### Biologics update 2019

**by Elise M. Craig, DO**

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<tr>
<td>Adalimumab (Humira)</td>
<td>TNF-α inhibitor</td>
<td>Dermatologic: Plaque psoriasis, Hidradenitis suppurativa (HS) (12 years and older)</td>
<td>PG → Behcet’s disease, Aphthous stomatitis</td>
<td>SubQ, store in refrigerator protected from light. Allow to reach room temp before injecting (~30 mins).</td>
<td>Before starting: Test for TB and hepatitis B. Consider CBC, Cr, LFT, hepatitis C and HIV.</td>
<td>Common: Injection site reaction, URI, rash, UTI, headache, nausea, HLD, abdominal or back pain, flu-like symptoms, HTN, hypersensitivity reactions.</td>
<td>Avoid live vaccines and concurrent administration with IL-1 antagonists (ie, anakinra). Certain needle covers contain latex. Efficacy may wane over time due to development of anti drug antibodies; can be given concurrent to decrease risk of antibody formation. Lupus-like syndromes and autoimmune hepatitis can arise in patients on TNF-α inhibitors. Should not be given with azathioprine, risk of hepatosplenic T cell lymphoma.</td>
</tr>
<tr>
<td>Certolizumab pegol (Cimzia)</td>
<td>TNF-α inhibitor</td>
<td>Dermatologic: Plaque psoriasis</td>
<td>SubQ, store in refrigerator protected from light. Allow to reach room temp before injecting (~30 mins). Molecular structure does not cross placental barrier.</td>
<td>Before starting: Test for TB and hepatitis B. Consider CBC, Cr, LFT, hepatitis C and HIV.</td>
<td>Interval monitoring: Annual TB Test, Routine TBE.</td>
<td>Common: Urti, abdominal pain, HA, nausea, allergic reactions, injection site reaction, URI, rash.</td>
<td>Avoid live vaccines and concurrent administration with IL-1 antagonists (ie, anakinra). The needle shield inside the removable cap of the prefilled syringe contains latex. May interfere with aPTT tests. Efficacy may wane over time due to development of anti drug antibodies; MTX can be given concurrent to decrease risk of Ab formation. Lupus-like syndromes and autoimmune hepatitis can arise in patients on TNF-α inhibitors. Should not be given with azathioprine, risk of hepatosplenic T cell lymphoma.</td>
</tr>
</tbody>
</table>

**Elise M. Craig, DO**, is a PGY-3 dermatology resident at Kansas City University of Medicine and Biosciences-GMEC/TCD-Apex Dermatology.

**Emily Milam, MD**, is currently a PGY-4 at New York University School of Medicine.
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## DRUG & TARGET

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<th>TNF-α inhibitors</th>
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<td><strong>Etanercept</strong> (Enbrel)</td>
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## CLASS & MECHANISM

**TNF-α** inactivates TNF biologically, rendering receptors, TNF-α and TNF-β binding of IgG1. Inhibits Fc portion of linked to the TNF receptor.

## FDA APPROVED INDICATIONS

**Dermatologic:**
- Adult plaque psoriasis
- Pediatric plaque psoriasis (4 years or older)

**Other:**
- AS
- JIA
- PsA
- RA

## OFF-LABEL USES IN DERMATOLOGY

**SubQ,** store in refrigerator protected from light. Allow to reach room temp before injecting (~30 mins).

## ROUTE & STORAGE

**Before starting:**
- Test for TB and hepatitis B. Consider CBC, Cr, LFT, hepatitis C and HIV.

## MONITORING

**Interval monitoring:**
- Annual TB Test. Routine TBSE.

## SIDE EFFECTS & ADVERSE EVENTS

**Common:**
- Diarrhea, pruritus, fever, urticarial reaction, injection site reaction, URI, rash.

**Rare but serious:**
- CHF; melanoma & NMSC; uveitis; central demyelinating disorders; cytopenias; new-onset psoriasis (especially palmoplantar pustulosis); cutaneous small vessel vasculitis; eczematous eruptions; lichenoid dermatitis.

**Black Box Warnings:**
- Serious and fatal infections
- Lymphoma and other malignancies
- Screen for: CHF, IBD, demyelinating diseases.

## NOTES

Avoid live vaccines and concurrent administration with IL-1 antagonists (ie; anakinra).

