Biologics in Rheumatoid arthritis...
Where are we 15 years later?

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Disclosures

• None
Objectives

• Disease of target
• What makes up a biologic
• Who are these drugs
• How do they work/ how are they used
• Safety
• Tidbits
Disease of Target

• Rheumatoid arthritis
  – First series of classic RA patients around 1800 by a French medical student Augustin-Jacob Landre-Beauvais in his doctoral thesis
  – The term “Rheumatoid Arthritis” introduced around 1859 by Gerrod
  – Many hypotheses, the new world, sugar, periodontal disease, infection, etc.

From: *The Rheumatologist, September 2012*
Why Did Rheumatoid Arthritis Begin in 1800?
by Richard S. Panush, MD
RA

• It is a disease much beyond the mechanical aspect of fixing damaged joints
• -Chronic systemic inflammation
  – Repercussions to the cardiovascular system
  – Incidence of malignancies particularly leukemias and lymphomas
• Direct effects to the vascular, cutaneous, ocular, cardiac, pulmonary, and so on
RA-Immunology

- In RA immune complexes produced by synovial lining cells and inflamed blood vessels
- Plasma cells produce antibodies such as RF and CCP that contribute to the complexes but destructive disease can occur in their absence
- Macrophages then migrate to the affected synovium mostly around vessel inflammation increasing macrophage-derived lining cells
- Lymphocytes particularly the CD4+T cells infiltrate the synovium as well
- Activated T-cells produce a variety of cytokines that promote B cell proliferation and differentiation
  - Leading to antibody-forming cells promoting local B-cell stimulation
- Both the macrophages and the lymphocytes start making pro-inflammatory cytokines and chemokines (tumor necrosis factors [TNF], granulocyte-macrophage colony-stimulating factor [GM-CSF], various ILs, interferon-γ
  - This is what likely leads to the systemic and local inflammatory response
RA- Immunology

• The synovium is normally quite thin, but with chronic disease this will proliferate with villous projections (pannus)
• The synovial lining cells produce collagenase and stromelysin
  – Contributing to cartilage destruction
• IL-1 and TNF-α stimulate the pannus to form more collagenase:
  • Cartilage destruction
• IL-1 and TNF-α together with IL-6
  • Osteoclast-mediated bone absorption and demineralization
    – Prostaglandins produced by fibroblasts and macrophages
  • Will also lead to demineralization
**Figure 1** Stepwise development of arthritis in RA

Burmester, G. R. *et al.* (2013) Emerging cell and cytokine targets in rheumatoid arthritis

Previous therapeutics

• NSAIDs/ ASA

• Gold

• Orals
  – Methotrexate, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine, mycophenolate, leflunomide

  – Getting better
Biologics!
Biologics

- Genetically engineered products from human genes that guide the production of immune products in non-human cell cultures (made in large quantities through a multi-stage process) to produce a drug that will act in the body as part of the immune system
- = tricking the immune system
Biologics

**Anti-TNF**
- Etanercept (Enbrel)
- Infliximab (Remicade)
- Adalimumab (Humira)
- Golimumab (Simponi)
- Certolizumab pegol (Cimzia)

**IL-6**
- Tocilizumab (Actemra)

**IL-1**
- Anakinra (Kineret)

**T-cell**
- Abatacept (Orencia)

**B-Cell**
- Rituximab (Rituxan)
What’s in a name?

• The endings in the names can tell you a lot...

