

## What's New with Biologic Agents for Inflammatory Diseases?

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Biological response modifiers have proven to be efficacious in treating a wide spectrum of autoimmune diseases including rheumatoid arthritis (RA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), ulcerative colitis (UC) and Crohn's disease (CD). Approaches to treating rheumatic diseases with biologic agents include interference with cytokine function, inhibition of T-cell activation, or depletion of B cells. In the past few years substantial information about specific agents within this class of drugs has been published due to expanded indications including new pediatric approvals. In addition, several new therapeutic agents including biosimilar products for infliximab, etanercept and adalimumab have received U.S. Food and Drug Administration (FDA) approval, adding to the complexity of this drug class. **Table 1** summarizes the various biologic agents and their FDA approved indications. The purpose of this newsletter is to summarize significant evidence published for biologic agents within the past 2 years for indications that may impact the Oregon Medicaid population.

**Table 1. Common Indications for FDA-Approved Biologics**

Ankylosing Spondylitis		
Adalimumab (HUMIRA) and biosimilars	Certolizumab pegol (CIMZIA)	Etanercept (ENBREL) and biosimilars
Golimumab (SIMPONI)	Infliximab (REMICADE) and biosimilars	Secukinumab (COSENTYX)
Crohn's Disease		
Adalimumab (HUMIRA)† and biosimilars	Certolizumab pegol (CIMZIA)	Infliximab (REMICADE)† and biosimilars†
Natalizumab (TYSABRI)	Ustekinumab (STELARA)	Vedolizumab (ENTYVIO)
Juvenile Idiopathic Arthritis		
Abatacept (ORENCIA)*	Adalimumab (HUMIRA)* and biosimilars‡	Canakinumab (ILARIS)*
Etanercept (ENBREL)* and biosimilars*	Tocilizumab (ACTEMRA)*	
Plaque Psoriasis		
Adalimumab (HUMIRA) and biosimilars	Brodalumab (SILIQ)	Etanercept (ENBREL)‡ and biosimilars
Guselkumab (TREMIFYA)	Infliximab (REMICADE) and biosimilars	Ixekizumab (TALTZ)
Secukinumab (COSENTYX)	Ustekinumab (STELARA) ^	
Psoriatic Arthritis		
Abatacept (ORENCIA)	Adalimumab (HUMIRA) and biosimilars	Apremilast (OTEZLA)
Certolizumab pegol (CIMZIA)	Etanercept (ENBREL) and biosimilars	Golimumab (SIMPONI)
Infliximab (REMICADE) and biosimilars	Ixekizumab (TALTZ)	Secukinumab (COSENTYX)
Ustekinumab (STELARA)		
Rheumatoid Arthritis		
Abatacept (ORENCIA)*	Adalimumab (HUMIRA)* and biosimilars‡	Anakinra (KINERET)
Certolizumab pegol (CIMZIA)	Etanercept (ENBREL) and biosimilars	Golimumab (SIMPONI)
Infliximab (REMICADE) and biosimilars	Rituximab (RITUXAN)	Sarilumab (KEVZARA)
Tocilizumab (ACTEMRA)		
Ulcerative Colitis		
Adalimumab (HUMIRA) and biosimilars	Golimumab (SIMPONI)	Infliximab (REMICADE) and biosimilars

Indications are for adults 18 years and older unless indicated.

Key: \* ≥ 2 years old, ‡ ≥ 4 years old, † ≥ 6 years old, ^ ≥ 12 years old

### Expanded Indications

#### Abatacept

The approved age for which subcutaneous (SC) abatacept (Orencia<sup>®</sup>) can be administered was lowered from 6 years to 2 years for patients with polyarticular juvenile idiopathic arthritis (JIA) in March 2017. Abatacept is a T-lymphocyte inhibitor which is also FDA approved for management of adults with PsA and RA. The intravenous (IV) formulation of abatacept is indicated in pediatric patients 6 years and older. Abatacept also received an expanded FDA indication for treatment of PsA in adults in June 2017. This approval was based on two randomized, double-blind, placebo-controlled studies in adult patients with active PsA despite prior disease modifying treatment.<sup>1,2</sup>

#### Adalimumab

Adalimumab (Humira<sup>®</sup>), a tumor necrosis factor (TNF) blocker, was originally approved for the treatment of rheumatoid arthritis (RA) in 2002. In 2016 adalimumab received FDA approval for treatment of non-infectious uveitis in adult patients. The approval was based on a Phase 3 randomized controlled trial (RCT) conducted at 62 study sites in 21 countries.<sup>3</sup> Adults with inactive, non-infectious intermediate, posterior, or panuveitic uveitis controlled by 10–35 mg/day of prednisone were randomly assigned to receive either subcutaneous adalimumab or placebo, with a mandatory prednisone taper from week 2.<sup>3</sup> The primary efficacy endpoint was time to treatment failure. Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.<sup>3</sup> Time to treatment failure was significantly improved in the adalimumab group compared with the placebo group (>18 months vs 8.3 months; hazard ratio (HR) 0.57, 95% CI 0.39–0.84; p=0.004).<sup>3</sup> Adalimumab significantly lowered the risk of uveitic flare or loss of visual acuity upon corticosteroid withdrawal in patients with inactive, non-infectious intermediate, posterior, or panuveitic uveitis controlled by systemic corticosteroids.<sup>3</sup>

#### Etanercept

Etanercept (Enbrel<sup>®</sup>), a TNF blocker, arrived on the U.S. market in 1998 for the management of adult RA. It is also indicated for adult PsA, PsO, AS, and JIA. In 2016, the FDA approved etanercept to treat pediatric patients 4 years and older with chronic moderate-to-severe PsO who are candidates for systemic therapy or phototherapy. Dosing of etanercept varies by indication and is administered via SC injection.

