oscar

Clinical Guideline

Guideline Number: CG064, Ver. 2

Concomitant (Concurrent) use of Biologics (Biologic Response Modifiers Therapies) and targeted synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Biologic response modifier therapies (biologics) are special drugs that are genetically engineered to target specific parts of the immune system, suppress the immune system and disrupt inflammation for autoimmune diseases. Biologics are also referred to as immunomodulators and cytokine inhibitors (anticytokine). They are used in treatment of various diseases such as axial ankylosing spondylitis, graft versus host disease, juvenile idiopathic arthritis, rheumatoid arthritis, psoriatic arthritis, psoriasis, and inflammatory bowel disease. They can also target specific cancer cells or lessen side effects of cancer treatment. Biologics can be given intravenously (through the vein), subcutaneously (injected into fatty tissue), or orally.

Definitions

"Concomitant" is the concurrent use of a drug with another drug.

Biologic drug class by type of therapeutic molecule/agent:

- "Soluble receptor antagonists"are molecules that bind the target cytokine while they are in the blood and prevent the cytokines from interacting with cell surface receptors.

- "Monoclonal antibodies"are modified antibodies from human or nonhuman species and mass produced in a laboratory to target and recognize specific antigens that cause disease. They have a higher affinity for antigens than soluble receptor antagonists.
- "Cell surface receptor antagonist proteins" are inactive proteins that compete with cytokines for binding to the cytokine's membrane receptor and must bind more than 90 percent of the cell surface receptors to be effective.

Biologic response modifier therapies (biologics) drug class by mechanism of action and area of target:

- "Anti-integrin antibody" binds and blocks the interaction between integrin alpha-4-beta-7 and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in the gut which reduces the chronic inflammatory process present in both ulcerative colitis and Crohn's disease. FDA approved anti-integrin drugs are natalizumab and vedolizumab.
- "B-cells inhibitors" prevent the activation of B-cells that activate T-cells that activate cytokines that affect interleukin,Tumor Necrosis Factor-alpha, vascular endothelial growth factor (VEGF), monocyte chemotactic protein (MCP), and macrophage migration inhibitory factor (MIF). B-cells start a chain reaction that causes inflammation. Common examples of B-cell inhibitors are rituximab and belimumab.
- "Interleukin (IL) inhibitors" target interleukins in the body that cause inflammation. Common IL-1 inhibitors are anakinra, canakinumab, and rilonacept. Common examples of IL-6 inhibitors are tocilizumab and sarilumab. Examples of IL-17 inhibitors are secukinumab, ixekizumab, or brodalumab. Common examples of IL-12/23 blockades are ustekinumab and guselkumab.
- "T-cells inhibitors" prevent activation of an array of specific cytokines which influence systemic inflammation. T-cells produce TNF and IL-2. B-cells produce IL-4, IL-5, IL-10, and IL-13. A T-cell co-stimulation blocker is abatacept.
- "Tumor Necrosis Factor (TNF) inhibitors" target tumor necrosis factor-alpha which is an inflammatory cytokine produced by macrophages/monocytes in the body during inflammation that lead to cell death. TNF inhibitors block this inflammatory process and slow disease progression. Common examples are infliximab, adalimumab, certolizumab, etanercept, golimumab.

"Disease-modifying antirheumatic drugs (DMARDs)" suppress the immune system and inflammatory response and they are grouped as 1) conventional/traditional DMARDs, 2) targeted synthetic DMARDs (tsDMARD), or 3) biologic DMARDs for treating rheumatoid arthritis. Conventional DMARDs are drugs such as methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide prescribed as an initial course of therapy. Targeted synthetic DMARDs are drugs such as baricitinib, tofacitinib, apremilast; they are typically prescribed as an alternative to members who failed or have contraindications to conventional DMARDs or biologic DMARDs. Biologic DMARDs refer to the biologic response modifier therapies above for rheumatoid arthritis typically prescribed for members who have resistance to initial therapy.

"Kinase inhibitors"are not made from recombinant DNA and are not proteins; they are not considered biologics. Kinase inhibitors interrupt Janus kinases (JAK) that are critical for signal transduction to the

nucleus from the common gamma chain of the plasma membrane receptors for interleukin (IL)-2, -4, -7, -9, -15, and -21. These medications can be taken orally as pills such as Tofacitinib and Baricitinib.