  – “cept” = fusion of a receptor to the Fc portion of human IgG1
  – “mab” = monoclonal antibody
  – “ximab” = chimeric monoclonal antibody
  – “zumab” = humanized monoclonal antibody
Etanercept (Enbrel)

- Approved for RA in 1998
- Is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1
- Inhibits binding of both TNF-α and TNF-β receptors rendering TNF inactive
- Can also modulate the biological responses to TNF including expression of adhesion molecules responsible for leukocyte migration (I-CAM, IL-6) and serum levels of matrix metalloproteinase-3
Etanercept (Enbrel)

- Given as a SQ injection once a week
Adalimumumab (Humira)

- Approved in 2002 for RA
- Produced by recombinant DNA technology in a mammalian cell expression system
- A recombinant human IgG1 monoclonal antibody specific for TNF
- Binds specifically to TNF-α and blocks interaction with p55 and p75 surface receptors
- It also lyses surface TNF expressing cells in vitro in the presence of complement
- Does not bind or inactivate TNF-β
Adalimumab (Humira)

- SQ injection every other week
- In combination with methotrexate mean steady-state trough concentrations were 8-9µg/mL compared to 5 with adalimumab alone
- Can be increased to once a week in patients not on MTX
Infliximab (Remicade)

- Approved for RA in 1999
- Is a chimeric IgG1κ monoclonal antibody (composed of human constant and murine variable regions) specific for human tumor necrosis factor-alpha (TNFα)
- Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors
Infliximab (Remicade)

- Given as an IV infusion
- Takes about 2 hours
- For RA given in loading dose of 3mg/kg at week 0, 2, 6, then every 8 weeks for maintenance
- Dose can be adjusted up to 10mg/kg and frequency up to every 4 weeks if needed
Golimumab (Simponi)

- Approved for RA in 2009
- A human IgG1κ monoclonal antibody specific for TNF-α that exhibits multiple glycoforms with molecular mass levels of approximately 150-151 kilodaltons
- It was created using transgenic technology, in which genetically engineered mice were immunized with human TNF-α, resulting in an antibody with human-derived variable and constant regions
- Binds to both the soluble and transmembrane bioactive forms of human TNF-α
Golimumab (Simponi)

- Given as a SQ injection every 4 weeks with methotrexate
Certolizumab Pegol (Cimzia)

- Approved for RA in May 2009
- Is a recombinant humanized antibody Fab1 fragment with specificity for human TNF-α conjugated to an approximately 40kDa polyethylene glycol.
- It binds to the TNF-α and selectively neutralizes it in a dose dependent manner without neutralizing TNF-β
- Incubation of monocytes with certolizumab pegol results in dose dependent inhibition of LPS-induced TNF-α and IL-1 β production in human monocytes
- Does not contain an Fc (fragment crystallizable) region which is normally present in a complete antibody therefore it does not fix complement or cause antibody-dependent cell-mediated cytotoxicity in vitro
  - No apoptosis in human peripheral blood-derived monocytes or lymphocytes and does not induce neutrophil degranulation
Certolizumab Pegol (Cimzia)

- Dosing is 400 mg loading at weeks 0, 2, and 4, followed by 200 mg every 2 weeks or 400 mg every 4 weeks
- Given SQ by pre-filled 200mg syringe or in-office administration of reconstituted lyophilized powder
Abatacept (Orencia)

- Approved for RA in 2005-infusion 2011-inj
- Fusion protein that consists of a soluble extracellular domain of human cytotoxic T lymphocyte associated antigen 4 (CTLA-4) linked to modified Fc portion of human immunoglobulin G1
- Selective costimulation modulator; inhibits T cell activation by binding to CD80 and CD86 blocking interaction with CD28
  - Decreases T cell proliferation and inhibits production of TNF-α, IFN gamma, IL-2, RF, CRP
Abatacept (Orencia)

- Given IV as a ~30 minute infusion at week 0, 2, 4 then every 4 weeks
  - Weight based dosing 500mg (<60 kg), 750mg (60-100kg), or 1000mg (>100kg)
- Or given in a weekly SQ injection 125mg
  - Injection may be given with or without an IV loading dose (weight based one day before first SQ injection)
Rituximab (Rituxan)

