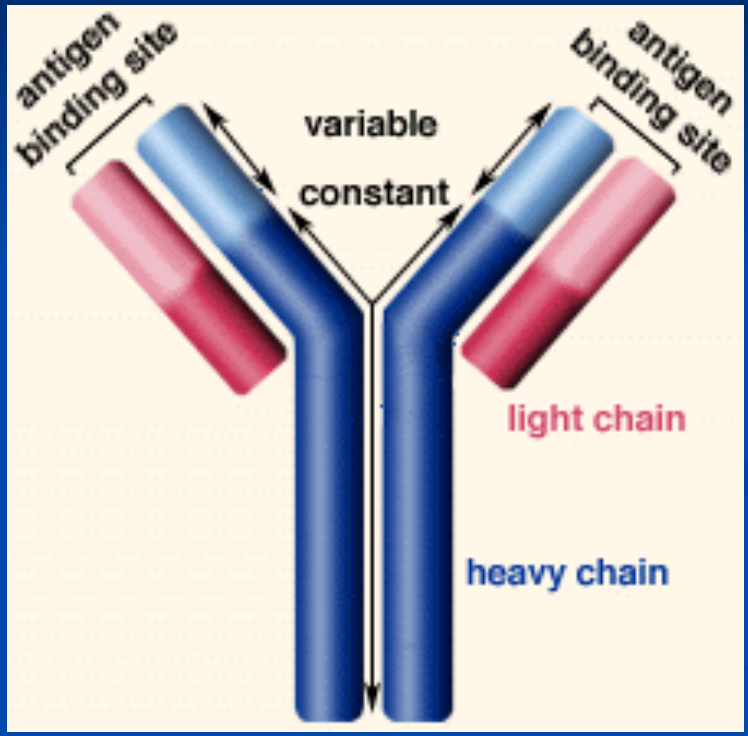
Biologics in Psoriasis

What is a BIOLOGIC?

Biologics

- Biologics are engineered proteins that are used to MODIFY immune reactions; target specific
  - E.g. antibodies, fusion proteins, cytokines
- Nomenclature
  - Chimeric monoclonal Ab end in "XIMAB"
  - Humanized monoclonals end in "ZUMAB"
  - Fully human monoclonals end in "UMAB"
  - Receptors end in "CEPT"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Psoriasis

- Chronic, immune mediated disease that affects skin and joints
- Initial source for activation unclear, but…
  - Activated T-cells found in psoriatic skin
  - TNF-alpha higher in lesional skin than normal

Biologic Therapy in Psoriasis

- It is a chronic disease
  - biologics seem to have long-term efficacy with few side effects
    - PUVA, methotrexate, and cyclosporine all carry significant long-term risks
- Psoriasis is due to a specific set of T-cell problems
  - can be specifically targeted