Experimental or Investigational / Not Medically Necessary

The Plan does not consider medically necessary the concurrent use of a biologic when the following criteria are met:

1. The use of two or more biologic agents (Anti-integrin antibody, B-cell inhibitors, IL inhibitors, T-cell inhibitors, TNF inhibitors), for purposes of the same diagnosis during the same time period (unless indicated that there is greater efficacy with concurrent use of biologics by FDA prescribing guidelines, compendia, national society guidelines, clinical criteria or high-quality clinical evidence); ***or***
2. The use of a biologic agent with a targeted synthetic DMARD (tsDMARD), for purposes of the same diagnosis during the same time period, (unless indicated that there is greater efficacy with concurrent use of biologics by FDA prescribing guidelines, compendia, national society guidelines, clinical criteria or high-quality clinical evidence) for the following, but not limited to:
    a. An oral Janus kinase (JAK) inhibitor (e.g., Olumiant (baricitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), Xeljanz XR (tofacitinib)); ***or***
    b. An oral phosphodiesterase-4 (PDE4) inhibitor (e.g., Otezla (apremilast)).

Oral tsDMARDs coverage is subject to plan benefits and are typically billed through a member's pharmacy benefits.

Concomitant Use of Biologics

There is limited research of the benefit from use of multiple biologics; the concomitant use of biologics increases the susceptibility to infection. Practice guidelines from national societies such as American College of Gastroenterology, American College of Rheumatology, American Academy of Dermatology, National Comprehensive Cancer Network, National Psoriasis Foundation, do not currently include the concurrent use of biologics (B-cell inhibitors, IL inhibitors, T-cell inhibitors, TNF inhibitors) as part of general guidance. Further guidance can be obtained by FDA prescribing labels for indications and contraindications, warnings and precautions.

Concomitant use of Anti-integrin antibody

The Plan does not consider medically necessary the use of anti-integrin antibodies (e.g., Tysabri (natalizumab), Entyvio (vedolizumab)) concurrently with another Anti-integrin antibody or TNF inhibitors due to risk of drug interactions and increased infections as per prescribing label.

Concomitant use of B-cells inhibitors

Other biologics

The Plan does not consider medically necessary the concomitant use of b-cell inhibitors with other biologics due to limited evidence.

***Concomitant** Use of IL inhibitors*

Other biologics

The Plan does not consider medically necessary the IL inhibitor (e.g., Kineret) with concurrent use of TNF blocker (e.g., Infliximab), as there is no added clinical benefit per the FDA label. IL inhibitor (e.g., Ustekinumab) with concurrent use of other biologic agents has not been evaluated in clinical studies of psoriasis.

Concomitant use a of Janus kinase (JAK) inhibitor

The Plan does not consider medically necessary the Rinvoq (upadacitinib) extended-release tablets, Olumiant (baricitinib), Xeljanz (tofacitinib) tablets, Xeljanz (tofacitinib) extended release tablets, or Xeljanz (tofacitinib) Oral Solution concurrently with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine as these combinations are not recommended for use in the prescribing label. described not recommended for use in the prescribing label.

Concomitant Use of T-cell co-stimulation blocker

TNF Inhibitor, Biologic DMARDs, JAK inhibitors

The Plan does not consider medically necessary the T-cell co-stimulation blocker when prescribed with a TNF inhibitor, biologic DMARDs, or Janus kinase inhibitors as it is not recommended as per FDA label. Clinical trials in ORENCIA STUDY IV have failed to show benefit and efficacy of concomitant use of T-cell co-stimulation blocker, Abatacept (Orencia), with TNF inhibitor therapy; the clinical trial showed patients experienced more infections, serious infections, and lack of enhanced efficacy with concurrent treatment.

Concomitant use of Otezla (apremilast)

A phosphodiesterase-4 (PDE4) inhibitor is not recommended for use concurrently with biologics for Behcet's Disease, moderate-to-severe plaque psoriasis, or active psoriatic arthritis, but as an alternative to members who failed or have contraindications to reach therapeutic targets with conventional DMARDs and/or biologics as per Clinical Pharmacology and Lexicomp drug interactions.

