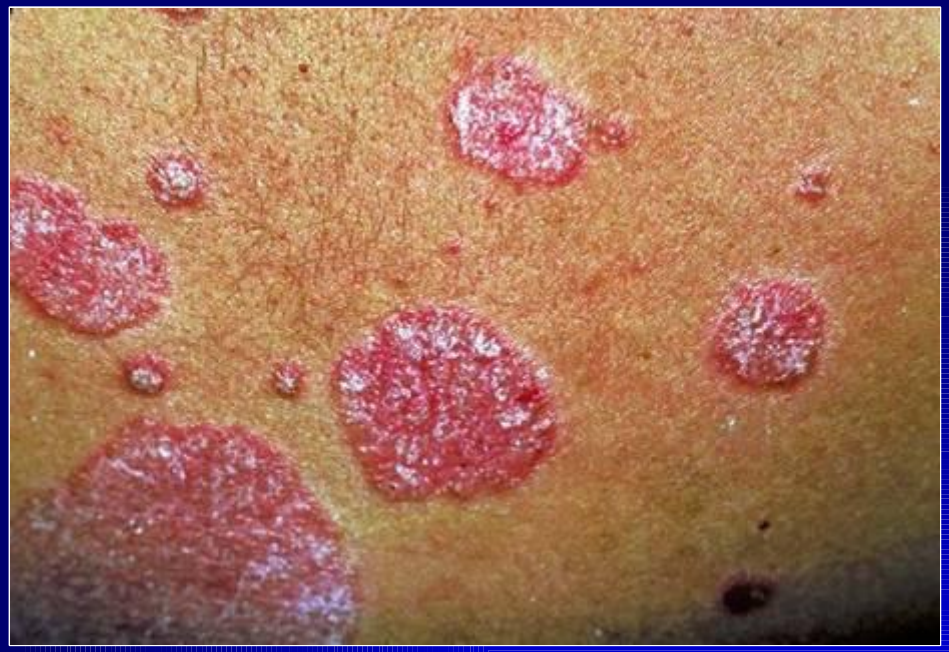
Phenotypical Expression

Griffiths CEM, Christophers E, Barker JNWN, Chalmers RJG, Chimenti S, Krueger GG, Leonardi C, Menter A, Ortonne JP, Fry L. A classification of psoriasis vulgaris according to phenotype. Br J Dermatol 2007;156:258-62.

Question: Are all the variants of psoriasis amenable to biological treatment?

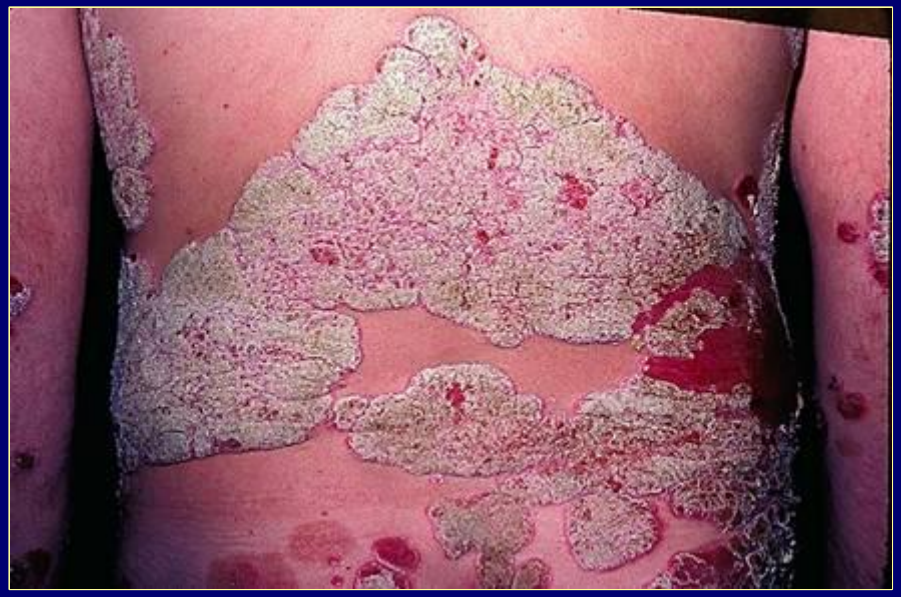
Small Plaque Psoriasis

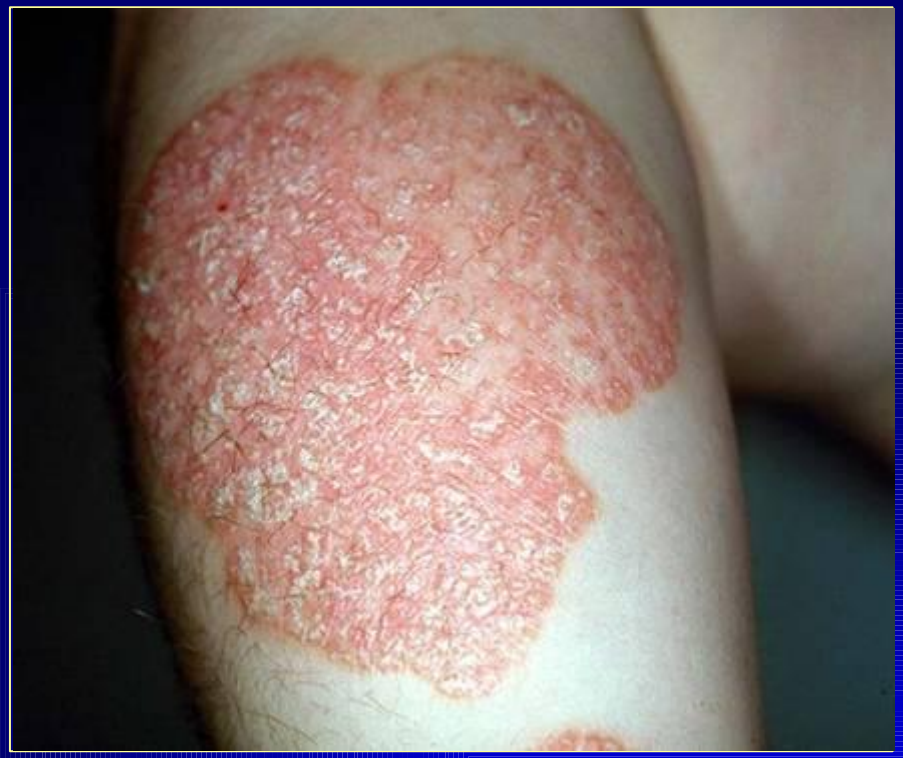




Therapy: Topicals vs. Systemic?
Phototherapy vs. Systemic?

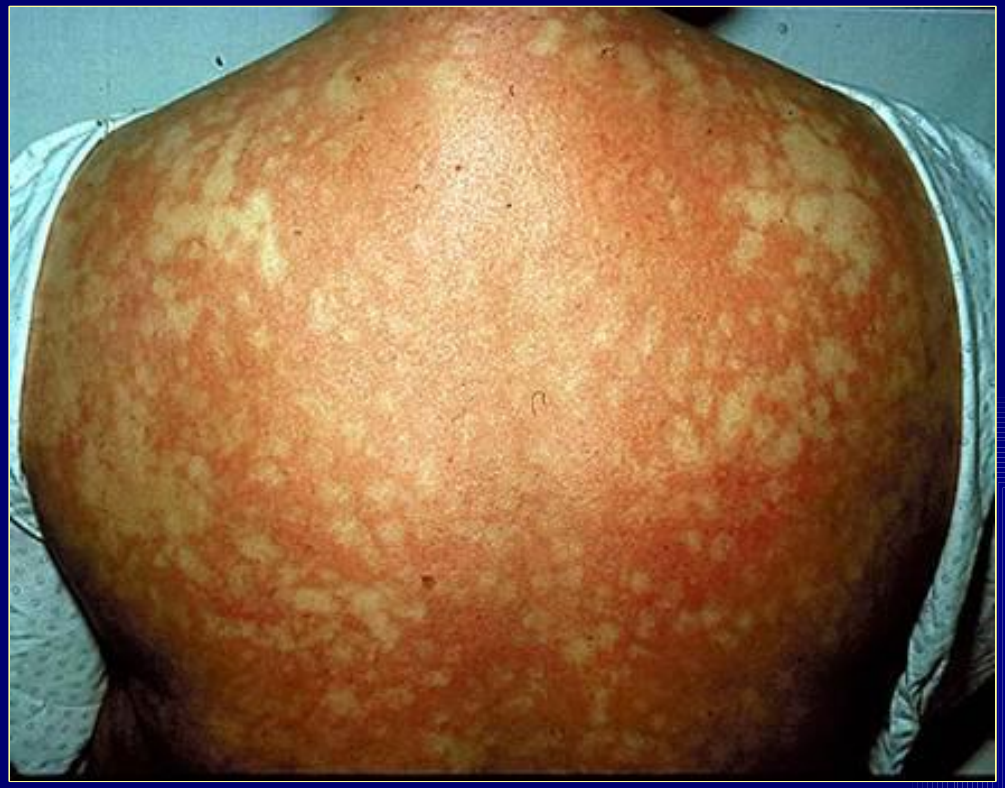
Large Plaque Psoriasis

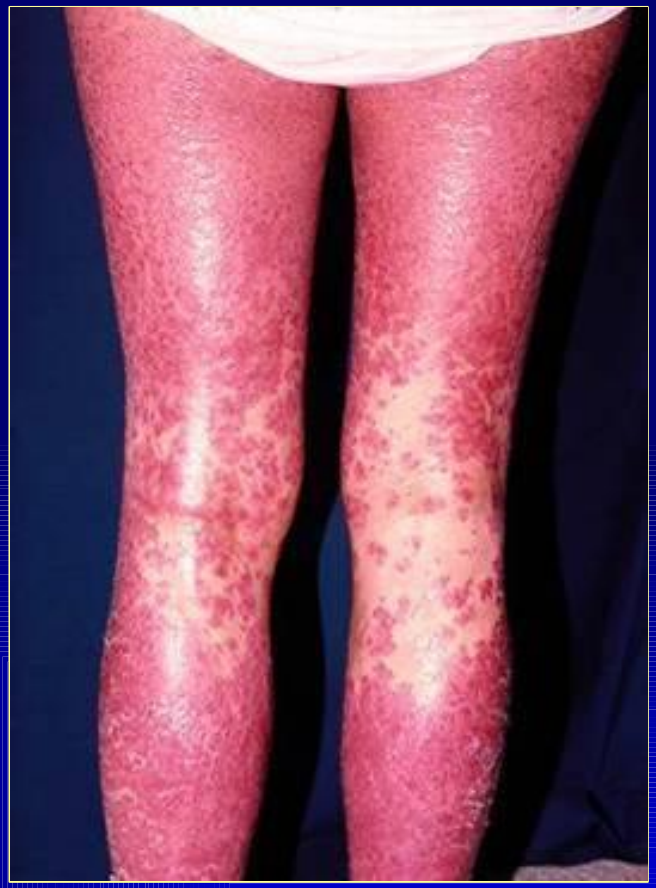




Do topicals have a role?

