



# WHAT INTERNISTS NEED TO KNOW ABOUT BIOLOGICS

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# POTENTIAL CONFLICTS

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# OVERVIEW

- BIOLOGIC THERAPY IN RA/AS/PSORIASIS AND PSORIATIC ARTHRITIS
- POTENTIAL USE IN OTHER DISEASES
- SIDE EFFECTS AND MANAGEMENT OF SIDE EFFECTS
- VACCINATIONS
- POTENTIAL NEW THERAPIES

# BIOLOGIC THERAPIES

- ETANERCEPT (ENBREL)
- INFLIXIMAB (REMICADE)
- ADALIMUMAB (HUMIRA)
- ANAKINRA (KINERET)
- ABATACEPT (ORENCIA)
- RITUXIMAB (RITUXAN)

# NOMENCLATURE

- CEPT – RECEPTOR DRUGS WHICH USUALLY BLOCK BINDING OF RECEPTOR TO CELL
- XIMAB – CHIMERIC MONOCLONAL ANTIBODY
- MUMAB – FULLY HUMANIZED MONOCLONAL ANTIBODY

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- Gastrointestinal
  - Ocular
  - Neurologic
  - Dermatologic

# DIAGNOSIS OF RA

SYNOVITIS: COMPRESSION TEST OF MCPs  
AND MTPs

ELEVATED INFLAMMATORY PARAMETERS:  
ESR/CRP. REMINDER: NORMAL IN 40%  
AT PRESENTATION

ANTI-CCP (CYCLIC CITRULLATED PEPTIDE  
ANTIBODY): specific for RA

# RHEUMATOID ARTHRITIS

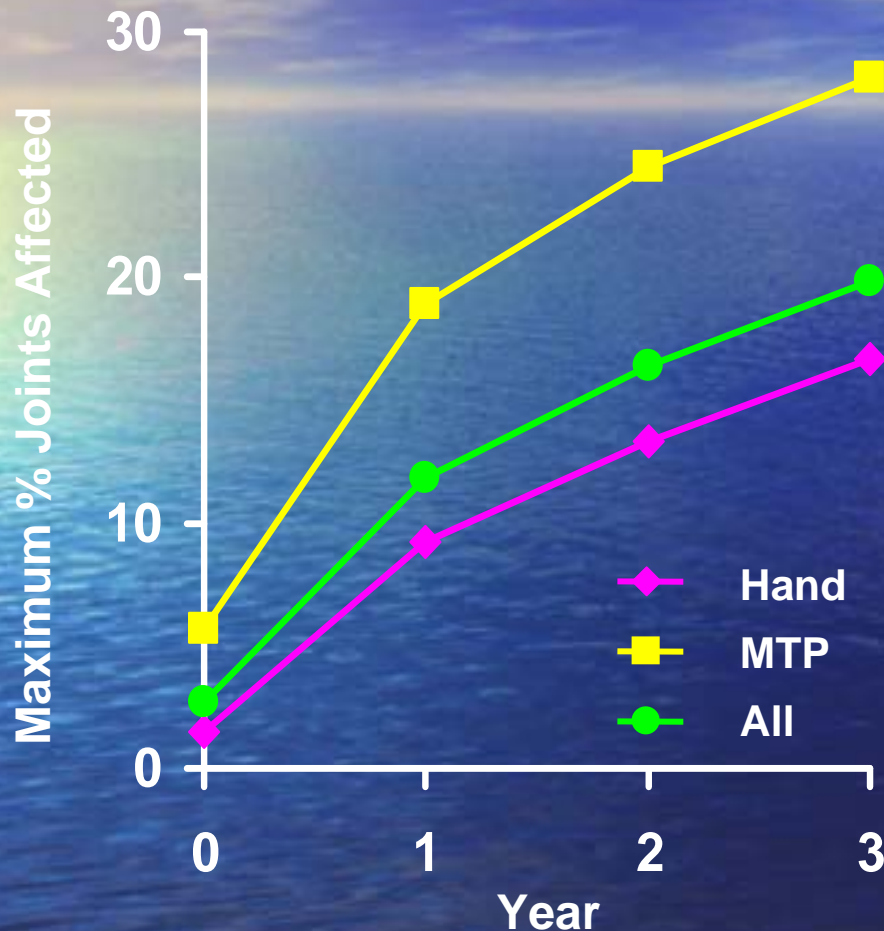
- MORBIDITY

- 75% RA patients changes job due to RA
- 50% RA patients disabled in 10 years
- Lifetime costs of RA comparable to those with CAD

- MORTALITY


- – life span 7 years less in men with RA compared to controls; 3 years less in women

