WEST VIRGINIA Department of Health & Human Resources
Bureau for Medical Services

DUR Capsules

News and Information for West Virginia Providers from the West Virginia Bureau for Medical Services (WVBMS)

Biologic Immunomodulators
June, 2013

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INTRODUCTION

Biologic immunomodulators are a significant advancement in the treatment of serious inflammatory disorders, such as rheumatoid arthritis (RA), psoriasis (PS), psoriatic arthritis (PA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), Crohn's disease (CD), and ulcerative colitis (UC).[1] Biologic agents are classified as anti-tumor necrosis factor (TNF) or non-TNF biologics. Anti-TNF biologics include adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®) and infliximab (Remicade®).[2] Non-TNF biologics include abatacept (Orencia®), anakinra (Kineret®), rituximab (Rituxan®), tolcilizumab (Actemra®), tofacitinib (Xeljanz®), and ustekinumab (Stelara®).[2] Alefacept (Amevive®) is a non-TNF biologic that was discontinued in the U.S. due to a supply distribution disruption.

Pharmacology

Biologic agents are genetically engineered protein molecules that block the proinflammatory cytokines TNF-α (etanercept, infliximab, adalimumab, certolimumab pegol, golimumab), Interleukin (IL)-1 (anakinra), IL-6 (tocilizumab), and IL-12 and IL-23 (ustekinumab), deplete peripheral B cells (rituximab), bind to CD80/86 on T-cells to prevent the costimulation needed to fully activate T-cells (abatacept), or inhibit janus kinase (tofacitinib)[1]. These agents may be effective when other non-biologic disease-modifying antirheumatic drugs (DMARDs) fail to achieve adequate response, but are considerably more expensive to use. The most commonly used non-biologic DMARDS include hydroxychloroquine (HCQ), leflunomide (LEF), methotrexate (MTX), minocycline, or sulfasalazine. Gold, cyclosporine, and azathioprine are infrequently used.[2] Biologic agents have no toxicity that requires laboratory monitoring, but have a small increased risk for infection.[1]

Cost Considerations

Biologics are classified as specialty drugs, which are the fastest-growing segment of drug expenditures in the U.S. In 2011, specialty medications accounted for 17.6% of total pharmacy costs.[3] The actual growth is masked because about 47% of specialty drugs are billed under medical benefits. Moreover, limited competition and an absence of generic alternatives are driving up the costs of these specialty administered drugs. Although new oral biologic therapies may offer simplified administration (tofacitinib), they are still more costly than more commonly prescribed therapies.

FDA-Approved Indications

Biologics should be properly selected according to FDA-approved product labeling, clinical guidelines and/or clinical trials for individuals who experience failure, allergy, contraindication or intolerance to conventional drug therapy. [1, 7-17] Prescribing these agents safely and cost-effectively requires meeting specific criteria which will be evaluated in this article. Biologic therapies have been shown to be efficacious for a number of FDA-approved indications. Off-label use of these expensive medications can lead to excessive use with a lack of proven clinical benefit. Table 1 lists the most common biologics on the market and the FDA approved indications.

Table 1: FDA-Approved Indications

	Route	Rheumatoid Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Ankylosing Spondylitis	Juvenile Idiopathic Arthritis	Crohn's Disease	Ulcerative Colitis
Abatacept (Orencia®)*	**SC,IV**	**X**				**X**		
Adalimumab (Humira®)*	**SC**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Anakinra (Kineret®)*	**SC**	**X**						
Certolizumab pegol (Cimzia®)*	***SC**	**X**					**X**	
Etanercept (Enbrel®)*	**SC**	**X**	**X**	**X**	**X**	**X**		
Golimumab (Simponi®)*	**SC**	**X**		**X**	**X**			
Infliximab (Remicade®)	**IV**	**X**	**X**	**X**	**X**		**X**	**X**
Rituximab (Rituxan) **#**	**IV**	**X**						
Tocilizumab (Actemra®)	**IV**	**X**				**X**		
Ustekinumab (Stelara®)*	**SC**		**X**					
Tofacitinib (Xeljanz®)**	**Oral**	**X**						

**SC injectable products allow for patient self-administration*
***First oral biologic available in US for rheumatoid arthritis*
 # Rituximab is also indicated as an antineoplastic.

