

NEW ORLEANS



Nuevos Horizontes en la Terapia de la Artritis Psoriatica

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**Ankylosing
Spondylitis**

**Psoriatic
Arthritis**

**Juvenile
SpA**

AAU

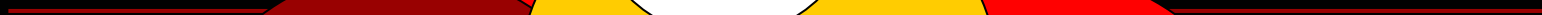
**Undifferentiated
SpA**

**Crohn's / UC
associated
Arthritis**

Sacroiliitis

Reactive arthritis

Arthritis



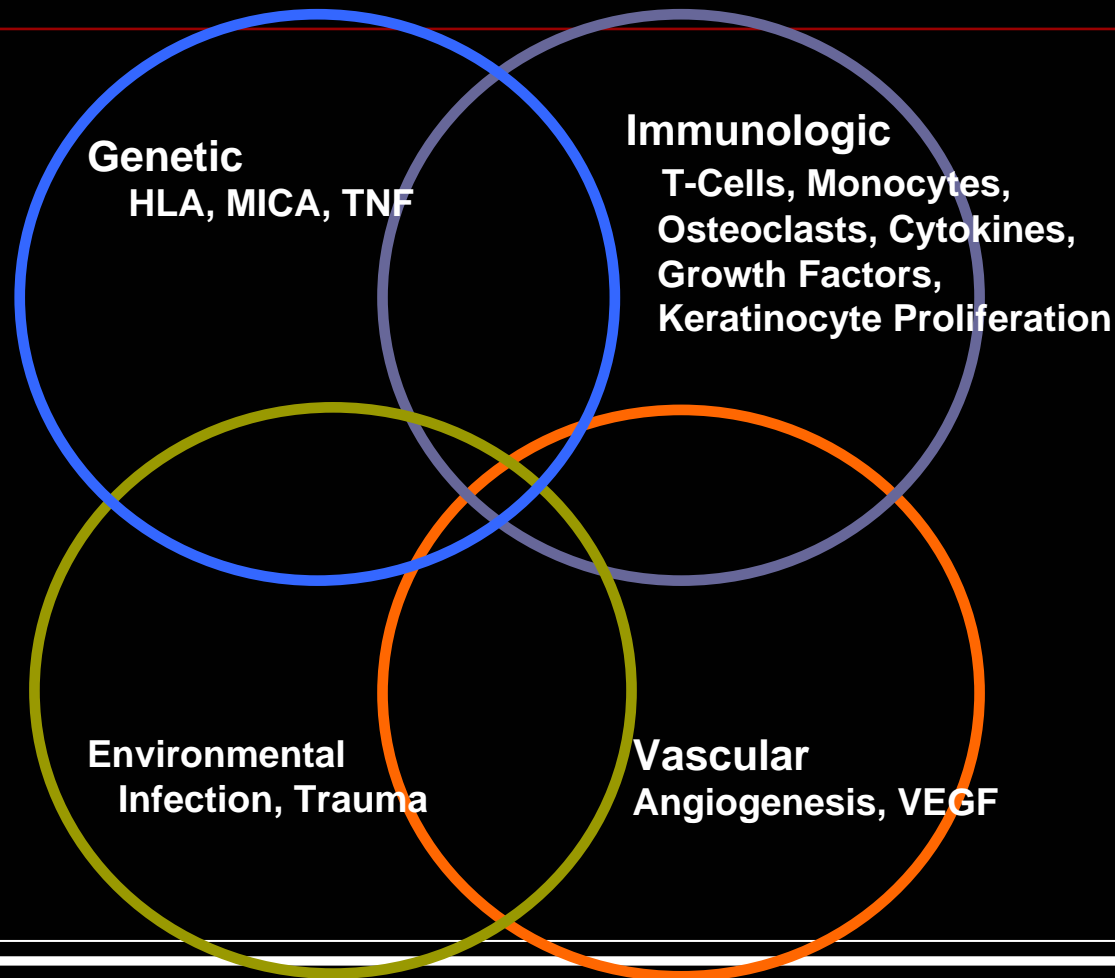
HISTORICAL ASPECTS

- Psora: itch
- 3rd Century A.D. Roman baths at Hammat Gader near sea of Galilee
- “Zaraat” - Leprosy- unclean
- 1674 Fray Felipe Colombo published a book by Royal Printing House of Madrid
- Narrates the life of Fray Pedro de Urraca
- Afflicted by severe and deforming cutaneous and arthritic condition

PSORIATIC ARTHRITIS: HISTORICAL CONSIDERATIONS

- Biblical times.
- 1818: Baron Jean Louis Alibert.
- 1818: Bourdillon.
- 1939: Bauer: PsA coincidence with RA.
- 1948: Leczinsky.
- 1956: Wright.
- 1963: Baker.
- 1964: Blumberg: PsA separate disease-ARA

Pathogenesis of Psoriatic Arthritis



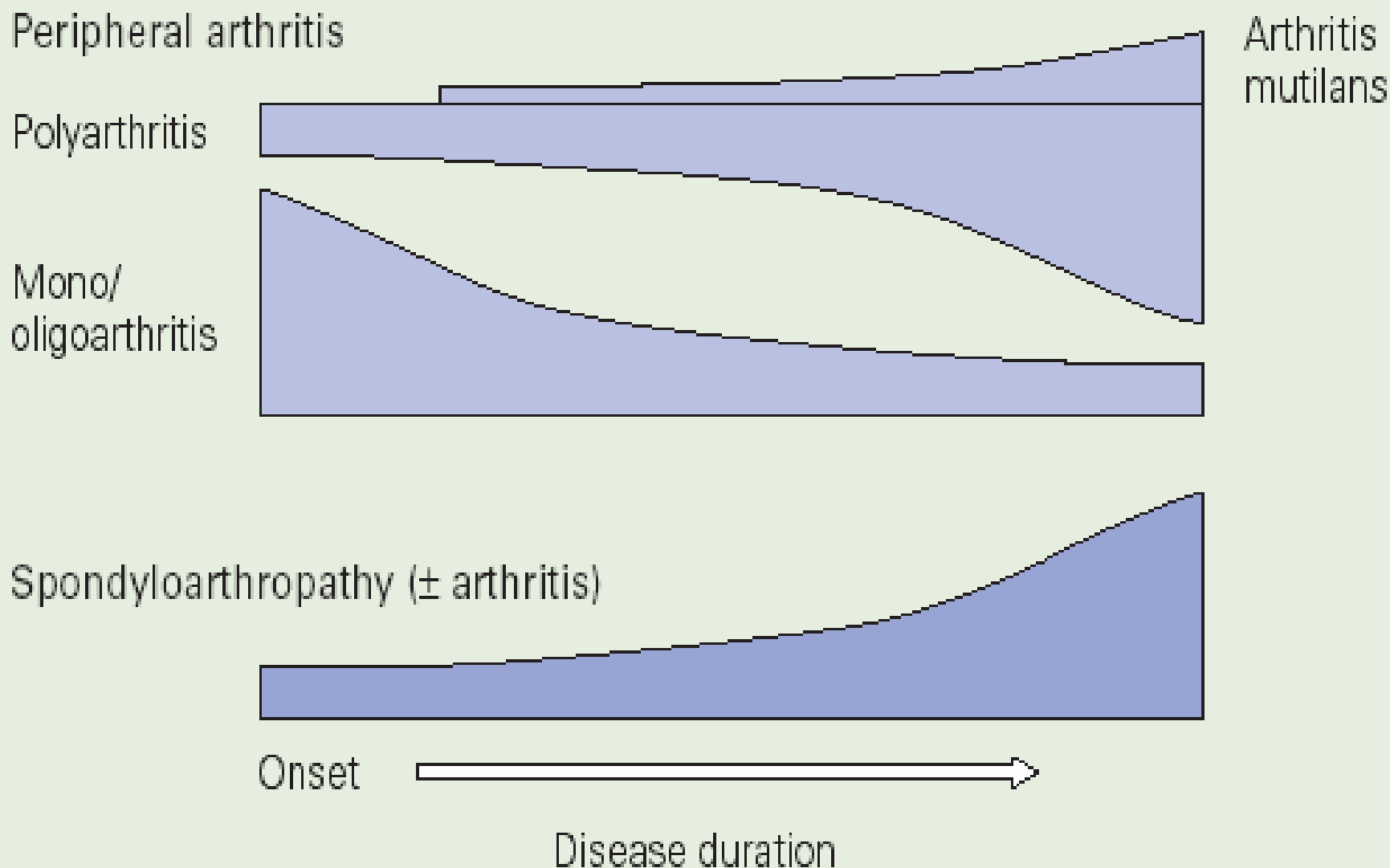
PSORIATIC ARTHRITIS: EPIDEMIOLOGY

- Psoriasis: prevalence 1-2% Caucasians.
- Much lower prevalence in African-Americans, Latin American Indians, Orientals.
- Similar prevalence in men and women.
- PsA: 5-7% in psoriasis.
- PsA: 0.1%- general population.
- PsA in children: 10-15/100,000.
- 20% seronegative arthritis have psoriasis.
- Olmsted County, MN: 6.6/100,000 per annum.
- Norfolk Arthritis Registry: 3.5/100,000 yearly.

PSORIATIC ARTHRITIS: CLINICAL FEATURES

- Onset: Usually insidious; acute in one-third
- Fever or malaise: Uncommon.
- Age of onset: Similar to RA.
- Male:female ratio: 1:1.
- Not as benign as once thought.
- Sizable proportion (30%): severe activity.
- Progression occurs over several years.

TIME-DEPENDENT TRENDS IN THE RELATIVE FREQUENCIES OF SPECIFIC SUBGROUPS OF PSORIATIC ARTHRITIS



PSORIATIC ARTHRITIS: NATURAL HISTORY

- PsA in population surveys: mild, self-limited
- PsA seen by rheumatologists: severe and progressive.
- Same prognosis as RA.
- Erosive disease appears early.
- Radiographic findings: progression inevitable.
- At 10 years: majority (>60%) remain active, deformities and erosions in over 50%.
- Functional disability: significant >10%.

PSORIATIC ARTHRITIS: CLASSIFICATION: Moll & Wright

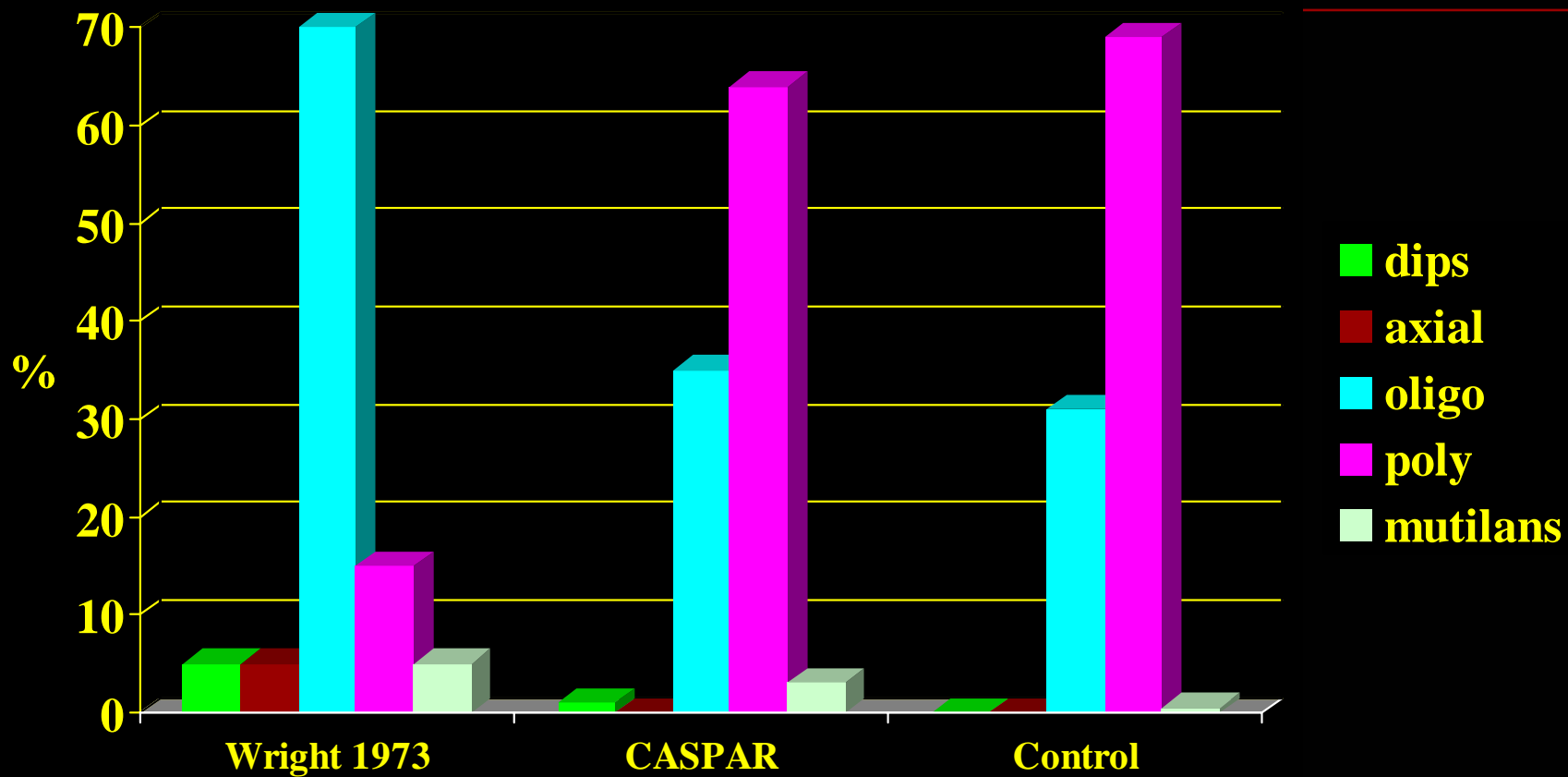
- Arthritis with predominant DIP involvement
- Arthritis mutilans.
- Symmetric polyarthritis- indistinguishable from RA.
- Asymmetric oligoarticular arthritis.
- Predominant spondylitis.
 - Sem Arthritis Rheum 1973; 3: 55-78.