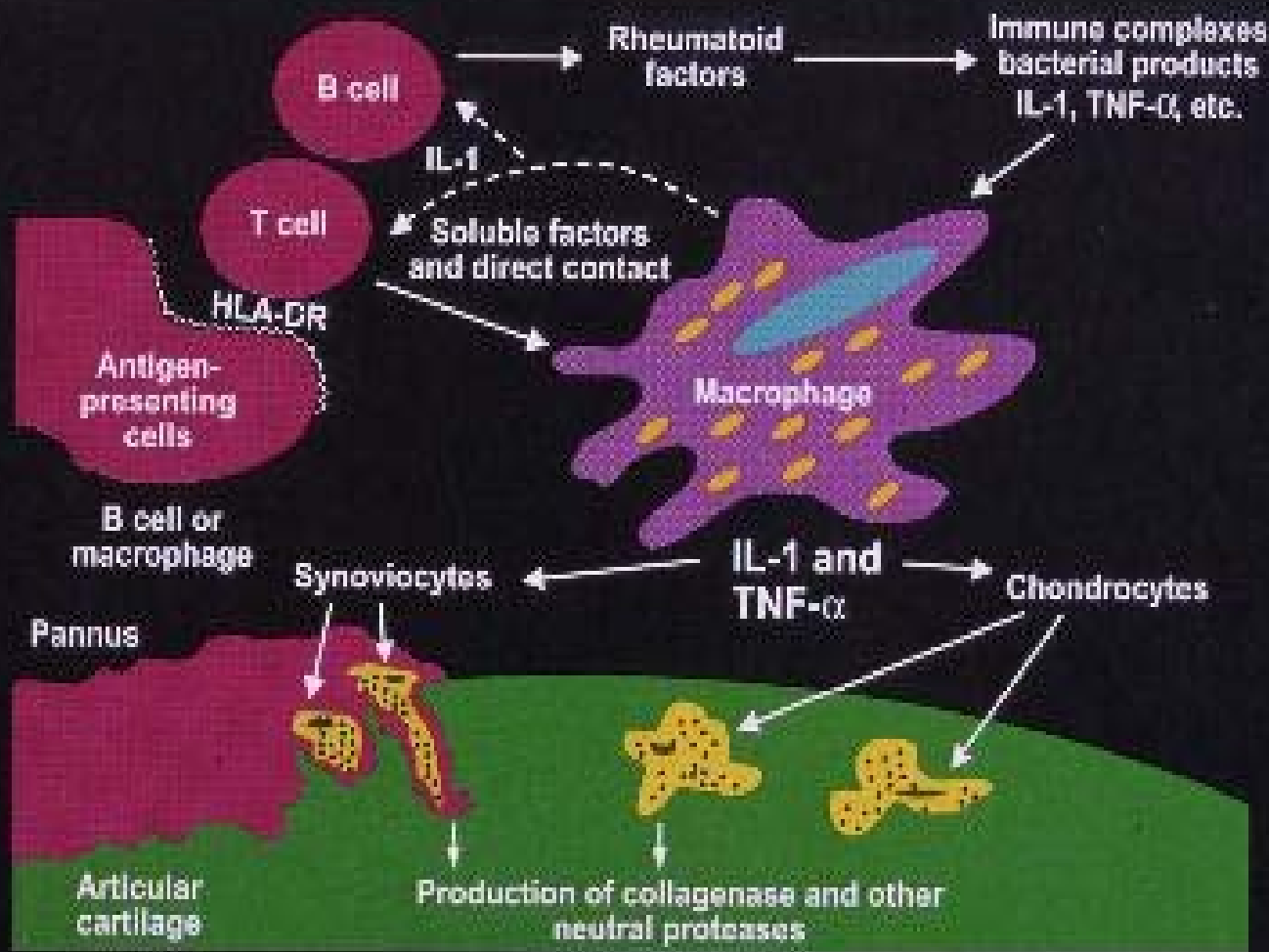
# Joint Erosions Occur Early in RA



- Up to 93% of patients with <2 years of RA may have radiographic abnormalities
- Erosions can be detected by MRI within 4 months of RA onset
- Rate of progression is significantly more rapid in the first year than in the second and

