Newer Medications in Rheumatology

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Mayo Clinic
April 9, 2016
Disclosures

• None
Outline

• Gout
• Rheumatoid arthritis
• Lupus
• Psoriatic arthritis/ankylosing spondyloarthritis
• Behcet's syndrome
• Repository corticotropin (ACTH analogue)
Gout

- Allopurinol - 1966
- Febuxostat – February 2009
- Pegloticase – September 2010
- Lesinurad – December 22, 2015
Gout: Febuxostat

• MOA: Xanthine oxidase inhibitor
• Administration: oral
• Dose: 40 or 80 mg daily
• Dose adjustments:
  • None for CrCl ≥ 30, Child-Pugh class A or B, or geriatric patients
• Potential toxicities: Elevated LFTs
• Side effects: Rash, nausea, arthralgias
• Use: *Failure or contraindication to allopurinol*

Gout: Pegloticase

• MOA: Uricase (uric acid → allantoin)
• Administration: IV
• Dose: 8mg q 2 weeks
• Dose adjustments: None for renal impairment or geriatric patients
• Pre-screen: G6PD deficiency (hemolysis and methemoglobinemia)

Sundy JS, et al. JAMA, 2011
Gout: Pegloticase

- Potential issues:
  - Immunogenicity
  - Infusion reactions (even with 1st dose)
  - Gout attack (75-80%) in 1st 3 months

- Requires SUA testing prior to every infusion
  - If SUA > 6 mg/dl...DO NOT GIVE

Sundy JS, et al. JAMA, 2011
Gout: Lesinurad

- MOA: URAT-1 inhibition
- Administration: oral
- Dose: 200 mg daily
- Concomitant XOI REQUIRED
- Dose adjustments:
  - Don’t give if CrCl <45ml/min or severe hepatic impairment
  - None for geriatrics
  - Not recommended if taking valproic acid

Gout: Lesinurad

• Potential toxicities:
  • Influenza (5%)
  • Headache (5%)
  • Elevated creatinine (4%)
  • Renal failure (1.2%)

• Ensure proper hydration: 2L/day
Rheumatoid arthritis

- Anti-TNF inhibitors
  - Etanercept – November 1998
  - Infliximab – November 1999
  - Adalimumab – December 2002
  - Certolizumab – October 2009
  - Golimumab – April 2009

- IL-1 inhibitor
  - Anakinra – November 2001
Rheumatoid arthritis

- T-cell co-stimulatory inhibition
  - Abatacept – December 2005
- B-cell targeting
  - Rituximab – February 2006
- IL-6 inhibition
  - Tocilizumab – January 2010
- JAK inhibition
  - Tofacitinib – November 2012
## RA: TNF-α Inhibitors

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chimeric anti-TNF-α mAb</td>
<td>Infliximab</td>
<td><img src="image" alt="Infliximab" /></td>
</tr>
<tr>
<td>TNF-receptor p75 IgG1 construct</td>
<td>Etanercept</td>
<td><img src="image" alt="Etanercept" /></td>
</tr>
<tr>
<td>PEGylated anti-TNF Fab</td>
<td>Certolizumab</td>
<td><img src="image" alt="Certolizumab" /></td>
</tr>
<tr>
<td>Fully human anti-TNF-α mAb</td>
<td>Adalimumab</td>
<td><img src="image" alt="Adalimumab" /></td>
</tr>
<tr>
<td></td>
<td>Golimumab</td>
<td><img src="image" alt="Golimumab" /></td>
</tr>
</tbody>
</table>

- Human
- Mouse
- Synthetic element
- Polyethylene glycol

RA: Abatacept

- MOA: CTLA-4 Ig to block activation of T-cells
- Administration: SC or IV
- Dosing schedule:
  - For IV: Wk 0,2,4 then every 4wk
  - For SC: 125 mg q7 days
- Dose adjustments: Weight based for IV
- Potential toxicity: COPD exacerbation
- Side effects: Nausea, headaches
RA: Abatacept
CTLA-4 Ig to Attenuate T-cell activation

- Similar efficacy to TNF-α inhibitors
RA: Rituximab

- MOA: B-cell depleter as an anti-CD20 chimeric mAb
- Administration: IV
- Dosing: 1000 mg IV day 0 and 14. q6 months.
- Dose adjustment: None
- Potential toxicity: Infusion reactions, PML
- Side effects: Numerous possible
- Efficacy similar to anti-TNF drugs in RA
RA: Rituximab