Biologic Therapy in Psoriasis

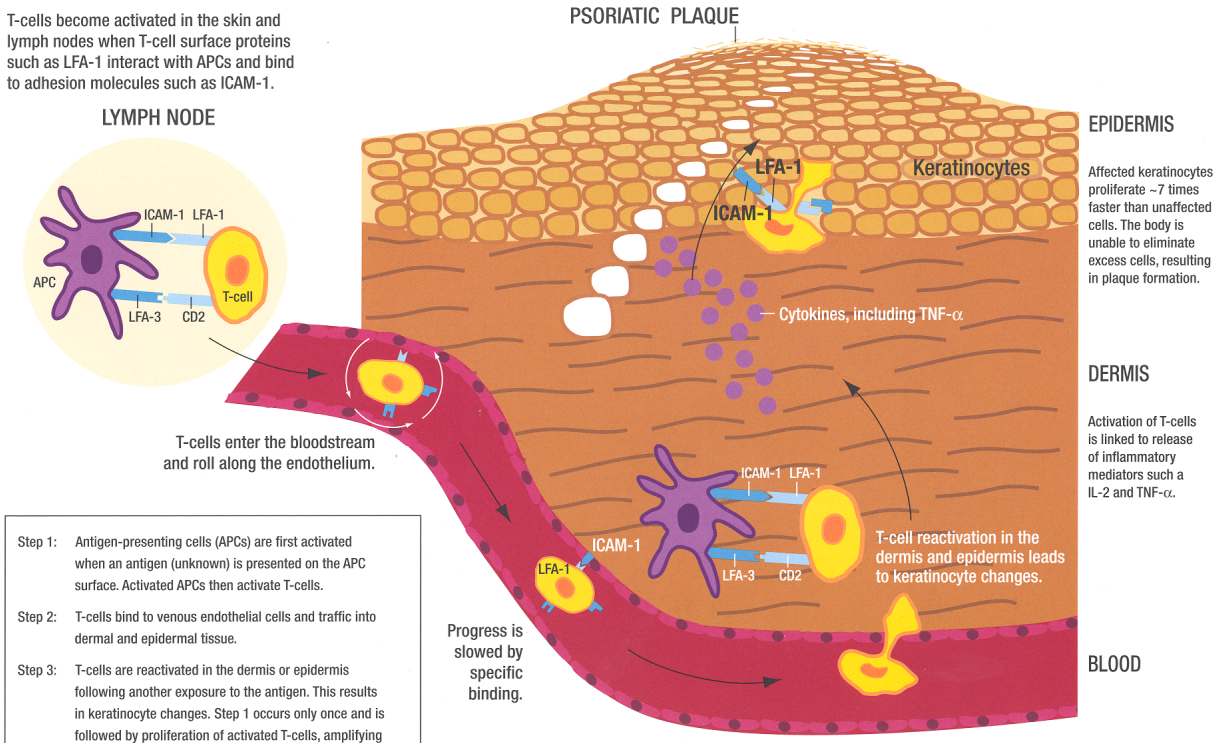
- Psoriasis is a widespread disease
  - systemic therapy often needed
  - quality of life scales indicate patient's frustration with current treatments options
  - biologics may be considered "convenient"

Biologic Therapy in Psoriasis

- Four approaches to drug mechanisms:
  - 1. Block cytokines
  - 2. Inhibit T-cell activation
  - 3. Reduce the number of pathogenic T-cells
  - 4. Promote immune “deviation”

Key steps in psoriasis pathogenesis

T-cells become activated in the skin and lymph nodes when T-cell surface proteins such as LFA-1 interact with APCs and bind to adhesion molecules such as ICAM-1.



Affected keratinocytes proliferate ~7 times faster than unaffected cells. The body is unable to eliminate excess cells, resulting in plaque formation.

Activation of T-cells is linked to release of inflammatory mediators such a IL-2 and TNF-α.

Step 1:	Antigen-presenting cells (APCs) are first activated when an antigen (unknown) is presented on the APC surface. Activated APCs then activate T-cells.
Step 2:	T-cells bind to venous endothelial cells and traffic into dermal and epidermal tissue.
Step 3:	T-cells are reactivated in the dermis or epidermis following another exposure to the antigen. This results in keratinocyte changes. Step 1 occurs only once and is followed by proliferation of activated T-cells, amplifying the process. Steps 2 and 3 occur over and over, causing the cyclic persistence of the disease.

Genentech

Biologics Research: background

- Study design
  - *After* extensive animal testing, drug companies petition the FDA for approval to begin human trials
    - Phase 1: Safety testing. Healthy volunteers are used to evaluate how the drug is absorbed, metabolized, & excreted. Small number of subjects (n= 20-100).
    - Phase 2: Efficacy testing. The drug is compared to a placebo in affected patients. Ideally, the study is blinded. Larger number of subjects (n= hundreds).

Biologics Research: background

- Study design
  - Human trials
    - Phase 3: Large scale evaluation over many years. Many patients are evaluated to have a better understanding of effectiveness and adverse events (n= thousands).
      - Once completed, may apply for FDA approval
    - Phase 4: Post-marketing. Drug comparison studies and long-term efficacy are evaluated.

