Novel Biologic Therapies for Rheumatic Diseases: An Overview

Jonathan Graf, MD
Professor of Clinical Medicine, UCSF
Division of Rheumatology San Francisco General Hospital
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Proliferation of Medications

• Explosion of new therapies have come to market in past decade

• Majority of these are in subspecialty areas:
  – Oncology
  – ID (HIV, Hepatitis C, etc...)
  – Immuno-therapeutics (Rheumatology, GI, Neurology, etc...)

• How do those in general medicine fields keep up to date?

“One thing we rabbits know how to Do is multiply....”
Growing List of FDA approved Biologics for Rheumatic Diseases

Rheumatoid Arthritis: Anti-TNFs
Etanercept 1998
Infliximab 1999
Adalimumab 2002
Certolizumab 2009
Golimumab 2009

SLE: Belimumab (anti-BLyS) 2011
ANCA vaculitis: Rituximab 2012
Psoriatic arthritis: Ustekinumab (anti iL-12/23) 2013
Periodic fever syndromes: CAPS, Muckle Wells, NOMID
Canakinumab (anti-iL1) 2009
Rilonacept (iL-1 TRAP) 2008

RA: Abatacept (CTLA4 Ig) 2005
RA: Tocilizumab (anti-iL6R) 2010
RA: Rituximab: depleting B cell Antibody 2006
RA: Anakinra: iL1-RA 2001
Importance of Understanding Biologics

• Their number has grown

• The number of indications for their use has grown
  – Anti-TNF therapies: rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, inflammatory bowel disease, juvenile idiopathic arthritis, and others)

• They are now being used by patients with chronic disease
  – Patients you will see in practice over many years (unlike oncology patients)

• They are $$$$ expensive. One medication (adalimumab/Humira) is the #1 selling drug worldwide by sales since 2012
Overview of Today’s Talk

• Anti-TNF therapy in detail
  – Most commonly used in practice

• When anti-TNF therapy for RA fails
  – Anti-IL6 directed therapy (although there are other options)
  – Use this as example to show how indications are likely to increase beyond RA for biologics like this
  – Segue into discussion below:

• New small molecule “biological response modifiers”

• A lot of long-worded medications that sound alike: “imabs, umabs.” Don’t fret – discuss general principles
Biologic Therapies

• What is meant by the term “Biologic Therapy”?

• Double meaning:
  – Large complex organic products (mostly but not necessarily proteins) synthesized by living cells
  – Target a gene or protein and modify biologic responses
    • Antibody-antigen interactions
    • Cytokine-receptor interactions (both ends)
    • Cell signaling proteins, inhibitors, or ligands
## Conventional vs. Biological Medication Comparison

<table>
<thead>
<tr>
<th>Conventional Medications</th>
<th>Biological Medications</th>
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<tr>
<td>• Small molecules</td>
<td>• Larger complex molecules</td>
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<tr>
<td>• Usually inorganic</td>
<td>• Often organic: usually peptides/proteins</td>
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<tr>
<td>• Synthesized and purified chemically from inorganic reactions</td>
<td>• Encoded genetically, transcribed, translated, and then post translationally modified by living cells</td>
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<td>• Structures can be identified = easily manufacture generic</td>
<td>• Often can be difficult to identify full structure of complex molecules that biologically constructed modified by cells</td>
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Families of biological medications for rheumatic diseases

- **Anti-cytokine therapies**
  - Block pro-inflammatory cytokines from binding their receptors
  - Anti-TNF, anti-IL6, anti-IL1, anti-IL 12/23, anti-IL 17

- **Cell-oriented therapies**
  - Removal of or prevent activation and/or proliferation of cells implicated in disease
  - Rituximab (B-cells), abatacept (T-cells)
Anti-cytokine therapies

- Pro-inflammatory cytokines bind to receptors on cells and mediate inflammatory responses from those cells

- Blockade of following cytokines significantly ameliorates these diseases
  - TNFa: RA, Psoriatic arthritis (PsA), psoriasis, ankylosing spondylitis, juv. arthritis, IBD
  - IL 17: Psoriasis and PsA
  - IL 12/23: Psoriasis and PsA
  - IL 6: RA, gout
  - IL 1: periodic fevers (gout)

McInnes et al. JCI 2008
Biological therapy for rheumatoid arthritis

- Approaching two decades of experience with first class of biological medications (anti-TNF medications)

- Data have shown significant benefits not only in treating disease-associated symptoms

- Significant prevention of joint erosion, narrowing, and ultimately disability
Benefits of adding an anti-TNF medication to conventional therapy with methotrexate
Biologic therapies for rheumatoid arthritis

• Anti-Tnf medications (5 total)
  – Etanercept (TNF decoy receptor fusion protein)
  – Infliximab, Adalimumab, certolizumab, golimumab
    (variations of anti-TNF antibodies or fragments)

• B-cell depleting agents
  – Rituximab

• T-cell costimulation inhibitors (receptor-ligand)
  – Abatacept

• Inhibitors of IL-6 signaling
  – Tocilizumab (anti IL-6 receptor antibody)

• IL-1 Inhibitors (IL-1 cytokine receptor decoy)
  – Anakinra
Biologic therapies for rheumatoid arthritis

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Where does it come from?