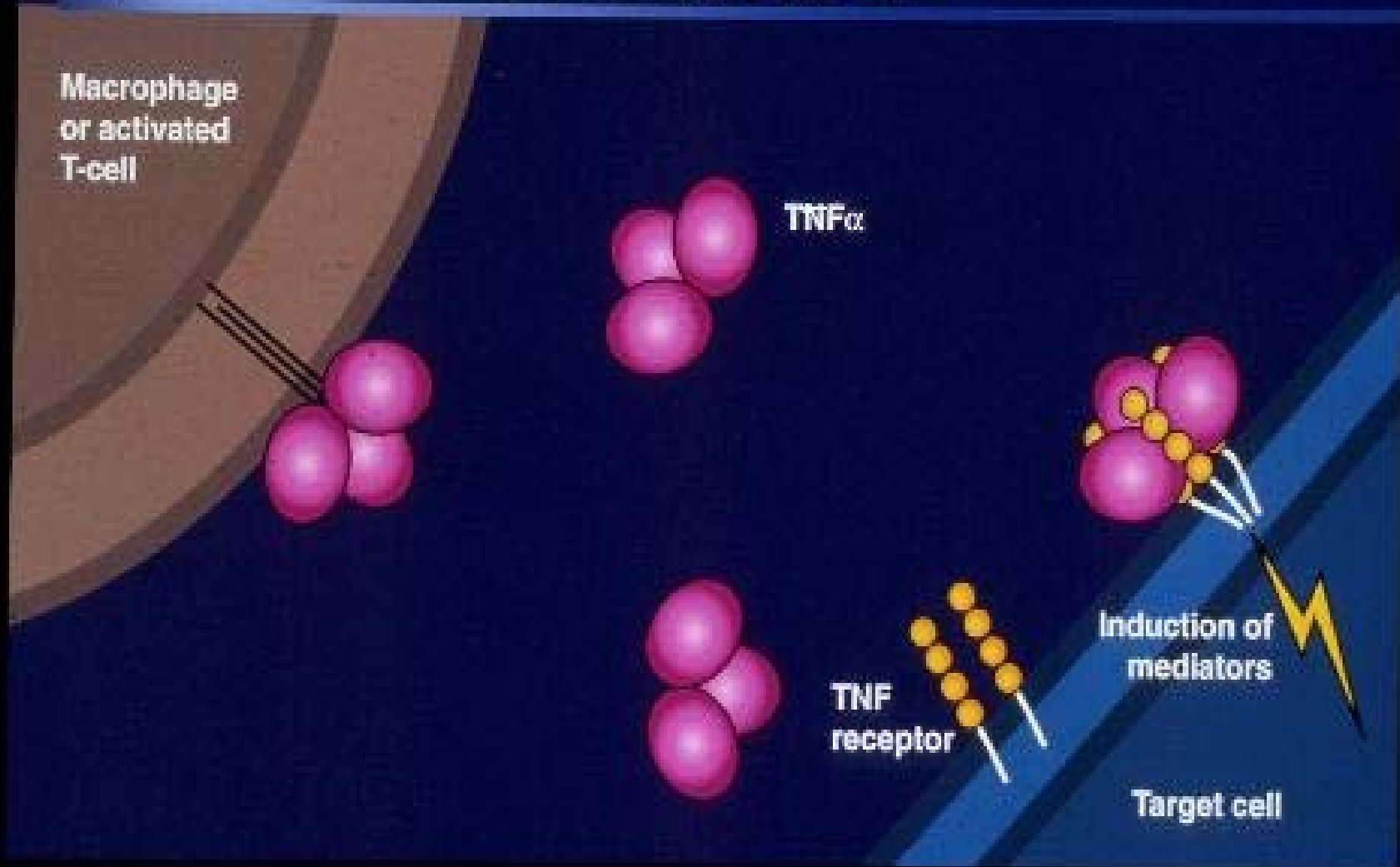
Fuchs HA et al. *J Rheumatol.* 1989;16:585-591.  
McQueen FM et al. *Ann Rheum Dis.* 1998;57:350-356.  
van der Heijde DM et al. *J Rheumatol.* 1995;22:1792-1796.

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- TREATMENT GOAL IS NOW REMISSION
  - ADJUST MEDICATIONS/COMBINE MEDICATIONS (BUT NEVER COMBINE BIOLOGIC THERAPIES) TO ACHIEVE GOAL
  - XRAYS NOW MORE COMMON BECAUSE WE NOT ONLY TREAT SYMPTOMS BUT ALSO TREAT TO PREVENT EROSIONS AND JOINT SPACE MARROWING