Biologics Research: background

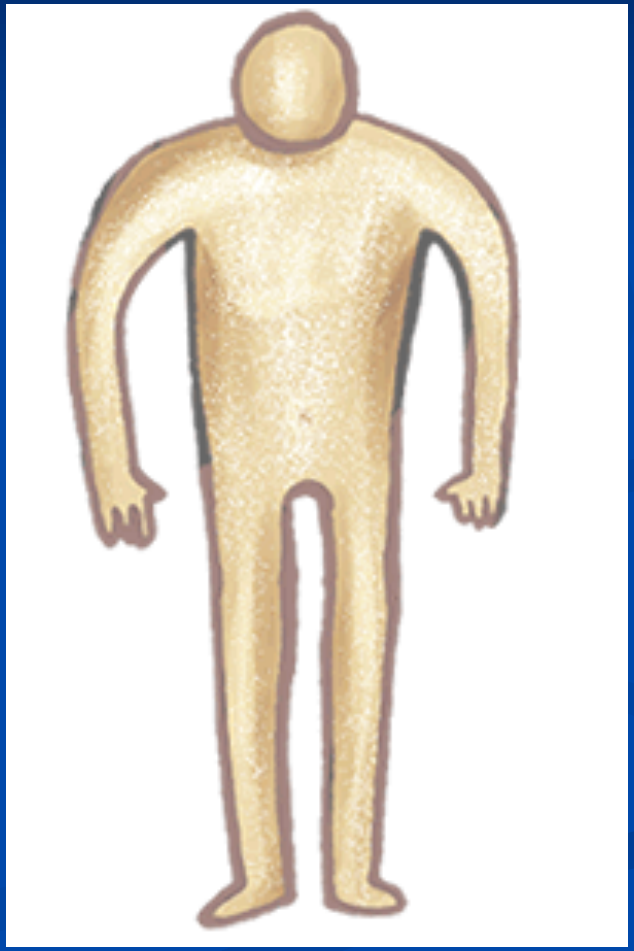
- PASI = Psoriasis Area and Severity Index
  - A tool used in research to quantify extent of disease
  - Calculated before, during, and after treatment

Biologics Research: background

- PASI
  - Components:
    - Area and severity scores are assigned for each body SECTION. Sections include legs, arms, trunk, and head.
    - **Area:** estimate a percentage of that section that is covered
    - **Severity**: based on itching, redness, scaling, and thickness

Biologics Research: background

- PASI
  - Scoring:
    - mathematical formula is used to weight the importance of each involved section
    - the final PASI score is between 0 (no psoriasis) and 96 (full body erythroderma).