Syringe contains latex.

Lupus-like syndromes and autoimmune hepatitis can arise in patients on TNF-α inhibitors. However, some case reports show improvement in SCLE with etanercept.

Avoid concomitant use with cyclophosphamide, and abatacept.

Efficacy may wane over time due to development of anti drug antibodies. MTX can be given concurrent to decrease risk of Ab formation.

Should not be given with azathioprine, risk of hepatosplenic T cell lymphoma.

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**Golimumab** (Simponi)

### TNF-α inhibitor

Fully humanized recombinant IgG1k monoclonal Ab that binds to both the soluble and transmembrane bioactive forms of human TNF-α.

### Dermatologic:

- Uveitis
- Crohn’s disease

### Other:

- AS
- PsA
- RA
- UC

### SubQ, store in refrigerator protected from light. Allow to reach room temp before injecting (~30 mins).

### Before starting:

- Test for TB and hepatitis B. Consider CBC, Cr, LFT, hepatitis C and HIV.

### Interval monitoring:

- Annual TB Test. Routine TBSE.

### Common:

- HSV outbreak, ALT/ALT elevation, HTN, fever, dizziness, paresthesias, injection site reaction, URI, rash.

### Rare but serious:

- CHF; melanoma & NMSC; uveitis; central demyelinating disorders; cytopenias; new-onset psoriasis (especially palmoplantar pustulosis); cutaneous small vessel vasculitis; eczematous eruptions; lichenoid dermatitis.

### Black Box Warnings:

1. Serious and fatal infections
2. Lymphoma and other malignancies

Screen for: CHF, IBD, demyelinating diseases.

Avoid live vaccines and concurrent administration with IL-1 antagonists (ie; anakinra).

Syringe contains latex.

Efficacy may wane over time due to development of anti drug antibodies. MTX can be given concurrent to decrease risk of antibody formation.

Lupus-like syndromes and autoimmune hepatitis can arise in patients on TNF-α inhibitors.

Should not be given with azathioprine, risk of hepatosplenic T cell lymphoma.