Arend WP, et al. Arthritis Rheum, 1990;33:305-315

# Synthesis and Actions of $\text{TNF}\alpha$

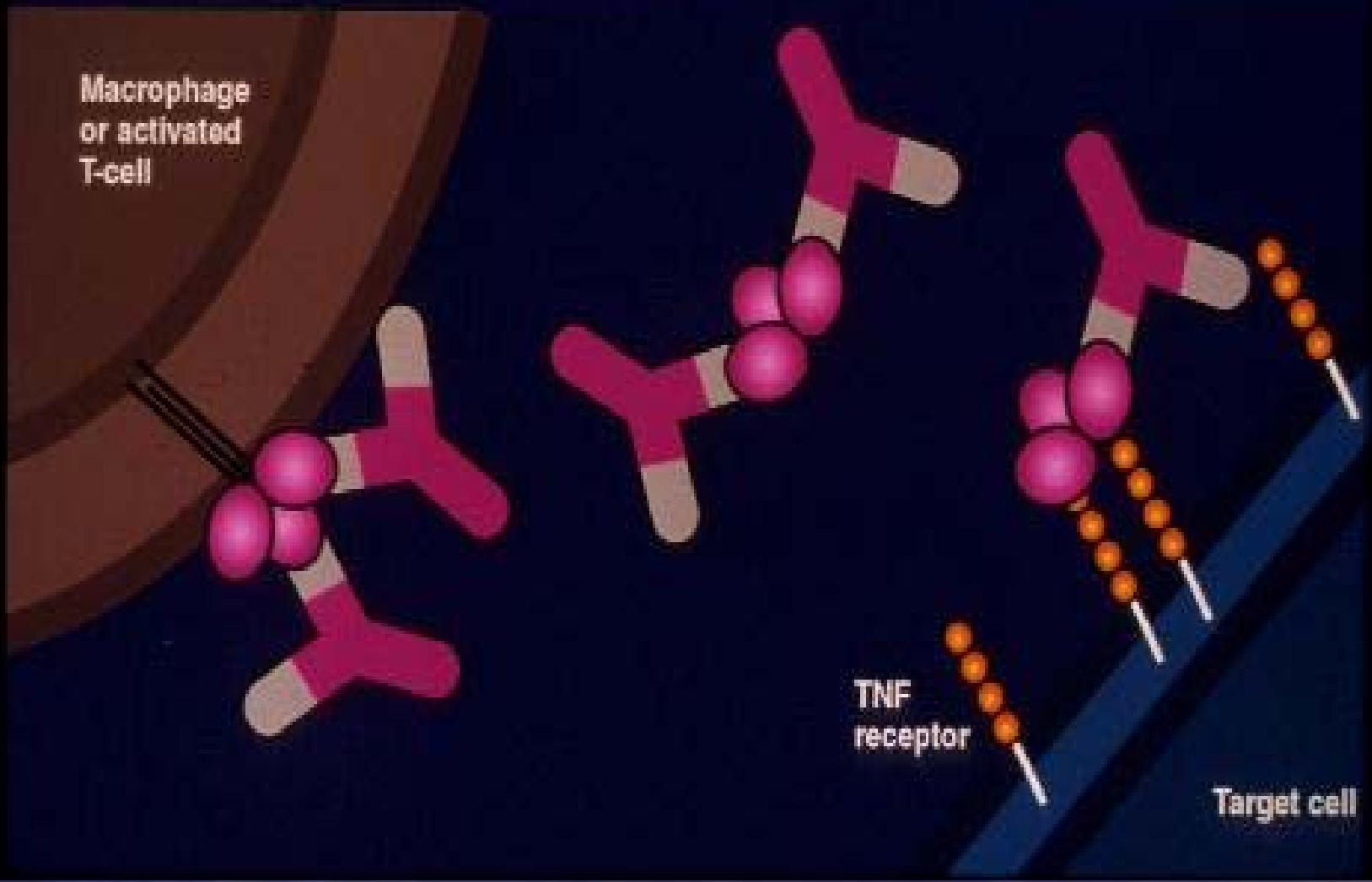


# Antibody Neutralization of $\text{TNF}\alpha$

Macrophage  
or activated  
T-cell

TNF  
receptor

Target cell



# TNF BLOCKADE THERAPY IN RA: SUMMARY

- SIGNIFICANT IMPROVEMENT IN SIGNS AND SYMPTOMS OF RA WITH COMBINATION THERAPY OF MTX AND ALL TNF ALPHA BLOCKERS
- SIGNIFICANT IMPROVEMENT IN FUNCTIONALITY WITH MTX AND TNF BLOCKERS
- HALTING OF JOINT DAMAGE IN RA WITH MTX/TNF BLOCKERS
- BEGINNING DATA TO SUGGEST DECREASED CARDIOVASCULAR EVENTS

# The Current Landscape of AS Therapies

- NSAIDs<sup>1</sup>
  - Effective in mild disease but may lose efficacy over time
- Corticosteroids<sup>1,2</sup>
  - Oral: limited effect
  - Systemic: temporary benefit, but potential for toxicity
- Other treatments<sup>1,3</sup>
  - Sulfasalazine: no proven benefit in axial disease
  - MTX: no large, placebo-controlled trials in AS
  - No therapies have been helpful in treating axial disease

**References:** 1. Dougados M, et al. *Ann Rheum Dis.* 2002;61(suppl III):iii40-iii50. 2. Sieper J, et al. *Ann Rheum Dis.* 2002;61(suppl III):iii8-iii18. 3. Toussirot E, et al. *Exp Opin Invest Drugs.* 2001;10:21-29.