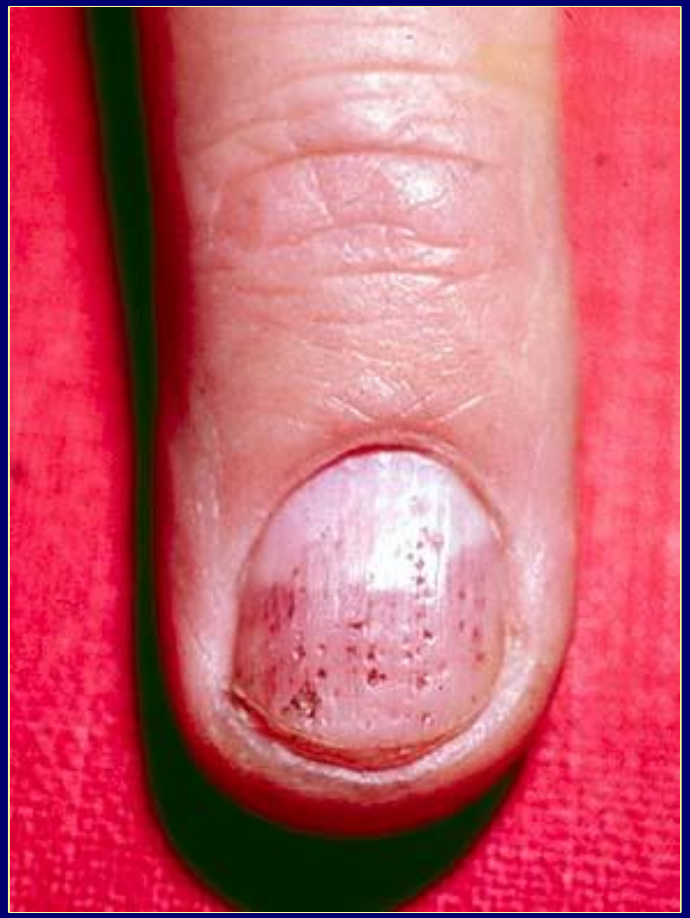
Erythrodermic Psoriasis

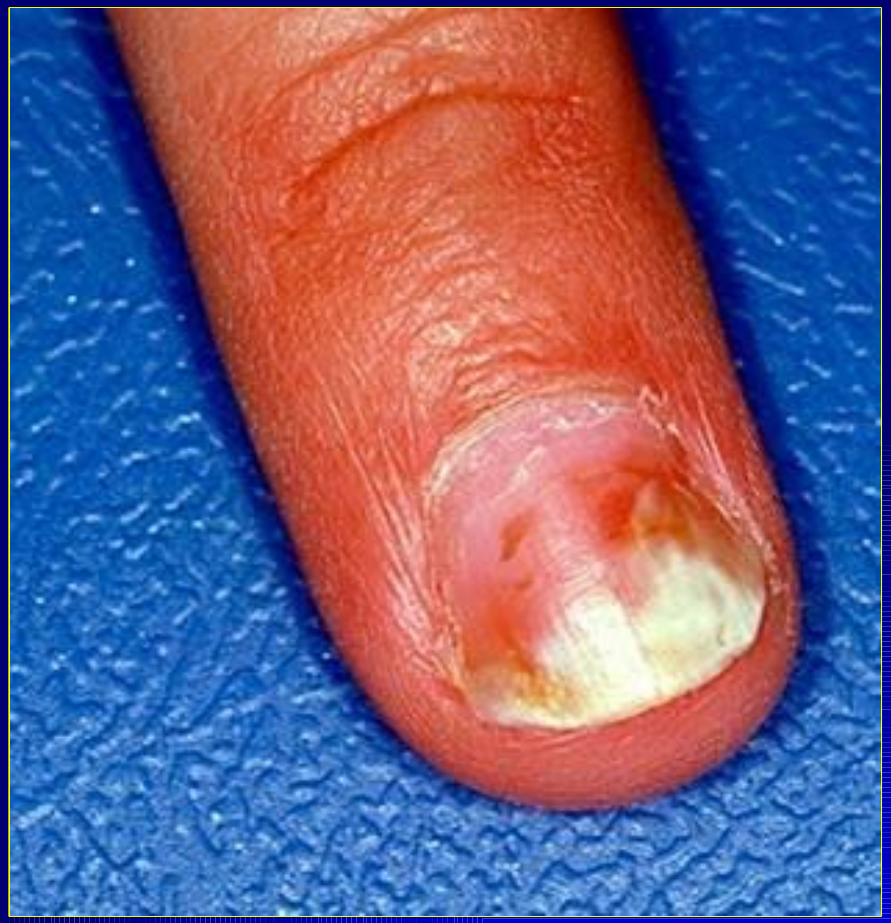




Therapy: Systemic & supportive topicals

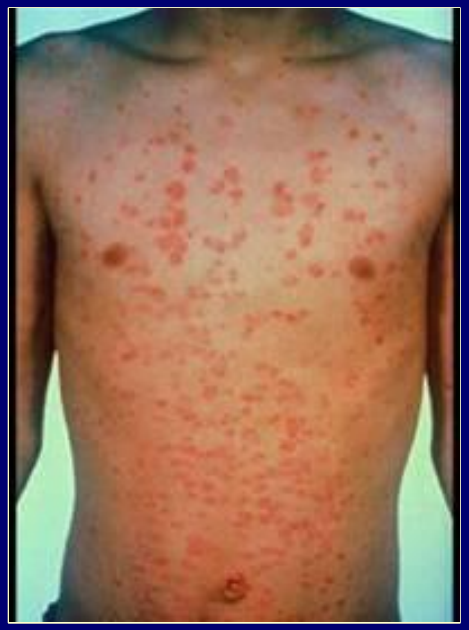
Nail Psoriasis

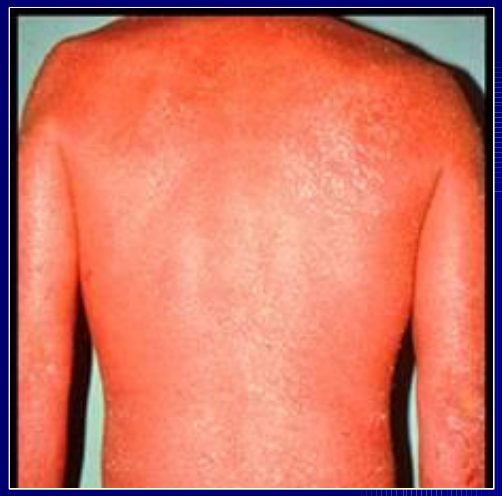


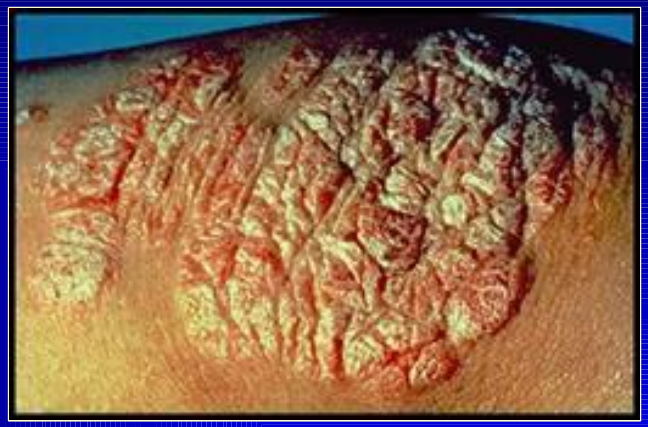


Therapy: Does anything really work?
TNF-α very promising.

The Many Faces Of Psoriasis







Is this one disease?
Does one therapy fit all?

Non-Biological Psoriasis Systemic Therapies

88 patient MTX and CyA study

Summary:

- Excellent - good PASI 75 scores (60-70%)
  - MTX + CyA
- Relapse occurs rapidly (6-12 weeks)
- Acute and cumulative toxicities (liver, bone marrow, kidney, hypertension) require safety monitoring and dose adjustments
- Moderate cost

Question: Do the risks outweigh the benefits?

Heydendael VM, et al. *N Engl J Med*. 2003;349:658-665.

CHAMPION Phase III Trial Results: Adalimumab Efficacy and Safety Compared with Methotrexate and Placebo in Patients with Moderate to Severe Psoriasis

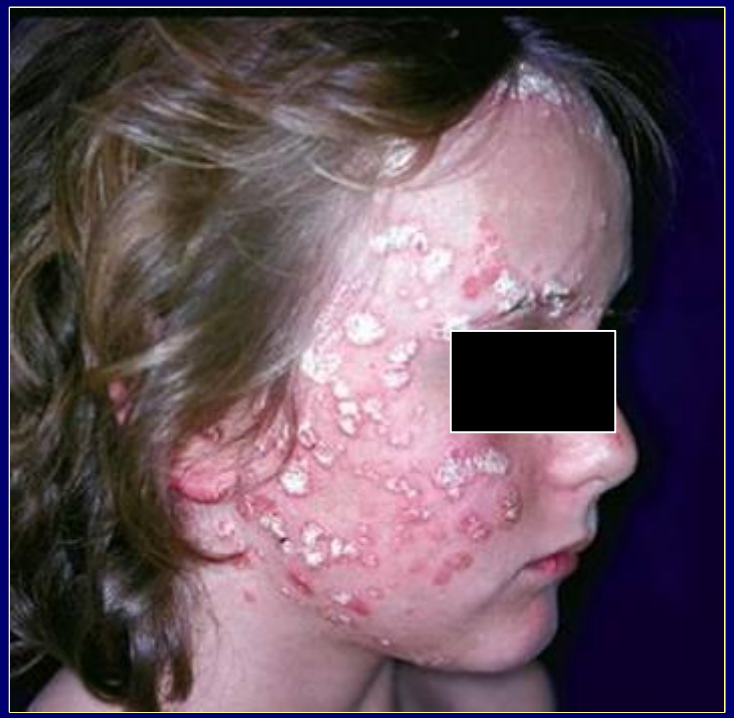
- Saurat J, Stingl G, Dubertret L, Papp K, Ortonne J, Unnebrink K, Kaul M, Camez A

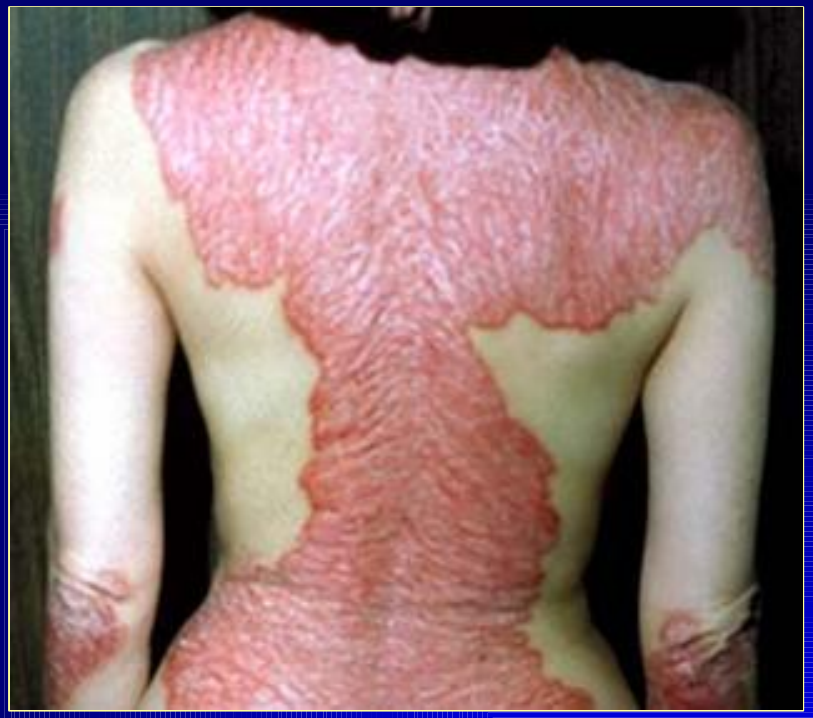
- Adalimumab demonstrated significantly superior efficacy in the treatment of moderate to severe psoriasis vs. MTX and vs. placebo
  - PASI 75 at Week 16: 80% for adalimumab vs. 36% for MTX and vs. 19% for placebo
- Response to adalimumab was rapid, with a mean percentage PASI improvement of 57% achieved at Week 4

Presented at the 15th Congress of the European Academy of Dermatology & Venereology, 2006

Biologics and Psoriasis

I would like to review our Dallas experience since the first biological agent, Alefacept*, was introduced (January 2003) in the USA.





Moderate-to-Severe Plaque Psoriasis

* Not licensed in the EU

Systemic Medications for Psoriasis

As of September 1, 2002

Patients on Monotherapy

MTX	212	Targretin	14
CyA	113	SSZN	7
Acitretin	87	Cellcept	1
6-Thioguanine	3	Azathioprine	2
Hydoxyurea	16		
		TOTAL	455

The “pre-biologic” era

Systemic Medications for Psoriasis

As of January 2007

Patients on Monotherapy

MTX	98	Hydroxyurea	7
CyA	44	SSZN	5
Acitretin	92	Cellcept®	7
6-Thioguanine	0		

TOTAL 253

44% reduction since 2002

Systemic Medications for Psoriasis

As of September 1, 2002

Patients on Combination Therapy

MTX	- CyA	14
	- Acitretin	5
CyA	- Acitretin	9
	- Hydroxyurea	3
	- 6 Thioguanine	1
Acitretin	- Hydroxyurea	20
	- 6 Thioguanine	2
	- SSZN	2
Hydroxyurea	- SSZN	1

TOTAL 57

The “pre-biologic” era

Systemic Medications for Psoriasis
As of January 2007

Patients on Combination Therapy

MTX	- CyA	2	Acitretin	- Hydroxyurea	3
	- Acitretin	3		- Azathioprine	1
CyA	- Acitretin	1		- SSZN	3
			TOTAL		13

79% reduction since 2002

Biological Therapy in Psoriasis & PsA
Our Dallas Patient Data
January 2007

	Monotherapy	In combination with traditional agents	TOTAL
• **Etanercept**	**145**	**21**	**166**
• Efalizumab	69	11	80
• **Adalimumab**	**99**	**13**	**112**
• **Infliximab**	**89**	**20**	**109**
• Alefacept *	7	1	8
Totals =	**409**	**66**	**475**

81% = TNFα drugs

*Not licensed in the EU

Alan Menter, MD, Personal data

Biological Therapy in Psoriasis & PsA
Our Dallas Patient Data
January 2007

Number of patients

- On biologics = **475**
- On traditional agents = **266**

Number of patients on systemic therapy = 741

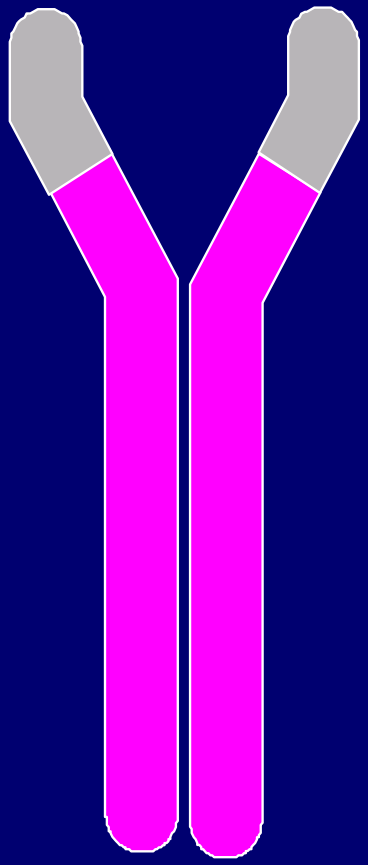
- This is a 45% increase over the past 3 ½ years
- Reduction in traditional monotherapy agents (MTX and CyA)
- 78% reduction in patients on traditional systemic combination agents (eg MTX + CyA)
- Acitretin remains unchanged

Practical Considerations in the Use of Biologicals

Let's Discuss The "Big Five"

Alefacept*

Portion of LFA-3



Fc Portion of IgG1

- Recombinant Fusion Protein
  - First extracellular portion of LFA-3
  - Fc portion of IgG1
- Binds to CD2 on T and NK Cells
  - Inhibits secondary signaling
  - Induces T-cell apoptosis
- Lymphocyte Depleting
  - Depletes memory-effector T-cells
- Administered by
  - IM injection
- Monitoring
  - CD_4+ T lymphocyte bi-weekly while on therapy
  - Hold therapy if CD4+ <250/µL
  - Discontinue if CD4+ <250/µL for 1 month

* Not licensed in the EU

Biological Agents in Psoriasis

- Alefacept* issues
  - Slow onset improvement
  - Poor PASI with single course (21% PASI 75); better with subsequent courses
  - Phototherapy accelerates initial response
  - 12 week courses likely incorrect, ie 16 weeks better
  - Bi-weekly CD4 counts likely unnecessary
  - Excellent safety record
  - Can we predict remissions in sub-group of patients, ie pharmacogenomics?