- Approved for RA in combination with MTX in 2006
- Chimeric murine/human monoclonal IgG1κ antibody directed against CD20 antigen
- Fab domain of rituximab binds specifically to CD20 antigen on B lymphocytes, and Fc domain recruits immune effector functions to mediate B cell lysis (pre-B and mature B cell lymphocytes)
- B cells are implicated in production of TNF, IL-6 and IL-2
Rituximab (Rituxan)

- Given as an infusion with methotrexate 1000mg 2 weeks apart every 4-6 months
- Recommended to pre-medicate with glucocorticoids, acetaminophen and an antihistamine
- May take up to 6 hours for infusion
Tocilizumab (Actemra)

- Approved for RA in 2010, inj in 2013
- Humanized anti-human IL-6 receptor antibody
- Binds specifically to both soluble & membrane bound IL-6 receptors and inhibits IL-6 mediated signaling through these receptors
Tocilizumab (Actemra)

- Both preparations given with or w/o MTX
- Given IV 4mg/kg every 4 weeks, and may be increased to 8mg/kg every 4 weeks
  - Takes about and hour
- Or given SQ 162mg every other week if less than 100kg with titration to every week if needed, and weekly to start if over 100kg
Anakinra (Kineret)

- Recombinant IL-1 receptor antagonist that blocks the biologic activity of both IL-1α and IL-1β
- Competitively inhibits IL-1 binding to the IL-1 type 1 receptor (IL-1R1)
- It blocks the IL-1 receptor without removing endogenous IL-1 from the circulation
- Given as a daily SQ injection
Safety

- Serious infection
- Opportunistic infections
- Malignancy
- PML
- Heart Failure
- Other
The Disease is not benign...

- Joint pain
- Joint destruction → Deformity → Disability
- Malignancy
- Extra-articular manifestations
  - Vascular/Cutaneous
  - Ocular
  - Cardiovascular
  - Pulmonary
## Serious infections Events

*(per product inserts)*

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<tr>
<td>Certolizumab pegol</td>
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RA and Serious Infections

• The best predictors for serious infections was not the DMARDs but:
  – RA duration and severity
  – Extra-articular manifestations
  – Leukopenia
  – Skin infections
  – Corticosteroid usage
  – Joint surgery
  – Comorbid diseases

Opportunistic Infections

- TB
- Non-TB Mycoplasma
- Fungal
- Viral - hepatitis, shingles
Opportunistic Infections

• 70 Randomized placebo controlled trials with biologics in RA patients
  – Highest Concern:
    • Mycobacterial (OR, 3.73; 95% CI, 1.72-8.13; I²=0)
    • Viral (OR, 1.91; 95% CI, 1.02-3.58; I²=0)
  – Less concerning were actually
    • Fungal infections (OR, 1.31; 95% CI, 0.46-3.72)
    • Invasive fungal infections (OR, 2.85; 95% CI, 0.68-11.91)
    • Pneumocystis jirovecii pneumonia (OR, 1.77; 95% CI 0.42-7.47)
    • Varicella-zoster virus (OR, 1.51; 95% CI 0.71-3.22)
TB

- Screen all patients with rheumatoid arthritis starting biologics regardless of risk
- Not only screening for active TB, but latent TB infection also poses a concern for re-activation
- Tuberculin skin test or interferon-γ-release assays are both appropriate however the IGRA is preferred in patients with previous BCG vaccination due to risk of false positive with TST
- If positive result, then appropriate imaging is necessary
- Cultures and referral to specialist may be next step if abnormal imaging
TB

- Latent TB
  - May start biologic as long as patient is on treatment for the latent TB, many providers choose to wait for one month
- Active TB
  - Treatment may commence once the patient has completed treatment
- Recommend screening patients annually for any individual at risk
- As patients with RA may be immunocompromised, if there is any clinical suspicion with negative testing either with the TST or the IGRA, may consider repeating testing in 1-3 weeks to ensure result
Mycobacterial

- Non-TB mycobacterial infections are often one of the more significant concerns in regards to opportunistic infection
- Even with treatment, may not be able to fully eradicate non-TB mycobacterial infections, best not to start anti-TNF agents
Fungal