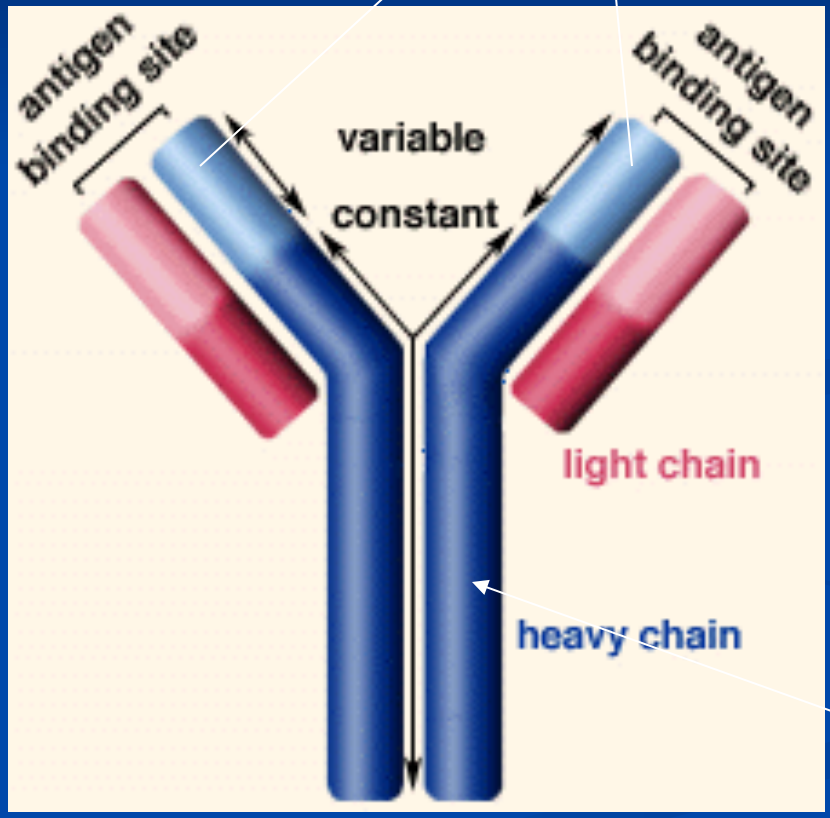
TNF-Alpha

- Inflammatory cytokine representative of TH1 response
- Exists in a soluble form (in blood) and a bound form (on membranes of activated T-cells)
- Effects:
  - Recruits other inflammatory cells
  - Amplifies production of IL-1, IL-6, IL-8
  - Increases keratinocyte proliferation and decreases apoptosis
  - Induces production of VEGF
  - Destroys cartilage and bone

Infliximab (Remicade)

- Mechanism
  - Chimeric antibody to TNF-alpha
    - MOUSE antigen binding region bound to HUMAN IgG constant region
  - One molecule infliximab binds to two TNFs
  - It can bind to soluble *and* bound TNF
    - Infliximab induces apoptosis of the cells with bound-TNF
      - May explain greater effect of this medication compared to other anti-TNF

Mouse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Human

Infliximab (Remicade)

- How it is used:
  - FDA approved for rheumatoid arthritis and Crohn's disease
  - 3-5 mg/kg IV infusion over 2-3 hours
    - Given at weeks 0, 2, 6 and then every 8 weeks (optimal?)
  - Pregnancy category B

Infliximab (Remicade)

- Results
  - PASI 75:
    - appr. 80% of patients after week 10
  - Onset: fast
  - Maintenance: unclear at this point
    - after 26 weeks, greater than half of patients were still at PASI 50
  - Cost: about $22,000 per year for drug alone

Infliximab (Remicade)

- Side effects
  - Infusion rxns
  - Infection
  - Antibody formation
  - SLE-like rxn
  - Demyelinating disease
  - CHF
  - Hepatic toxicity **

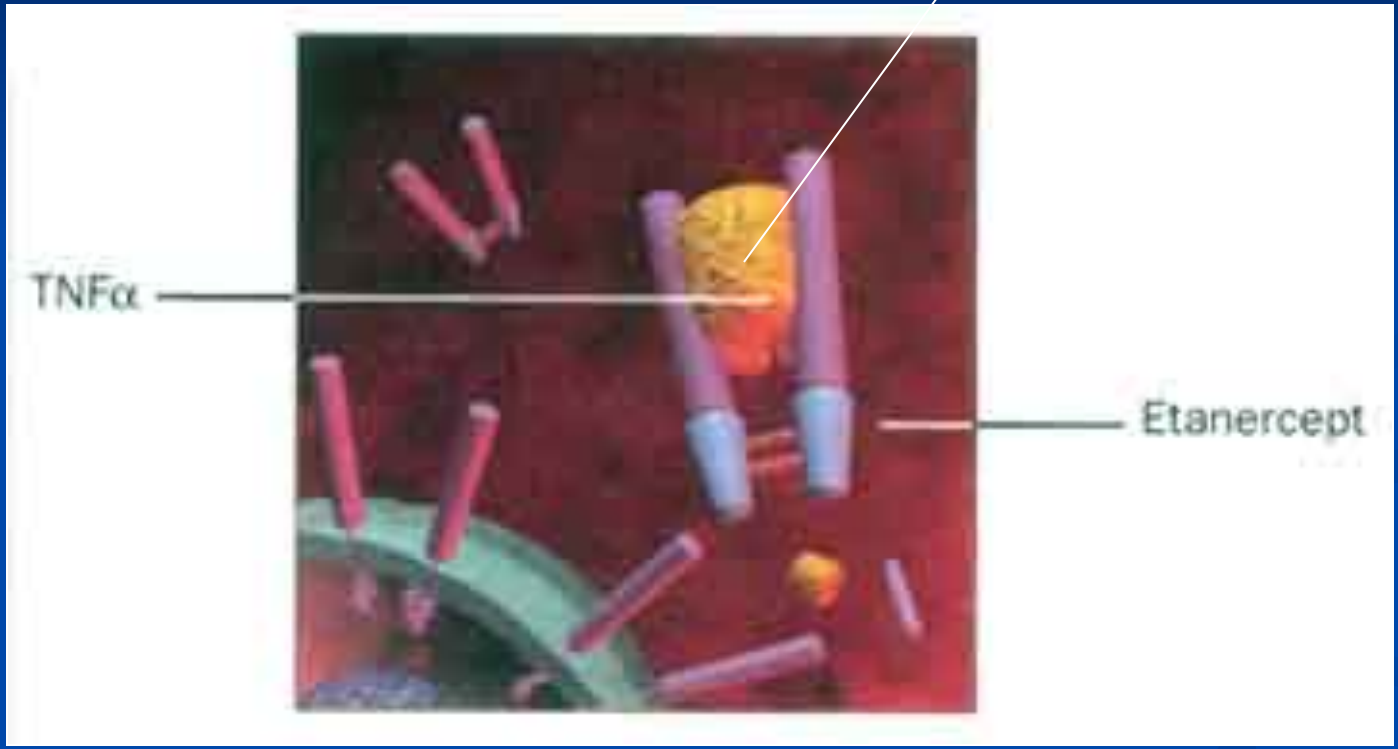
Infliximab (Remicade)