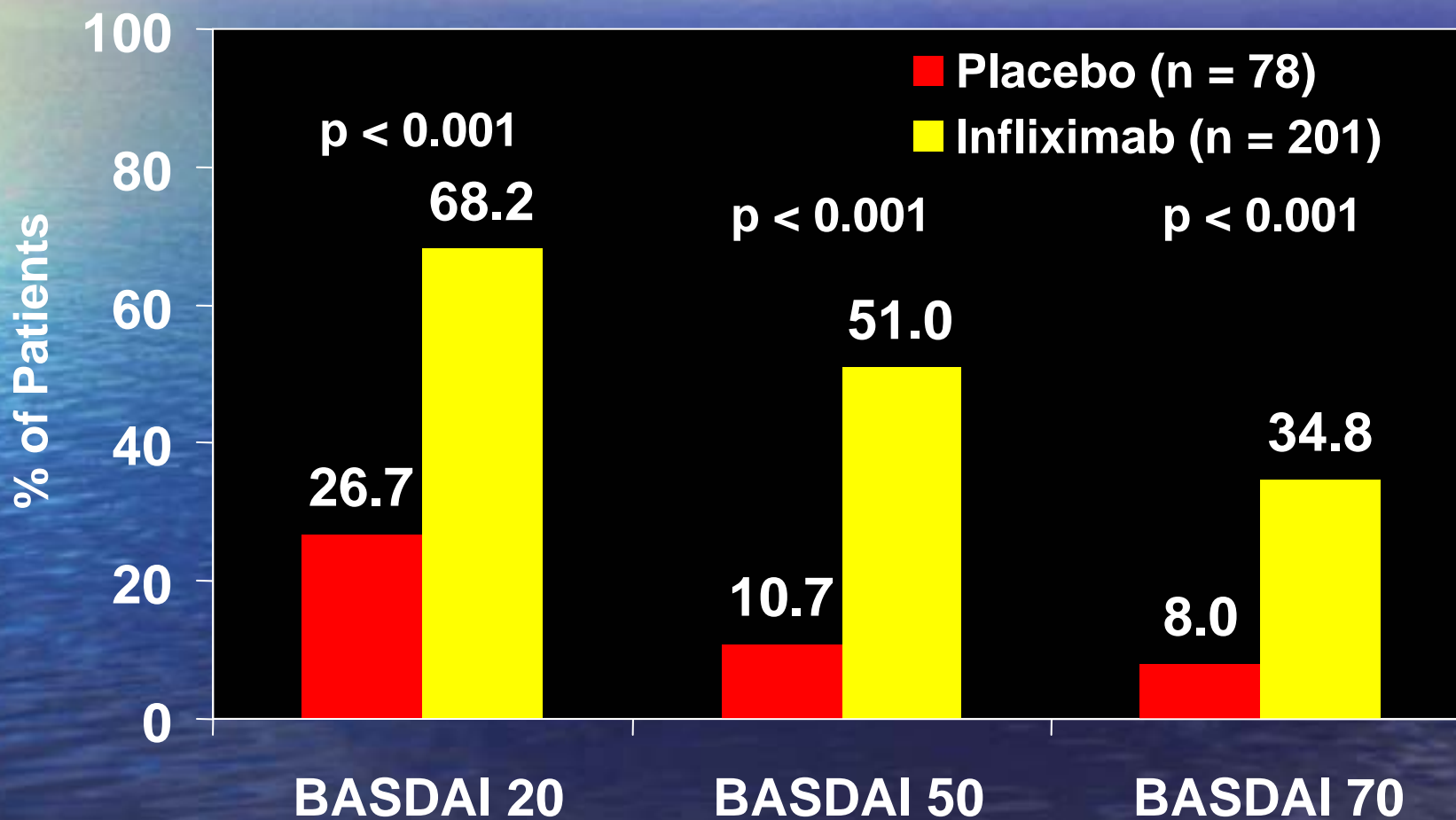
# AS: Burden of Disease

- Rates of pain and disability are similar to those in RA<sup>1</sup>
- U.S. prevalence is estimated to be >300,000<sup>2</sup>
- Diagnosis may be delayed for up to 10 years after onset<sup>3</sup>
- Spinal damage is cumulative, irreversible, and independent of symptoms<sup>4</sup>
- Most patients who progress to fusion had severely restricted spines within the first 10 years<sup>5</sup>

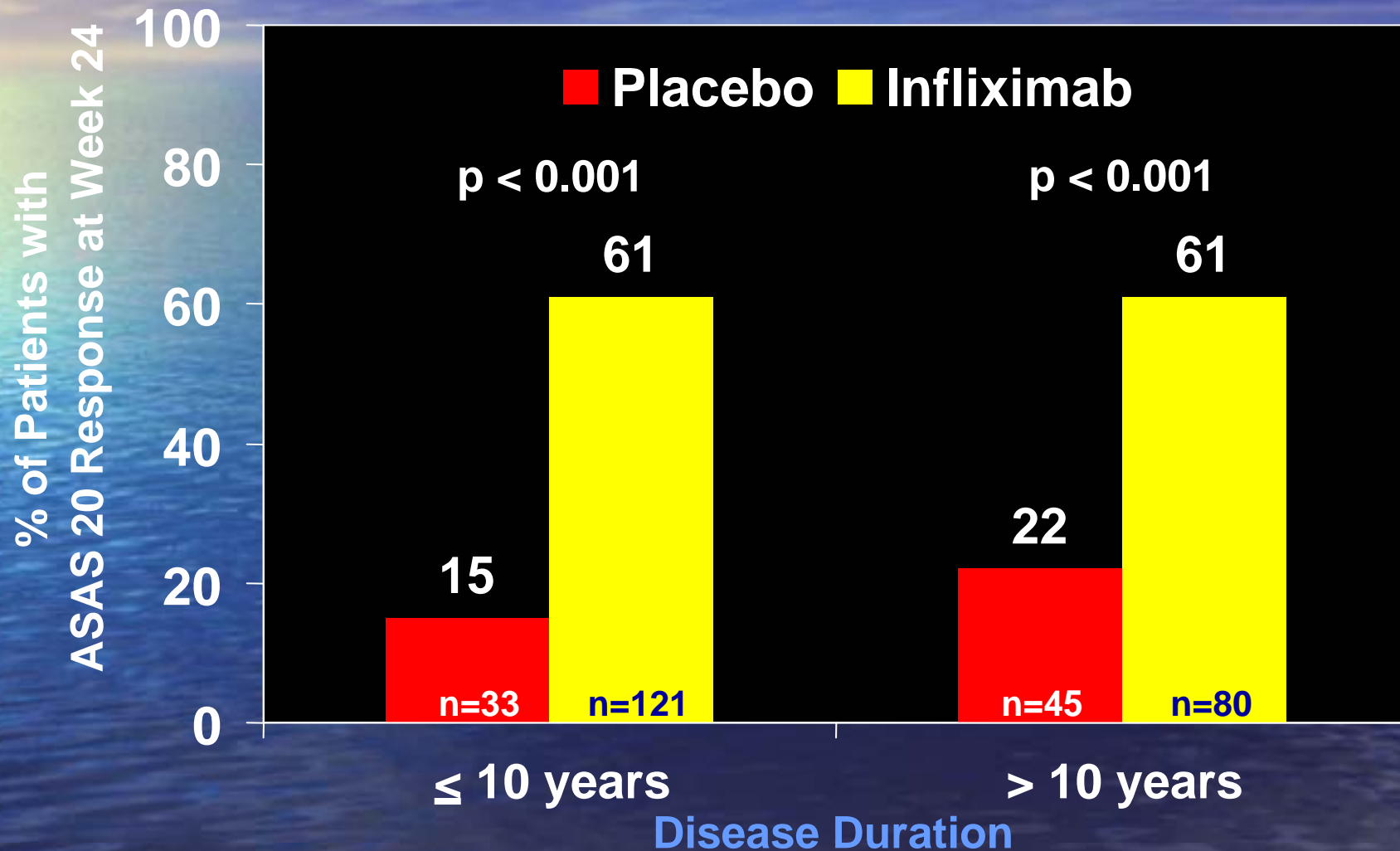
**References:** 1. Gorman JD, et al. *N Engl J Med.* 2002;346:1349-1356. 2. Spondylitis Association of America. Available at: <http://www.spondylitis.org/html/htmlpages.asp?load=whatisas.htm>. 3. Spondylitis Association of America. October 22, 2002. 4. Brophy S, et al. *J Rheumatol.* 2002;29:1236-1243. 5. Sieper J, et al. *Ann Rheum Dis.* 2002;61(suppl III):iii8-iii18.