PSORIATIC ARTHRITIS: CLASSIFICATION

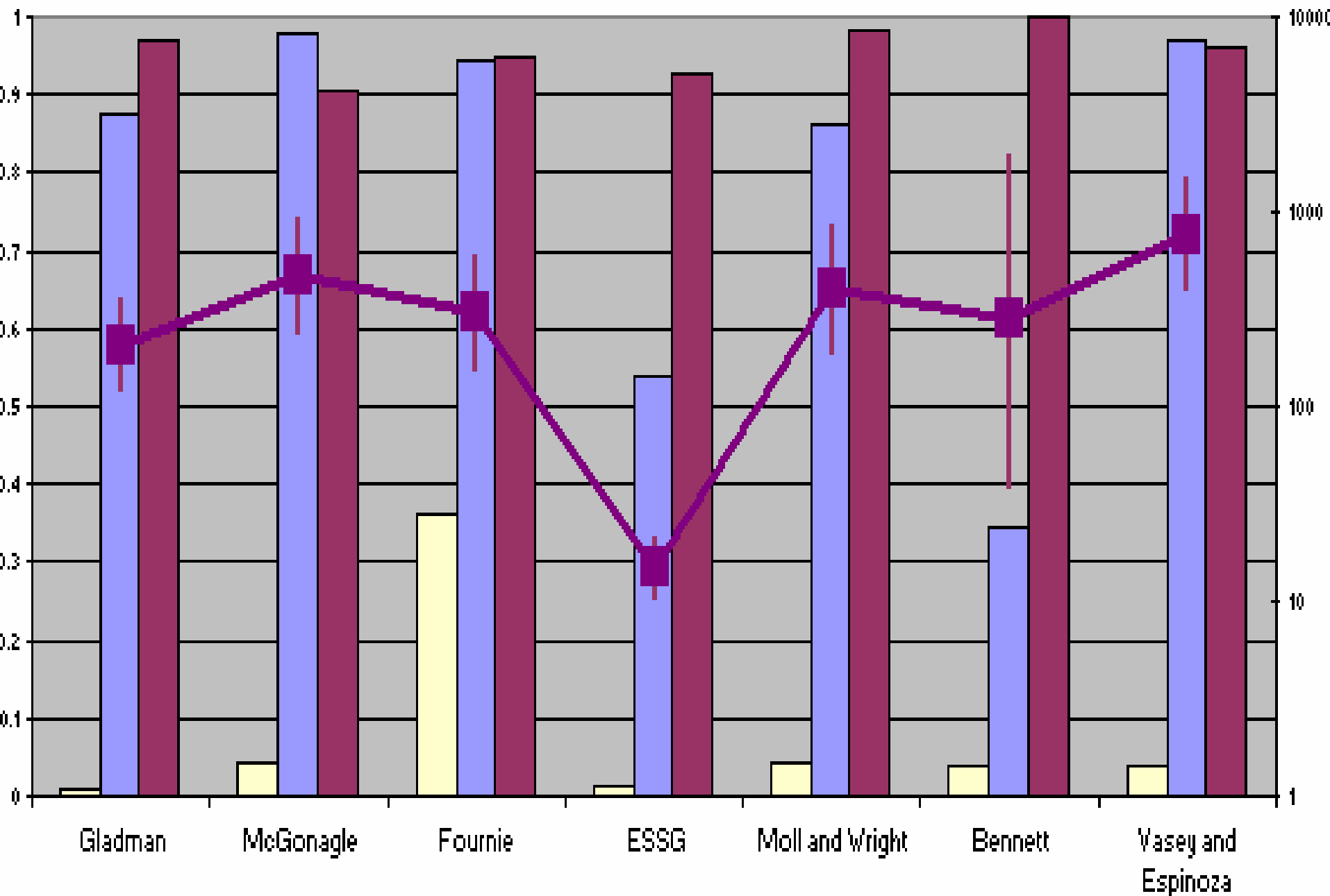
- 1- Mandatory: Psoriatic skin or nail involvement.
- 2- One other feature from the following:
 - A) Pain and soft tissue swelling of DIP>4w
 - B) Pain and soft tissue swelling of peripheral joints in an asymmetric pattern>4 weeks.
 - C) Symmetrical peripheral arthritis>4 weeks in the absence of RF or subcutaneous nodules.
 - D) Peripheral radiological features: pencil in cup deformity, erosions of terminal phalanges, bony ankylosis.
 - E) Spinal pain and stiffness with restriction of motion>4w
 - F) Spinal radiological features: grade 2 bilateral sacroiliitis, or 3 or 4 unilateral sacroiliitis.

- Vasey FB & Espinoza LR: Psoriatic Arthritis in the Spondyloarthropathies, ed Calin A. Grune&Stratton, New York, 1985

Percentage of subgroups



Percentage not able to be classified Sensitivity Specificity DOR



Overview of Some PsA Clinical Features



- A. Sharp demarcated erythematous plaque covered by silver white scales
- B. Scalp involvement in 50%
- C. Psoriatic arthritis
- D. Psoriatic nail pitting
- E. Nail Involvement

PsA: Who will progress?

- Findings at presentation.
- Lack of response to initial Rx.
- Previous steroids use.
- Erosions on x-ray.
- Elevated ESR or CRP.
- Gender: Male sex protective.
- Clinical subset: Polyarthrititis.
- Inadequate response to serial Rx.
- Progression of erosions on x-ray.

Definition of Patients with Active PsA

- Regardless of current therapy, active PsA patients may be defined by:¹ *
 - ≥ 3 swollen or ≥ 3 tender joints at two or more visits at least a month apart
 - Dactylitis (=1 joint)
 - Active skin disease
- Consideration should also be given to elevations in acute-phase reactants (e.g., C-reactive protein, ESR)²

PsA: Choosing therapy

- Considerations in choice of Rx.
- Efficacy in joints and skin.
- Addressing risk of progression.
- Quality-of-life considerations.
- Safety factors.
- Methods of administration.
- Economic realities.

TABLE 112.1 THERAPEUTIC MANAGEMENT OF PSORIATIC ARTHRITIS

Patient education	Assistive devices and educational material
Rehabilitation and physical therapy	Early and aggressive active and passive physical therapy Dynamic strengthening exercises Preservation of a normal upright posture Avoidance of contact sports and heavy physical activity
Pharmacologic measures	Non-steroidal anti-inflammatory drugs Selective COX-2 inhibitors Disease-modifying drugs
Dermatologic measures	Photochemotherapy with psoralen Steroids
Surgical measures	Synovectomy Joint arthroplasty

Early institution of an aggressive comprehensive medical management program may prevent the development of serious joint deformity and disability

TABLE 112.2 DISEASE-MODIFYING DRUGS IN PSORIATIC ARTHRITIS

- Methotrexate
- Sulfasalazine
- Cyclosporin A
- Azathioprine
- Leflunomide
- Biological agents
 - Etanercept (Enbrel)
 - Infliximab (Remicade)
 - Alefacept
- Gold compounds
- Retinoid treatment
- Corticosteroids
- Colchicine

The most common agents used in treatment of psoriatic arthritis – alone or in combination

TABLE 112.3 MISCELLANEOUS AGENTS USED IN THE TREATMENT OF PSORIATIC ARTHRITIS

- Antimalarials
- Vitamin D derivatives
- D-penicillamine
- Apheresis
- Antibiotics
- Non-selective inhibitors of TNF- α
 - Pamidronate?
 - Thalidomide?
- Alternative treatment?
- Autologous stem cell transplantation

The use of some of these agents and treatment modalities, such as alternative therapy, autologous stem cell transplantation and non-selective inhibitors of TNF- α , requires further investigation

Measuring Response

- ACR Response Criteria
- Both:
 - 20% improvement in tender joint count.
 - 20% improvement in swollen joint count.
- Plus: 20% improvement in 3/5:
 - Patient pain assessment.
 - Patient global assessment.
 - Physician global assessment.
 - Patient self-assessment disability.
- Acute phase reactant value(ESR or CRP)

Psoriatic Arthritis Response Criteria (PsARC)

- Improvement in at least 2 of 4 criteria, 1 of which must be tender-or-swollen-joint score
- Physician global assessment (>1 unit).
- Patient global assessment (>1 unit).
- Tender-joint score (>30%).
- Swollen-joint score (>30%).
- No worsening in any criterion.

BIOLOGIC AGENTS

- ANTI-CYTOKINES
- T-CELL INTERFERENCE
- CELL MIGRATION INTERFERENCE
- B-CELL DEPLETION
- TRANSCRIPTION FACTOR INTERFERENCE

Biologic Agents: Anti-Cytokines

- Kineret: IL-1R antagonist; 4-6 h Daily sc
- Etanercept: TNF-R blocker; 4 d Week-sc
- Infliximab: mAb TNF blocker; 9 d IV: 0,2,4..
- Adalimumab: mAb TNF blocker; 2 w sc
- Certolizumab: peg mAb TNF blocker; 2w sc
- Golimumab: mAb TNF blocker; 7-20 d sc-iv
- Tocilizumab: mAb IL-6R; 10 d IV 4 weeks
- Ustekinumab: IL-12/23 inhibitor; 20-39 d 8-12 w

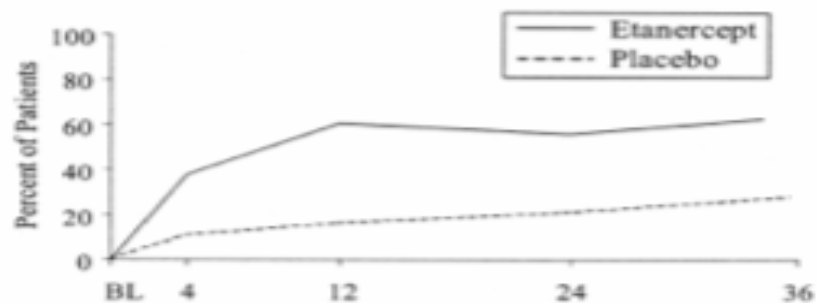
PsA: Etanercept Phase III

- 6 month RDBPCT
- Placebo vs. etanercept 25 mg 2x/week.
- Open-label extension.
- Two co-primary endpoints.
- Improvement of signs and symptoms.
- Prevention of structural damage.

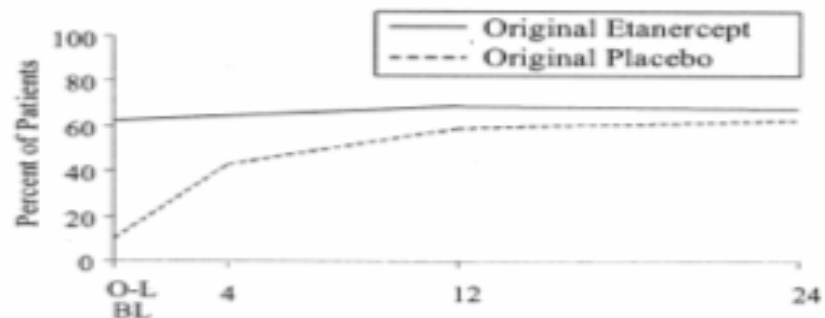
- Mease PJ et al. A&R 2004

Controlled and Maintenance Periods

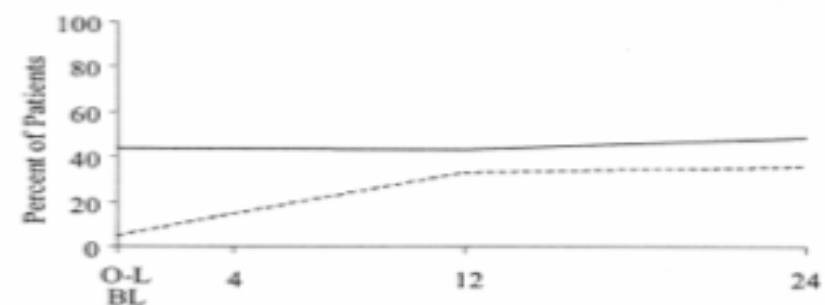
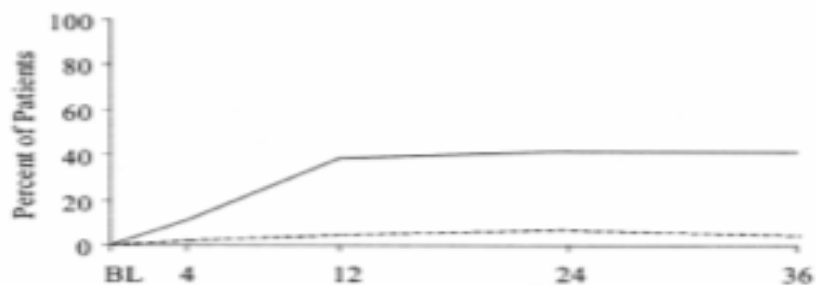
ACR 20



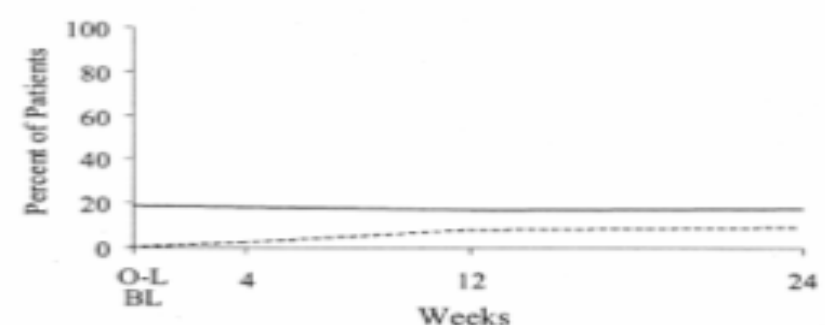
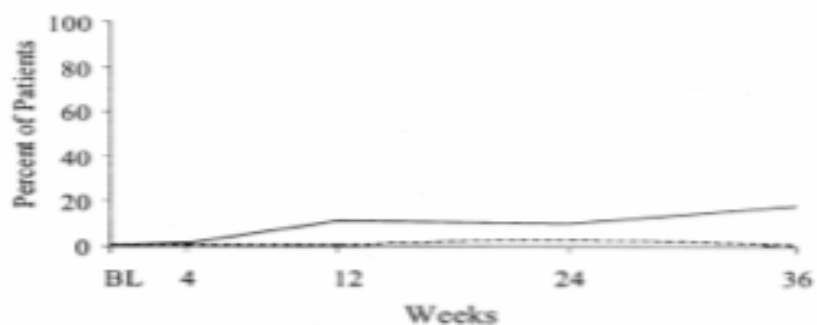
Open-label Etanercept



ACR 50

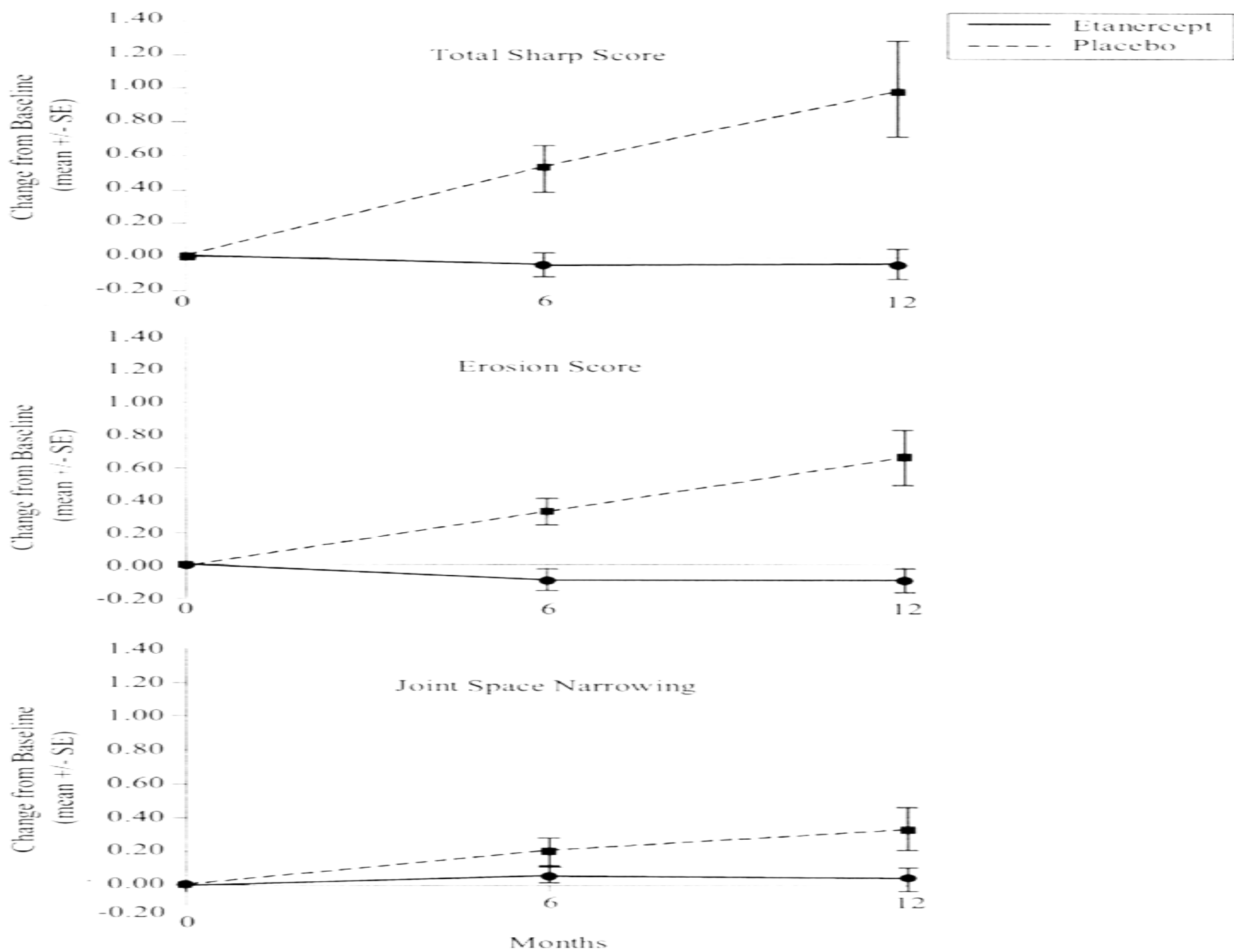


ACR 70



Number Patients Over Time:				
	wk 4	wk 12	wk 24	wk 36
Etanercept	100	99	90	78
Placebo	101	97	65	49