#### Ixekizumab

Ixekizumab (Taltz<sup>®</sup>), an IL-17 inhibitor, is a recent addition to the biologic agent class. It first received approval to treat adult PsO in 2016 and received an expanded indication for the treatment of adults with active PsA in December 2017. Dosing of ixekizumab varies by indication and is administered via SC injection. Ixekizumab was studied in two phase 3 randomized controlled trials (RCTs) in adult patients with PsA naive to biologic therapy and in patients with inadequate response to TNF inhibitors.<sup>4,5</sup> The primary endpoint in both trials was the percentage of patients achieving at least 20% improvement in American College of Rheumatology (ACR20) response criteria at week 24. In both studies, patients treated with ixekizumab demonstrated a greater clinical response compared to placebo. In the SPIRIT-P1 trial, significantly more patients naive to biologic therapy and treated with ixekizumab achieved an ACR20 response with ixekizumab 80 mg every 4 weeks (57.9%) than placebo (30.2%; p<0.001).<sup>4</sup> In the SPIRIT-P2 trial, a higher proportion of patients who had not responded to TNF inhibitor therapy attained ACR20 with ixekizumab every 4 weeks (53%) than did placebo-treated patients (20%; 95% CI 22.4 to 45.2; p<0.0001).<sup>5</sup>

*Biologic agents with pediatric indications include abatacept, adalimumab, canakinumab, etanercept, infliximab, and ustekinumab.*

### Tocilizumab

Tocilizumab (Actemra®), an IL-6 receptor inhibitor, first was received FDA approval to manage RA via IV infusion in 2010. In May 2017, tocilizumab was approved for the treatment of adult patients with giant cell arteritis (GCA) via subcutaneous injection. This approval was based on a randomized, double-blind, multicenter study in which patients with active GCA were randomized to either tocilizumab 162 mg every week, tocilizumab a 162 mg every other week, or two different placebo groups (pre-specified prednisone-taper regimen over 26 weeks and 52 weeks).<sup>6</sup> The primary outcome was the rate of sustained glucocorticoid-free remission at week 52. The proportion of patients achieving the primary efficacy endpoint of sustained remission for those treated with tocilizumab weekly was 56.0%, for those treated with tocilizumab every other week was 53.1%, placebo-treated with 26-week prednisone taper was 14.0% and 18% for patients in the placebo group with the 52-week prednisone taper ( $p < 0.001$  for comparisons of either active treatment with placebo).<sup>5</sup> The FDA approved dose of tocilizumab for GCA is 162 mg SC given once a week in combination with a glucocorticoid taper.<sup>7</sup>

### Ustekinumab

Ustekinumab (Stelara®), an interleukin (IL)-12/23 inhibitor, was originally approved by the FDA to manage adult patients with moderate to severe PsO when given by SC administration in 2009. Ustekinumab was also approved for the treatment of adults with moderate to severe CD in patients who have failed other treatments in late 2016. Induction dosing for CD begins with a single weight-based IV infusion followed by maintenance dosing of ustekinumab 90 mg SC every 8 weeks.<sup>8</sup> In October 2017, ustekinumab was approved for treatment of adolescent patients aged 12-17 years with PsO.<sup>8</sup> This approval was based on a phase 3 RCT trial of 110 adolescent patients randomized to either placebo or weight-based ustekinumab with a minimum body surface (BSA) involvement of 10%, Psoriasis Area and Severity Index (PASI) score  $> 12$ , and a Physician's Global Assessment (PGA) score  $> 3$  whose disease was inadequately controlled by topical therapy.<sup>9</sup> A greater proportion of ustekinumab-treated patients compared to placebo-treated patients achieved a PGA score of cleared or minimal (69.4% vs. 5.4%;  $p < 0.001$ ), PASI 75 (80.6% vs. 10.8%;  $p < 0.001$ ), and PASI 90 (61.6% vs. 5.4%;  $p < 0.001$ ) at week 12.<sup>9</sup> The only other biologic agent with FDA approval for treatment of PsO in pediatric patients is etanercept.

*Preferred biologic agents for Medicaid Fee-For-Service include etanercept and adalimumab.*

### Conclusion

In the past 2 years adalimumab, ixekizumab, tocilizumab, and ustekinumab have received expanded indications beyond their initial FDA approvals. Etanercept and ustekinumab have received approval for use in pediatric patients with PsO older than 4 and 12 years, respectively. Abatacept is now approved for SC administration in pediatric patients with JIA and is approved to treat PsA.

The biologic agents are available for patients with Medicaid Fee-For-Service insurance through the Oregon Health Plan (OHP). All of the biologic agents require prior authorization but adalimumab and etanercept are preferred agents. Trial and failure of adalimumab and etanercept may be required before advancing to other therapies for AS, PsO, RA or PsA.

Complete evidence reviews are available at [www.orpd.org/drugs/](http://www.orpd.org/drugs/).  
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