- In use for treatment of B cell lymphomas
- Rituximab reduces number of mature activated B cells (CD20-positive) but not memory B cells or plasma cells, so humoral immunity is not affected (fewer infections)
- Option for TNF failures
- *Patients with history of malignancies*
MOA: Rituximab
RA: Tocilizumab

- **MOA:** IL-6R inhibitor
- **Administration:** SC or IV
- **Dosing:**
  - For IV: 4mg/kg or 8mg/kg monthly
  - For SC: 162 mg q7 or q14 days
- **Potential toxicity:** GI perforation, neutropenia, elevated LFTs
- **Side effects:** Abd pain, HA, dizziness
Reducing pro-inflammatory cytokines
Tocilizumab – IL-6 Receptor mAb

Blockade of IL-6 signals by anti-IL-6 receptor antibody (MRA, Tocilizumab). h, human; IL, interleukin; sIL-6R, soluble interleukin-6 receptor.

Binds to both soluble and membrane-bound IL-6R
RA: Tofacitinib

• MOA: JAK1 and JAK3 inhibition
• Administration: Oral
• Dose: 5 mg BID
• Dose adjustments:
  • Mod-severe renal or moderate hepatic impairment: give 5 mg daily
  • Severe hepatic impairment: do not give
  • If taking potent CYP3A inhibitors: 5 mg daily
  • If taking potent CYP3A inducers: do not give
RA: Tofacitinib

- Potential toxicities: Myelosuppression, elevated LFTs, elevated lipids
- Side effects: HA, GI perforation
Screening and Vaccinations prior to initiation of therapy

- Hepatitis B and C serologies
- Test for latent TB
- CBC
- Renal and liver profile

- Influenza
- Pneumococcal
- Zoster
<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
<th>TNF-inhibitors</th>
<th>Rituximab</th>
<th>Abatacept</th>
<th>Tofacitinib</th>
<th>Tocilizumab</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>+/-</td>
<td>OK</td>
<td></td>
<td></td>
<td>OK</td>
<td>OK</td>
<td>All patients regardless of immunosuppression, ideally before biologics or MTX, yearly</td>
</tr>
<tr>
<td>Pneumococcus*</td>
<td></td>
<td>OK</td>
<td></td>
<td>**</td>
<td></td>
<td>OK</td>
<td>All patients regardless of immunosuppression, ideally before biologics or MTX</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All at-risk patients regardless of immunosuppression</td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All patients age ≤26, regardless of immunosuppression</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All patients ≥50 not on biologics or high dose corticosteroids. Should be given ≥2 weeks before starting biologics or ≥4 weeks after stopping biologics</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contraindicated for patients on immunosuppression</td>
</tr>
</tbody>
</table>

Table 1: Impact of RA therapy on vaccine immunogenicity and indications for vaccination. Indications for vaccination based on ACR and EULAR guidelines (10,11). Methotrexate decreases pneumococcal vaccine humoral response, and may also decrease humoral response to influenza vaccination. (29, 35, 36) TNF inhibitors do not significantly impact response to influenza or pneumococcal vaccines, though two small studies showed a negative effect on hepatitis B vaccine response. (15-24, 29, 35-38, 72, 73) Rituximab significantly decreases humoral response to both influenza and pneumococcal vaccines. (25-29) Abatacept decreases humoral response to influenza and pneumococcal vaccines. (17, 32, 40) Tofacitinib does not have a negative effect on influenza vaccine but does decrease immunogenicity of pneumococcal vaccines. (31) Tocilizumab has not been shown to have a detrimental effect on influenza or pneumococcal vaccine immunogenicity. (30, 39-41)

MTX: methotrexate, TNF: Tumor necrosis factor.
+/-: Limited data suggests this medication might negatively impact immunogenicity, though more data is needed.
*: No data regarding vaccine immunogenicity in this setting
OK: Vaccine does not impair immunogenicity.
*Polysaccharide pneumococcal vaccine data only, the 13-valent conjugate vaccine immunogenicity has not been evaluated in the setting of RA
**Abatacept and influenza vaccine immunogenicity has only been evaluated for the H1N1 vaccine, not the new trivalent or quadrivalent vaccines.
Medication Risks: Infection

Figure 1. Cumulative Incidence of Hospitalized Infection during One Year Follow-up

Table 2: Events, person years, crude incidence rate and adjusted hazard ratio \(^*\) of hospitalized infection by biologic agent