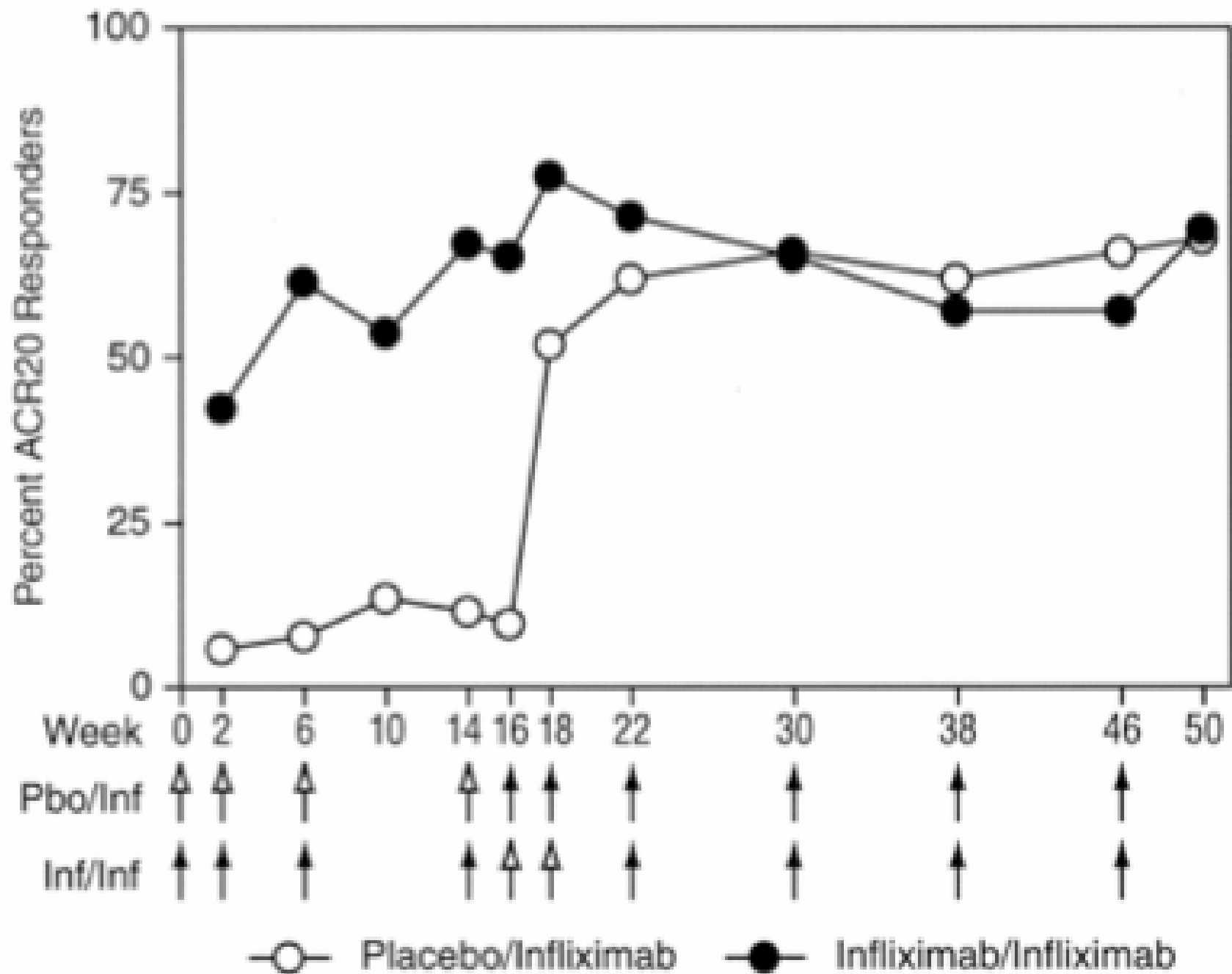
Number Patients Over Time:				
Original group	BL	wk 4	wk 12	wk 24
Etanercept	85	85	81	78
Placebo	81	80	79	70



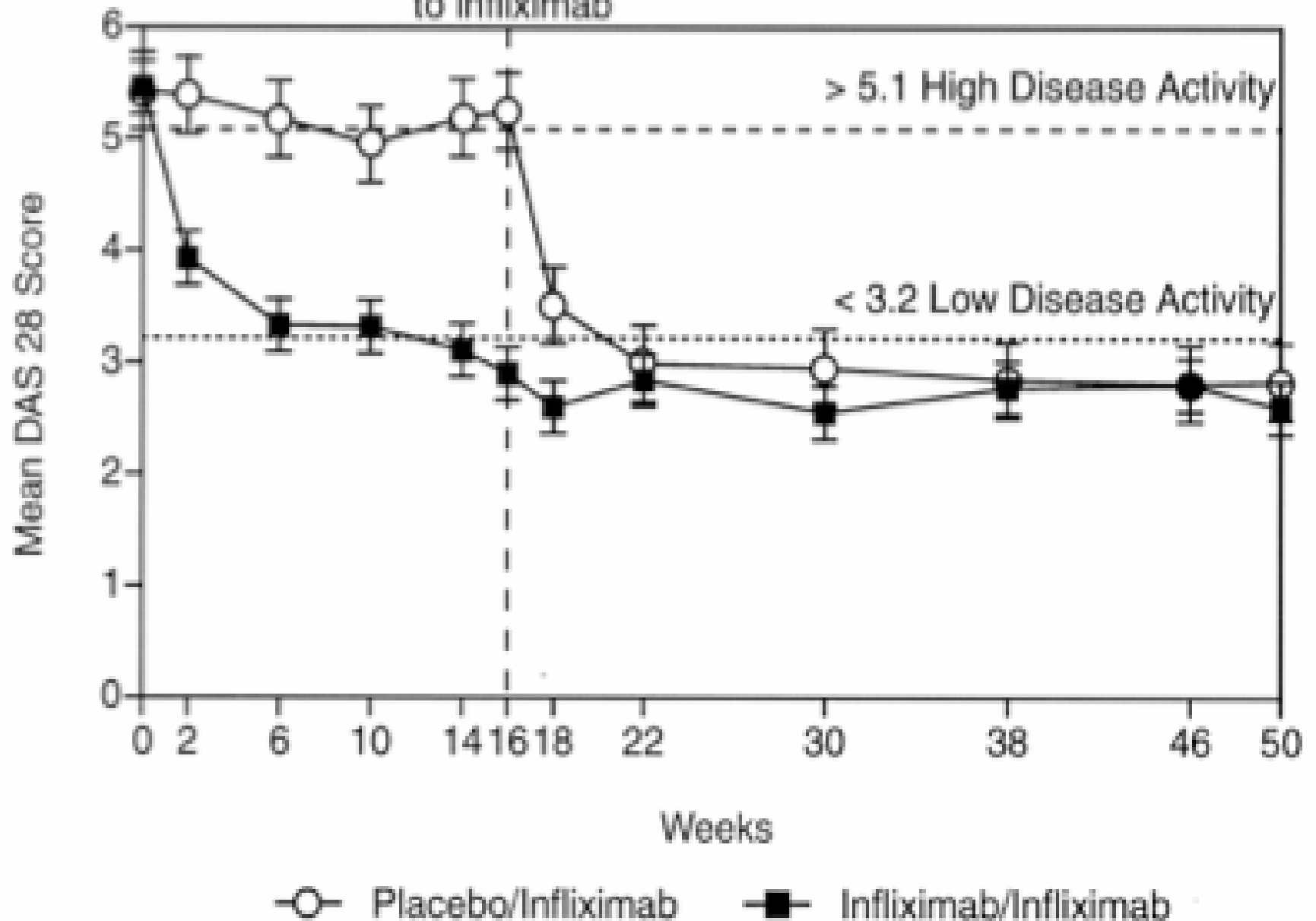
PsA: Infliximab Phase III (IMPACT)

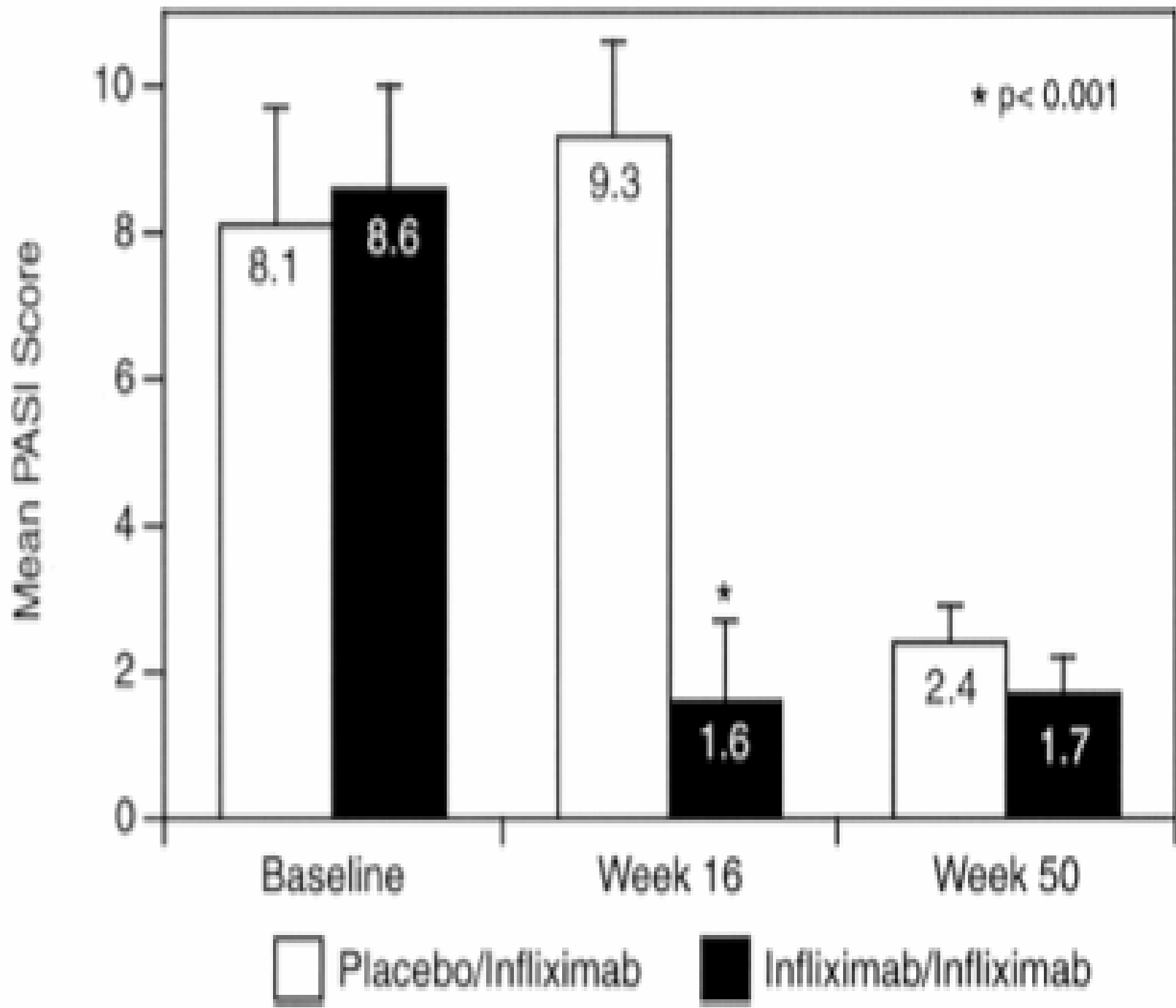
- 200 pts. with active disease and inadequate response to NSAIDs or DMARDs.
- RDBPCT for 24 wks, open label to 54 weeks.
- Infliximab 5mg/kg at 0,2,6,14, and Q8wks.
- Escape pts. Loaded at wks 16 and 18
- Stable DMARDs, NSAIDs, steroids<10mg.
- MTX not required.

- Primary endpoint ACR 20 at 12 weeks.