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TNF-α continued on p. 3
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<tr>
<td><strong>TNF-α (cont.)</strong></td>
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<tr>
<td><strong>Infliximab (Remicade)</strong></td>
<td>TNF-α inhibitor</td>
<td>Chimeric (human-mouse) IgG1 monoclonal Ab specific for human TNF-α. Neutralizes the biological activity of TNF-α by binding with high affinity to the soluble and transmembrane forms of TNF-α, inhibiting it from binding with its receptors.</td>
<td>Dermatologic: &gt; Psoriasis &gt; Other: &gt; ADULT and pediatric Crohn’s &gt; Adult and pediatric UC &gt; AS &gt; PsA &gt; RA</td>
<td>IV</td>
<td>Before starting: Test for TB and hepatitis B. Consider CBC, Cr, LFT, hepatitis C and HIV. Interval monitoring: Annual TB Test, Routine TBSE.</td>
<td>Common: Infusion-related reactions, including fever, chills, pruritus, hyp- or hypertension, chest pain, urticaria, shortness of breath; nausea, headache, abdominal pain, dyspepsia, rash, urthralgia. Rare but serious: Anaphylaxis; CHF; malignancies (i.e., lymphoma). Black Box Warnings: 1. Serious and fatal infections 2. Lymphoma and other malignancies</td>
<td>Avoid live vaccines and concurrent administration with IL-1 antagonists (i.e., anakinra). Efficacy may wane over time due to development of neutralizing anti-chimeric antibodies. MTX can be given concurrent to decrease risk of antibody formation.</td>
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<tr>
<td><strong>CD20</strong></td>
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<tr>
<td><strong>Rituximab (Rituxan)</strong></td>
<td>CD20 inhibitor</td>
<td>Chimeric monoclonal Ab that binds to CD20 antigen found on surface of mature B cells and causes apoptosis of these cells or existing plasma cells.</td>
<td>Dermatologic: &gt; Psoriasis &gt; Other: &gt; CCL &gt; Non-Hodgkin B-cell lymphoma &gt; RA</td>
<td>IV</td>
<td>Before starting: Test for TB and hepatitis B. Consider testing hepatitis C &amp; CBC. Interval monitoring: Annual TB and consider semi-frequent CBCs.</td>
<td>Serious infections (bacterial, fungal, and viral) can occur up to 1 year after completing therapy, or reactivation of viral infections (especially hepatitis B). Reported cases of bowel obstruction and perforation, cardiac arrhythmias and angina, SJS/TEN, and onset of paraneoplastic pemphigus.</td>
<td>Avoid live vaccines. Cases of PML have been reported. Tumor lysis syndrome can occur in lymphoma patients. Efficacy may decrease over time due to development of neutralizing anti-chimeric antibodies.</td>
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<td><strong>IgE</strong></td>
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<tr>
<td>Omalizumab (Xolair)</td>
<td>IgE inhibitor</td>
<td>Humanized IgG1 recombinant monoclonal Ab. Blocks IgE high affinity Fc receptor, decreasing IgE and blocking its attachment to mast cells, basophils, and dendritic cells.</td>
<td>Dermatologic: Chronic idiopathic urticaria Other: Asthma</td>
<td>SubQ Chronic urticaria 150 or 300 mg q4 weeks (max of 150 mg per injection site). Doses in CIU are not dependent on serum IgE or body weight.</td>
<td>Before starting: Consider serum total IgE levels and PFTs.</td>
<td>Common: Injection site reactions, arthritis, rash, fever, pruritus, URI. Rare but serious: Anaphylaxis and malignancy. Black Box Warnings: 1. Anaphylaxis after first dose, and even after &gt;1 year of treatment 2. Live virus vaccines should be given cautiously during omalizumab treatment until more data are available.</td>
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<td><strong>IL-1</strong></td>
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<tr>
<td>Anakinra (Kineret)</td>
<td>IL-1 receptor inhibitor</td>
<td>Recombinant form of human IL-1 receptor antagonist.</td>
<td>Dermatologic: None Other: RA, Neonatal onset multisystem inflammatory disease (NOMID). Urticarial lesions associated with Schnitzler’s Syndrome Periodic fever syndromes. PG</td>
<td>SubQ Adult RA Dose 100 mg q2 weeks. For CrCl &lt;30, consider q48h dosing. Pediatric Dose: 1-2mg/kg</td>
<td>Before starting: Baseline Cr, CBC, TB. Interval monitoring: CBC and Cr monthly x 3 months, then q3 months.</td>
<td>Common: Injection site reaction, URI, HA, nausea, vomiting, diarrhea, fever, rash, arthralgia, abdominal pain, flu-like symptoms. Rare but serious: Malignancy, neutropenia, &amp; thrombocytopenia. Avoid in patients with severe renal impairment, active infections, asthma, or hypersensitivity to E. coli proteins.</td>
<td>Avoid live vaccines. Syringe contains latex. Do not give concurrently with other TNF-α modifiers. Efficacy may wane due to development of anti drug antibodies.</td>
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<tr>
<td><strong>IL-4</strong></td>
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<tr>
<td>Dupilumab (Dupixent)</td>
<td>IL-4 receptor inhibitor</td>
<td>Humanized IgG1 monoclonal Ab that binds to and inhibits the alpha subunit of the IL-4 receptor, which interferes with IL-4 and IL-13 cytokines.</td>
<td>Dermatologic: Adult atopic dermatitis (18+) Adolescent atopic dermatitis (ages 12-17) Other: Asthma CRSwNP</td>
<td>SubQ, store in refrigerator protected from light. Allow to reach room temp before injecting (~30 mins) Adult AD 600 mg (two 300 mg injections) week 0, then 300 mg q2 weeks.</td>
<td>No baseline or routine tests recommended. Consider CBC with diff q6 months.</td>
<td>Common: Injection site reactions, conjunctivitis, HSV outbreak, dry eyes. Rare but serious: Keratitis, serum sickness-like reaction, hypersensitivity reaction. Use with caution in patients with acute asthma or possible helminth infection.</td>
<td>Avoid live vaccines.</td>
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<td><strong>Uses</strong></td>
<td><strong>Route &amp; Storage</strong></td>
<td><strong>Monitoring</strong></td>
<td><strong>Side Effects &amp; Adverse Events</strong></td>
<td><strong>Notes</strong></td>
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<tr>
<td>Ustekinumab</td>
<td>Stelara</td>
<td>IL-12/IL-23 antagonist</td>
<td>Adolescents (12 years or older)</td>
<td>SubQ, store in refrigerator protected from light. May be stored at room temp for 4 hours in original carton protected from light, if needed.</td>
<td>Before starting: Test for TB. Interval monitoring: Annual TB test.</td>
<td>Common: URIs, HA, injection site reaction, back pain, fatigue. Rare but serious: Possible increased risk of adverse cardiovascular events, severe infections, NMSC, malignancy, hypersensitivity reactions including anaphylaxis, non-infectious pneumonia, and eczematous eruptions.</td>
<td>Avoid live vaccines. Syringe contains latex. Patients deficient in IL-12/IL-23 have increased risk of severe infections with mycobacteria and Salmonella.</td>
</tr>
</tbody>
</table>

