Biological Agents for Rheumatic Diseases: A Primary Care Primer 2019

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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?

Growing List of FDA approved Biologics for Rheumatic Diseases

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

Importance of Understanding Biologics

• Their number has grown
• The number of indications for their use has grown
  – Anti-TNF therapies: rheumatoid arthritis, psoriatic arthritis, spondylarthropathies, 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 molecules (usually proteins or protein-based) that are 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

Conventional medications
- Small molecules
- Usually simple chemical structure
- Synthesized and purified from simple chemical reaction in lab
- Structures can be identified = easily manufacture generic

Biological medications
- Larger complex molecules
- Larger complex macromolecules: usually peptides/proteins
- Encoded genetically, transcribed, translated, and then posttranslationally modified by living cells
- Often can be difficult to identify full structure of complex molecules that biologically constructed modified by cells

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:
  - TNFα: RA, Psoriatic arthritis (PsA), psoriasis, ankylosing spondylitis, sju. arthritis, IBD
  - IL 17: Psoriasis and PsA
  - IL 12/23: Psoriasis and PsA
  - IL 6: RA, giant cell arteritis
  - 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

Biologic therapies for rheumatoid arthritis

- Anti-Tnf medications (5 total + new “biosimilars”)
  - Etanercept (TNF decoy receptor fusion protein)
  - Infliximab, Adalimumab, certolizumab, golimumab (variations of anti-TNF antibodies or fragments)
  - Biosimilars
- B-cell depleting agents
  - Rituximab
- T-cell costimulation inhibitors (receptor-ligand)
  - Abatacept
- Inhibitors of IL-6 signaling
  - Tocilizumab and others (anti IL-6 receptor antibody)
- IL-1 Inhibitors (interfere with IL-1 activity)
  - Anakinra, Canakinumab, and others

Benefits of adding an anti-TNF medication to conventional therapy with methotrexate

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)
  - Biosimilars (new)

- Because of structural & manufacturing complexities, these biological products are considered as similar, but not generic equivalents of parent biologics

- FDA definition: Highly similar to the reference product without clinically meaningful differences in safety, purity and potency

- Somewhat more streamlined process of providing analytical, pharmakokenetic/dynamic, and toxicity data

- Extrapolation allowed

FDA approved biosimilars as of 11/17

Tumor Necrosis Factor-a

- 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

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-alpha 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)
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- Golimumab (anti-TNF antibody)

Anti-TNF medications
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, (infiximab, 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

- Assess 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
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)

Specifics: 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
Question

You are caring for a 52 YO female with a history of RA and progressive interstitial lung disease for which she is currently receiving treatment with methotrexate 20 mg/week and prednisone 30 mg/day. Her rheumatologist would like to switch her from methotrexate to an anti-TNF therapy in a few weeks and is requesting that you make sure her vaccinations are up to date. All of the following would be acceptable EXCEPT:

A. Injectable influenza vaccine
B. Herpes zoster vaccine
C. PCV-13 conjugated pneumococcal vaccination
D. Pneumococcal 23-valent polysaccharide vaccine

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Specifics: Vaccination

- Yearly vaccination with influenza vaccine strongly recommended
- Vaccination with pneumococcal vaccines (PCV-13 conjugate and pneumococcal 23-polyvalent) strongly recommended per CDC schedule
- Recommended NOT to receive live, attenuated vaccines during therapy within two weeks of initiating therapy (ACR)
  - Zoster vaccine is recommended at least 2 weeks prior to starting therapy (Age >50).
  - OK with modest level immune suppression (conventional DMARDs like MTX and prednisone doses <20 mg/day)
  - Shingrix vaccine: Under CDC review until better efficacy data published (1/2018)

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 (Wolle 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)

IL-1 Inhibitors (IL-1 cytokine receptor decoy)
Anakinra

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

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IL-6 is an important cytokine

**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

Blocking IL6: predictable biology of inhibiting the acute phase response

Tocilizumab very effective in treating RA

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
GiACTA Tocilizumab (TCZ) vs. placebo for GCA

Cytokine Signaling through Kinases

Current Biologic Therapies

Cytokine: e.g. TNF/IL6

Kinases

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
IL-6 and other cytokines signal through JAK upon binding their receptors

Overview of cytokine signaling through Jak and selective inhibition by JAKi’s

- Pan selective JAKi’s have advantage of knocking down multiple cytokine pathways vs more selective JAKi’s or single anti-cytokine therapy (eg. Anti-TNF)
- Also come with risk of inhibiting important constitutive functions (JAK2 and hematopoiesis)


Pipeline of Oral Small Molecule Inhibitors

- Tofacitinib (PAN JAKi: JAK 1/3 >2 kinase inhibitor)
  - Rheumatoid Arthritis (FDA approved 2012; Failed twice to get approval in Europe until 2017)
  - Now also approved for psoriatic arthritis and ulcerative colitis (2018)
  - Potential future indications: psoriasis, atopic dermatitis, and alopecia areata

- Baricitinib (Pan JAKi: JAK 1/2 kinase inhibitor)
  - FDA approved for RA 2018*

- In development
  - Upadacitinib (JAK 1 selective: approval expected 2019)
  - Filgotinib (JAK 1 selective: approval expected in 2019-2020)


- 40% of MTX naive patients with active RA achieved a 70% response on Tofacitinib 10 mg vs. 10% on MTX.
- Predictable adverse events similar to anti-IL6 therapy
  - Gastroenteritis, headache, infections, etc.
  - Caution that JAK signaling more widespread than for IL6 alone
Baricitinib: RA-BEACON
Genovese et al. NEJM 2016
Active RA refractory to conventional DMARDs and biological DMARDs

Baricitinib: RA-Beam
Taylor et al. NEJM 2017
Active RA despite MTX: Comparing Baricitinib to Adalimumab and PBO

Baricitinib: A cautionary tale
FDA approval blocked 2017

Baricitinib: Analysis of VTE/PE events
6/997 patients: 4 mg @24 wk
0 PBO/2 mg @ 24 wk
Taylor et al. Arth & Rheum 2019 in press
FDA approves amended application for Baricitinib 2018

- FDA originally required new clinical safety trial but changed its mind and accepted amended application with additional secondary analyses of existing clinical trial data.
- Black box warning for serious infections and VTE/PE risk.
- Only 2 mg (low dose) approved in US. 2 & 4 mg doses already approved in Europe since 2017 and safety surveillance ongoing.
- Based upon additional data: Baricitinib should be used with caution in patients with risk factors for DVT/PE:
  - older age, obesity, a medical history of thrombosis, hypercoagulable state, recent surgery or immobilization.

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, but oral small molecule biologic response modifiers are increasingly making their way to market and into clinical practice.
- Primary care providers should be aware of how to follow patients on these medicines.

Multiplication!