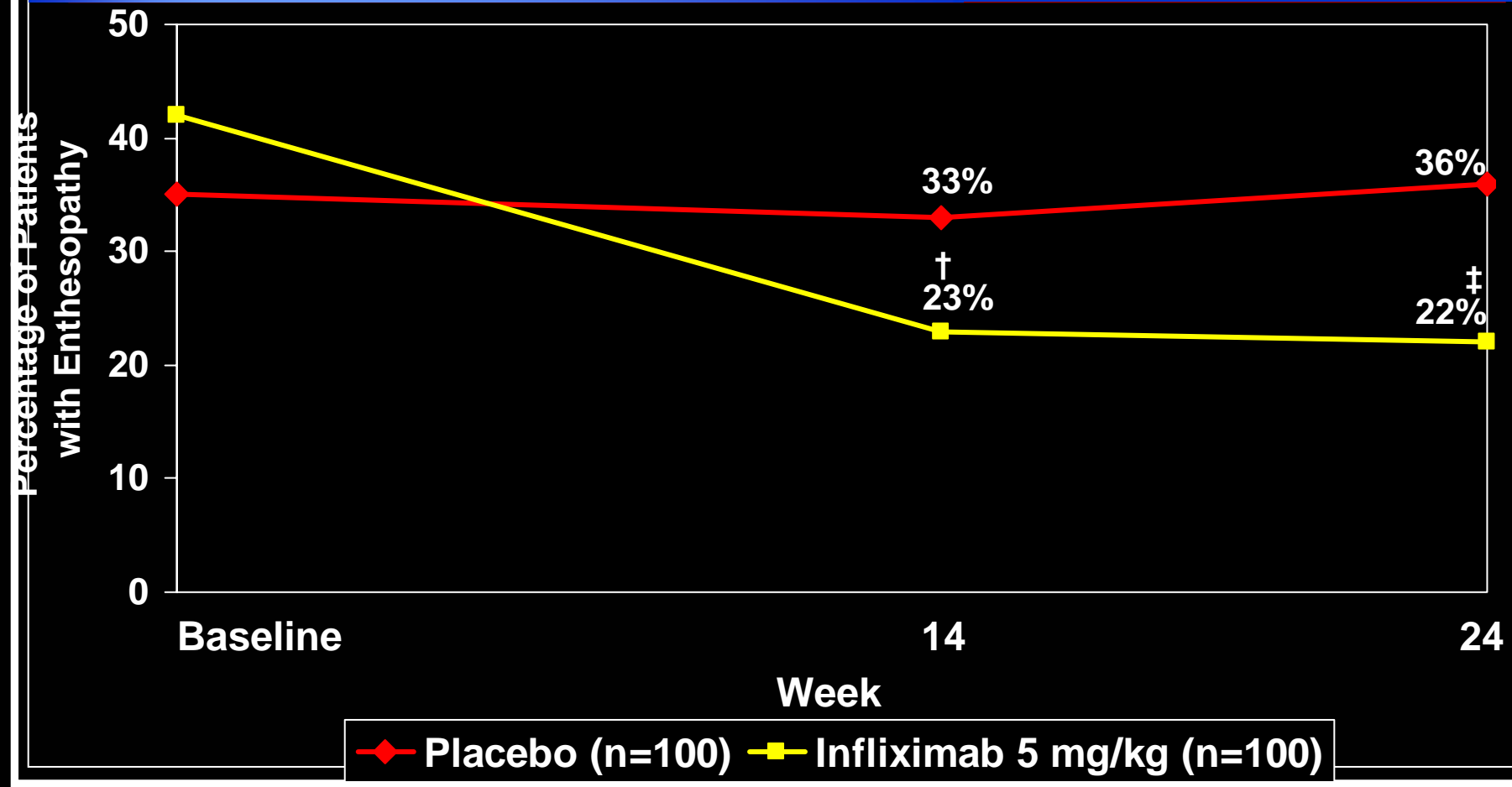
Placebo cross-over
to infliximab





IMPACT 2

Percentage of Patients with Enthesopathy Over Time



† p=0.023

‡ p=0.004

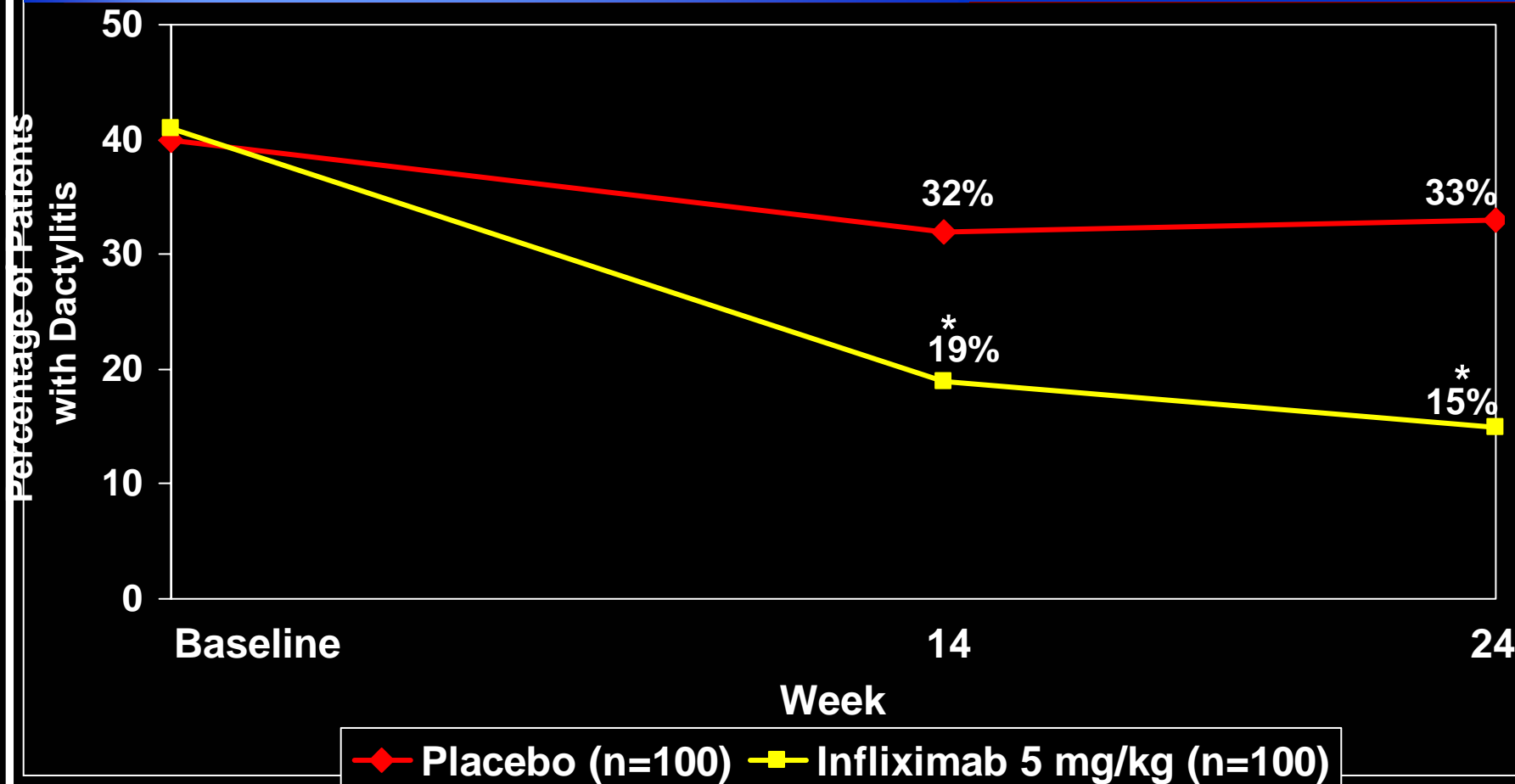
REMICADE [package insert]. Malvern, PA: Centocor, Inc.; 2004.

Data on File, Centocor, Inc.

Antoni C, et al. *Ann Rheum Dis*. 2005;64:1150-1157.

IMPACT 2

Percentage of Patients with Dactylitis Over Time



REMICADE [package insert]. Malvern, PA: Centocor, Inc.; 2004.

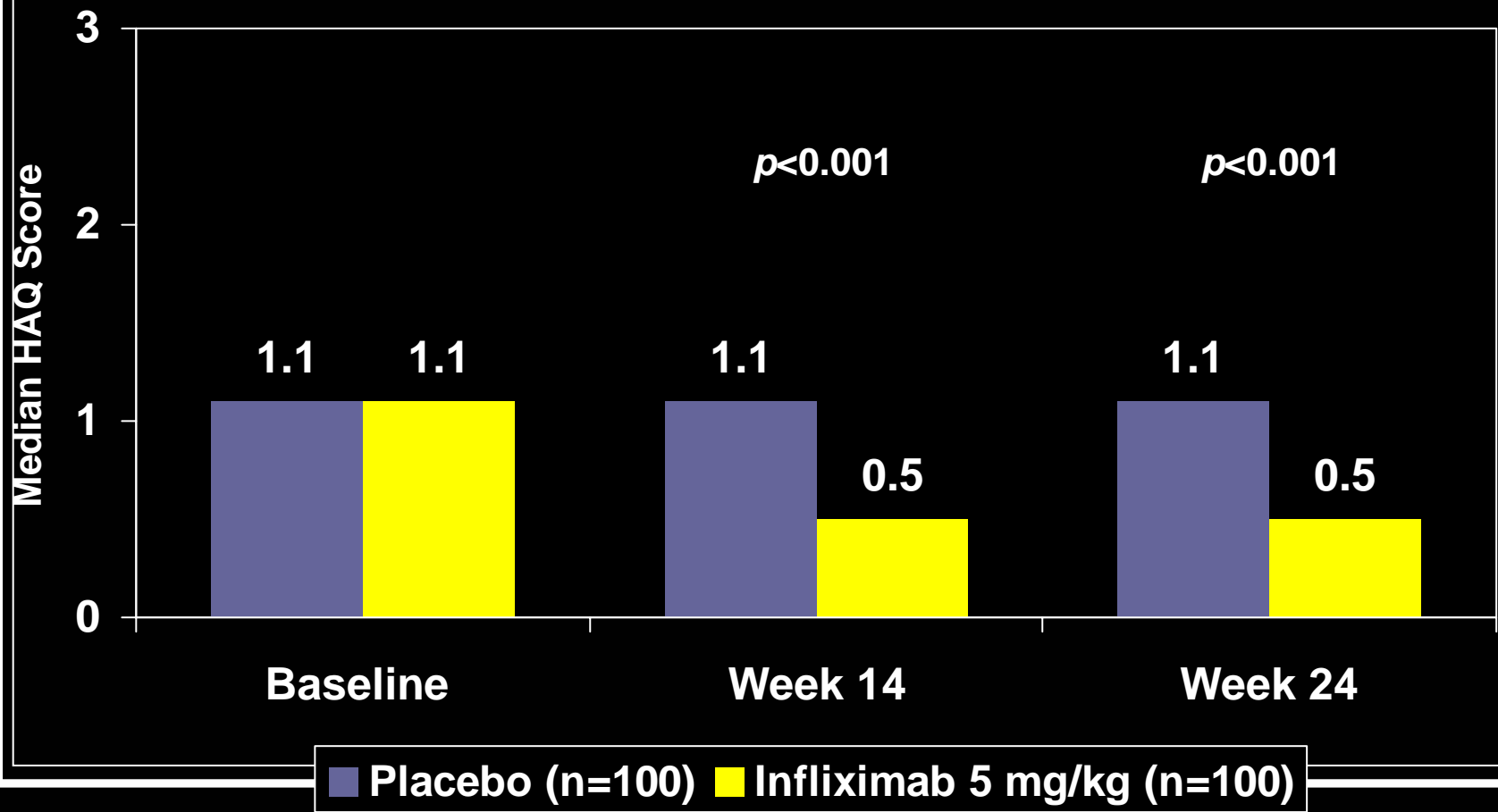
Data on File, Centocor, Inc.

Antoni C, et al. *Ann Rheum Dis*. 2005;64:1150-1157.

*p<0.05

IMPACT 2

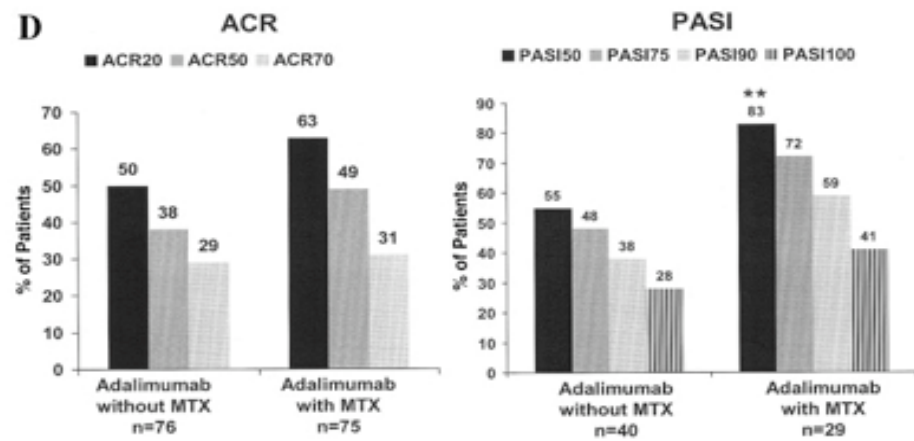
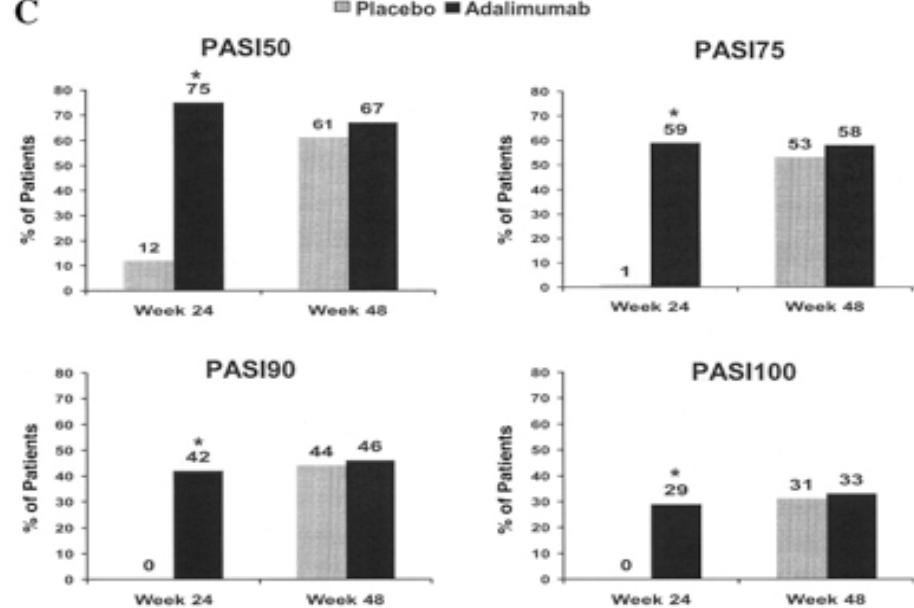
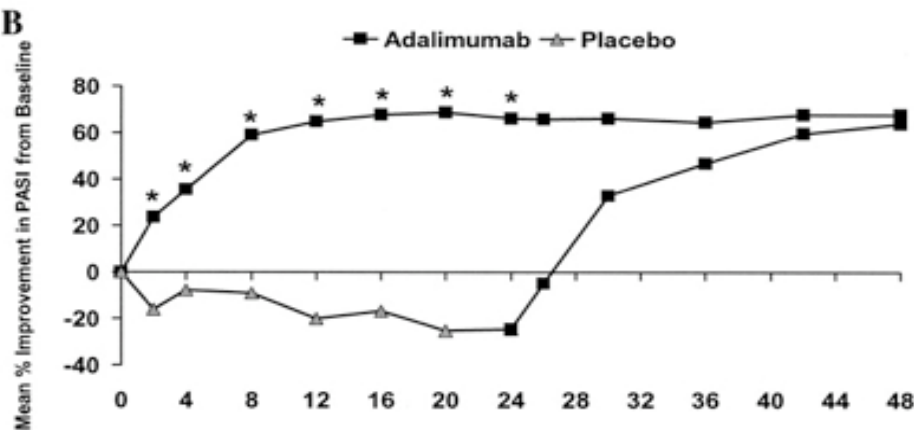
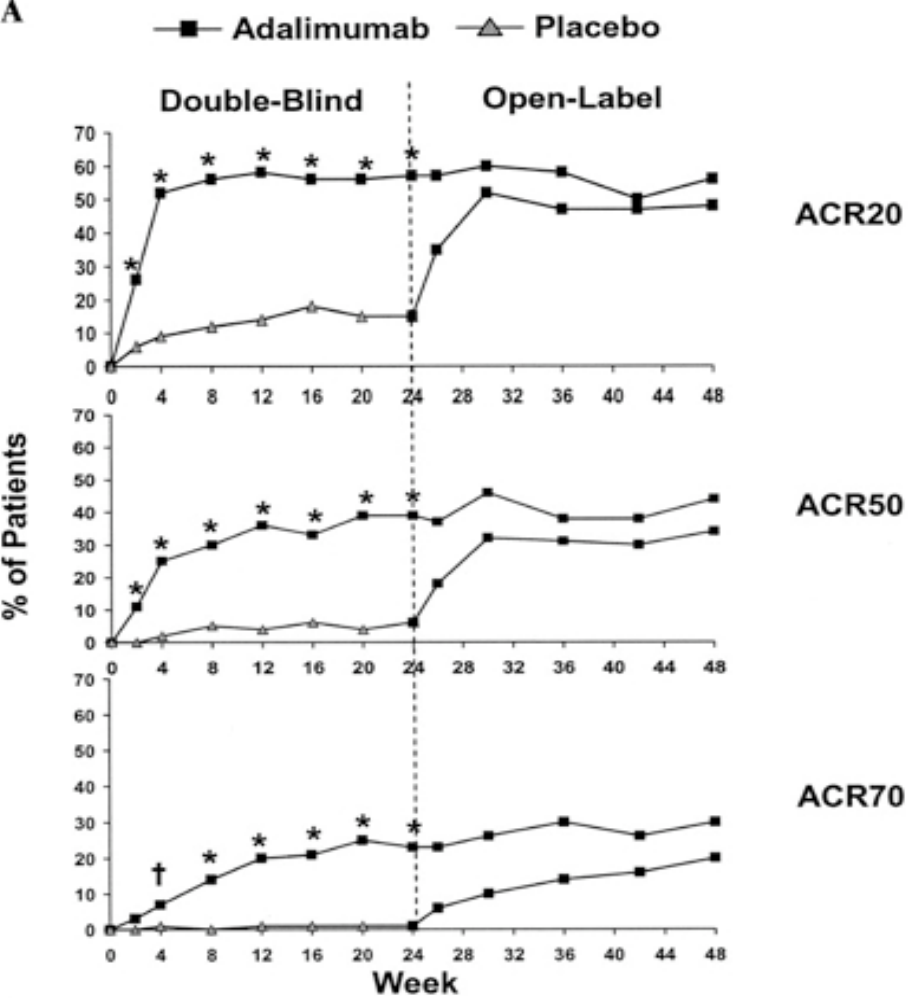
Median HAQ Score at Baseline, Week 14, and Week 24