| **IL-17** | **Drugs** | **Target & Mechanism** | **Uses** | **Route & Storage** | **Monitoring** | **Side Effects & Adverse Events** | **Notes** |
| Brodalumab | Siliq | IL-17 receptor | Psoriasis | SubQ, store in refrigerator protected from light. Allow to reach room temp before injecting (~30 mins) | Before starting: Test for TB. Interval monitoring: Annual TB test. | Common: Injection site reaction, increased risk of infection, arthralgia, HA, fatigue, diarrhea, nausea, oropharyngeal pain, myalgia, influenza, and tinea infections. Rare but serious: neutropenia. Black Box Warnings: 1. Suicidal ideation and behavior. | Avoid live vaccines. Efficacy may decrease over time due to development of neutralizing antibodies. Only available through a restricted program, Siliq Risk Evaluation & Mitigation Strategy (REMS), because of risk of suicidal behavior and ideation. Screen for history of IBD. IL-17 treatment may develop new or cause flaring. |
| Ixekizumab | Taltz | IL-17 inhibitor | Psoriasis | SubQ, store in refrigerator protected from light. Allow to reach room temp before injecting (~30 mins) | Before starting: Test for TB. Interval monitoring: Annual TB test. | Common: Injection site reactions, increased risk of infection, URI, nausea, tinea infections. Rare but serious: New or exacerbated cases of IBD, hypersensitivity reaction, neutropenia, thrombocytopenia. | Avoid live vaccines. Efficacy may decrease over time due to development of neutralizing antibodies. Screen for history of IBD. IL-17 treatment may develop new or cause flaring. |

**IL-17** continued on p. 6
### IL-17 (cont.)

**Secukinumab (Cosentyx)**
- **Drug: IL-17 inhibitor**
- Humanized IgsG1 monoclonal Ab that binds to IL-17A cytokine and inhibits its interaction with IL-17 receptor.
- **Indications:**
  - Dermatologic: Psoriasis
  - Other: AS, PsA
  - RA, HS

**DRUG & TARGET** | **CLASS & MECHANISM** | **FDA APPROVED INDICATIONS** | **OFF-LABEL USES IN DERMATOLOGY** | **ROUTE & STORAGE** | **MONITORING** | **SIDE EFFECTS & ADVERSE EVENTS** | **NOTES**
--- | --- | --- | --- | --- | --- | --- | ---
IL-17 | IL-17 inhibitor | Dermatologic: Psoriasis | Other: AS, PsA | RA, HS | SubQ, store in refrigerator protected from light. Allow to reach room temp before injecting (~30 mins) | Common: Injection site reactions, increased risk of infection, HSV, nasopharyngitis, diarrhea, URIs. Rare but serious: Anaphylactic or hypersensitivity reactions, severe infections, eczematous reactions, and neutropenia. | Avoid live vaccines. Removable cap of pen and prefilled syringe contains latex. Efficacy may decrease over time due to development of antibodies. Screen for history of IBD. IL-17 treatment may develop new or cause flaring.