<table>
<thead>
<tr>
<th>Biologic agent</th>
<th>Events</th>
<th>Person years</th>
<th>Crude IR per 100 Pys (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>275</td>
<td>2020.9</td>
<td>13.8 (12.1-15.3)</td>
<td>1.07 (0.92-1.28)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>95</td>
<td>706.6</td>
<td>13.4 (11.0-16.4)</td>
<td>1.08 (0.87-1.35)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>236</td>
<td>1621.0</td>
<td>14.8 (12.8-16.5)</td>
<td>1.23 (1.04-1.44)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>77</td>
<td>572.3</td>
<td>13.4 (10.8-16.8)</td>
<td>1.15 (0.90-1.47)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>327</td>
<td>2029.2</td>
<td>16.1 (14.5-18.0)</td>
<td>1.38 (1.19-1.60)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>482</td>
<td>2741.7</td>
<td>17.8 (16.1-19.2)</td>
<td>1.37 (1.21-1.56)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>112</td>
<td>816.7</td>
<td>13.7 (11.4-16.5)</td>
<td>1.10 (0.86-1.36)</td>
</tr>
<tr>
<td>Abatacept</td>
<td>632</td>
<td>5071.6</td>
<td>12.5 (11.5-13.5)</td>
<td>Ref</td>
</tr>
</tbody>
</table>

\(^*\) Adjusted for infection risk score decile, disability status, glucocorticoids use during baseline, methotrexate use during baseline, most recent biologic during baseline and Medicaid eligibility.
## Herpes Zoster

**Events, absolute incidence rate and adjusted hazard ratio of Herpes Zoster infection by different types of biologics and other RA Medication**

<table>
<thead>
<tr>
<th>Biologic Exposures</th>
<th>Events</th>
<th>Person years (pys)</th>
<th>Absolute incidence rate per 100 pys (95% CI)</th>
<th>Adjusted hazard ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Anti TNF mechanism of action</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abatacept</td>
<td>142</td>
<td>7614</td>
<td>1.87 (1.58-2.20)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>82</td>
<td>3611</td>
<td>2.27 (1.83-2.82)</td>
<td>1.20 (0.88-1.63)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>18</td>
<td>839</td>
<td>2.15 (1.35-3.40)</td>
<td>1.05 (0.60-1.84)</td>
</tr>
<tr>
<td><strong>Anti-TNF mechanism of action</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>46</td>
<td>2638</td>
<td>1.74 (1.31-2.33)</td>
<td>1.04 (0.72-1.51)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>19</td>
<td>774</td>
<td>2.45 (1.57-3.85)</td>
<td>1.30 (0.77-2.23)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>48</td>
<td>2229</td>
<td>2.15 (1.62-2.86)</td>
<td>1.26 (0.87-1.81)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>11</td>
<td>683</td>
<td>1.61 (0.89-2.91)</td>
<td>0.91 (0.47-1.76)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>57</td>
<td>3135</td>
<td>1.82 (1.40-2.36)</td>
<td>0.98 (0.69-1.39)</td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>128</td>
<td>8548</td>
<td>1.50 (1.26-1.78)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>≤ 7.5mg/day</td>
<td>209</td>
<td>9841</td>
<td>2.12 (1.85-2.43)</td>
<td>1.55 (1.25-1.93)</td>
</tr>
<tr>
<td>&gt; 7.5mg/day</td>
<td>86</td>
<td>3134</td>
<td>2.74 (2.22-3.39)</td>
<td>2.35 (1.81-3.04)</td>
</tr>
</tbody>
</table>