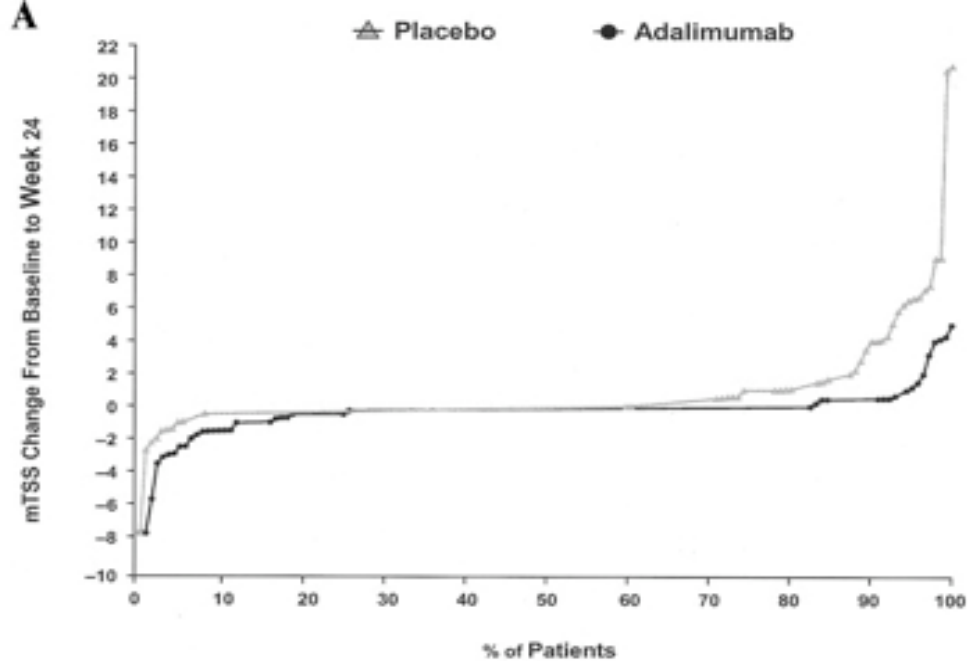


Adalimumab for long-term treatment of PsA

- Forty-Eight week data from the adalimumab effectiveness in PsA trial
- Aim: Assess efficacy & safety
- ADEPT: followed up for 48 wks
- Open label 40mg Qo2w
- Radiograph at 48 weeks
- Improved joint and skin, reduced disability, and inhibited radiographic progression. Good safety profile

- Gladman DD et al A&R 2007; 56: 476-488

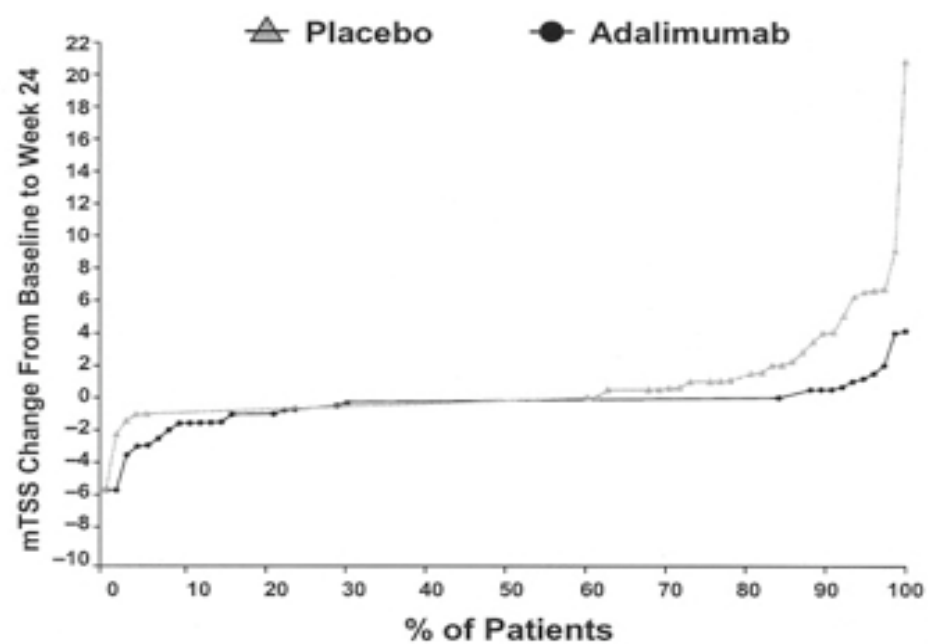
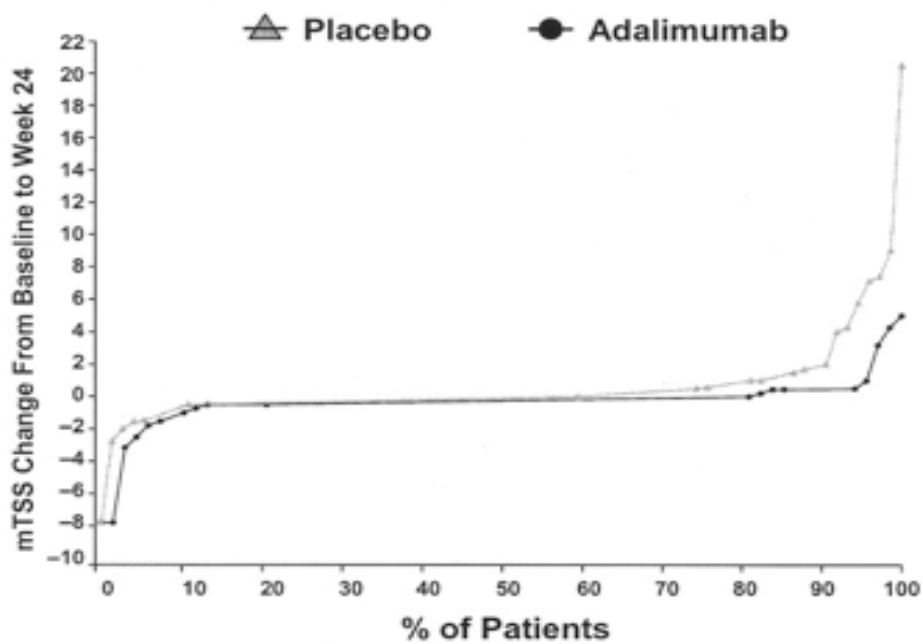


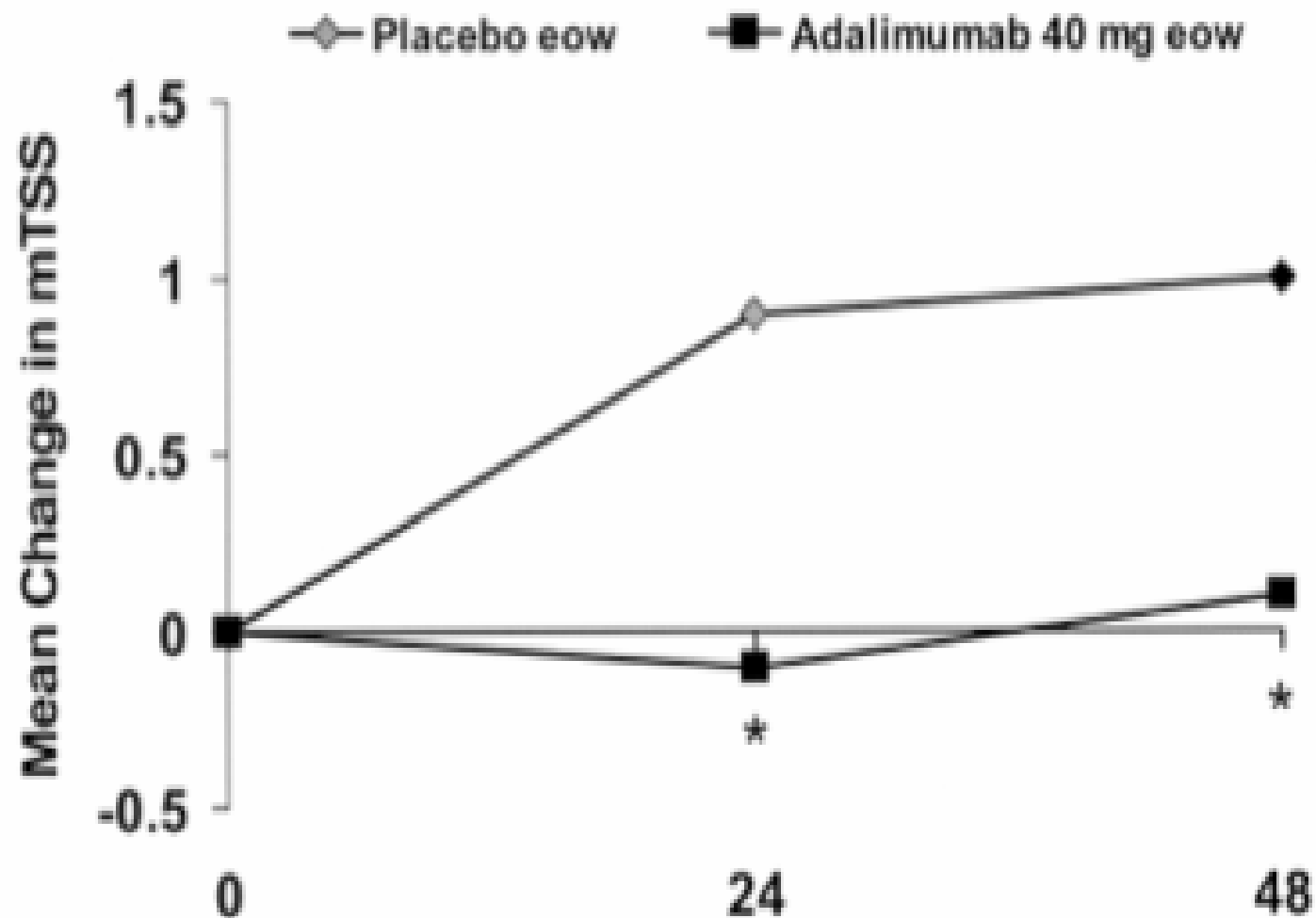


B

No MTX

With MTX





	N	Baseline	Week 24 Mean Change	Week 48 Mean Change
Placebo/adalimumab	141	22.1	0.9	1.0
Adalimumab	133	23.4	-0.1*	0.1*

PsA: GO-REVEAL STUDY

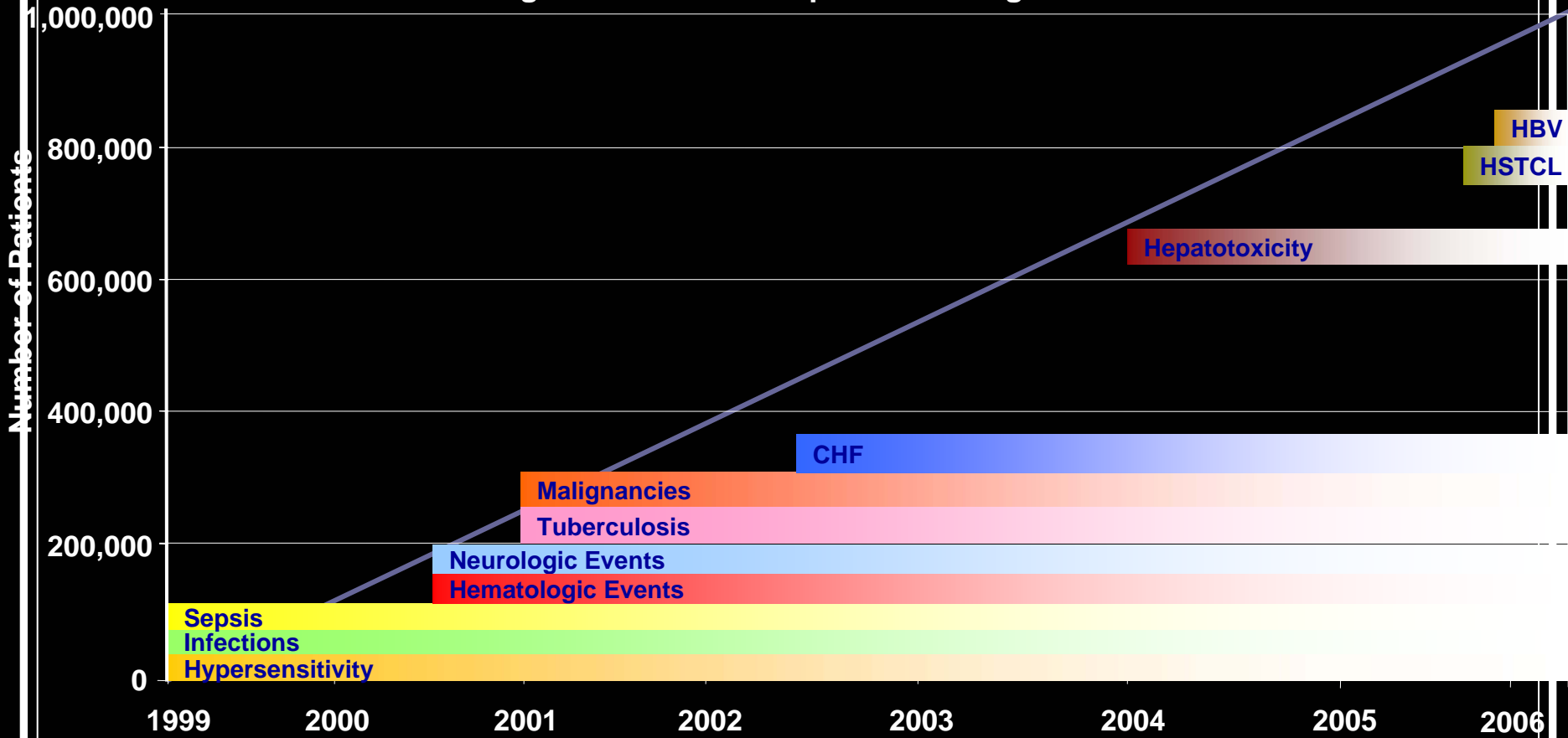
- Golimumab improves active PsA and psoriatic skin disease
- 405 patients with active PsA received sc placebo or golimumab (50 mg or 100 mg) injections every 4 weeks.
- Aim: to assess safety and efficacy
- Golimumab was significantly superior to placebo at weeks 24 and maintained at 52
- Safety: at week 24, 2.4% SAEs vs 6.2% placebo
- Nail, enthesitis, and dactylitis: improved
- No reports of TB or opportunistic infections
- Kavanaugh et al Arthritis Rheum October 2008

The comparative one-year performance of anti-TNF drugs in patients with RA, PsA, and AS

- What is the survival of anti-TNF therapy in clinical practice, and what are the predictors of successful long-term use?
- RA patients require change sooner-65% vs 77% (PsA and AS)
- Etanercept: best crude survival rates
- Concomitant MTX use: greater longevity
- Factors associated with early termination: female gender and higher disease activity
- Improvement in health-related quality of life with TNF therapy was greater in PsA and AS, accounting, perhaps for the improved duration of therapy
- Heiberg et al. Arthritis Rheum 2008; 59: 234-240