- Monitoring guidelines
  - Pre-treatment
    - TB test *required*; infection warning
    - Evaluate for demyelinating disease
    - Evaluate for CHF
  - On-going
    - Lymphoma risk

Etanercept (Enbrel)

- Mechanism
  - Fully human TNF antibody receptor
  - One etanercept molecule binds one TNF
  - Only binds to the soluble TNF
    - Prevents it from ever getting to cell-surface receptors

One binding site, soluble TNF only



Etanercept (Enbrel)

- How it is used:
  - Psoriatic arthritis
    - 25 mg sc injection BIW
  - Psoriasis
    - 50 mg sc injection BIW for 3 months, then decrease to 25 mg BIW
  - Pregnancy category B

patient may opt to treat once per week instead

Etanercept (Enbrel)

- Results
  - PASI 75:
    - 49% of the 50 BIW and 34% of the 25 BIW at week 12
  - Onset: changes noted by week 2
  - Maintenance: will relapse within 2-3 months; no rebound
  - Cost: about $14,000 for the 25 BIW and $28,000 for 50 BIW

Etanercept (Enbrel)

- Side effects
  - Injection site reaction
  - Pancytopenia
  - CHF
  - Infection
  - Malignancy
  - Demyelinating

Etanercept (Enbrel)

- Monitoring guidelines
- Pre-treatment
  - None required by FDA
  - Caution in person with CHF, demyelinating disorder
  - Consider:
    - PPD, +/- chest XRay
    - CBC
- On-going
  - Consider CBC for pancytopenia

Adalimumab (Humira)

- Mechanism
  - Fully human monoclonal antibody to TNF-alpha
  - Blocks TNF interaction with p55 and p75 cell surface receptors
  - Lyses cells expressing TNF

Adalimumab (Humira)

- How it is used:
  - 40 mg SC injection weekly or every other week
    - Studies on-going
  - Pregnancy category: hasn't been tested

Adalimumab (Humira)

- Results
  - PASI 75:
    - 80% at week 12 in the weekly group
    - 43% at week 12 in the every other week
  - Onset: relatively fast
  - Maintenance: on-going
  - Cost:

Adalimumab (Humira)

- Side effects
  - Injection site reactions
  - Infection?
  - Lymphoma?
  - Demyelinating disease?
- Monitoring guidelines
  - Pretreatment ppd

Efalizumab (Raptiva)

- Mechanism
  - Humanized monoclonal antibody to CD11a of LFA1
  - Works in two ways:
    - Interferes with T-cell activation
    - Interrupts T-cell trafficking to the skin