- TNF genes located on chromosome 6 (MHC)
- Primarily Macrophage and Monocyte derived
- Some also produced in T Cells and Synoviocytes
Natural Biological Effects of TNF

Release of TNF-α

- Membrane bound TNF-α
- Cleavage by specific metalloproteinases
- Immunologically active?
- Immunologically active, free TNF-α

Activated macrophage

- Proinflammatory cytokine release (including IL-1, IL-6, IL-23, and GM-CSF)
- Chemokine release (including RANTES, MCP-1, IL-8, and SDF-1)
- Leukocyte accumulation
- Endothelial cell activation
- Upregulation of E-selectin and VCAM-1
- Leukocyte accumulation
- Induction/maintenance of HLA class II expression
- Angiogenesis
- Osteoclast activation
- Bone resorption
- Chondrocyte activation
- Metalloproteinase production
- Cartilage destruction
- PGE₂ production
- Hepcidin induction
- Acute-phase response

McInnes et al. JCI 2008
TNF Effects: Good and the Bad

**GOOD**

- TNF-alpha regulates biological functions necessary for normal inflammatory, immune, and tumor surveillance responses.
  - TNF-alpha absolutely essential for granulomatous host defenses against intracellular bacteria (MTb, fungal infections, listeria)
  - Explains infection-related toxicity profile of these medications

**BAD**

- TNF-a binds membrane-bound TNF receptors and mediates pro-inflammatory processes implicated in inflammatory arthritis.
Anti-TNF Family

Anti-Tnf medications

- Etanercept (TNF receptor fusion protein)
- Infliximab (anti-TNF antibody)
- Adalimumab (anti-TNF antibody)
- Certolizumab pegol (anti-TNF Fab-PEG)
- Golimumab (anti-TNF antibody)
Anti-TNF medications

Etanercept

Most of other anti-TNF monoclonal Abs
Practical issues to consider in patients on long term anti-TNFs: Pharmacokinetics...

- Anti-TNF medications have long half lives

- This is important for duration of the biologic effect

- Also important in case someone develops a side effect or infection while on one of these medicines
  - Etanercept 4.25 days
  - Infliximab 8-12 days
  - Adalimumab 14 days

- Many patients, especially those on IV therapy, (infliximab, rituxan, etc…) may not mention to their MD that they are on therapy
Contraindications

• History of latent tuberculosis unless/until they have completed an adequate courses of prophylactic therapy (Duration up for debate)

• Active acute or chronic infections (HCV exception)

• Active or suspected malignancies.

• Anti-TNFs are generally contraindicated in patients with moderate or severe congestive heart failure (some have black box warning)

• History of demyelinating disease
Initiating Anti-TNF Therapy

• Asses Latent TB status at baseline
  – PPD or interferon release assay
  – Follow up CXR if necessary (I recommend CXRs on all high risk patients)

• Initiate treatment for LTBI if necessary (I recommend holding therapy in high risk patients until they have completed a significant amount of their regimen)

• Other intracellular organisms with latent infection:
  – Consider coccidiomycosis and histoplasmosis in endemic regions before prescribing (should weigh into decision of risks/benefits)

• Age appropriate cancer screening - good idea
Initiating and monitoring therapy

• Screening for active infections by history in all patients on active therapy
  – Hepatitis B (will be discussed shortly)

• If patients are being treated in our office, screen for illness (history, temperature and blood pressure) before infusions or injections
  – Counsel patients to do the same if being treated at home and hold doses if ill. If truly sick – seek MD attention

• Recommended NOT to receive live vaccines within two weeks of initiating therapy
  – CDC does recommend zoster vaccine prior to starting therapy
Anti-TNFs: Adverse Events

• Most common: Injection site reactions
  – Tend to wane over time and with use

• Most serious: Increased risk of infections! (OR of 2.0 for serious infection in large meta analysis published in JAMA 2006)
  – Most common URIs
  – Problematic: mTB and other intracellular organisms for which TNF is necessary for immune containment

• Increased malignancy risk: Controversial

• May worsen symptoms of congestive heart failure.
Infliximab and TB


56% Extra Pulmonary TB
24% Disseminated disease
Patients don’t make granulomas (atypical appearance)
Average onset 12 weeks after initiation (3-4th dose)
Specifcics: Hepatitis B

• Patients with chronic hepatitis B infections are at risk for re-activation and liver injury

• Risk is highest for those who are hepatitis B surface antigen positive and/or DNA positive

• Risk is lowest for those who are surface antigen negative and surface antibody positive
Hepatitis B Recommendations:

• We screen all patients for HBV serologies

• Follow LFTs in “carriers” who are Hep B Core Ab+, even if also SAb+. Ensure viral load undetectable

• Avoid anti-TNF therapy in patients who have chronic active infection (Hep B Sag+) unless:

  • If use anti-TNFs in Hep B Sag+ patients:
    – we initiate anti-Hep B therapy (RT inhibitors)
    – Follow Hep B DNA PCR for log changes in viral copies
Specifics: Anti-TNFs and Malignancy