Addition of Warnings and Precautions Information in Anti-TNF α Labels Over Time

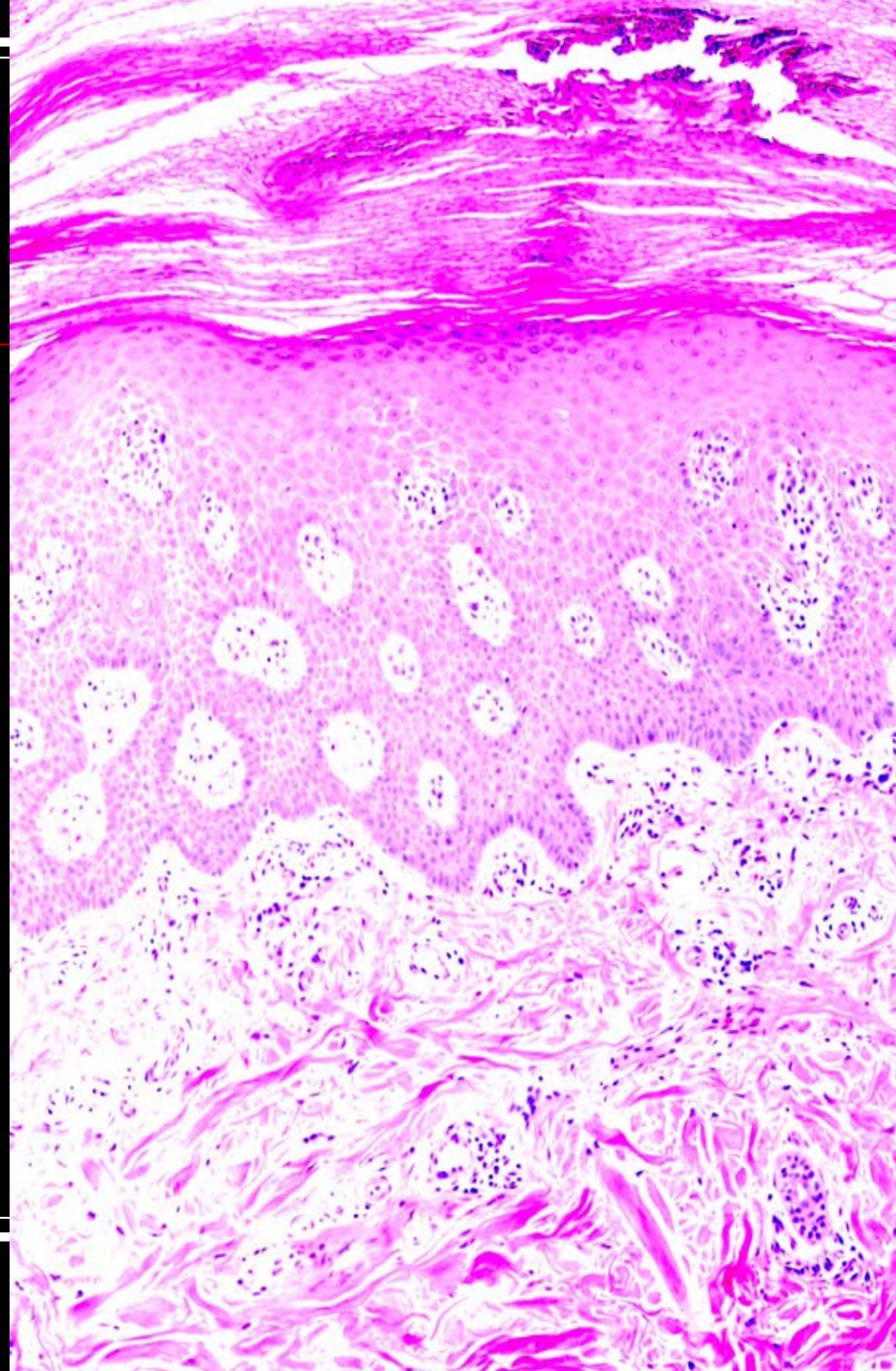
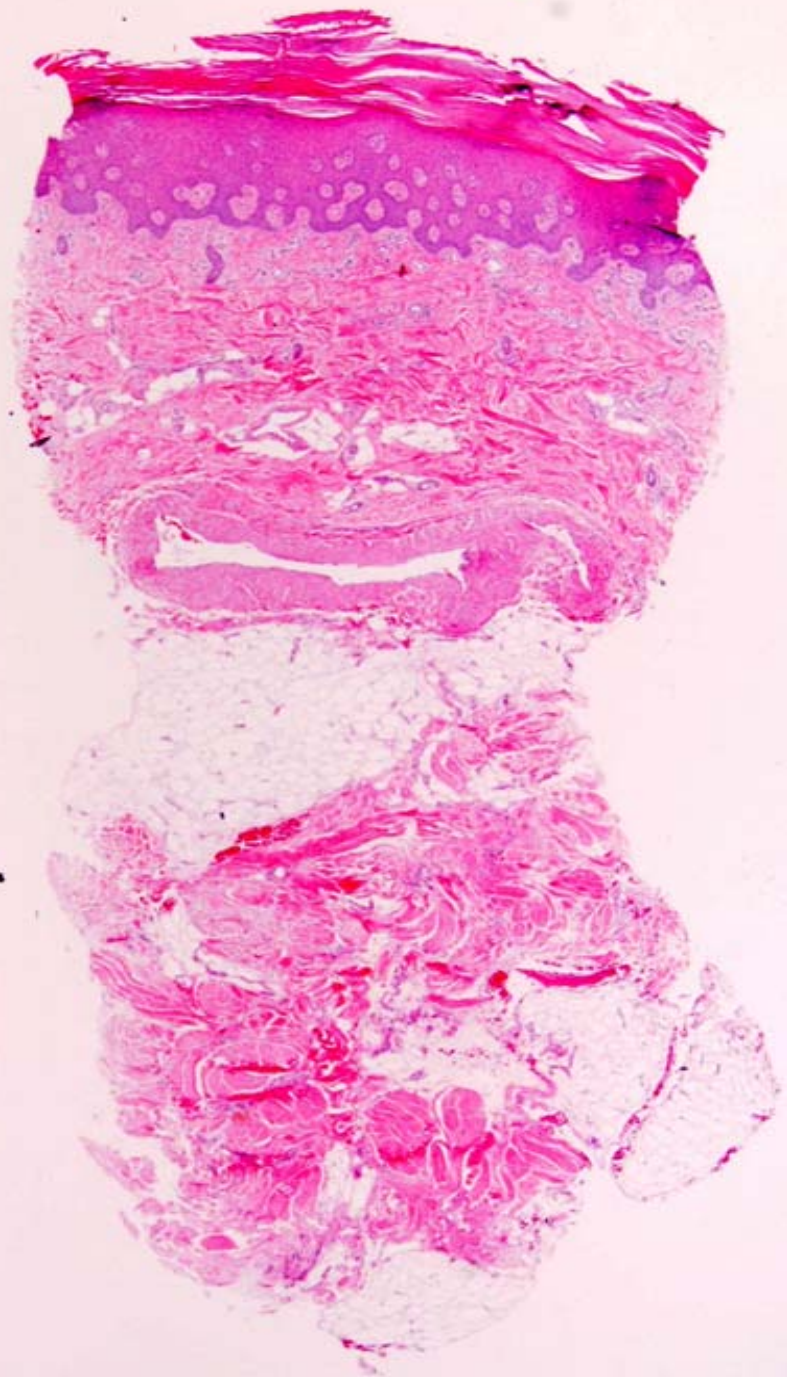
Warnings and Precautions information is based on data collected during clinical trials and postmarketing surveillance

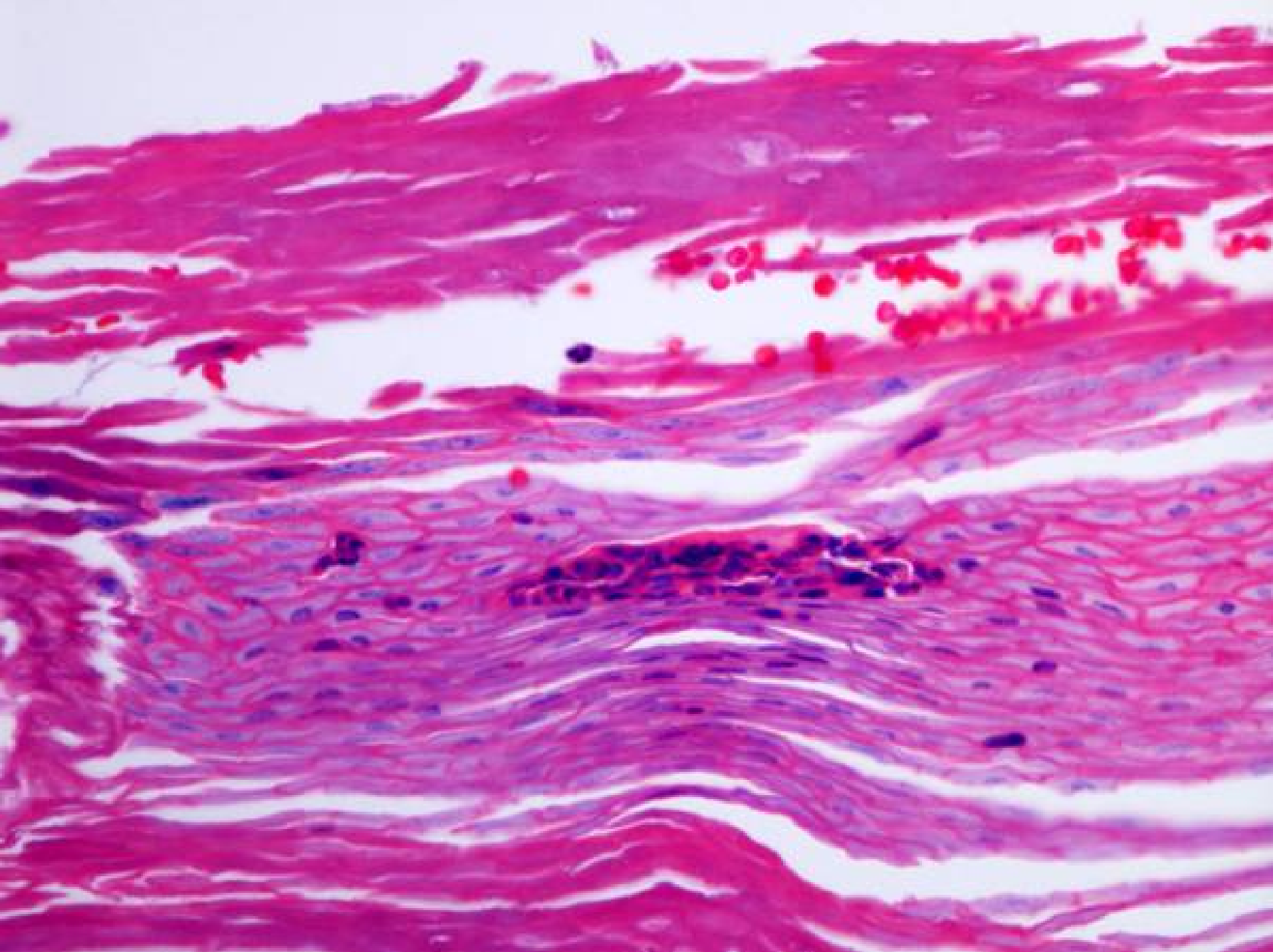


FDA web site. Available at: <http://www.fda.gov>. Accessed September 2006.
 REMICADE® (infliximab) Prescribing Information, Centocor, Inc. August 2006.
 ENBREL® (etanercept) Prescribing Information, Immunex Corporation. June 2006.
 HUMIRA® (adalimumab) Prescribing Information, AbbVie Inc. August 2006.