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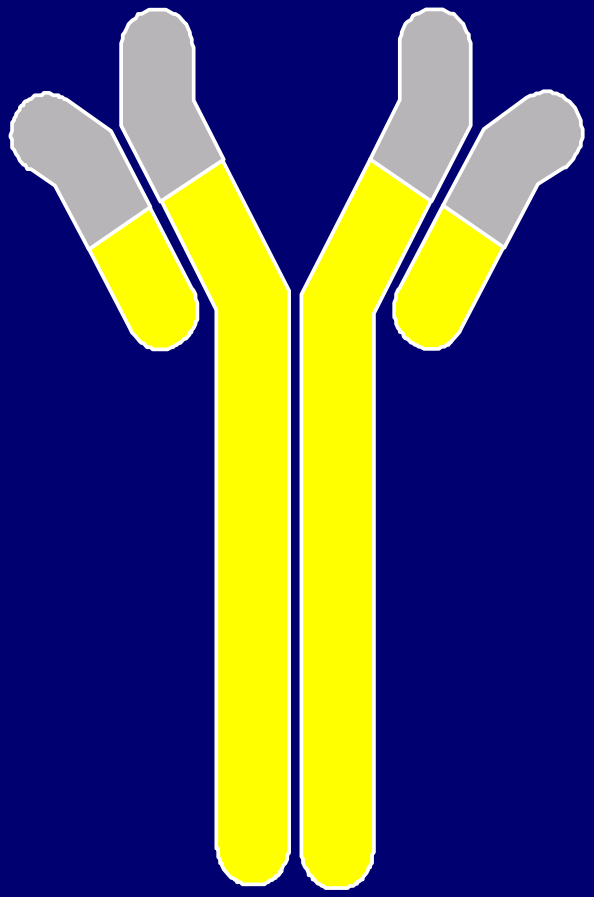
Practical Considerations in the Use of Biologicals

EFALIZUMAB

Biologic Drug Strategies for Psoriasis
Strategy 2
Block T-Cell Migration:

Murine Binding Site for CD11a



Human IgG1

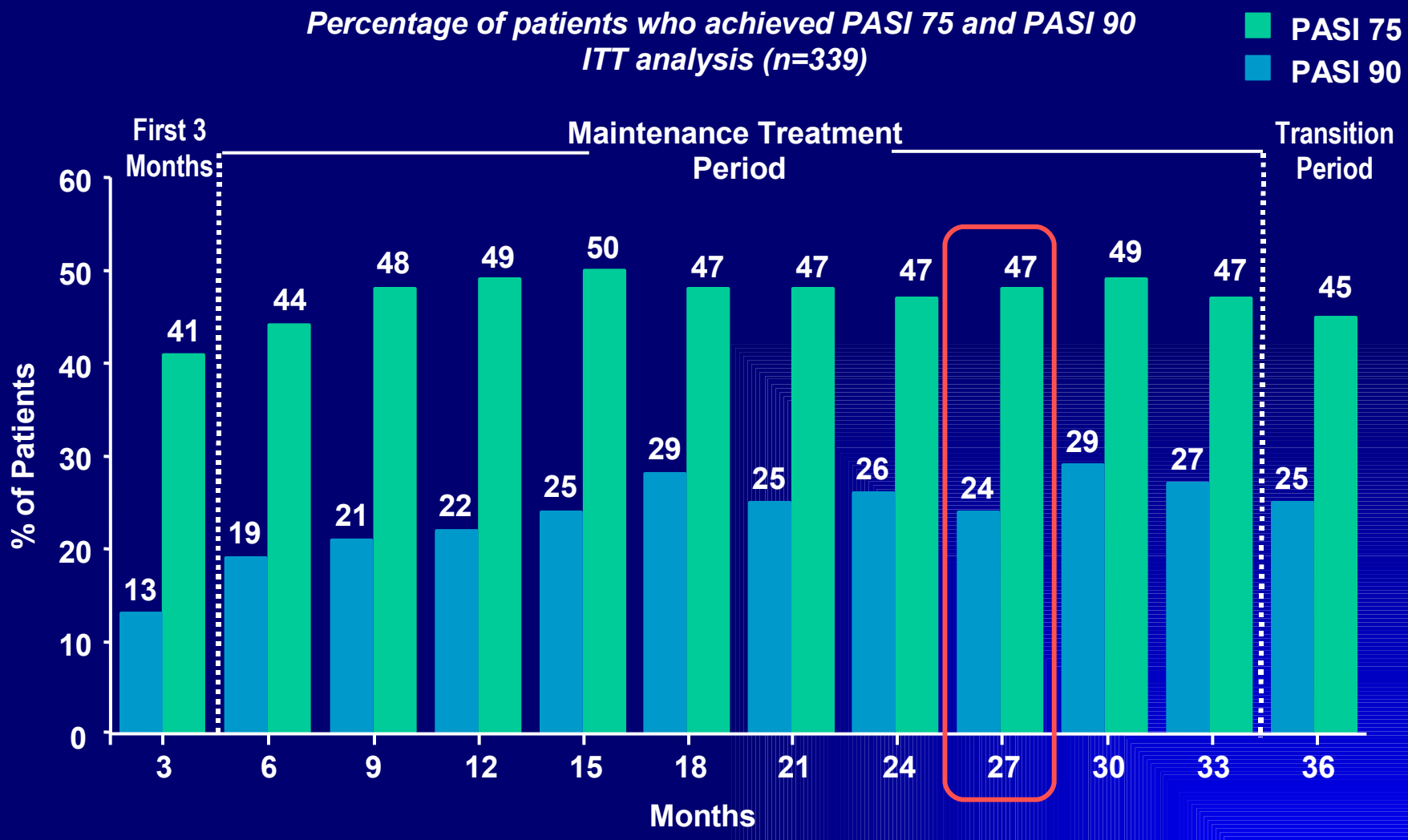
Efalizumab

- Humanized Mab against CD11a chain of LFA-1
- Non-lymphocyte depleting

∀↓ Lymphocyte trafficking into dermis/epidermis

Efalizumab 2007
New Considerations

Efalizumab Efficacy During 3 Years of Therapy (Intent-to-Treat Analysis)



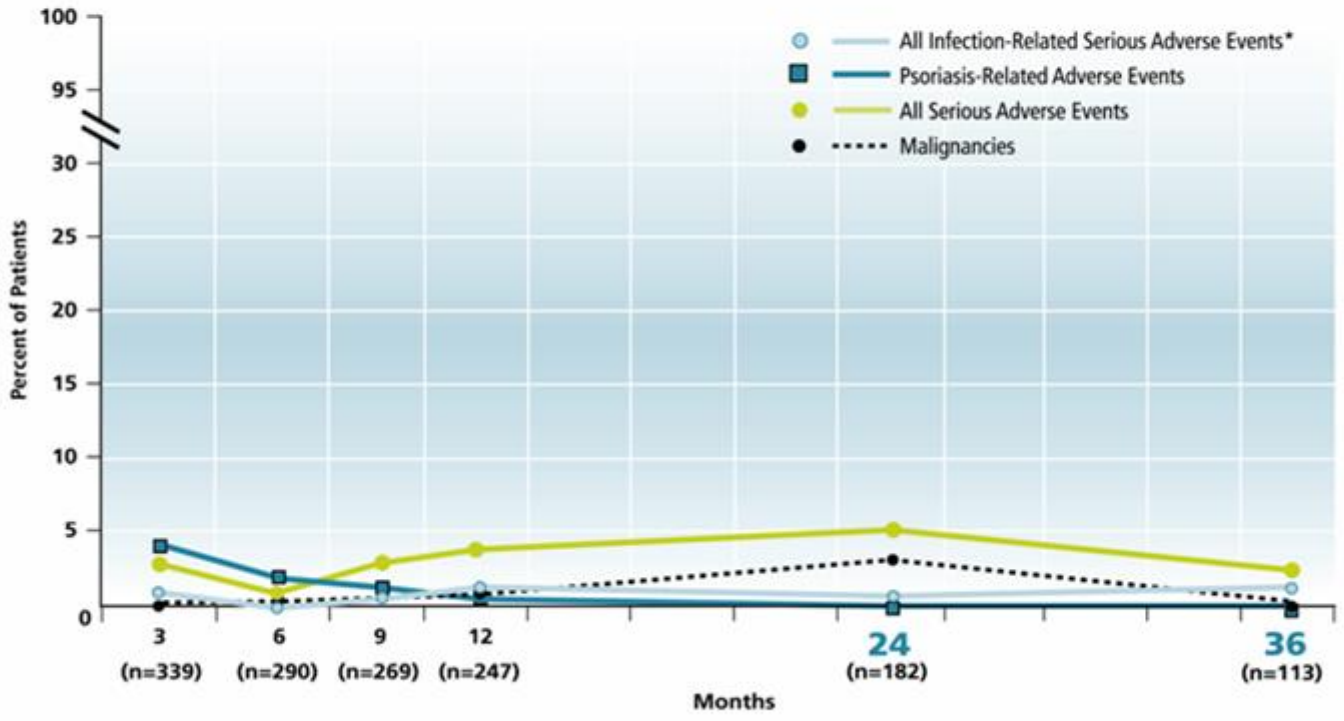
Gottlieb A, et al. AAD Annual Meeting 2005; Poster 4.

J Am Acad Dermatol. 2006 Apr;54(4 Suppl 1):S154-63

Efalizumab in Psoriasis – *JAAD* Manuscript # 1

Incidence of adverse events remain low over time (Note: manuscript results through 27-months only)

Incidence of adverse events during 36 months of continuous therapy with RAPTIVA® [efalizumab][8]



JAAD Manuscript # 3
Psoriasis adverse events during efalizumab therapy

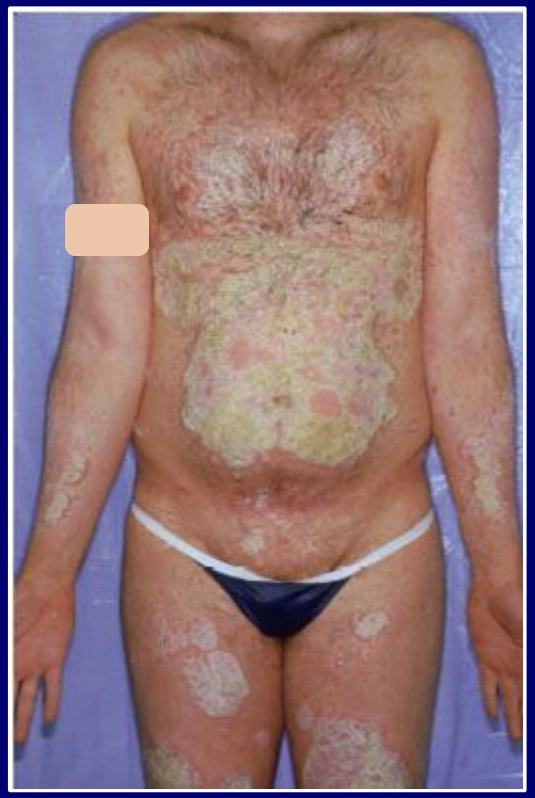
A. Localized mild breakthrough (LMB)

- Occurs in 1/3 to 1/4 of patients
- Transient
- Manifests during the first 4-8 wks
- Presents on neck, torso, or flexural areas
- Papular in nature
- Occurs in responders or non-responders
- Can be effectively “treated through” with low potency topical steroids
- Does not signal impending GIF

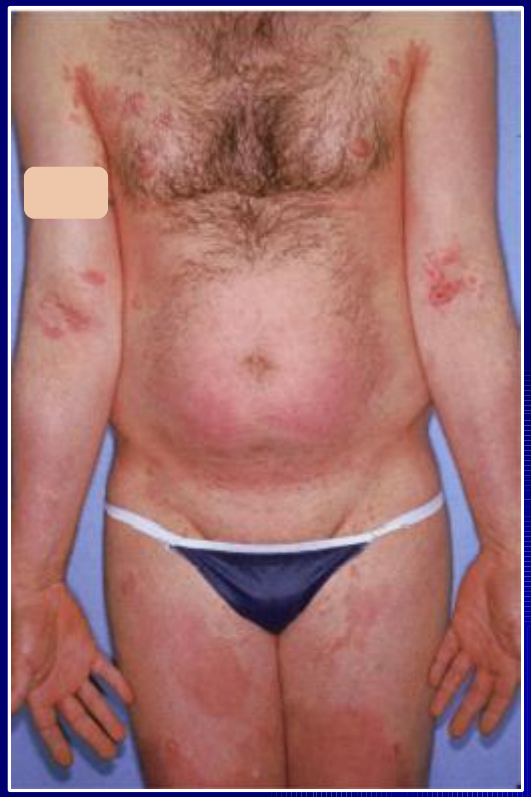
Menter A, Leonardi CL, Sterry W, Bos JD, Papp KA. Long-term management of plaque psoriasis with continuous efalizumab therapy. *J Am Acad Dermatol*. 2006 Apr ;54(4 Suppl 1):S182-8.

Localized mild breakthrough (LMB)

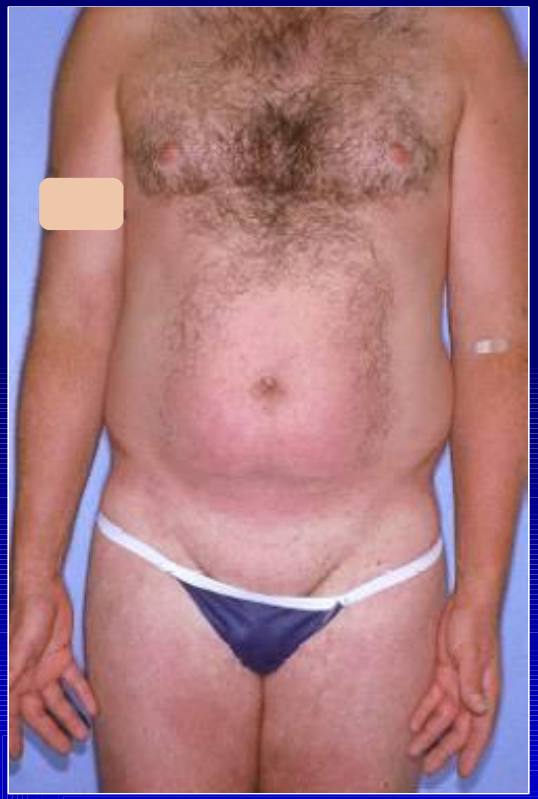
Patient Treated for 6 Months



Baseline
PASI 42.8



Month 3
PASI 14.1



Month 6
PASI 6.8

Courtesy of SD Glazer, MD. Buffalo Grove, Illinois.