Perioperative DMARD management

Biologics

• Paucity of high-quality studies

• Recommendation to temporarily hold agent based on half-life prior to surgery

• Restart agent 2 weeks postoperatively

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pharmacologic $t_{1/2}$</th>
<th>Dosing interval</th>
<th>Pre-operative Withhold</th>
<th>Continue</th>
<th>Special considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>3–15 h, dose dependent</td>
<td>Weekly</td>
<td>None</td>
<td>Yes</td>
<td>Monitor renal function</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>14 Days</td>
<td>Daily</td>
<td>1 Week</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>32–50 Days</td>
<td>Daily</td>
<td>None</td>
<td>Yes</td>
<td>Monitor renal function</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>5 h</td>
<td>Daily</td>
<td>None</td>
<td>Yes</td>
<td>Monitor renal function</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>7–15 h dependent on acetylation rate</td>
<td>Daily</td>
<td>None</td>
<td>Yes</td>
<td>Monitor renal function</td>
</tr>
<tr>
<td><strong>TNFα inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>3–5.5 Days</td>
<td>Weekly</td>
<td>2 Weeks</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>7–20 Days</td>
<td>Monthly</td>
<td>6 Weeks</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>10–20 Days</td>
<td>2 Weeks</td>
<td>3 Weeks</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>7–12 Days</td>
<td>4–8 Weeks</td>
<td>6 Weeks</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>14 Days</td>
<td>4 Weeks</td>
<td>6 Weeks</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>SC: 5–13 days</td>
<td>SC: 1–2 weeks</td>
<td>SC 3 weeks</td>
<td>No</td>
<td>Signs of inflammation like temperature and CRP may be masked</td>
</tr>
<tr>
<td></td>
<td>IV: 11–13 days</td>
<td>IV: every 4 weeks</td>
<td>IV 4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>18–32 Days</td>
<td>16–24 weeks</td>
<td>None</td>
<td>Yes</td>
<td>Infection risk not related to interval between dose and surgery</td>
</tr>
<tr>
<td>Abatacept</td>
<td>13–14 Days</td>
<td>SC: 1 week</td>
<td>SC 2 weeks</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV: 4 weeks</td>
<td>IV 4 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Systemic lupus: Belimumab

- FDA approved in March 2011
- Approved for antibody-positive patients who continue to have active disease despite maximal standard therapy
- Skin, joint, mucocutaneous disease
- Not approved for renal or CNS lupus disease
- Can be useful as steroid-sparing agent
- Not particularly effective in pts of African decent
Systemic lupus: Belimumab

- MOA: BLyS inhibition
- Administration: IV
- Dose: 10mg/kg q 2 wks x 3 doses, then monthly
- Dose adjustments: None
- Potential toxicities:
  - Infusion rx (anaphylaxis, hypersensitivity)
  - PML
- Side effects:
  - Nausea, diarrhea, nasopharyngitis, fever, depression
Systemic lupus: Belimumab
Psoriatic Arthritis

- TNF-α inhibitors: etanercept, infliximab, adalimumab, certolizumab, golimumab
- Ustekinumab – 9/2013
- Apremilast – 3/2014
- Secukinumab – 1/2016
Psoriatic Arthritis: Ustekinumab

- **MOA**: IL-12 and IL-23 inhibition
- **Administration**: SC
- **Dose**: 45mg SC with repeat dosing 4 weeks later, then every 12 weeks.
- **Dose adjustment**: Can give 90mg SC for pts >100kg (220lbs)
- **Potential toxicities**: Similar to TNF-α inhibitors
- **Screen for latent TB**
Ustekinumab
Ustekinumab
Psoriatic Arthritis: Apremilast

• MOA: Phosphodiesterase 4 inhibitor
• Administration: oral
• Dosing: Starter pack* followed by 30 mg BID
• Dose Adjustment:
  • 30 mg daily in pts with CrCl <30 ml/min
  • Avoid strong CYP450 inducers
• Potential side effects: Depression, Weight loss, Diarrhea, Headache

*Day 1, 10 mg in AM; Day 2, 10 mg BID; Day 3, 10 mg in AM, 20 mg in PM; Day 4, 20 mg BID; Day 5, 20 mg in AM, 30 mg in PM
Apremilast
Psoriatic Arthritis/Ankylosing Spondyloarthritis: Secukinumab

- MOA: IL-17 inhibitor
- Administration: SC
- Dosage:
  - Loading dose: 150 mg/wk x 4 then q 4wks
  - No loading dose: 150 mg q 4 wks
  - Can also use 300 mg if needed in PsA
- Screen for latent TB
- May cause flare or de novo IBD
Figure 4. Radiographic classification in the evaluation of sacroiliac joints. Grade 0 – normal (A); grade I – suspicious; grade II – mild irregularity and sclerosis of articular surfaces, with preserved joint space (B); grade III – joint space narrowing, besides intense irregularity and subchondral sclerosis (C); grade IV – bilateral ankylosis (D).
Behcet's Syndrome: Apremilast

- Orphan Drug Status
  - Mucocutaneous disease
  - Skin lesions
  - Inflammatory arthritis
  - Inflammatory eye disease
ACTH analogue

• Indications:
  • Acute exacerbation or maintenance therapy
    • Dermatomyositis/polymyositis
    • Lupus
  • Short-term administration
    • Rheumatoid arthritis
    • Psoriatic arthritis

• Side effects: typical steroidogenic
Take Home Points

• Multiple new medications for treatment of rheumatic diseases over the past 10+ years
• Most common adverse events are infections
• Advise influenza/pneumococcal +/- Zoster immunizations prior to starting
Questions?