Biologicals and Psoriasis

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Patient 18 months ago







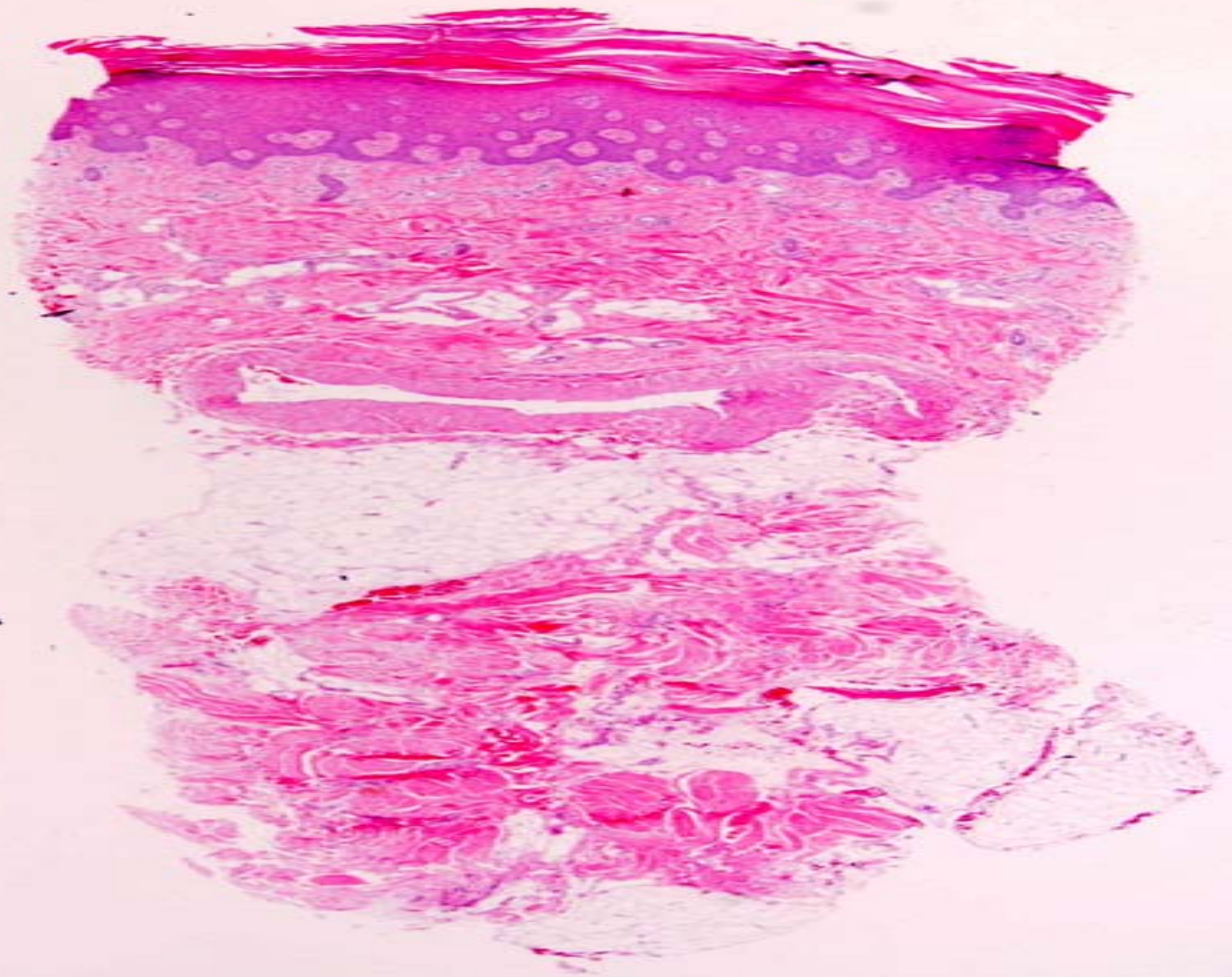
One week after adalimumab



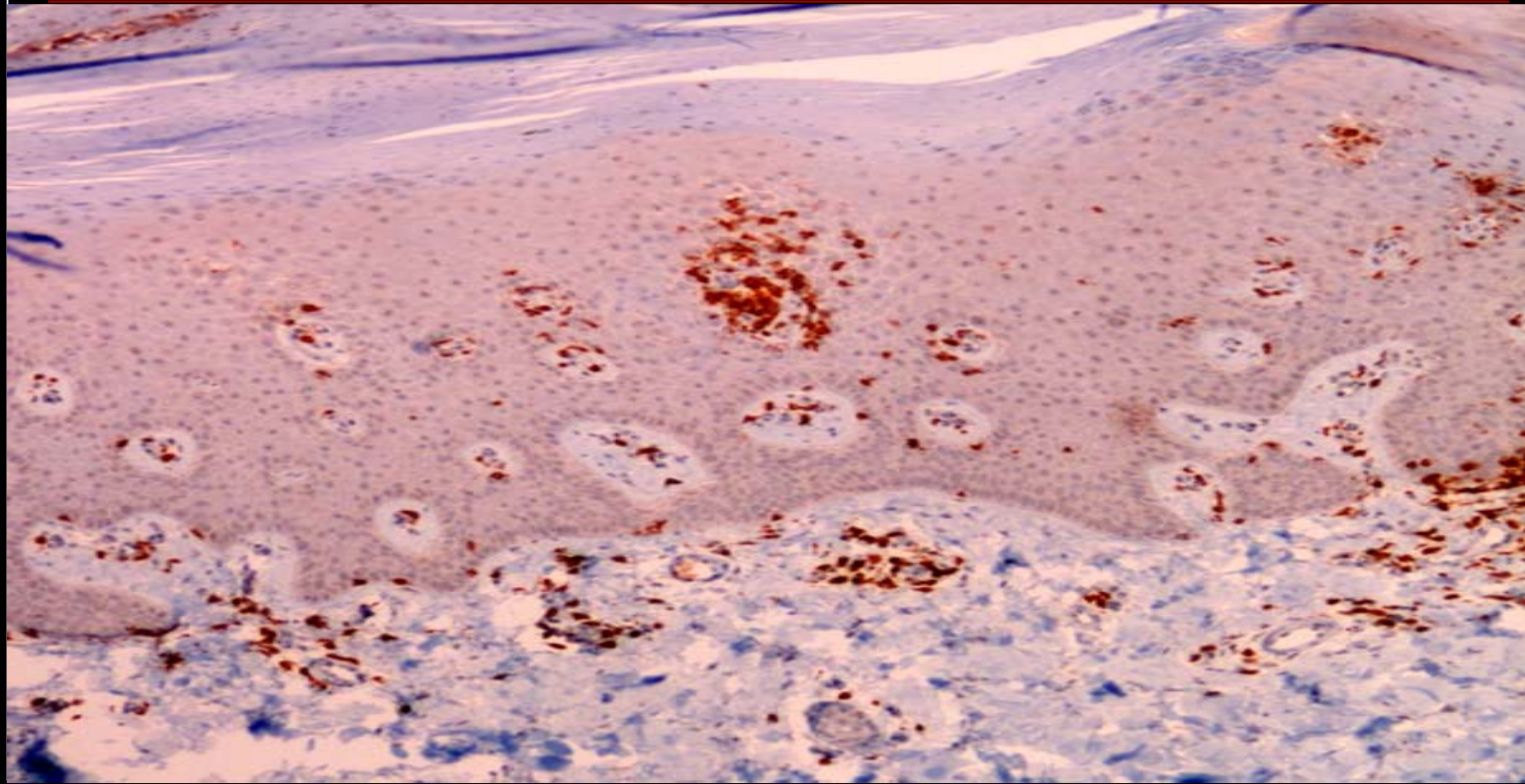




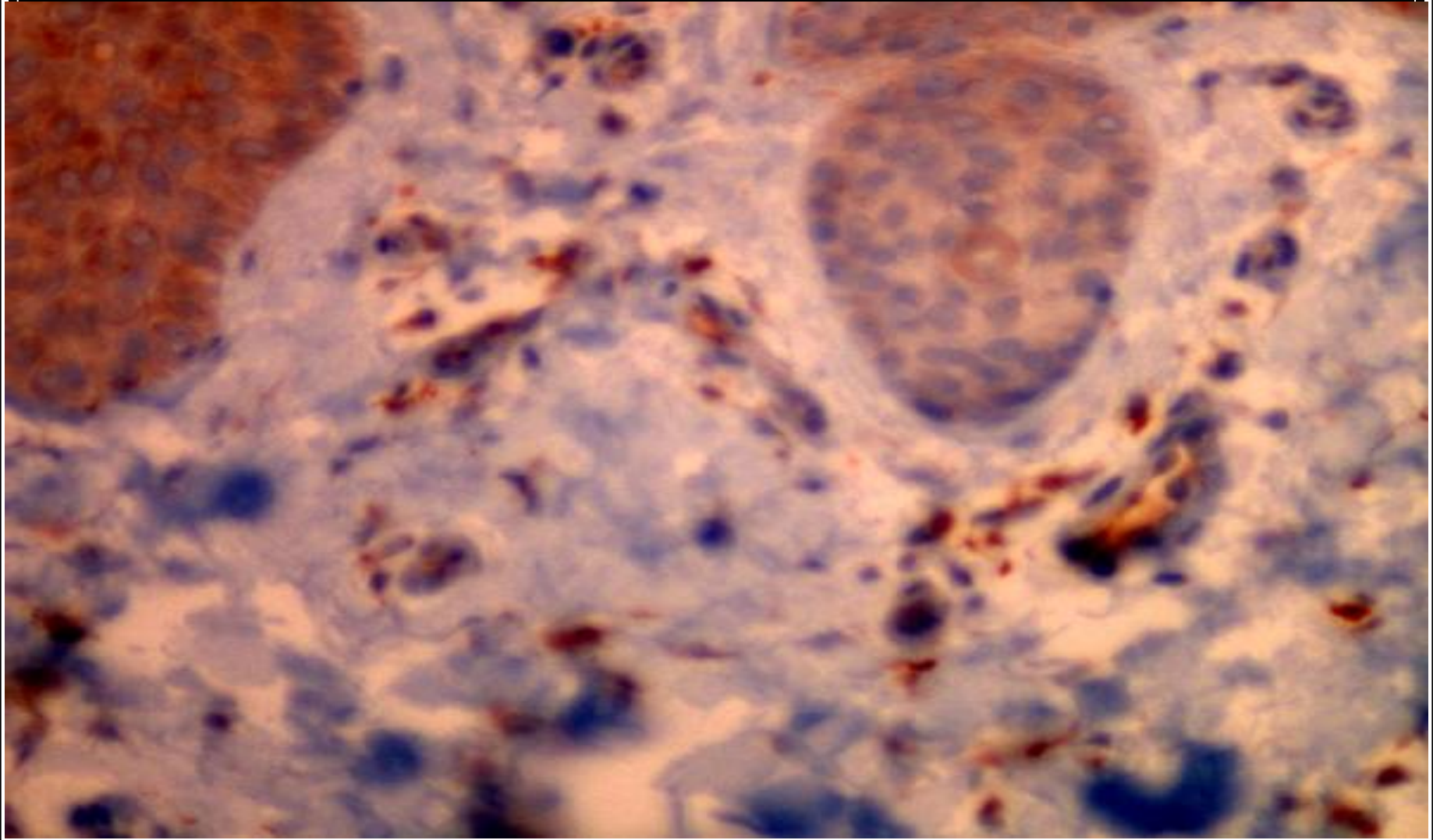




CD3- T cells



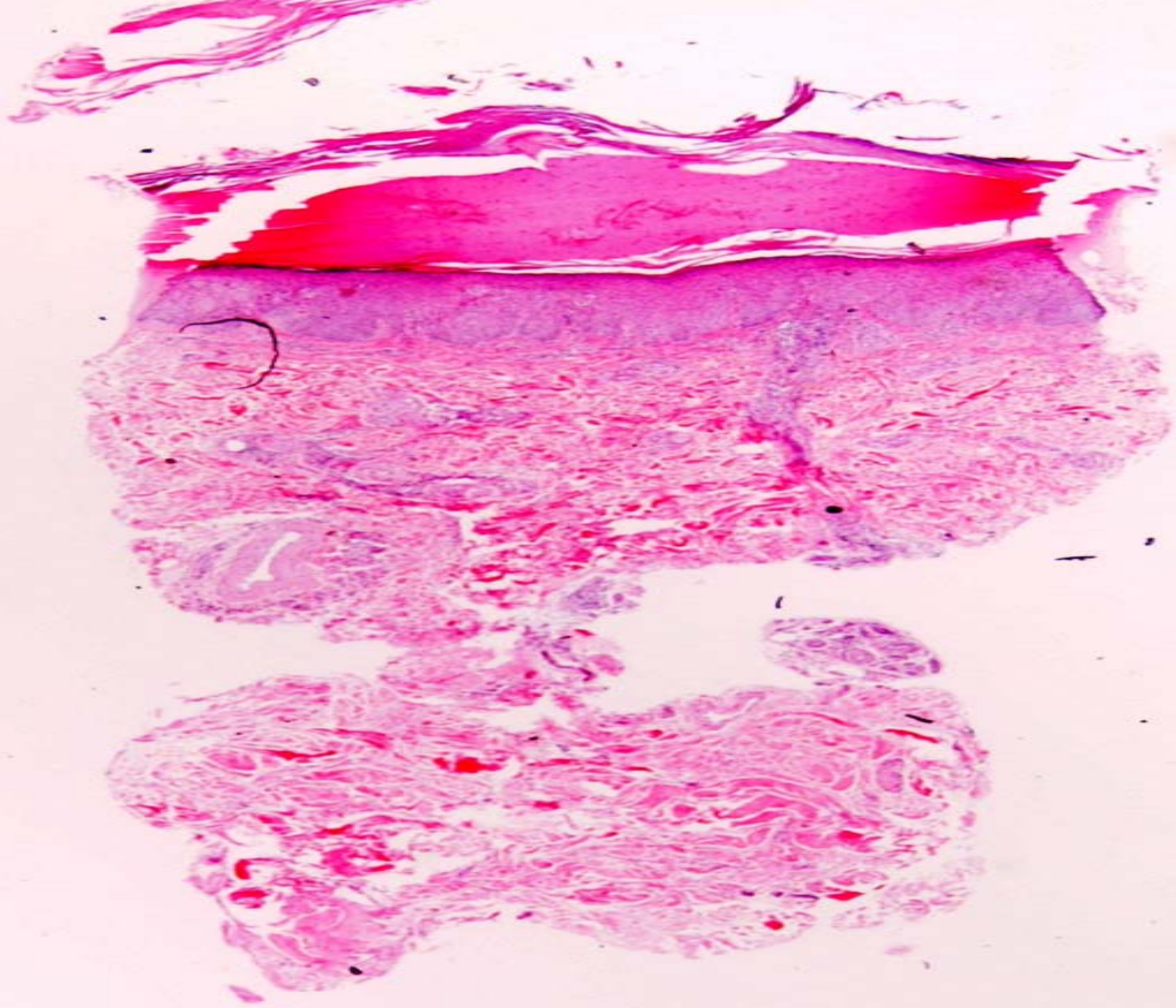
CD68-macrophages/histiocytes

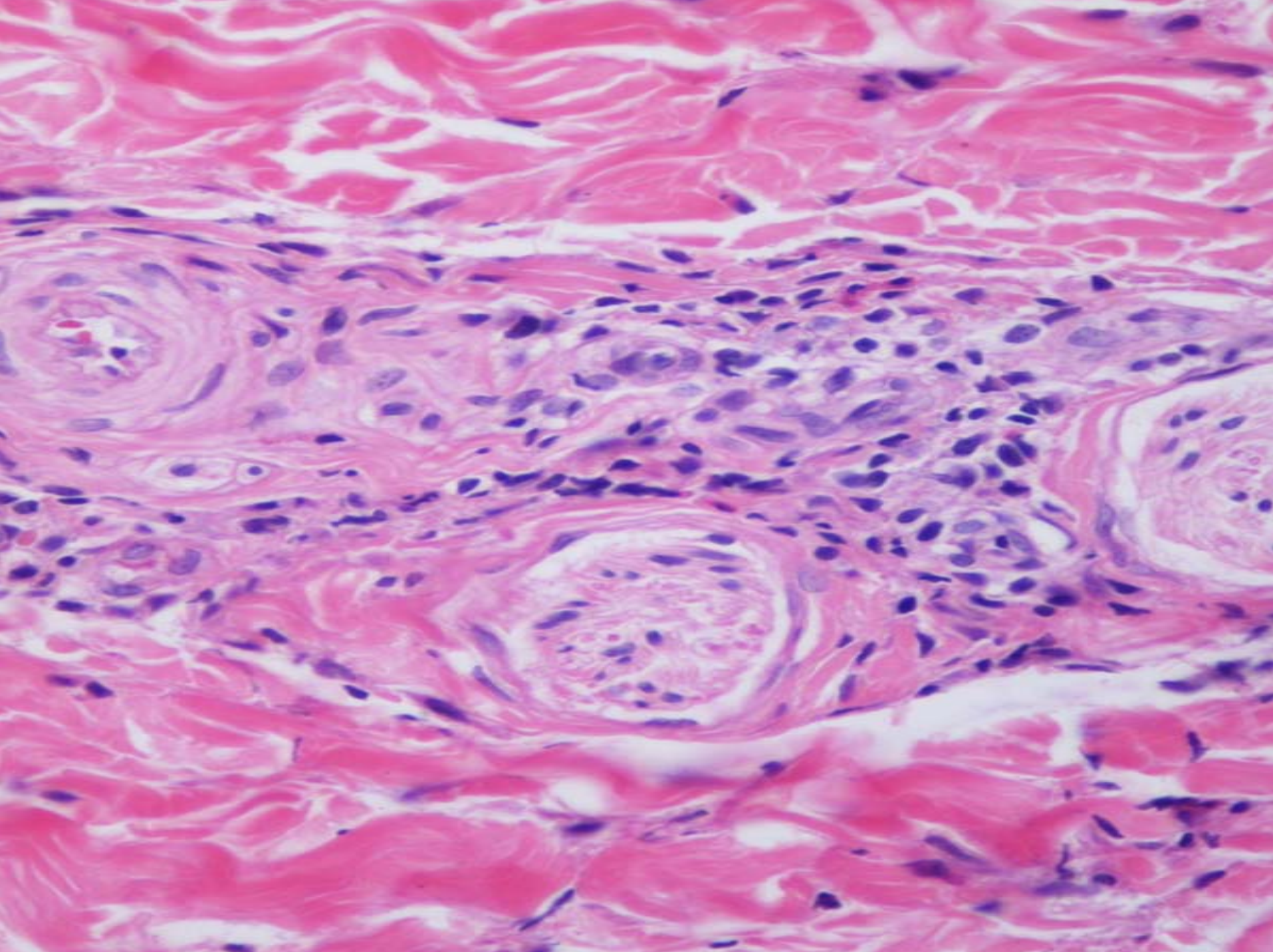




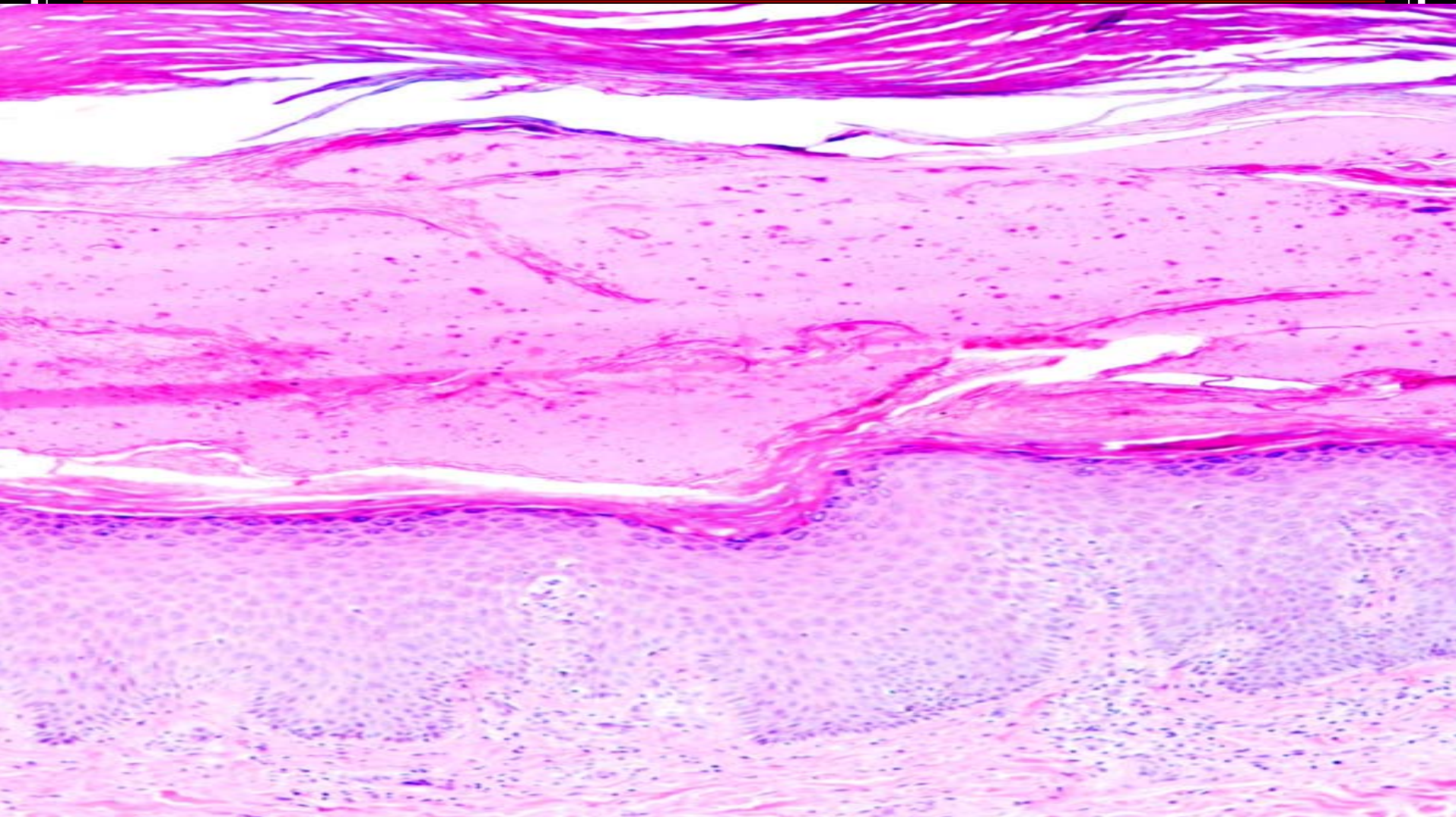








Spongiotic psoriasiform dermatitis intracorneal vesicles with eosinophils



Cuchacovich R, Espinoza CG, Virk Z,
Espinoza LR.