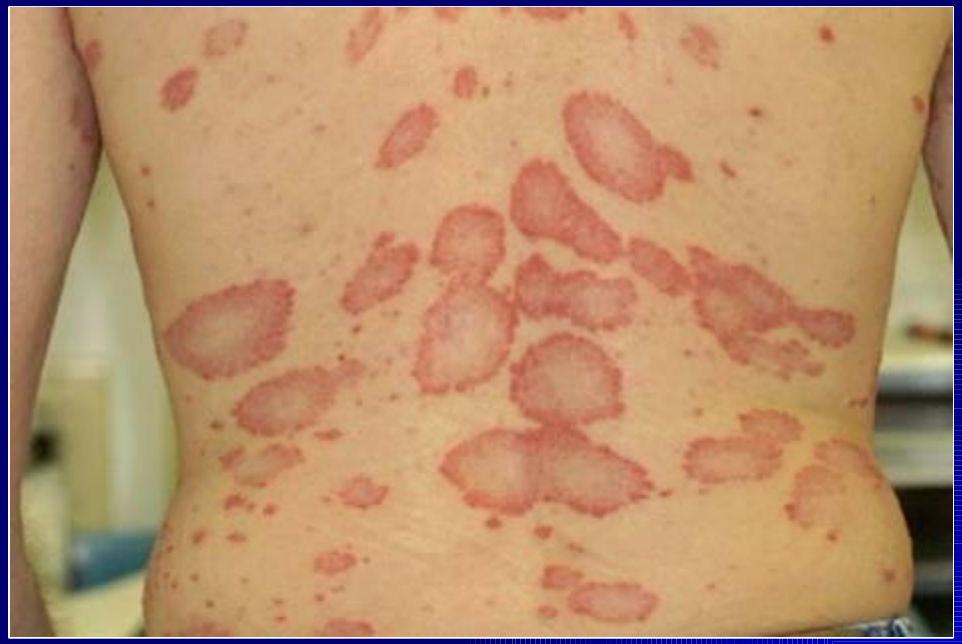
Psoriasis adverse events during efalizumab therapy

B. Generalized Inflammatory flare

Clinical Experience

- Occurs in up to 5% of efalizumab patients
- Less frequent than localized mild breakthrough, but more severe
- More common in partial or nonresponders
- Therapy:
  - Transition patient to another agent
  - Add concomitant systemic agent
- Observe patients closely following discontinuation of efalizumab

Efalizumab
Generalized Inflammatory Flare
Personal Case



Week 10 of efalizumab therapy

- CyA “rescue” initiated with rapid response
- Efalizumab discontinued

Biologicals in Plaque Psoriasis

- Efalizumab issues
  - Quicker onset of action vs alefacept
  - Continued response up to 24 weeks
  - Palmar-plantar psoriasis efficacy
  - Excellent 3 year safety data (thrombocytopenia, hemolytic anemia) with no loss clinical efficacy
  - Localized mild breakthrough (2-3 weeks duration)
  - Generalized inflammatory flare – non-responders (CyA, MTX “rescue”)
  - Rebound?
  - Potential in Atopic Dermatitis

T-Cell Orientated Therapies Summary

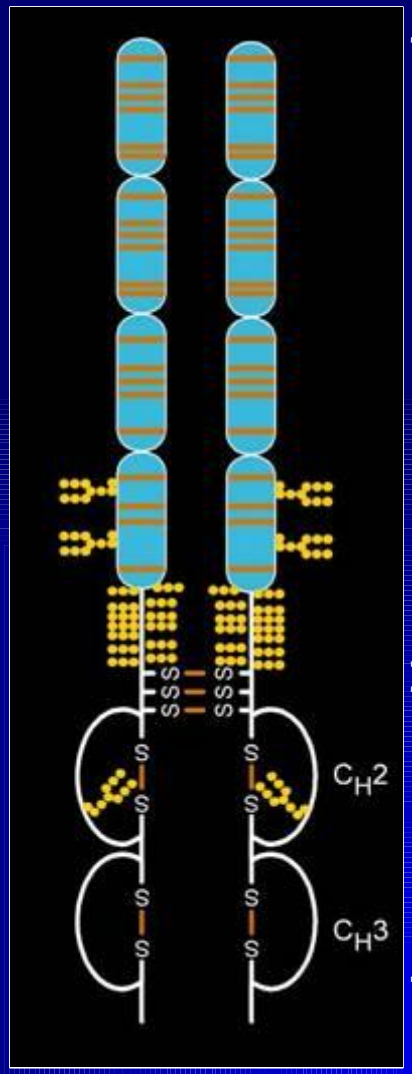
- Question: Can Alefacept* and Efalizumab measure up to the “TNF Agents” over the next 5 years?
  - Safety data?
  - Durability of response?
  - Palmar-plantar psoriasis
  - Efficacy in other T-cell mediated diseases?
    - Alopecia Areata
    - Atopic Dermatitis
    - Vitiligo
    - Pyoderma Gangrenosum
    - GVHD, CTCL, etc.
  - Psoriatic Arthritis?
    - Alefacept – favorable
    - Efalizumab – Nil response

*Not licensed in the EU


Practical Considerations
in the Use of Biologicals
ETANERCEPT

Etanercept 2007
New Considerations

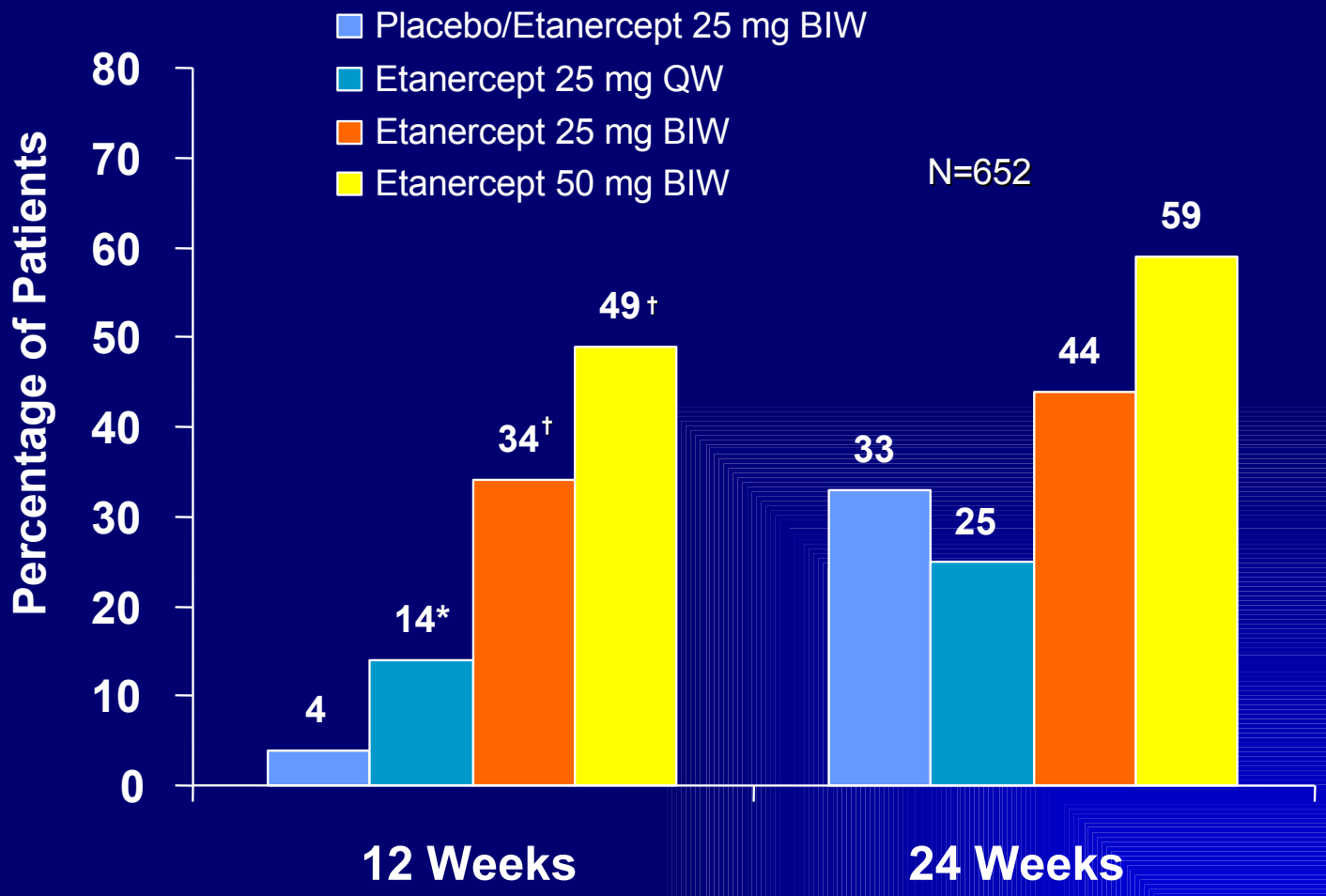
- Indications
  - RA, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile RA
- Administration
  - Subq injections 50 mgs 2 times a week for first 3 months, weekly thereafter



Extracellular domain of high-affinity human p75 TNF receptor

Fc region of human IgG_1

Etanercept in Plaque Psoriasis (Phase III US Study)
PASI 75 Response



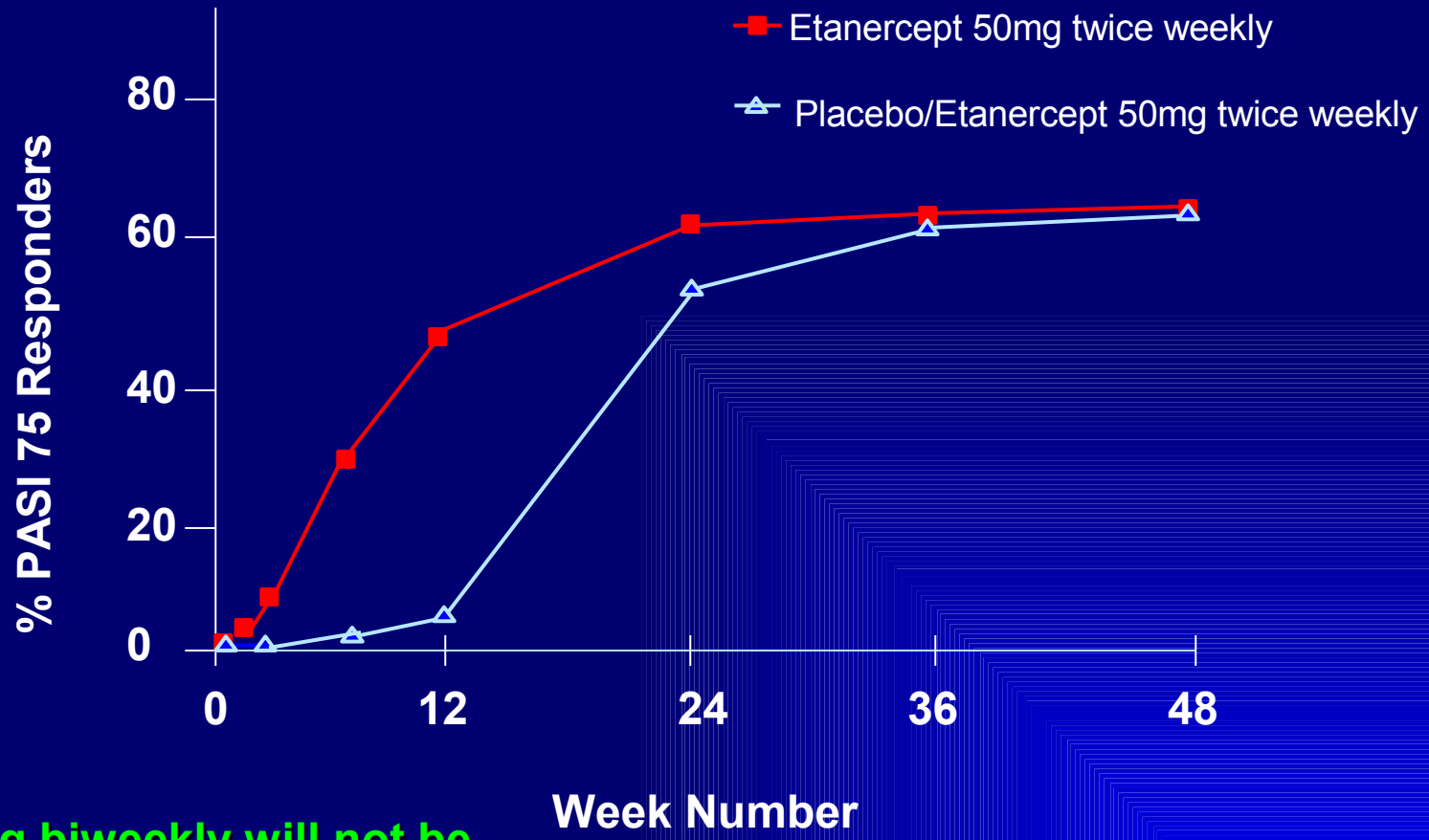
*P=0.0006; †P<0.0001 vs placebo

Leonardi C, et al. *N Engl J Med.* 2003;349:2014-2022.