# Proportion of Patients Achieving BASDAI 20, 50, and 70 Response

Week 24



# ASSERT Subgroup Analysis: Primary Endpoint by Disease Duration

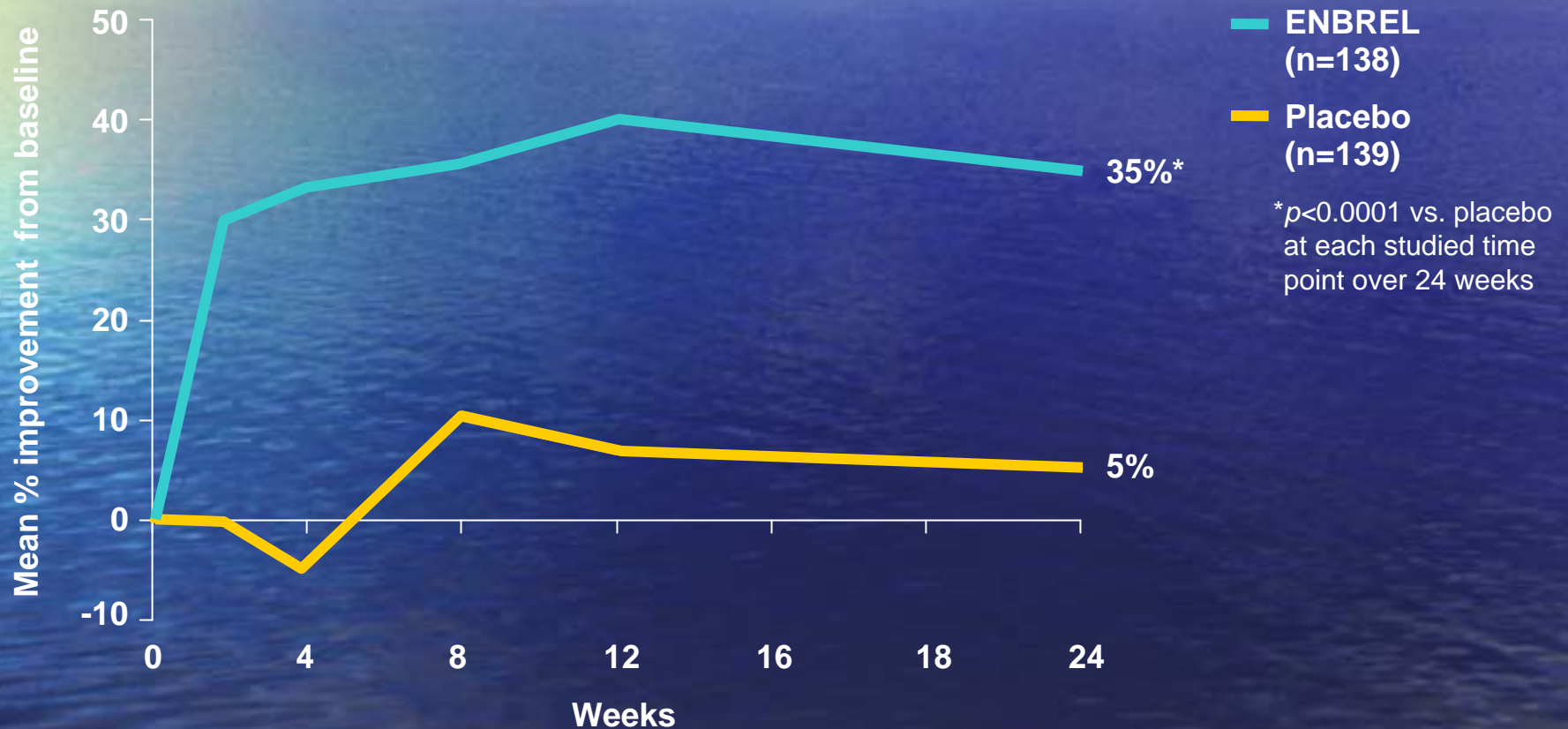


Prespecified Subgroup Analysis

EULAR 2004 Abstract: SAT0051

# Significant Improvement in Axial Pain With ENBREL<sup>1</sup>

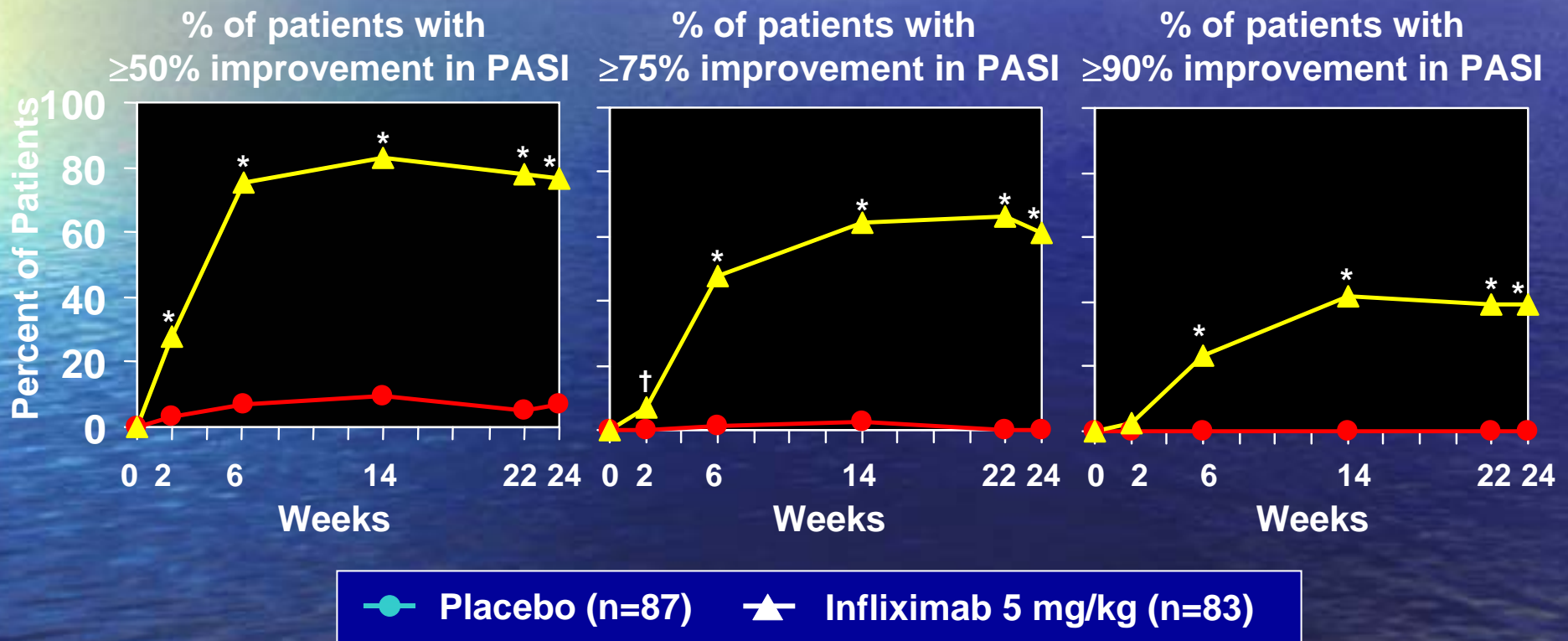
Improvement in Average of Nocturnal and Total Back Pain Scores



Reference: 1. Data on file, Amgen, Thousand Oaks, Calif.

IMPACT 2

# PASI Response Through Week 24



\*  $p < 0.001$   
†  $p = 0.011$

# Global Phase 3 Study: Patient 3066<sup>1</sup>



PASI Score	31.6	5.7	1.3	0.6
PASI % Improvement		82	96	98

Patient was initially treated with Enbrel® (etanercept) 50 mg twice weekly and was stepped down to 50 mg weekly (25 mg BIW) at 3 months.

<sup>1</sup>Data on file, Amgen, Thousand Oaks, Calif.

# Safety Issues

- Administration reactions
- Oppportunistic infections (TB)
- Infections
- Malignancies
- Demyelination
- Hematologic abnormalities
- Hepatotoxicity
- Congestive heart failure

# Administration reactions

- For injectables: hive or redness at site of injection (or past injections) usually occurs the first two months then decreases. Risk about 25%
- For infusions: headache, BP variations, rash most common (10%) rare to see fever, chills, chest pain, SOB

# Infections

- Increased risk of all infections – about 32% risk without TNF blocker and 35% with TNF blocker
- Risk of serious infection – about 3% without TNF blocker and 5% with TNF blocker
- STOP TNF blocker at any signs of infection and restart only when infection cleared. Avoid TNF blocker in any patients with chronic infection (eg, osteomyelitis, bronchiectasis)