- Biologic therapy (TNF-alpha antagonists)-
induced psoriasis: a cytokine imbalance
between TNF-alpha and IFN-alpha? J Clin
Rheumatol 2008; December (in press)

Ustekinumab in Psoriatic Arthritis

- Recent identification and characterization of Th17 cells as the main pathogenic effectors in several autoimmune disorders, including psoriasis and PsA, have provided new avenues of therapeutic interventions
- Psoriatic skin and synovial fluid from patients with PsA are rich with IL17, 23, and 6 and ROR gamma t (NFkb and STAT signaling)

Ustekinumab for PsA

- Novel biologic for psoriasis shows superiority over current best-seller
- Trial Watch
- Nature: November 2008. Volume 7

Ustekinumab in Psoriatic Arthritis

- Phase II, randomized, double-blind, placebo-controlled study of ustekinumab, a human interleukin-12/23 monoclonal antibody, in psoriatic arthritis.
- Gottlieb A, Menter A, Mendelsohn A et al. Lancet November 11, 2008

Ustekinumab in Psoriatic Arthritis

- Increase concentration of p40 subunit of IL-12/IL-23 and IL-17 in psoriasis skin and psoriatic joints
- Ustekinumab is a human monoclonal antibody that neutralizes IL-12 and IL-23

Ustekinumab in Psoriatic Arthritis

- 146 patients included; active PsA and moderate to severe psoriasis that had no responded to DMARDs and TNF blockers
- Group 1 in weeks 0, 1, 2, and 3, received ustekinumab 90 or 63 mg sc
- Group 2 received placebo 3 mg
- In weeks 12 and 16, group 1 received placebo and group 2 received ustekinumab 6
- Primary endpoint was ACR 20% at week 12
- Patients were followed up until week 36

Ustekinumab in Psoriatic Arthritis

- ACR 20% at week 12, greater response in group 1 (42% vs 14%; difference 28.0%, 95%CI 14.0-41.6%)
- Response was maintained for 26 weeks
- Results in group 2, at weeks 24 (51%, 28/55), 28 (45%, 24/53), and 36 (42%, 21/50) after 2 ustekinumab doses (weeks 12 and 16) were similar to group 1

Ustekinumab in Psoriatic Arthritis

- In patients with psoriasis, covering more than 3% of their body-surface area, a PASI 75 was achieved in 52% of group 1 compared with 5% in group 2
- Patients in group 2 with at least 3% BSA involvement at base line also experienced improvement at 36 weeks with the 2 doses of ustekinumab at weeks 12 and 16

Table 1. Development Status of IL12 and IL23 antagonists

■ Drug(Company)	Indication	Status
■ Ustekinumab	Psoriasis	P-registration
■ (J&J)	PsA, C, MS	Phase II
■ ABT-874(Abbott)	Psoriasis	Phase III
■	Crohn'	Phase II
■ Apilimod	Crohn'	Phase II
■ (Synta Ph.)		

Ustekinumab in Psoriatic Arthritis

- Frequency of adverse and serious adverse events was similar in both groups, and therapy was discontinued in 1% of patients in group 1 and 6% in group 2

USTEKINUMAB IN PSORIATIC ARTHRITIS

Raquel S. Cuchacovich, Luis R. Espinoza

Lancet 2008, Nov 11 (in press)

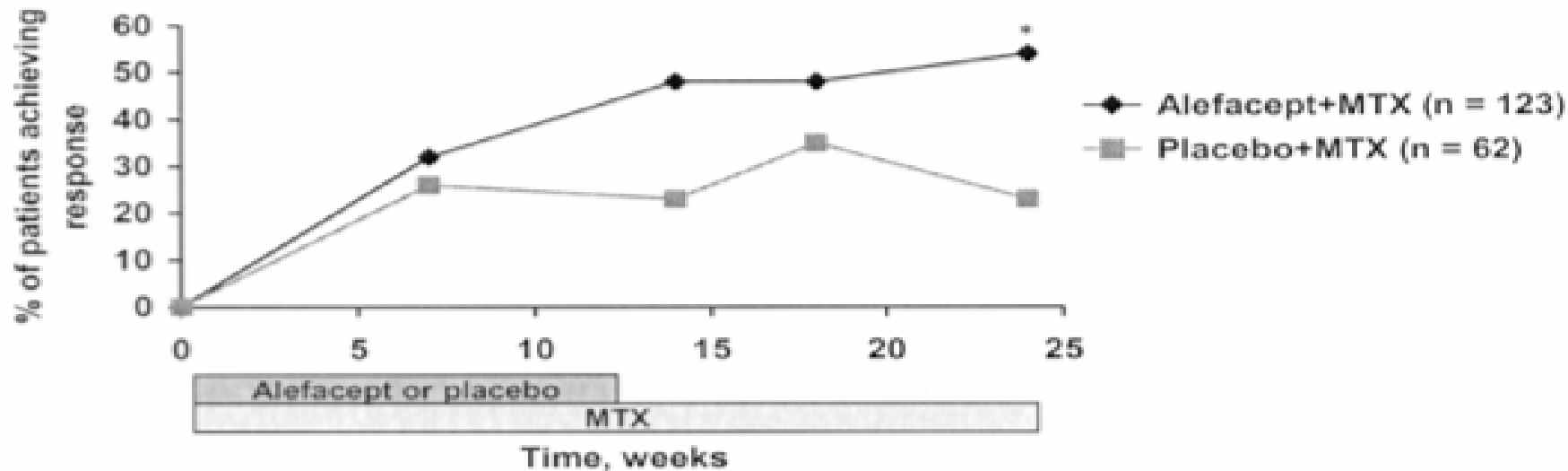
Biologic Agents: T-Cell Interference

- ABATACEPT:
- Fusion protein: mimics natural CTLA-4
- Blocks CD80 and CD86 on APC
- Prevents binding to CD28 on T-cells
- Thus co-stimulation and activation
- Half-life: 8-25 days
- IV: at weeks: 0, 2, 4 and then every 4 weeks

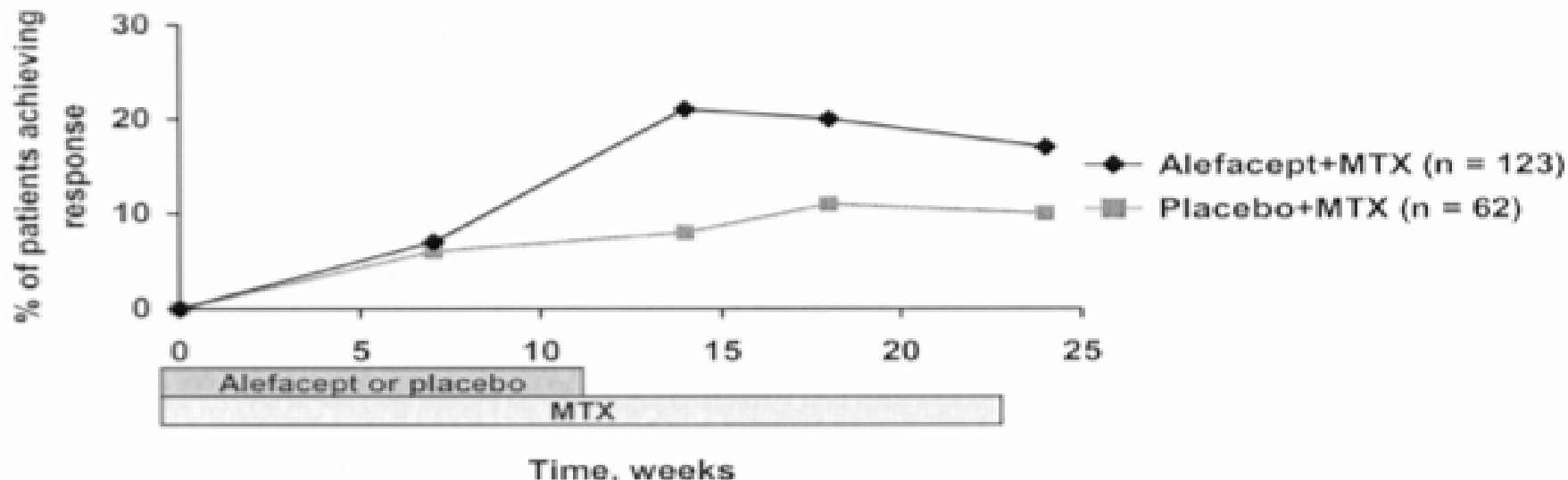
Biologic Agents: Cell Migration Interference

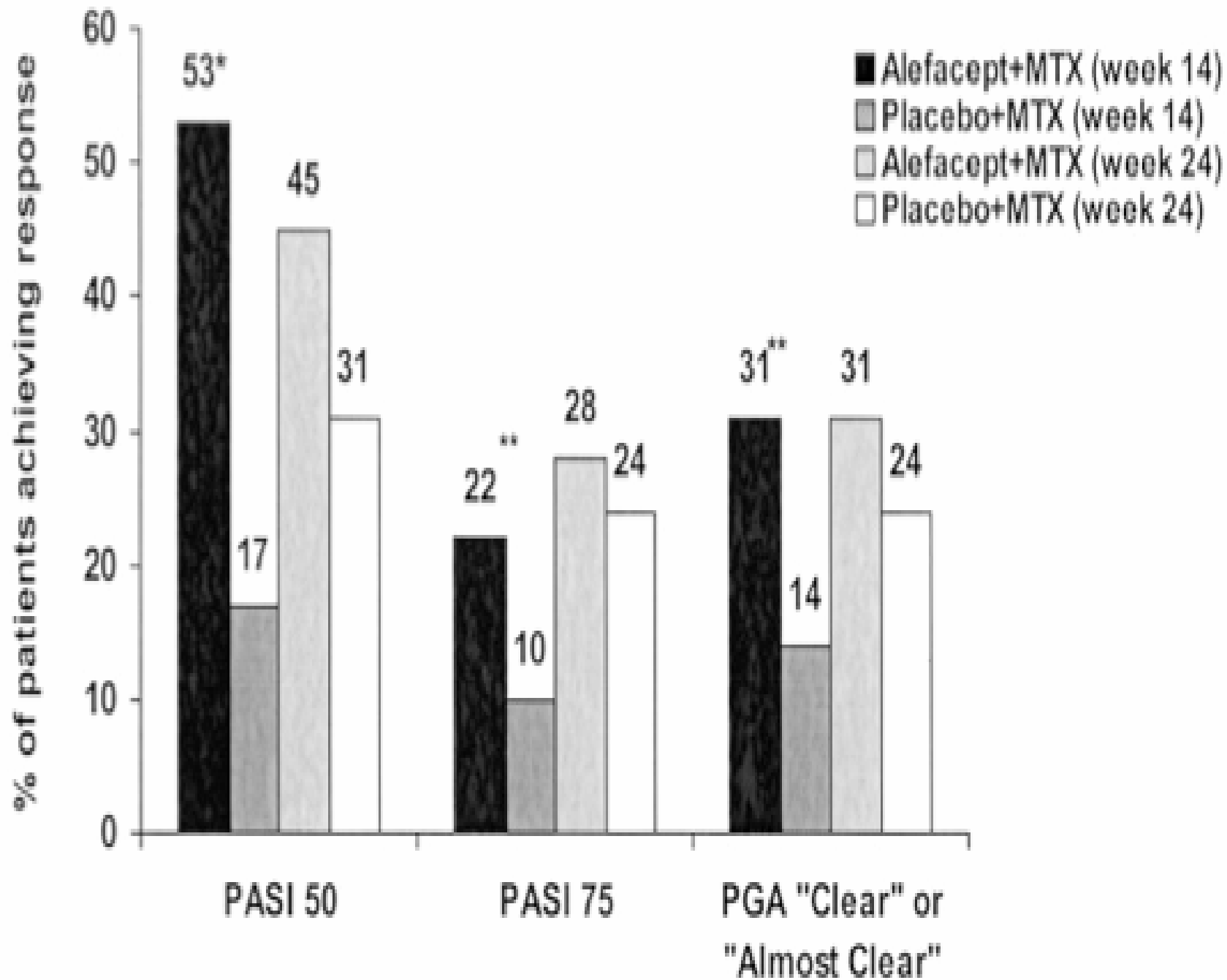
- ALEFACEPT:
- Inhibits T lymphocyte activation and proliferation
- Binding to lymphocyte CD28
- Blocking interaction with LFA-3
- Half-life: 11-12 days
- Administration: IV or IM x 12 weeks
- Induces selective T cells apoptosis: “memory”
- Effectively reduces activity of skin psoriasis

ACR 20 response during treatment and follow-up



ACR 50 response during treatment and follow-up





Biologic Agents: Cell Migration Interference

- EFALIZUMAB:
- Binds to CD-11a of LFA-1 on lymphocytes
- Thus interfering with multiple aspects of T cell activation and migration
- Half-life: 5-8 days
- Administration: weekly sc injections

Biologic Agents: Cell Migration Interference

- NATALIZUMAB:
- mAb to alpha-4 integrin molecules
- Blocks T-cell migration into extravascular tissue
- Half-life: 7-15 days
- Administration: IV infusion every 4 weeks

Biologic Agents: B-Cell Depletion

- RITUXIMAB:
- Induces B-cell lysis via chimeric antibody to CD20
- Interferes with B- and T-cell functions
- Half-life: 80-400 hours
- Administration: 2 IV infusions, 2 weeks apart

Biologic Agents: Transcription Factor Interference

- ANTI-JANUS KINASE 3 (JAK3):
- Inhibits activity of tyrosine kinase required for JAK3
- Block multiple inflammatory pathways
- Half-life: unknown
- Administration: Daily oral

PsA Therapy: Summary

- Traditional DMARDs, including SSZ and MTX, can be effective
- Adalimumab, etanercept, and infliximab are effective in PsA.
- Unlike RA, there is no compelling evidence to suggest synergy with MTX.
- No direct comparison with MTX.
- TNF antagonists slow radiographic progression in PsA, but only a portion of these patients will actually progress.
- No firm clinical or biologic markers of aggressive disease.
- Pharmaco-economic studies need further investigation

Saketkoo L, Cuchacovich R, Espinoza LR.

- Methotrexate therapy for psoriatic arthritis: Reappraisal of an old remedy.
- J Rheumatol 2008, JANUARY

PsA 2008 Where do we stand?

- All 3 available TNF antagonists shown in RCTs to be effective.
- All slow radiographic progression.
- There appear to be differences in skin response
- Initial ideal therapy: not clear.
- In US, TNF antagonists are the only approved DMARDs for PsA.
- Coordination of treatment for skin and joint disease is critically important.
- Promising agents with unique mechanisms of action will become available in near future

Mardi Gras-New Orleans