Etanercept in Plaque Psoriasis

48 Weeks Data (50mg biw)

Proportions of Patients Attaining PASI 75



NOTE: 50mg biweekly will not be covered for 48 weeks by majority of insurance companies in the US.

Papp et al. Poster, July AAD 2005

Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial

Methods

- 618 patients, placebo vs. 50 mg twice-weekly etanercept

Outcome Measures

FACIT- F (Functional Assessment of Chronic Illness Therapy Fatigue scale)

- 13 questions, self administered
- How fatigue affects the patient's activities

Ham-D (Hamilton rating scale for Depression)

- 17 questions, administered by Healthcare Professional
- Determines level of depression

BDI (Beck Depression Inventory)

- Patient administered
- 21 symptoms and attitudes

Tyring S, et al. *Lancet* 2006 ;367:29-35.

Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial

Results

Week 12

- 50% improvement in Ham-D or BDI vs. placebo
- 5 point improvement FACIT vs. 1.9 placebo improvement

Conclusions

- Etanercept treatment relieves fatigue and symptoms of depression associated with this chronic disease
- Likely other TNF-α agents will show a similar response

Tyring S, et al. *Lancet* 2006 ;367:29-35.

Utilization of Narrow-Band UVB Light Therapy and Etanercept for the Treatment of Psoriasis (UNITE): Characteristics of PASI Responders

- Kircik L, Elmets C, Koo J, MD; Menter A, Bagel J, Korman N, Boer Kimball A, Yang YC, Chiou CF, Dann F, Stevens SR

Poster presented at 2007 AAD

Utilization of Narrow-Band UVB Light Therapy and Etanercept for the Treatment of Psoriasis (UNITE): Characteristics of PASI Responders

STUDY DESIGN

- 12-week, open-label, single-arm, prospective study
- Etanercept (50 mg twice weekly, administered subcutaneously) and NB-UVB phototherapy (three times weekly with dose escalation)
- 86 patients enrolled

RESULTS

- 26% of patients achieved PASI 100
- 60% of patients achieved PASI 75

Poster presented at 2007 AAD

Biologicals Case Study

KA

Prior Therapy

- Topical therapy: Multiple
- Phototherapy excluded due to travel distance
- Systemic therapy: Methotrexate
  - 10 years
  - Accumulated dose 4.5gm
  - Liver biopsy @ 2.5gm – Grade 1

Biologicals Case Study

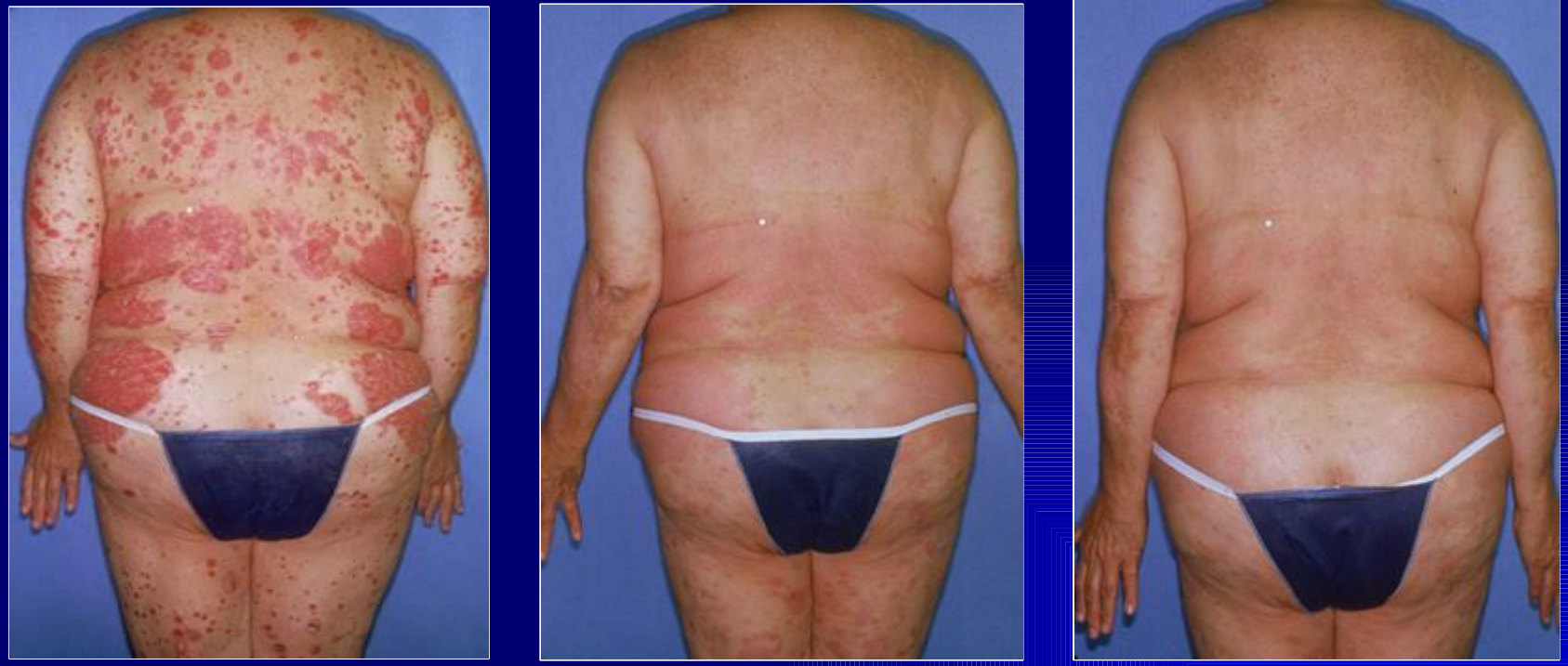
KA

Biologic Therapy

- Jan 03 etanercept - initiated with MTX dose stable @ 10mg/wk
- May 03 MTX - reduced to 5mg/wk, then discontinued
- Feb 05 – BSA now 3%
- Psoriatic Arthritis – Rapid response – asymptomatic at week 4 of etanercept therapy

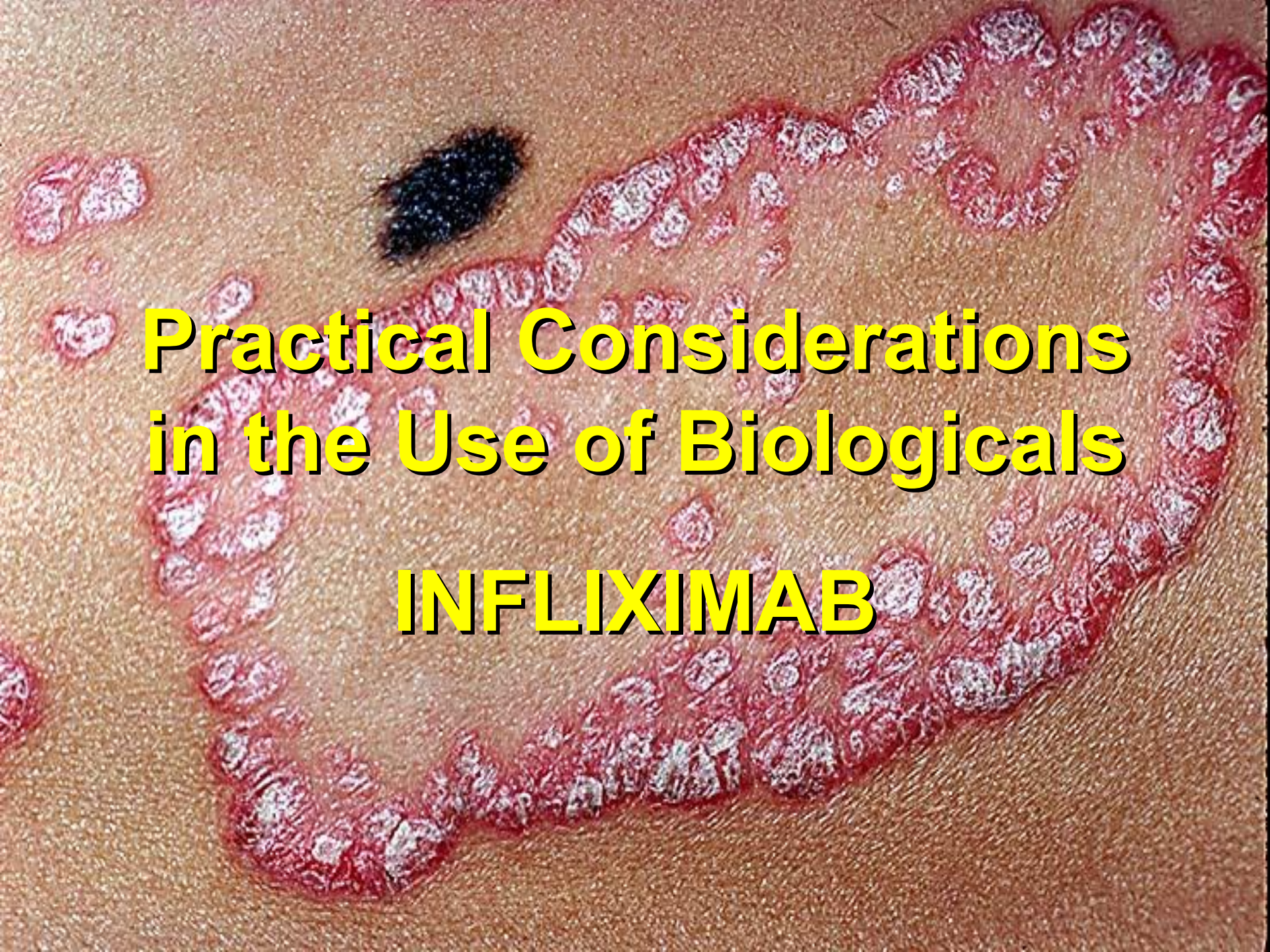
Biologicals Case Study

KA



Wk 0 Wk 12 Wk 24

Etanercept Therapy


Practical Considerations
in the Use of Biologicals
INFLIXIMAB

Treatment of Immune-Mediated Inflammatory Diseases with Infliximab

Data on file, Centocor, Inc.

THE LANCET

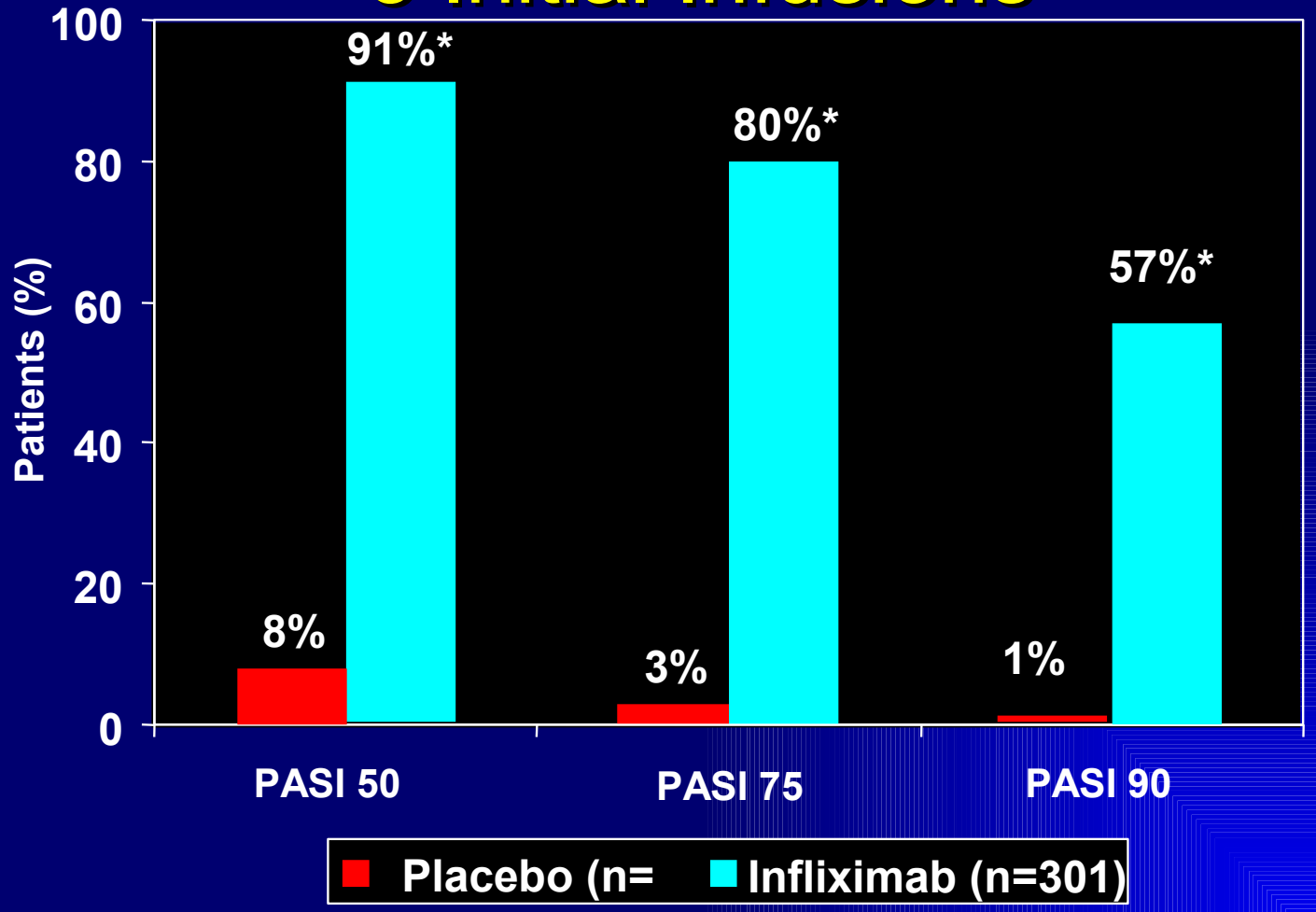
Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial

*Kristian Reich, Frank O Nestle, Kim Papp, Jean-Paul Ortonne, Robert Evans, Cynthia Guzzo, Shu Li, Lisa T Dooley, Christopher E M Griffiths, for the EXPRESS study investigators**

Lancet 2005; 366: 1367–74

The "EXPRESS" Study

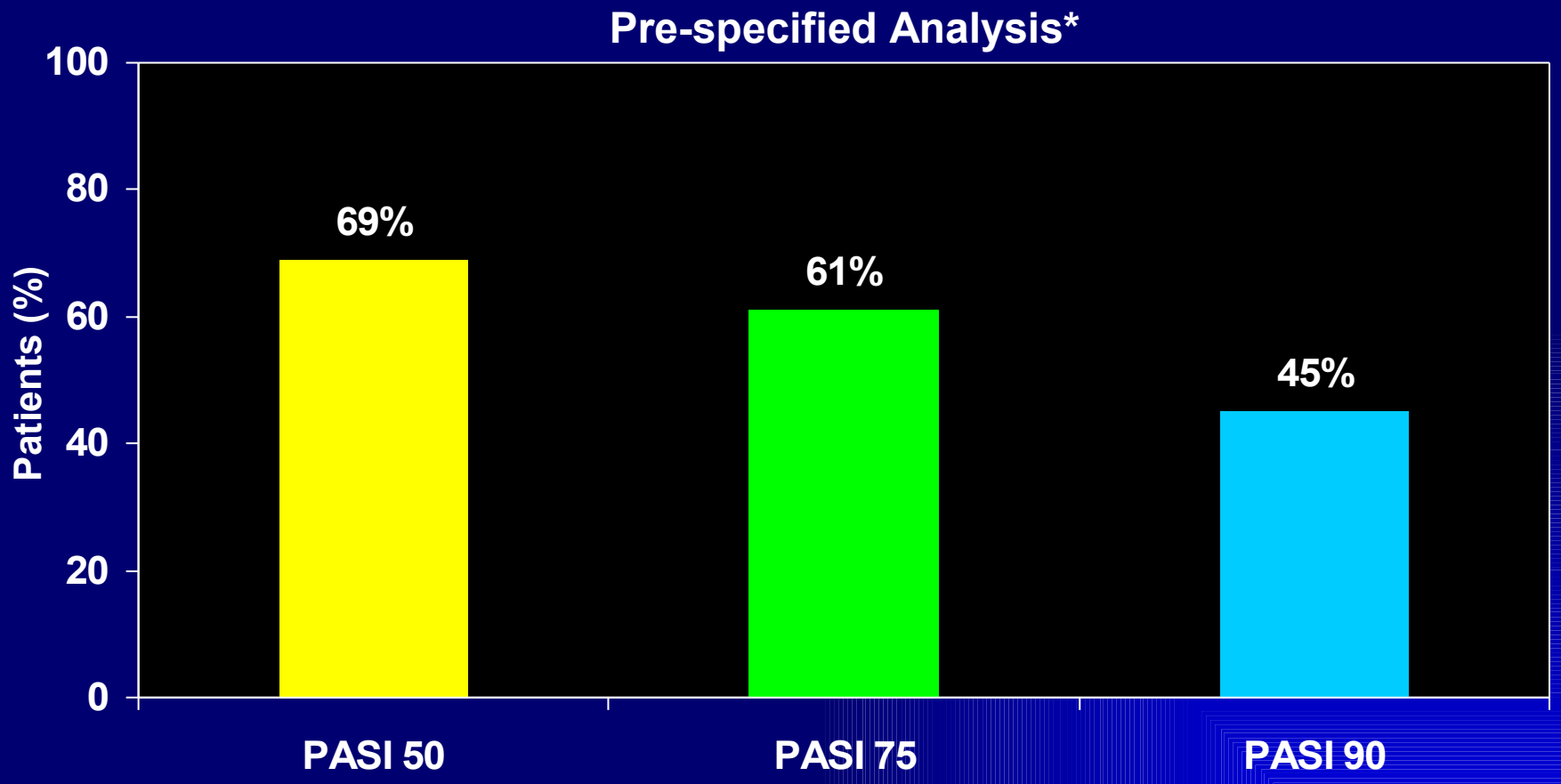
Study – Infliximab 5mg/Kg vs. Placebo PASI Response at Week 10 3 Initial Infusions



*p<0.0001 vs. placebo

Reich K, et al. *Lancet.* 2005;366:1367–1374.

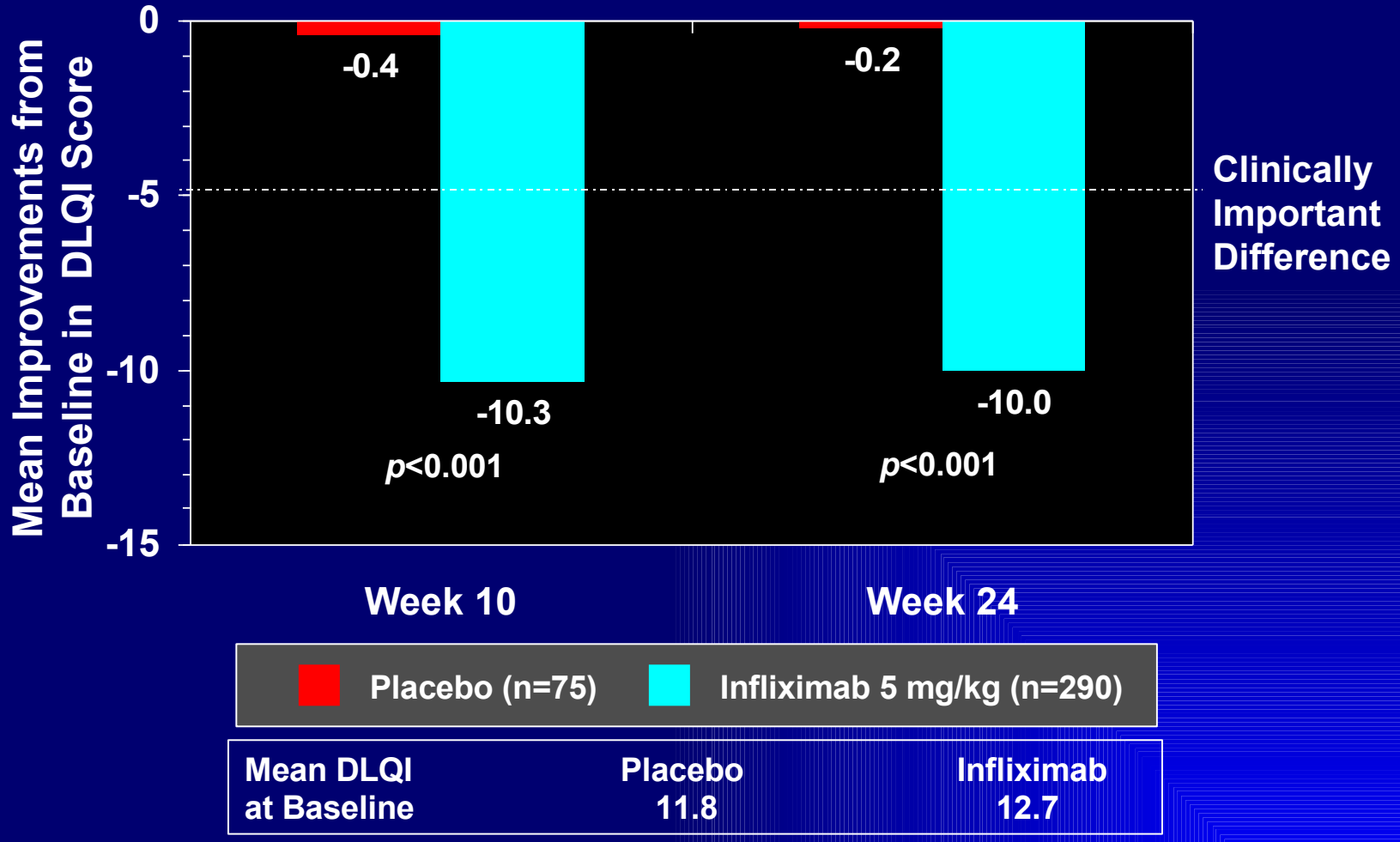
Lancet Study
PASI Responses at Week 50



*Pre-specified of patients randomized to infliximab 5 mg/kg (n=281)

Reich K, et al. *Lancet.* 2005;366:1367–1374.

Lancet Study
Mean Improvement from Baseline in DLQI



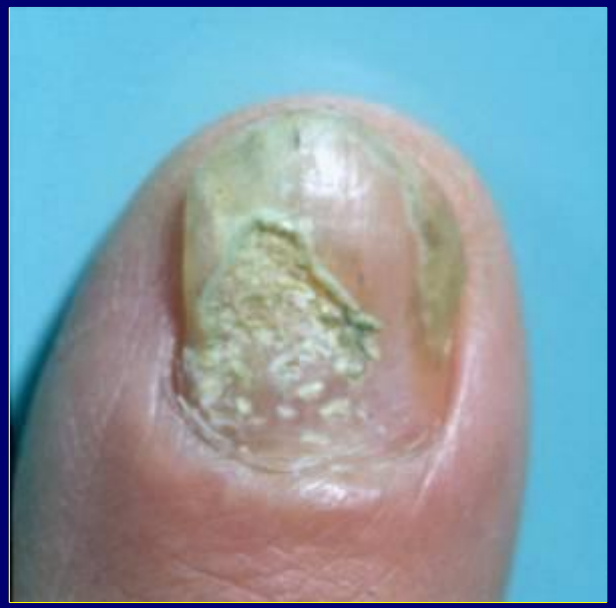
Data on File, Centocor, Inc.

Lancet Study Maintenance of Response Through Week 50

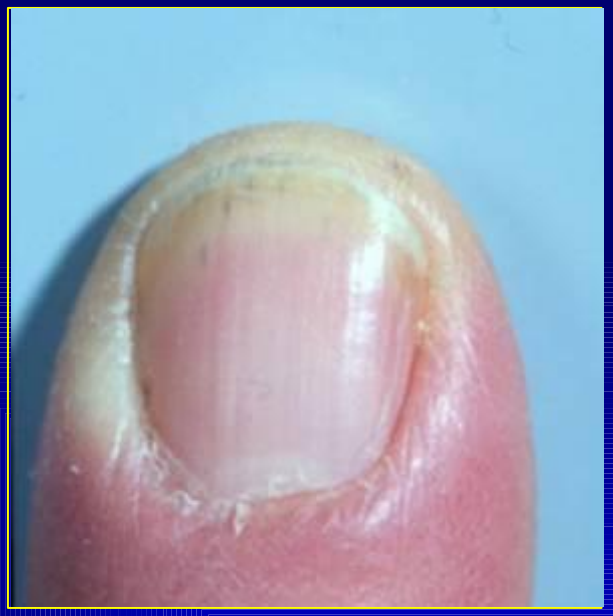
- About 25% of patients will lose PASI 75 response over 1 year
- Persistence of a PASI 75 response through Week 50 is associated with the maintenance of detectable serum levels of infliximab between infusions
- Undetected levels can occur in patients that are both antibody-to-infliximab (ATI) positive or ATI negative (“fast metabolizers”)

Lancet Study
Target Nail at Baseline and Week 24

Baseline



Week 24



Does this also occur with the other 2 TNF-α inhibitors?

Reich K, et al. *Lancet.* 2005;366:1367–1374.

A Randomized Comparison of Continuous vs. Intermittent Infliximab Maintenance Regimens Over 1 Year in the Treatment of Moderate-to-Severe Plaque Psoriasis (EXPRESS II)

Study:

- 5mg/kg vs 3mg/kg dosages
- Every 8 week infusions vs as needed infusions (PRN)

Conclusion:

- 75% of patients maintain excellent PASI 75 over 50 weeks
- 5mg/kg q8 weeks optimal
- No unexpected side effects

Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, et al. *J Am Acad Dermatol* 2007 January; 56(1):31.e1-15.

Infliximab EXPRESS II Study Safety Summary

Liver Functions:

- Markedly abnormal ALTs in approximately 5% of patients
  - No infliximab subjects had markedly abnormal bilirubin or liver failure

Infusion Reactions:

- Highest in 3mg/kg prn group
- Lowest in 5mg/kg every 8 weeks group

Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, et al. *J Am Acad Dermatol* 2007 January; 56(1):31.e1-15.

Infliximab
Infusion Reactions

Infliximab Infusions
Our TDA (Dallas) Experience (2003-06)

- **Total patients treated** — **136**
- **Total number of infusions** — **861**
- **Patients discontinued** — **28**
  - **Infusion reaction** — **7 (5.14% of patients)**
  - **Worsening of disease** — **11**
  - **Increased liver function** — **1**
  - **Hospitalization** — **3 (1 unrelated cause)**
  - **Moved from area** — **3**
  - **Unrelated death** — **1**
  - **Insurance change (large out of pocket** — **2**

Thus, 10/136 patients (7%) discontinued as a direct result of infliximab-related issues.

Infliximab Therapy Improves Patient Productivity Among Those with Moderate to Severe Psoriasis

Menter A, Feldman SR, Wu Y, Bala M

Poster presented at 2007 AAD.