- Large meta-analysis suggested an OR 3.3 for all malignancies in patients using anti-TNF, especially “high doses.” (Bongartz et al., JAMA 2006)

- Longitudinal analysis of 20,000 patients from the National Databank of Rheumatic Diseases found no increased risk of lymphoma compared to general population or those with RA (Wolfe et al., A&R 2007)

- Two studies published in 2011 (including large Danish registry) corroborate lack of evidence linking cancer to anti-TNF therapy in adult RA patients

- Possible evidence of increased risk of non-melanoma skin cancer
When patients fail anti-TNF therapy…

• Up to 30% of patients fail to respond or lose response to anti-TNF therapy

• Additional patients are intolerant or have contraindication to anti-TNF therapy

• There are now many other biologic therapies available
When Patients fail anti-TNF therapy:

B-cell depleting agents
   Rituximab

T-cell costimulation inhibitors (receptor-ligand)
   Abatacept

Inhibitors of Il-6 signaling
   Tocilizumab (anti Il-6 receptor antibody)

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Interleukin-6 Biology

• Cytokine with pleiotropic effects

• Secreted by activated T-cells and macrophages

• Triggers acute phase inflammatory response
  – Fever, acute phase proteins, host defense against pathogens, tumor surveillance

• Basal IL-6 secretion also required for normal homeostatic functions
  – hematopoiesis
  – regenerative processes (liver)
  – neural development
IL-6 is an important cytokine.
Measuring the Acute Phase Response Directly

INFLAMMATION

Anti-Inflammatory Cytokines
IL-1  IL-6  TNF

Positive Acute Phase Reactants
Fibrinogen  Serum amyloid A

Liver

C-reactive protein

Source: Adv Neonatal Care © 2003 W. B. Saunders
IL-6 Signaling

• Most cells do NOT express an IL6 receptor

• Rather, the IL6 receptor is secreted and soluble

• Unlike soluble TNF receptor (of which etanercept is based), sIL6-R is NOT an antagonist/anti-inflammatory; it potentiates the IL6 signal
How IL6 transmits its signal
Tocilizumab

- Antibody that binds to the iL6 receptor and prevents IL6/IL6R complex from forming
Tocilizumab very effective in treating RA

Genovese et al. Arth Rheum 2008
Blocking IL6: predictable biology of inhibiting the acute phase response

Genovese et al. Arth Rheum 2008
Tocilizumab: Predictable (and not so predictable side effects)

- 34% of patients had significant drop in neutrophil counts
- Significantly higher percentage of patients on tocilizumab has transaminase elevations
- 23% patients on tocilizumab vs. 4% controls had fasting total cholesterol >240 (increases in LDL and HDL)
- Infections more common in tocilizumab vs. placebo
- Unusual side effect: intestinal perforations have led to caution with use in patients susceptible to diverticulitis
7 patients with refractory large vessel vasculitis (including GCA, TA) despite trials of other corticosteroid sparing agents

All patients responded after 8-12 weeks of therapy and remained in clinical remission on therapy

All patients tapered their prednisone dose from mean 20 mg/day to <6 mg/day

One patient died of preoperative MI and on autopsy was found to have ongoing vasculitis despite being “in clinical remission”
Cytokine Signaling through Kinases

Cytokine: eg. TNF/IL6

Kinases

Current Biologic Therapies

Transcription

Biologic Effect:
- Proliferation
- Activation
- Cytokine production
Oral Small Molecule Inhibitors

• Not proteins but are small molecules

• Taken orally and can act intracellularly

• “Biologic-like” effects by blocking downstream events initiated by cytokine-receptor engagement

• Emerging term: “Biologic response modifiers”
  – Not organic, complex macromolecules but have similar effects to biological molecules
Cytokine Signaling through Kinases

Current Biologic Therapies

Cytokine: eg. TNF/IL6

Kinases

New Kinase Inhibitors
IL-6 and other cytokines signal through JAK upon binding their receptors
• 40% of MTX naïve patients with active RA achieved a 70% response on Tofacitinib 10 mg vs. 10% on MTX.

• Predictable adverse events similar to anti-iL6 therapy
  - Liver, neutropenia, lipids, infections, etc.
  - Caution that JAK signaling more widespread than for IL6 alone
Pipeline of Oral Small Molecule Inhibitors

• Tofacitinib (JAK 1/3 kinase inhibitor)
  – Rheumatoid Arthritis (FDA approved 2012; Failed twice to get approval in Europe)

• Apremilast (Phosphodiesterase 4 inhibitor)
  – Psoriatic Arthritis (FDA approved 2014)

• In development
  – Syk kinase inhibitors
  – CSF1-receptor (c-FMS) inhibitors
Summary

• Biological medications and non-biological therapies with biologic-like effects are increasingly used to treat a wide-variety of chronic diseases (RA, psoriasis, IBD, MS, etc...)

• Anti-Cytokine therapies are most prevalent

• Primary care providers should be aware of how to follow patients on these medicines
Multiplication!