RHEUMATOID ARTHRITIS TREATMENT GUIDELINES AND RECOMMENDATIONS

Guidelines and recommendations for use of biologic agents in the treatment of rheumatoid arthritis were developed by American College of Rheumatology.[2] Guidelines are also available for treatment of psoriasis and psoriatic arthritis[4], juvenile idiopathic arthritis[5], and Crohn's Disease.[6] Recommendations for RA include indications for use, monitoring of side effects, assessment of the clinical response, screening for tuberculosis, and assessment of the roles of cost and patient preference in decision making. Adherence to guidelines and recommendations are voluntary with the ultimate determination for use to be made by the physician in regards to each patient's individual circumstances.

Step Therapy

Recommendations for appropriate use of non-biologic DMARDs and biologic agents in patients who qualify for treatment of RA are as follows:[2]

For patients with early RA (< 6 months), non-biologic DMARD monotherapy is recommended for low, moderate, and high disease activity with absence of poor prognostic features. Non-biologic DMARD combination therapy is recommended with moderate or high disease activity plus poor prognostic features. Combination therapy may include double therapy with MTX + HCQ, MTX + LEF, MTX + sulfasalazine, or sulfasalazine + HCQ or triple therapy with MTX + HCQ + sulfasalazine. Anti-TNF biologics with or without methotrexate are also recommended for high disease activity with poor prognostic features. Infliximab is the only exception and the recommendation is to use it in combination with methotrexate, but not as monotherapy.

In patients with established RA (> 6 months) and low disease activity with absence of poor prognosis after 3 months of therapy with non-biologic DMARD monotherapy, who deteriorate from low to moderate/high disease activity, add MTX, HCQ, or LEF. If after 3 months of MTX or MTX combination therapy and the patient has moderate or high disease activity, add or switch to another non-MTX DMARD.

For patients with established RA (> 6 months) and moderate/high disease activity after 3 months of non-biologic DMARD monotherapy or MTX combination therapy, add or switch to another non-MTX DMARD or as an alternative switch to an anti-TNF biologic, abatacept, or rituximab. If after 3 months of intensified non-biologic

DMARD combination therapy and a patient still has moderate or high disease activity, add or switch to an anti-TNF biologic. If a patient still has moderate or high disease activity after 3 months of anti-TNF biologic therapy and this is due to a lack or loss of benefit, switch to another anti-TNF biologic or a non-TNF biologic. If a patient still has moderate or high disease activity after 6 months of non-TNF biologic and failure is due to lack or loss of benefit, consider switching to another non-TNF biologic or an anti-TNF biologic. A 6 month assessment period is recommended because non-TNF biologics are anticipated to take longer to show efficacy. Combination therapy with more than one biologic agent is not recommended due to risk of serious infections.

If a patient has high disease activity after failing an anti-TNF biologic because of a serious adverse event, switch to a different class, such as a non-TNF biologic. The FDA definition of serious adverse event includes death, life-threatening event, initial or prolonged hospitalization, disability, congenital anomaly, or an adverse event requiring intervention to prevent permanent impairment or damage. If a patient has moderate or high disease activity after failing an anti-TNF biologic because of a nonserious adverse event, switching to another anti-TNF biologic or a non-TNF biologic is acceptable. If a patient has moderate or high disease activity after failing a non-TNF biologic because of an adverse event either serious or nonserious, switching to another non-TNF biologic or an anti-TNF biologic is acceptable.

Disease-Related Concerns[2]

Biologics are associated with risk of adverse events in certain disease states. Recommendations on use of biologic agents in RA patients with comorbidities such as hepatitis, malignancy, or CHF are as follows:

- *Hepatitis B or C.* In patients with untreated chronic hepatitis B and in patients with treated chronic hepatitis B with Child-Pugh class B and higher, biologic agents are not recommended. In RA patients with hepatitis C requiring RA treatment, etanercept could potentially be used.
- *Malignancy.* Biologic agents can increase the risk of developing a malignancy. In RA patients treated for a solid malignancy or nonmelanoma skin cancer greater than 5 years ago, any biologic agent may be initiated or resumed if appropriate. Rituximab is the only biologic agent that is recommended for RA patients with a previously treated solid malignancy or nonmelanoma skin cancer within the last 5 years, or a previously treated melanoma skin cancer or lymphoproliferative malignancy.
- *Congestive Heart Failure.* The anti-TNF biologic agents can worsen heart failure and are not recommended in RA patients with New York Heart Association (NYHA) class III or IV CHF, who have an ejection fraction of 50% or less.
- *Chronic Obstructive Pulmonary Disease (COPD).* Abatacept is associated with an increased risk of adverse effects such as COPD exacerbations including cough, dyspnea, and rhonchi in patients with COPD. In patients with RA and COPD, abatacept should be used with caution and closely monitored for worsening of respiratory status.
- *Demyelinating Central Nervous System Disorders.* Certain biologics, such as adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and tocilizumab can exacerbate demyelinating central nervous system disorders and should be used with caution.