Infliximab Therapy Improves Patient Productivity Among Those with Moderate to Severe Psoriasis

Methods

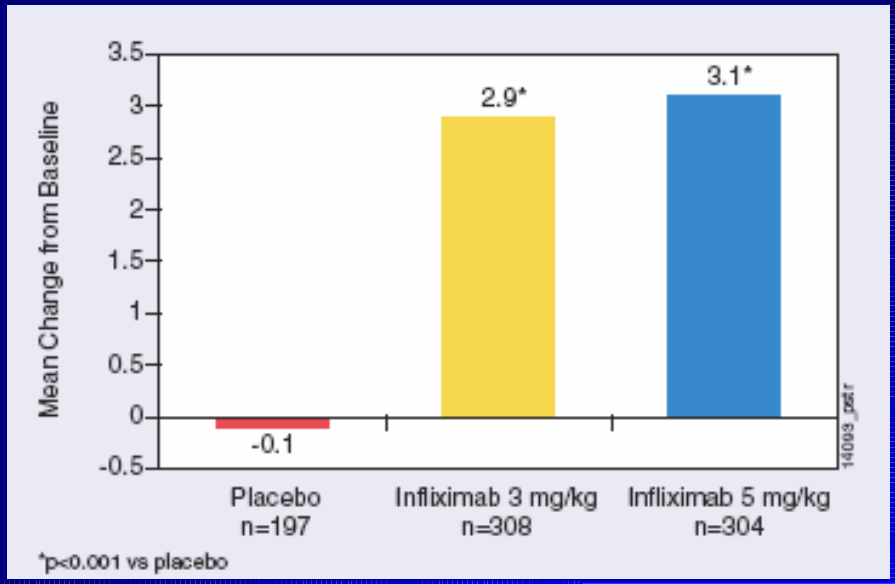
- 835 patients in EXPRESS II: Double-blind, placebo-controlled study with two doses of infliximab (3 or 5mg/kg)

Productivity Assessments

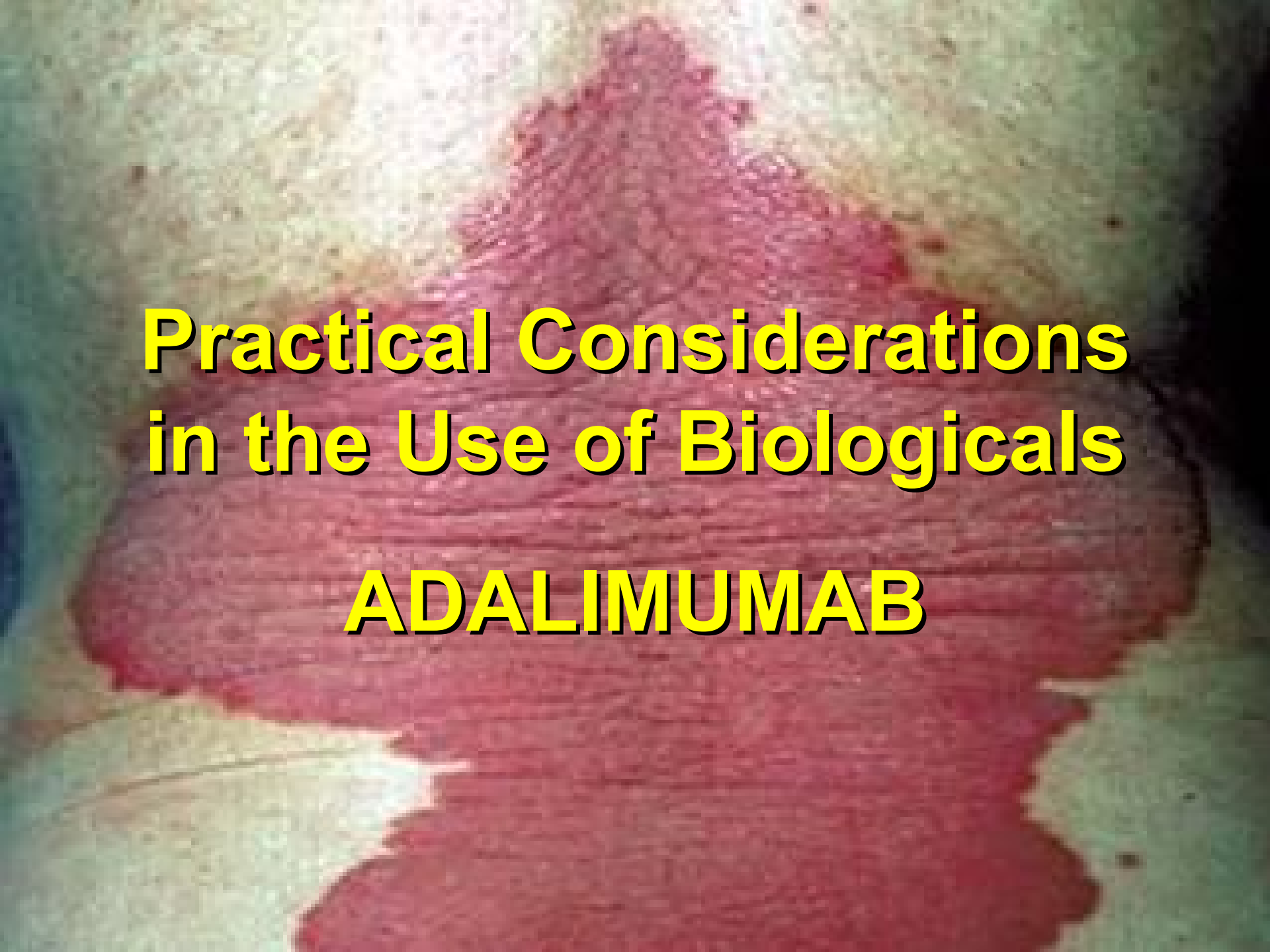
- Patients were asked to assess how much psoriasis affects their productivity at work, school, or home

Results

- Improvement in productivity VAS at Week 10



Poster presented at 2007 AAD.


Practical Considerations
in the Use of Biologicals
ADALIMUMAB

“Short- and Long-Term Efficacy and Safety of Adalimumab in a Pivotal Phase III Study in Adult Patients With Moderate to Severe Chronic Plaque Psoriasis”

- A Menter, KA Papp, CL Leonardi, Y Gu, SJ Rozzo

Poster 19 presented at AAD, Washington, DC, February 4, 2007.

"Short- and Long-Term Efficacy and Safety of Adalimumab in a Pivotal Phase III Study in Adult Patients With Moderate to Severe Chronic Plaque Psoriasis"

METHODS

- **REVEAL** was a multi-center, 52-week, randomized, placebo-controlled trial
- **Main Inclusion Criteria**
  - Clinical diagnosis of psoriasis for ≥6 months
  - Affected body surface area (BSA) ≥10% and PASI ≥12
  - Physician's Global Assessment (PGA) of at least "moderate"
- **Main Exclusion Criteria**
  - Prior use of anti-TNF therapy
- **Washout Period**
  - Two weeks for topical agents and UVB
  - 4 weeks for PUVA and non-biologic systemic therapies
  - 12 weeks for all biologic therapies

Menter A, et al. P19 presented at AAD, Washington, DC, February 4, 2007.

"Short- and Long-Term Efficacy and Safety of Adalimumab in a Pivotal Phase III Study in Adult Patients With Moderate to Severe Chronic Plaque Psoriasis"

Treatment Period 1

- Period A (Double-blind, placebo-controlled, Weeks 0–16)
  - Patients were randomized 2:1 to adalimumab or placebo
  - Patients in the adalimumab arm received:
    - Week 0: 80 mg subcutaneously (sc)
    - Weeks 1–15: 40 mg every other week (eow)
  - At Week 16, patients who achieved:
    - ≥PASI 75 improvement continued into Period B
    - <PASI 75 improvement entered the open-label extension (OLE) study

Menter A, et al. P19 presented at AAD, Washington, DC, February 4, 2007.

"Short- and Long-Term Efficacy and Safety of Adalimumab in a Pivotal Phase III Study in Adult Patients With Moderate to Severe Chronic Plaque Psoriasis"

Treatment Period 2

- Period B (Open-label, Weeks 17–33)
  - Adalimumab 40 mg eow sc
  - Patients who achieved:
    - ≥PASI 75 response at Week 33 entered Period C
    - PASI 50–<75 response at the end of Period B entered the OLE
    - <PASI 50 response discontinued the study

Menter A, et al. P19 presented at AAD, Washington, DC, February 4, 2007.

"Short- and Long-Term Efficacy and Safety of Adalimumab in a Pivotal Phase III Study in Adult Patients With Moderate to Severe Chronic Plaque Psoriasis"

Treatment Period 3

- Period C (Double-blind, placebo-controlled, Weeks 34–52)
  - Patients randomized to adalimumab treatment in Period A and who achieved ≥PASI 75 at Week 33 were re-randomized 1:1 to either continue adalimumab 40 mg eow or receive placebo treatment
  - Patients randomized to placebo treatment in Period A and who received adalimumab in Period B, continued adalimumab treatment in Period C if they achieved a ≥PASI 75 in Period B

Menter A, et al. P19 presented at AAD, Washington, DC, February 4, 2007.

"Short- and Long-Term Efficacy and Safety of Adalimumab in a Pivotal Phase III Study in Adult Patients With Moderate to Severe Chronic Plaque Psoriasis"

MALIGNANCIES

- No lymphomas were diagnosed in REVEAL.
- The percentages of patients with non-melanoma skin cancers and the percentages of patients with all other types of malignancies (excluding nonmelanoma skin cancers and lymphomas) were comparable among placebo- and adalimumab-treated patients in Period A, and for Period A vs. the entire 52-week study (Adalimumab Treatment Group).

INFECTIONS

- One case of oral candidiasis (opportunistic infection) was diagnosed
- One case of presumptive tuberculosis (–ve AFB and –ve culture, with clinical course suggestive of tuberculosis) was diagnosed in a patient who was PPD+ve at baseline and who was noncompliant with INH prophylaxis
- No cases of rebound were noted among patients re-randomized to placebo in Period C

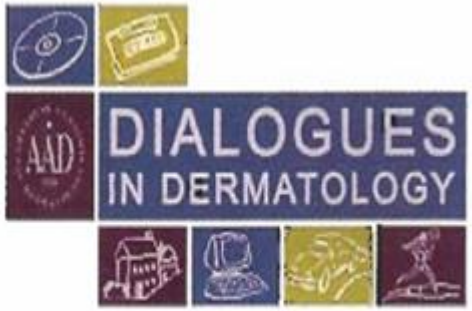
Menter A, et al. P19 presented at AAD, Washington, DC, February 4, 2007.

Clinical Response to adalimumab: The relationship with anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis

Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, Kijkmans BAC AC, Tak PP, Wolbink GJ

- METHODS
  - 121 consecutive RA patients treated with adalimumab
  - Serum adalimumab concentrations and antibodies against adalimumab together with clinical response parameters before and up to 28 weeks
  - 79% on methotrexate
- RESULTS
  - ATAs were detected in 21 patients during 28 weeks of treatment
  - EULAR non-responders significantly more often had ATAs than good responders
  - Patients with ATAs had less improvement in DAS28 score than patients without ATAs
  - Patients with ATAs during follow-up had lower serum adalimumab concentrations at 28 weeks than patients without ATAs
  - Good responders had higher serum adalimumab concentrations than non-responders

Ann Rheum Dis, published online 14 Feb 2007.



This month's selected commentary

Side effects of the biologics

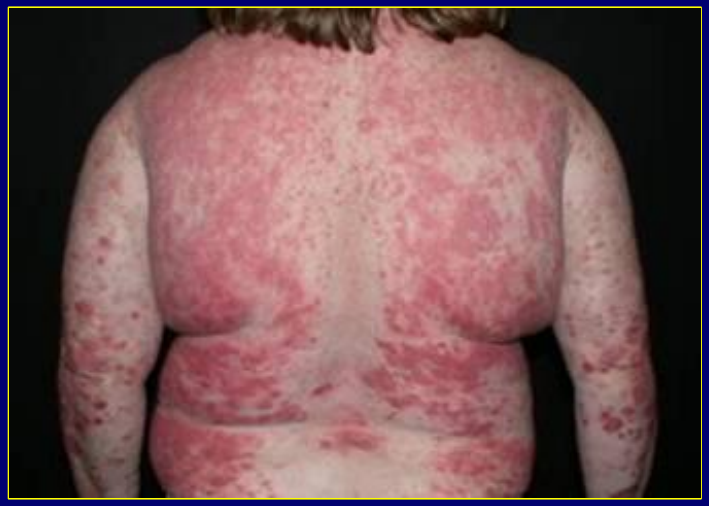
Warren R. Heymann, MD
Based on a dialogue between
Drs Stephen E. Wolverton and Gary Brauner

J Am Acad Dermatol 2005;53:692-3

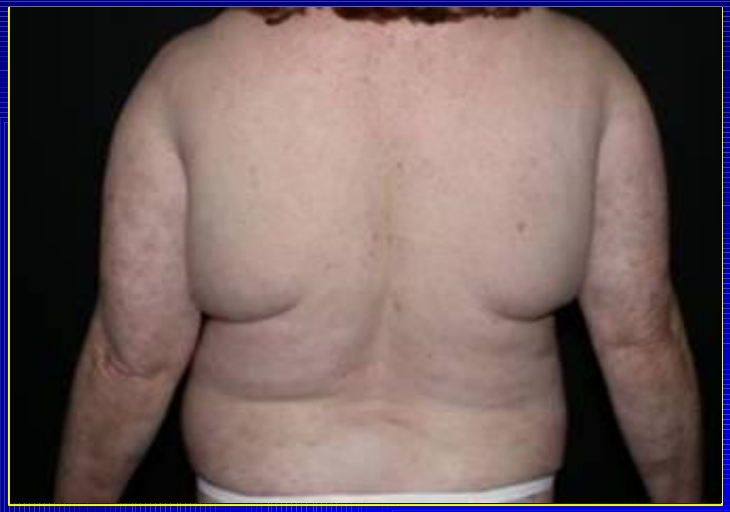
TNF-α Inhibitor Safety Issues

A Dermatologist's Perspective

We know they work very well in psoriasis and psoriatic arthritis



Pre-Rx



16 weeks Rx

Anti-TNF-α treated patient

Safety Issues with TNF-α Inhibitors
Our Dermatology Perspective

4 Main Categories

- Cardiac failure
- Infections
- Lymphoma
- Neurologic issues

NOTE: 1) Infliximab infusion reactions: 2.8% patient discontinuation in clinical trials
2) Auto-immunity – Rare clinical cases

Safety Issues with TNF-α Inhibitors

- What lessons can dermatologists learn from our Rheumatology and GI colleagues, recognizing that over 1,300,000 patients have been treated worldwide?