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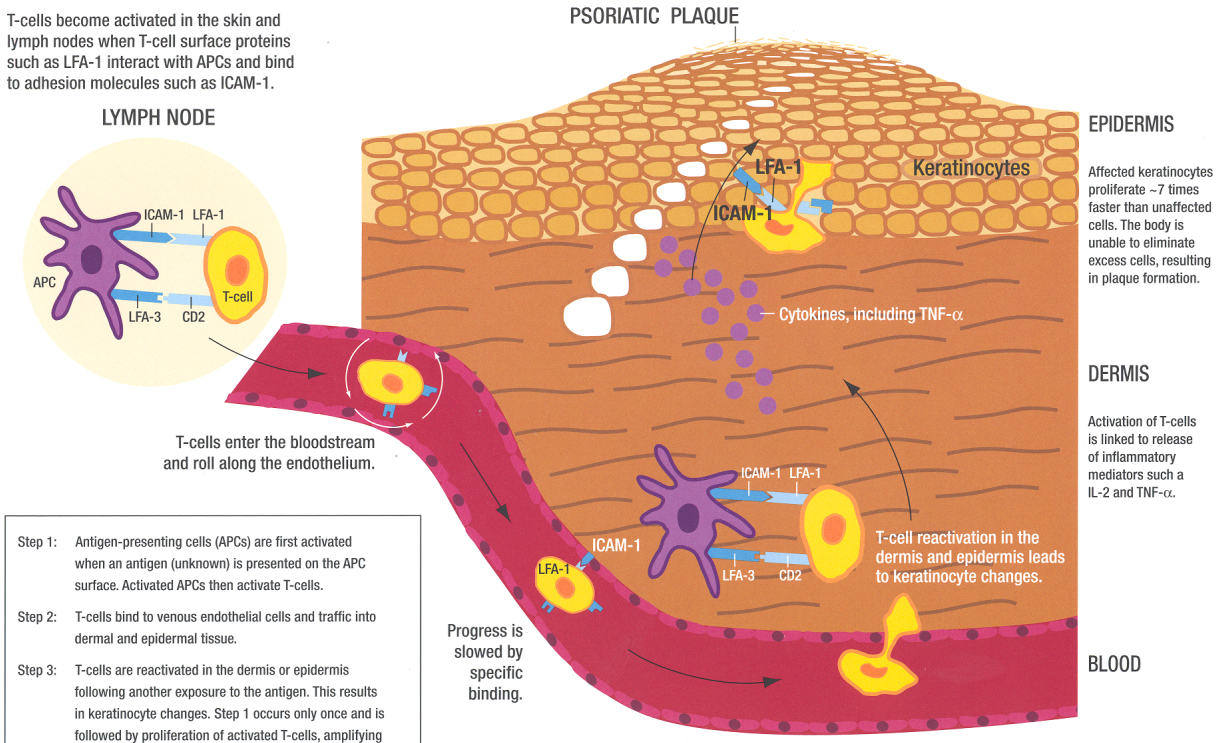

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Genentech

Efalizumab (Raptiva)

- How it is used:
  - 1mg/kg sc injection weekly
    - "Conditioning dose" of 0.7mg/kg for first week
  - Pregnancy category C

Efalizumab (Raptiva)

- Results
  - PASI 75:
    - Approx. 30% at 12 weeks, improving with cont therapy
  - Onset: improvements by 2 weeks
    - May be most rapid, after infliximab
  - Maintenance: long-term data is promising
    - Rebound v. relapse
  - Cost: $16-18,000 per year

Efalizumab (Raptiva)

- Side Effects
  - Flu-like symptoms
  - Thrombocytopenia
  - (Artificial) Lymphocytosis
  - Rebound (>125% of original or new form)
  - No evidence of serious infection or malignancy
- Monitoring guidelines
  - Check platelets monthly for 3 months, then additionally every 3 months

Alefecept (Amevive)

- Mechanism
  - Fully human protein of LFA3
  - Binds to CD2
    - Blocks T-cell activation at LFA3 site
    - Induces apoptosis of NK cells via FcG portion

Alefecept (Amevive)

- How it is used:
  - 15 mg IM injection weekly for 12 weeks
    - IM found to be comparable to IV data
  - Repeated after 12 week interval
  - Pregnancy category B
    - amevive has a pregnancy registration protocol

Alefecept (Amevive)