### IL-23

**Guselkumab (Tremfya)**
- **Drug: IL-23 inhibitor**
- Recombinant humanized monoclonal Ab; selectively blocks IL-23.
- **Indications:**
  - Dermatologic: Psoriasis, HS, Pediatric psoriasis, Oral lichen planus, PsA

**Risankizumab (Skyrizi)**
- **Drug: IL-23 inhibitor**
- Humanized IgsG1 monoclonal Ab that selectively binds to the p19 subunit of IL-23 cytokine and inhibits its interaction with IL-23 receptor.
- **Indications:**
  - Dermatologic: Psoriasis, PsA, Crohn’s disease

**Tildrazkizumab (Ilumya)**
- **Drug: IL-23 inhibitor**
- Humanized IgsG1/k monoclonal Ab that selectively binds to the p19 subunit of IL-23 and inhibits its interaction with IL-23 receptor.
- **Indications:**
  - Dermatologic: Psoriasis

**DRUG & TARGET** | **CLASS & MECHANISM** | **FDA APPROVED INDICATIONS** | **OFF-LABEL USES IN DERMATOLOGY** | **ROUTE & STORAGE** | **MONITORING** | **SIDE EFFECTS & ADVERSE EVENTS** | **NOTES**
--- | --- | --- | --- | --- | --- | --- | ---
## JAK Inhibitors

### Baricitinib (Olumiant)

- **Dermatologic:** None
- **Other:** RA
- **Route & Storage:** PO
- **Before starting:** Test for TB, CBC w. diff, hepatitis panel, and lipids.
- **Interval Monitoring:**
  - CBC at 4 and 8 weeks, then q3 months.
  - Periodic CMP
  - Lipids 4-6 weeks after starting.
- **Common:** URI, UTI, herpes zoster, lipid elevations, nausea, herpes simplex, AST/ALT increase.
- **Rare but serious:** Increased risk of infections, NMSC, pancytopenia, reactivation of TB, arterial and venous thrombosis, viral reactivation, GI perforation.
- **NOT recommended** for patients with severe hepatic or renal impairment.
- **Avoid live vaccines.**

### Ruxolitinib (Jakafi)

- **Dermatologic:** None
- **Other:** Polycythemia vera → Myelofibrosis → Chronic GVHD (12 years or older)
- **Route & Storage:** PO
- **Before starting:** Test for TB, CBC w. diff, hepatitis panel, and lipids.
- **Interval Monitoring:**
  - CBC at 4 and 8 weeks, then q3 months.
  - Periodic CMP
  - Lipids 4-6 weeks after starting.
- **Common:** URI, nausea, UTI, herpes zoster, lipid elevations, HA, diarrhea, transient lymphocytosis, bruising, dizziness.
- **Rare but serious:** Increased risk of infections, NMSC, pancytopenia, reactivation of TB, thrombosis.
- **NOT recommended** for patients with severe hepatic or renal impairment.
- **Avoid live vaccines.**
- **Avoid use with fluconazole doses of greater than 200 mg daily.**

### Tofacitinib (Xeljanz)

- **Dermatologic:** None
- **Other:** RA → PsA → UC
- **Route & Storage:** PO
- **Before starting:** Test for TB, CBC w. diff, hepatitis panel, and lipids.
- **Interval Monitoring:**
  - CBC at 4 and 8 weeks, then q3 months.
  - Periodic CMP
  - Lipids 4-6 weeks after starting.
- **Common:** URI, nausea, UTI, herpes zoster, lipid elevations, HA, diarrhea, ALT/AST increase, Cr increase, transient lymphocytosis.
- **Rare but serious:** Increased risk of infections, NMSC, pancytopenia, reactivation of TB, GI perforation, blood clots, and death.
- **NOT recommended** for patients with severe hepatic or renal impairment.
- **Black Box Warnings:**
  1. Serious & fatal infections (including new TB or reactivation)
  2. Lymphoma and other malignancies

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## PDE-4

### Apremilast (Otezla)

**PDE-4 inhibitor**

Small molecule that selectively inhibits PDE-4, increasing intracellular cAMP, which decreases inflammatory TNF-α and IL-23, and increases anti-inflammatory IL-10.

**Dermatologic:**
- Psoriasis
- Behcet’s disease
- PsA

**Other:**
- AA
- HS
- AD

**Route:** PO

**Before starting:** None indicated

**Interval monitoring:** None indicated

**Common:** Diarrhea, nausea, vomiting, weight loss, HA, back pain, fatigue, insomnia, URI.

Use with caution in patients with depression, suicidal ideation, and CrCl <30.

GI side effects often improve after first few weeks of treatment.

Use with cytochrome P450 enzyme inducers (rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended as they reduce systemic exposure of apremilast.