• Rare

• No general screening recommendations
  – Consider patient risk prior to initiation
    • Do they live in an endemic region

• If at risk patient on biologic with undiagnosed systemic illness, consider empiric antifungal treatment while evaluating
  – Delay in treatment may lead to severe and deadly complications
Hepatitis

• Hepatitis C – mostly case reports with the use of biologics in regards to safety
  – Risk and benefit have to be weighed, re-activation
  – ACR 2012 RA guidelines recommend etanercept as first line biologic agent

• Hepatitis B
  – Untreated Hep B- biologics not recommended
  – Currently treated or resolved Hep B - Risk and benefit has to be weighed
    • Still not recommended for Child-Pugh class B and higher
Malignancy in RA

- Meta analysis of 21 publications in standardized incidence ratios of RA
  - RA patients have approximately a two-fold increase in lymphoma risk (SIR 2.08, 95% confidence interval [CI] 1.80 to 2.39)
  - Greater risk of Hodgkin than non-Hodgkin lymphoma
  - Lung cancer was also increased with an SIR of 1.63 (95% CI 1.43 to 1.87)

Malignancy

• In general we don’t really know what the biologics pose in regards to risk of malignancies (solid tumors or NMSK within the past 5 years)

• Cases of melanoma and non-melanoma skin cancer have been reported with the anti-TNFs
  – Generally not recommended for patients with melanoma history

• For patients who have a history of solid tumor or NMSC within the past 5 years, hx lymphoproliferative malignancy, or tx melanoma the ACR 2012 guidelines suggest Rituximab

• Others you will have to weight the risk and benefit
PML

• Progressive multifocal leukoencephalopathy (PML) is a rare, typically fatal, opportunistic infection caused by the JC virus
• Although very rare, there is no real known prevention, treatment or cure which make it particularly devastating
• At risk conditions include HIV/AIDS, cancer and organ transplant patient
• Of the 15 patients on biologics, 14 had received RTX (6 of which had previously been on anti-TNF), one had been on anti-TNF and concomitant CYC
• It is listed as a warning on rituximab package insert

Heart Failure

• Due to potential for anti-TNFs to instigate CHF, ACR 2012 RA tx guidelines recommend
  – Not using an anti-TNF biologic in RA patients with CHF that is New York Heart Association (NYHA) class III or IV and who have an ejection fraction of 50% or less

• Patients very sensitive to fluid shifts, a consideration will have to be given to the fluid given with IV biologics as well
Vaccination

• Patients on immunosuppressives such as anti-TNFs are considered to be with “altered immunocompetence”

• Lives are a No

• Inactive are a yes (although Rituximab suggests even getting inactive vaccines performed 4 weeks prior to initiation)
Live vs. inactive vaccines

• Live Vaccines = No
  – Yellow fever, BCG, rubella, polio, cholera, typhoid, and varicella, MMR, BCG, polio, smallpox, anthrax

• Inactive Vaccines = Yes
  – Flu (IM not nasal), Typhoid, Tetanus/diphtheria/pertussis, pneumococcal, HPV, hepatitis B, hepatitis A, HIB, meningococcus, rabies
Herpes Zoster

• Due to increased incidence of HZ in RA patients particularly on immunosuppressives/biologics probably a good idea to immunize those eligible for vaccine

• Good suggestion may be to wait 2 weeks after vaccine before starting biologic
Tidbits

• No head to head trials for anti-TNFs that reveals one is better than another in RA
• No one drug/biologic class is better than another in RA, it just may be better for each specific patient
• New pharmaceuticals open a world of new opportunities in the treatment of RA today
• Our goal is no longer to improve quality of life, but to put the disease into remission
References

• The Rheumatologist, September 2012 Why Did Rheumatoid Arthritis Begin in 1800? by Richard S. Panush, MD


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