- Results
  - PASI 75:
    - Maximum benefit 6-8 weeks after course of treatment
    - 20-30% achieve PASI 75
  - Onset:
    - Slow. Maximum benefit at 18 weeks into therapy; may have greater benefit with subsequent courses
  - Maintenance:
    - Only biologic that may be remittive. Patient may not need retreatment for 7-8 months! Results even better after 2 courses.
  - Cost: $6600 for 12 week course (expect twice per year)

Alefecept (Amevive)

- Side effects
  - Chills/flu-like
  - Decrease in CD4 count
  - *No* increased infection or malignancy rate noted
- Monitoring guidelines
  - Check CD4 weekly
    - Hold if CD4<250; resume next week and count as total
    - D/C if CD4<250 on 4 consecutive occasions

Comparisons: Efficacy

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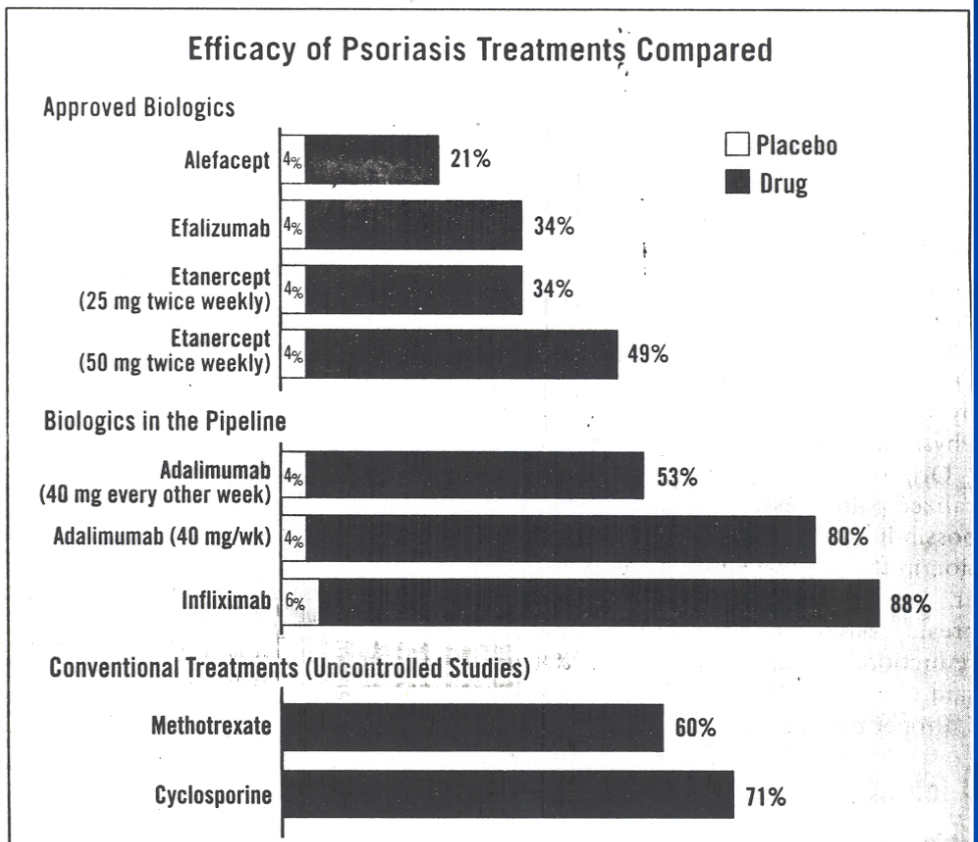

Comparisons: Annual Price

- Infliximab: $ 22,000
- Etanercept: $28,000
- Efalizumab: $18,000
- Alefecept: $13,000
- Adalimumab: ?
- Cyclosporine: $7200
- Methotrexate: $1100
- Acitretin: $4800

Note: prices do not include administration fees, office visit, or labs

Conclusion

- The biologics are a new and exciting field for the treatment of psoriasis
  - Long term treatment, fewer(?) side effects
- They carry their own risks that must be considered
  - Platelets, CD4 counts, antibody formation, infection, malignancy risk, etc…
- They carry a LARGE price tag!!!

References

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