### Abbreviations:
- AA = Alopecia areata
- Ab = Antibody
- AD = Atopic dermatitis
- AS = Ankylosing spondylitis
- CD = Crohn’s disease
- CRSwNP = Chronic rhinosinusitis with nasal polyposis
- GVHD = Graft versus host disease
- HS = Hidradenitis suppurativa
- HSV = Herpes simplex virus
- IBD = Inflammatory bowel disease
- JIA = Juvenile idiopathic arthritis
- MRH = Multicentric reticulohistiocytosis
- PDE = Phosphodiesterase
- PG = Pyoderma gangrenosum
- PRP = Pityriasis rubra pilaris
- PsA = Psoriatic arthritis
- RA = Rheumatoid arthritis
- SCLE = Subacute cutaneous lupus erythematosus
- TEN = Toxic epidermal necrolysis

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**Psoriasis** guide on p. 7
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**TNF = Tumor necrosis factor**

### PSORIASIS DOSING GUIDE

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<th>Second 52 Weeks</th>
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<td>Tildrakizumab (Ilumya)</td>
<td>100 mg administered at week 0, week 4, and q12 weeks thereafter</td>
<td>6 doses</td>
<td>4 doses</td>
</tr>
<tr>
<td>Ustekinumab (Stelara)</td>
<td>For pts &gt;100kg, 90 mg administered at week 0, week 4, and q12 weeks thereafter. For pts 60-100kg, 45 mg administered at week 0, week 4, and q12 wks thereafter. For adolescents &lt;60kgs, 0.75 mg/kg administered at week 0, week 4, and q12 wks thereafter.</td>
<td>6 doses</td>
<td>4 doses</td>
</tr>
<tr>
<td>Rizankizumab (Skyrizi)</td>
<td>150 mg (two 75 mg injections) administered at week 0, week 4, and q12 weeks thereafter.</td>
<td>6 doses</td>
<td>4 doses</td>
</tr>
<tr>
<td>Guselkumab (Tremfya)</td>
<td>100 mg at week 0, week 4, then q8 weeks thereafter</td>
<td>8 doses</td>
<td>6 doses</td>
</tr>
<tr>
<td>Ustekinumab (Stelara)</td>
<td>For pts &gt; 100kg, 90 mg administered at week 0, week 4, and q12 weeks thereafter. For pts 60-100kg, 45 mg administered at week 0, week 4, and q12 wks thereafter. For adolescents &lt;60kgs, 0.75 mg/kg administered at week 0, week 4, and q12 wks thereafter.</td>
<td>6 doses (2 injections/dose)</td>
<td>4 doses (2 injections/dose)</td>
</tr>
<tr>
<td>Rizankizumab (Skyrizi)</td>
<td>150 mg (two 75 mg injections) administered at week 0, week 4, and q12 weeks thereafter.</td>
<td>6 doses (2 injections/dose)</td>
<td>4 doses (2 injections/dose)</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>400 mg (2 injections of 200 mg) each other week. With body weight &lt; 90 kg, consider a dose of 400 mg (2 injections of 200 mg each) at weeks 0, 2, and 4, followed by 200 mg every other week.</td>
<td>26 doses (2 injections/ dose)</td>
<td>26 doses (2 injections/ dose)</td>
</tr>
<tr>
<td>Certolizumab pegol (Cimzia)</td>
<td>80 mg week 0, followed by 40 mg every other week (starting 1 week after initial dose).</td>
<td>27 doses</td>
<td>26 doses</td>
</tr>
<tr>
<td>Brodalumab (Silq)</td>
<td>210 mg at weeks 0, 1, and 2, followed by 210 mg q2 weeks.</td>
<td>28 doses</td>
<td>26 doses</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>Adult: 50mg weekly x 3 months, followed by 50mg once weekly. Pediatric: -63kg: 0.8mg/kg weekly (maximum of 50mg). &gt;63kg: 50mg weekly.</td>
<td>64 doses</td>
<td>52 doses</td>
</tr>
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</table>
| Apremilast (Otezla)    | 10 mg on day 1, 10 mg BID day 2, 10 mg in the am and 20 mg in the pm day 3, 20 BID day 4, 20 mg in the am and 30 mg in the pm day 5, 30 mg BID day 6, and continue with 30 mg BID daily.  
  - If CrCl ≤30, start 10mg daily x 3 days, then 20mg daily x 2 days, then 30mg daily. | 729 doses 26 doses | 730 doses 26 doses |

**Sources:**