Tuberculosis (TB) Screening[2]

Active TB and reactivation of latent TB infection (LTBI) have been reported with biologic therapy. All RA patients being considered for therapy with biologic agents, regardless of the presence of risk factors for LTBI should be screened. The tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) are recommended as the initial tests in all RA patients starting biologic agents, regardless of risk factors for latent TB infection. The IGRA is recommended over TST in patients who had previously received a BCG vaccination, due to a high false-positive test rates for TST. RA patients with a positive initial or repeat TST or IGRA should have a chest radiograph and if suggestive of active TB, a subsequent sputum examination to check for the presence of active TB is recommended.

RA patients with a negative screening TST or IGRA may not need further evaluation in the absence of risk factors and/or clinical suspicion, such as in patients who may be immunocompromised. Accordingly, a repeat TST or IGRA could be considered 1-3 weeks after the initial negative screening. If the RA patient has active or latent TB based on the test results, appropriate antitubercular treatment and referral to a specialist is recommended. Treatment with biologic agents can be initiated or resumed after 1 month of latent TB treatment with antitubercular medications and after completion of the treatment of active TB, as applicable. Annual testing

in RA patients who live, travel, or work in situations where TB exposure is likely while they continue treatment with biologic agents is recommended.

Age-Related Recommendations [7-17]

Biologics should be prescribed within the age range for which they were approved per manufacturer labeling.

- Anakinra, certolizumab pegol, golimumab rituximab, ustekinumab, and tofacitinib are approved for use in patients 18 years of age and older.
- Infliximab is approved for use in patients with Crohn's disease 6 years of age and older.
- Adalimumab is approved for use in patients with JIA 4 years of age or older.
- Etanercept and tocilizumab are approved for use in patients with JIA 2 years of age or older.
- Abatacept is approved for use in patients with JIA 6 years of age or older.

Vaccinations[2]

It is recommended that all killed (pneumococcal, influenza intramuscular, and hepatitis B) and recombinant (human papillomavirus [HPV] vaccine for cervical cancer) vaccinations should be administered before starting a non-biologic or biologic DMARD, if not previously done to prevent blunting of the vaccination effectiveness. Live vaccines (varicella-zoster, live attenuated influenza) should not be given concurrently with biologic agents or within 3 months of discontinuation to prevent possible risk of secondary transmission of infection.

CONCLUSION

Many state Medicaid programs are improving patient therapeutic outcomes by including biologic immunomodulators on their drug formularies. Because biologic agents are so specialized and costly, the West Virginia Medicaid program requires use of a preferred drug list. Preferred and non-preferred agents and prior authorization criteria are listed in table 2. Our goals are to guide health care providers to prescribe the right drug at the right time.

Table 2: Cytokine and Cell Adhesion Molecule (CAM) Antagonists

Preferred	Non-Preferred	PA Criteria
ENBREL (Etanercept) HUMIRA (Adalimumab)	CIMZIA (Certolimumab pegol) KINERET (Anakinra) ORENCIA (Abatacept) SIMPONI (Golimumab) STELARA (Ustekinumab) XELJANZ (Tolfacitinab)	Thirty (30) day trials of each of the preferred agents are required before a non-preferred agent will be approved.
Xeljanz will be approved after a thirty (30) day trial of one of the preferred agents if each of the following criteria are met: 1. Diagnosis of moderately or severely active rheumatoid arthritis 2. Negative tuberculin skin test before initiation of therapy 3. Intolerance to or an inadequate response to a sixty (60) day trial methotrexate 4. The patient is eighteen (18) years of age or older 5. There are no plans to use tolfacitinab in combination with biologic DMARDS or potent immunosuppressants (i.e. azathioprine or cyclosporine) 6. The dose is limited to two (2) tablets daily		
Enbrel and Humira will be authorized for the treatment of psoriasis or psoriatic arthritis if the following criteria are met: 1. Patient is eighteen (18) years of age or older 2. Diagnosis of moderate to severe psoriasis (≥10% of the body affected) 3. Initial treatment plan is done in consultation with a dermatologist or rheumatologist 4. Prior treatment with a potent topical corticosteroid plus calcipotriol 5. Prior treatment with a Vitamin D analogue 6. Prior treatment with phototherapy 7. Prior treatments with a disease-modifying agent (DMARD) such as methotrexate, cyclosporine, acitretin, etc.		

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