# TB and TNF Blockers

- Not initially detected in clinical trials
- Reactivation of latent TB
- Higher incidence in Europe
- >50% extra-pulmonary sites
- Possibly higher incidence with MAb blockers
- Usually occurs within first 6 months of therapy
- Now screen all patients with PPD (> 5mm considered positive) prior to initiation of therapy
- Consider CXR in area with fungal disease

# TB and TNF blockers

- Recent new cases of TB in patients initially PPD negative on TNF blockers – usually high risk patients – endemic area, travel etc.
- ?? Annual PPD in patients on TNF blockers

# MALIGNANCY AND TNF BLOCKERS

	• SEER	Observed
• Placebo	• 5.0	5.0
• Infliximab	• 30.1	27

# Lymphomas and TNF Blockers

- Between 5-26-fold increase in lymphomas in RA patients
- Although observed lymphomas increased in patients on TNF blockers, data is compared to SEER which is normal patients
- Observed lymphomas 2.56-5.66 fold increase

# CANCER and TNF blockers

- Bottom line: patient with active malignancy should NOT receive TNF blocker (consider rituximab) until malignancy cured
- Patients with lymphomas should not be retreated with TNF blocker even after remission of lymphoma (consider rituximab)

# Hematologic abnormalities with TNF blockers

	• Placebo	Infliximab
• Anemia	• 3.3%	3.8%
• Leukopenia	• 1.0	1.4
• Neutropenia	• 0.4	1.0
• Thrombocytopenia	• 0.4	0.9
• pancytopenia	• 0.1	0.1

# Hepatotoxicity with TNF blockers

- 34 cases out of 575,000 treated patients
- 3 cases required liver transplant and all on other hepatotoxic drugs and all received no more than 5 doses of TNF agent
- 2 deaths – 1 with significant EtOH intake and 1 elderly woman with severe CHF and elevated LFTs

# NEUROLOGIC COMPLICATIONS

- Previous TNF receptor blocker (lenercept) associated with worsening of MS in MS patients
- Rare case reports of CNS demyelinating disorders with TNF blockers

# CHF and TNF blockers

- Studies with TNF blockers in NYHA functional class III/IV CHF patients demonstrated no improvement of worsening of CHF with TNF blockers
- Post-marketing data has shown some cases of increased CHF with TNF blockers
- Should not use TNF blockers in patients with severe CHF

# ANA/DIL and TNF blockers

- 10-12% with TNF blockers
- More likely in patients receiving intermittent therapy
- Lower incidence if on concomitant immunosuppressive
- Those with ANA more likely to have infusion reactions
- Rare case of Drug-induced lupus (DIL) seen which resolved with steroids and discontinuation of drug

# VACCINATIONS

- IMPORTANT FOR PATIENTS TO BE CURRENT ON FLU AND PNEUMOVAX VACCINATIONS
- AVOID LIVE VIRUS VACCINATIONS SUCH AS SHINGLES VACCINE

# PERIOPERATIVE MANAGEMENT

- General recommendation has been to hold the TNF blocker one week prior to surgery and the week of surgery if injectable and at least two weeks prior to surgery and one week after surgery if infusion
- Recent data suggests that holding TNF blockers for one month decreases incidence of peri-operative infections to normal (no matter the half-life of the agent)

# OTHER USES FOR TNF BLOCKER THERAPY

- DEFINITE: INFLAMMATORY BOWEL/PSORIASIS
  - ❖ DISEASE (MAb BETTER THAN RECEPTOR)
- PROBABLY: UVEITIS/IRITIS
- BEHCET'S DISEASE
- POSSIBLE: SARCOIDOSIS
- SJOGREN'S SYNDROME
- WEGENER'S GRANULOMATOSIS

# Rituximab

- FDA approved for B cell lymphomas 1997
- FDA approved for RA 2006
- Clinical trials in progress for SLE, myositis, ANCA vasculitis and multiple sclerosis
- Administered two doses two weeks apart then none for 4-12 months (until disease reactivates)

# Side effects of Rituximab

- Similar risk of infection with TNF blockers
- BUT no risk of TB or opportunistic infection EXCEPT two SLE patients and about 20 lymphoma patients (no RA patients reported) and one SLE patient with soft tissue infection with histoplasmosis

# Side Effects of Rituximab

- About 25 cases of PML (JC virus) reported in Imphoma and 2 cases in SLE patients who have received rituximab
- Possible long-term IG depletion

# Side effects of Rituximab

- Infusion reactions similar to infliximab – do NOT see reactions as seen in lymphoma patients (probably due to tumor burden)
- Do not see worsening of CHF, DIL, malignancy increase or neurologic symptoms

# Side effects of Abatacept

- Similar risk of infections, including Tb and opportunistic infections as with TNF blockers
- Increased risk of infections in patients with severe COPD
- ? Increased risk of Lung cancer in COPD patients
- Similar risks of infusion reactions

# New therapies

- Tocilizimab (IL6 RA)
  - Expected to be released in the near future
  - Infusion reactions similar to other biologic agents
  - Increased LFTs (transient)
  - Increased apolipoproteins (but some data to suggest decreased CV events)
  - Neutropenia

# New therapies

- Newer TNF blockers to be released
  - Certolizimab will not cross placenta so should be safe in pregnancy
  - Golimumab will be monthly injection