TNF-α Inhibitors in Patients with CHF

- Mild CHF and stable
  - Document risk
  - Follow patient carefully
- Moderate - Severe CHF
  - Consult Cardiologist

Thus, 1) Evaluate patients at each visit and at each infliximab infusion

2) Work closely with primary physician or cardiologist

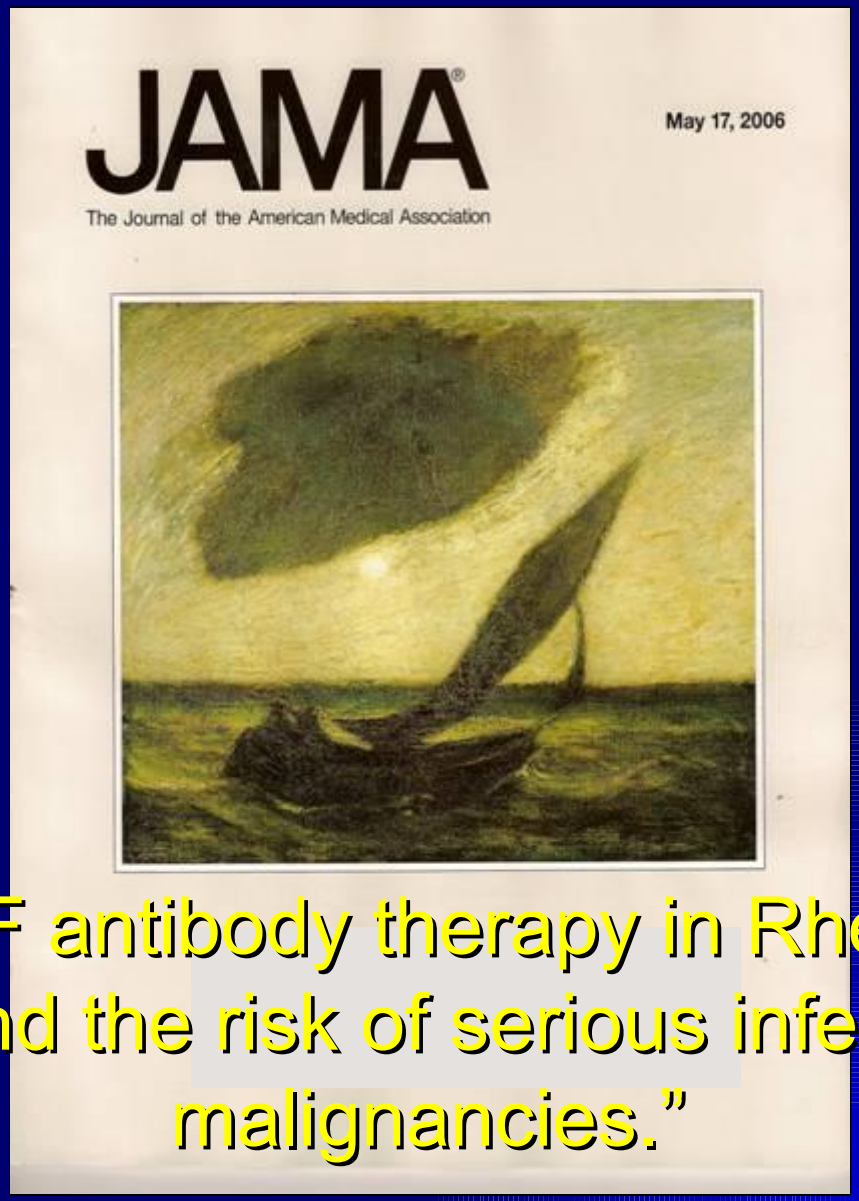
- **Answer: *Exercise Caution***

"Risk of Myocardial Infarction in Patients with Psoriasis"

Gelfand JM, Neimann AL,
Shin DB, Wang X, Margolis DJ, Troxel AB

- **Objective**
  - To determine if within a population-based cohort psoriasis is an independent risk factor for MI when controlling for major cardiovascular risk factors.
- **Design**
  - A prospective, population-based cohort study in the United Kingdom of patients with psoriasis aged 20 to 90 years, comparing outcomes among patients with and without a diagnosis of psoriasis.
- **Patients**
  - A total of 556 995 control patients and patients with mild (n=127 139) and severe psoriasis (n=3837) were identified.
- **Conclusion**
  - Psoriasis may confer an independent risk of MI. The RR was greatest in young patients with severe psoriasis.

JAMA. 2006;296:1735-1741



"Anti-TNF antibody therapy in Rheumatoid Arthritis and the risk of serious infections and malignancies."

Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V.

***JAMA* 2006 May. 295(19):2275-85**

Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies

Systematic Review and Meta-analysis of Rare Harmful Effects in Randomized Controlled Trials

Bongartz T, et. Al. *JAMA* 2006; 295:2275-85

- Adalimumab, Infliximab only
- Meta-analysis of 'sparse adverse events'
- Different RCTs
- Different dosages
  - Adalimumab: 80 qw → 20 qeow
  - Infliximab: 3 mg/kg → 10 mg/kg
- 6/9 studies had combination therapy, ie MTX, steroids, etc

"Anti-TNF antibody therapy in Rheumatoid Arthritis and the risk of serious infections and malignancies."

- Conclusions
  - Evidence of increased risk of serious infections
  - Evidence of increased dose-dependent risk of malignancies
- How relevant is this paper to psoriasis and psoriatic arthritis?
- Await meta-analysis of etanercept

Bongartz T, et. Al. *JAMA* 2006; 295:2275-85

Etanercept: New Safety Concerns

Malignancy

- RCT for Wegener's Granulomatosis patients
- ↑ non-cutaneous solid malignancies compared to placebo
- Most patients were receiving concomitant immunosuppressants
  - Cyclophosphamide
  - Methotrexate
  - Corticosteroids

Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med.* 2005 Jan 27;352(4):351-61.

Infliximab: New Safety Concerns

Malignancy

- Exploratory RCT for COPD:
  - 9/157 patients developed malignancy
  - 1: Lymphoma
  - 8: SCC of lung or head and neck.
  - 0: Placebo group
- Aggressive Lymphomas in Pediatric Crohn's

Hepatotoxicity

- Elevations of transaminases have been observed
  - Wide variety disease states
  - With and without concomitant immunosuppressants
  - In psoriasis trials, 5% have 5x ULN for transaminases
  - Some decreased/resolved spontaneously while continuing Infliximab
- Hepatitis B warning

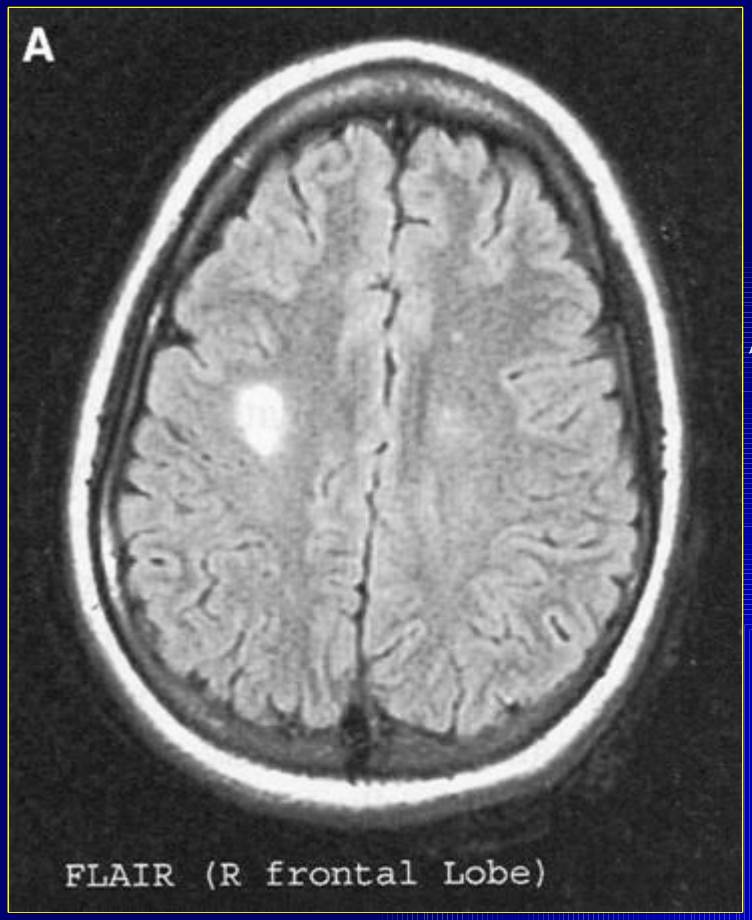
TNF-α Inhibitors: New Safety Concerns

Hepatitis B Reactivation

- Health Canada
- Boxed warning
- Based on post-marketing data
- Latent HBV reactivation
  - 3 weeks – 20 months after initiating therapy
  - Majority cases treated with other immunosuppressants
    - MTX
    - Azathioprine
    - Corticosteroids
  - Several cases with fatal outcomes

TNF-α Inhibitors & Demyelination

Axial FLAIR image shows large right frontal lobe white matter lesion



A psoriasis patient!

Sukal SA, Nadiminti L, Granstein RD. *JAAD* 54(1):160-164

USA – FDA
"Black Box" Warnings

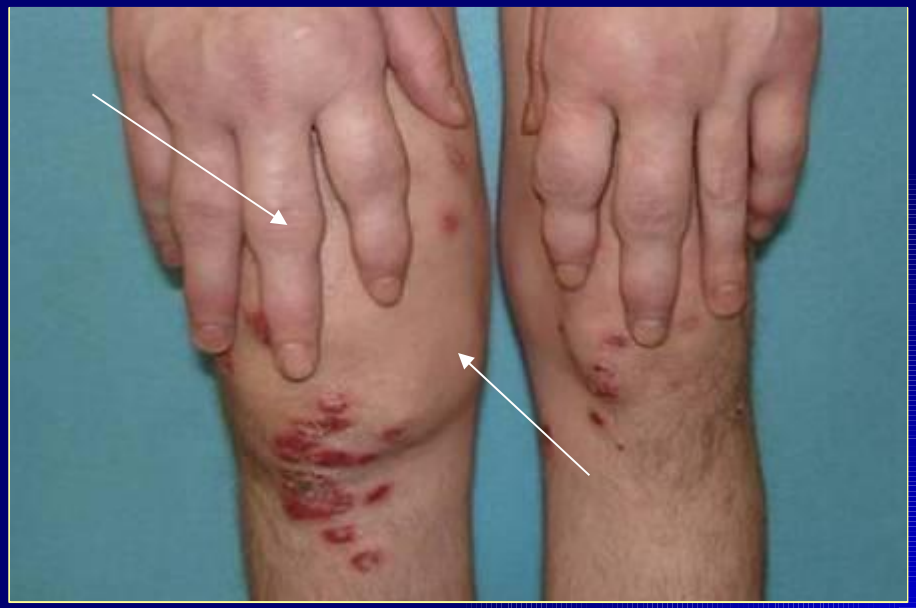
Traditional Agents

- Methotrexate 11
- Cyclosporine 3
- Acitretin 1
- Methoxsalen 3

Biologic Agents

- Infliximab 1
- Adalimumab 1
- Alefacept 0
- Etanercept 0
- Efalizumab 0

Practical Considerations in the Use of Biologics



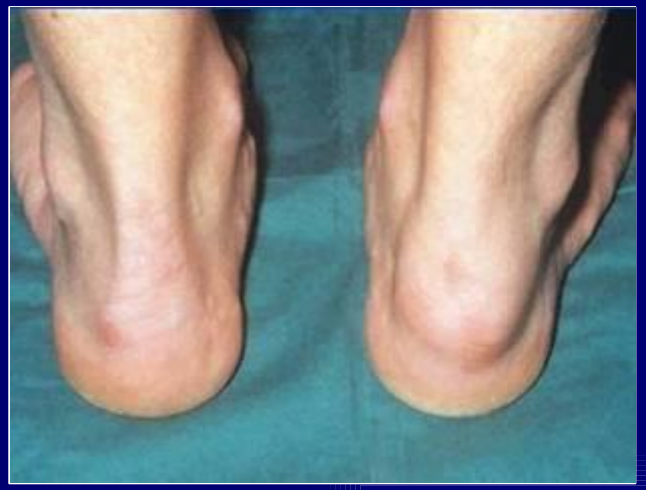
What role does a definite diagnosis of psoriatic arthritis have in the choice of TNF-α therapy?

Alan Menter, MD, Personal patient

More Derm-Rheum Relationship Questions for Consideration

- Does early morning stiffness for 30 minutes, eg hand, feet, hips, without clinical signs = PsA?
- Should dermatologists be ordering X-rays for suspected psoriatic joint disease?
- At what point is a rheumatologic consultation indicated?
- PsA usually improves more dramatically and completely than psoriasis. When does the Rheum refer to the Derm?

Psoriatic Arthritis



- Dermatologists must continue to play a major role in the systemic and biologic therapy of Psoriasis and be fully conversant with the features of PsA
- Derm-Rheum interaction and cooperation is essential for creating guidelines for therapy and for optimal management of our patients

Mease PJ, Menter MA. *JAAD* April 2006. 54(4):685-704


Progress and Promise
A Decade of Scientific Innovation
15 – 17 March 2007 – Munich, Germany

Dermatology Workshop Streams
Friday 15.00 – 16.15hrs

Workshop A	**Optimising the use of traditional systemic therapies**	
	Hervé Bachelez	Room 11a
	Jonathan Barker	Room 11b
	Alberto Giannetti	Room 12a
Workshop B	**Pratical considerations in the use of biologics**	
	Rana Anadolu-Brasie	Room 21a
	Carlos Ferrándiz	Room 12b
	Alan Menter	Room 2
Workshop C	**Long-term treatment strategies and efficacy of etanercept**	
	Knud Kragballe	Room 21b
	Lluís Puig	Room 22a
	Robert Strohal	Room 22b


Progress and Promise
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