***Concomitant** Use of TNF inhibitors*

Other biologics

The Plan does not consider medically necessary the TNF inhibitors (e.g., Infliximab, Etanercept) when prescribed with another biologic agent such as IL inhibitors (e.g., Kineret) or other biologic agents in different drug classes due to insufficient evidence on concurrent use as per the FDA. Evidence for the treatment of inflammatory bowel disease with TNF inhibitors and concurrent IL inhibitors have been limited to case reports and small case series that raise safety concerns as per Clinical Gastroenterology and Hepatology in 2018.

Applicable Billing Codes (HCPCS/CPT Codes)

The following codes are used for the medications considered biologics in this guideline. Concurrent use of biologics is not considered medically necessary. Coverage of one biologic is subject to members' plan benefits, the Plan Clinical Guideline: Preferred Physician-Administered Drugs (CG052, Ver. 6), and medical necessity criteria. This is not an exhaustive list of all biologics.

CPT/HCPCS Codes for biologics	
Anti-integrin antibodies	
J2323	Injection, natalizumab, 1 mg
J3380	Injection, vedolizumab, 1 mg
B-cell inhibitors	
Code	*Description*
J0490	Injection, belimumab, 10 mg
J9311	Injection, rituximab 10 mg and hyaluronidase
J9312	Injection, rituximab, 10 mg
IL inhibitors	
C9399/J3590	[Anakinra] Unclassified biologics
C9399/J3590	[Brodalumab] Unclassified biologics
C9399/J3590	[Ixekizumab] Unclassified biologics
C9399/J3590	[Risankizumab] Unclassified biologics
C9399/J3590	[Sarilumab] Unclassified biologics
C9399/J3590	[Secukinumab] Unclassified biologics
J0638	Injection, canakinumab, 1 mg
J1628	Injection, guselkumab, 1 mg
J2793	Injection, rilonacept, 1 mg
J3262	Injection, tocilizumab, 1 mg
J3357	Ustekinumab, for subcutaneous injection, 1 mg

J3358	Ustekinumab, for intravenous injection, 1 mg
T-cell inhibitors	
J0129	Injection, abatacept, 10 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
TNF inhibitors	
J0135	Injection, adalimumab, 20 mg
J0717	Injection, certolizumab pegol, 1 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J1438	Injection, etanercept, 25 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J1602	Injection, golimumab, 1 mg, for intravenous use
J1745	Injection, infliximab, excludes biosimilar, 10 mg
Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg
Q5109	Injection, infliximab-qbtx, biosimilar, (Ixifi), 10 mg
Q5121	Injection, infliximab-axxq, biosimilar, (AVSOLA), 10 mg

References

1. Arthritis Foundation. *Biologics.* Arthritis.org. https://www.arthritis.org/drug-guide/biologics/biologics
2. Ballow, M., & Fleisher, T.A. (April 2021). *Secondary immunodeficiency induced by biologic therapies.* UpToDate.com. https://www.uptodate.com/contents/secondary-immunodeficiency-induced-by-biologic-therapies?search=B-cell%20inhibitors%20concomitant&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2
3. Burmester, G.R. (Nov. 2020). *Overview of biologic agents and kinase inhibitors in the rheumatic diseases.* UpToDate.com. https://www.uptodate.com/contents/overview-of-biologic-agents-and-kinase-inhibitors-in-the-rheumatic-diseases?search=biologics&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H3220612907
4. Cohen, S., & Cannella, A. (Dec 2019). *Patient education: Disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (Beyond the Basics).* UpToDate.com. https://www.uptodate.com/contents/disease-modifying-antirheumatic-drugs-dmards-in-rheumatoid-arthritis-beyond-the-basics#H2
5. Cohen, S., & Cannella, A. (Jan 2020). *Treatment of rheumatoid arthritis in adults resistant to initial conventional nonbiologic DMARD therapy.* UpToDate.com.

https://www.uptodate.com/contents/treatment-of-rheumatoid-arthritis-in-adults-resistant-to-initial-conventional-nonbiologic-dmard-therapy?search=targeted%20synthetic%20disease-modifying%20antirheumatic%20drug&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

6. Elsevier. (Oct 2019). *Apremilast, Otezla, Description/Classification*. www.clinicalkey.com. https://www.clinicalkey.com/pharmacology/monograph/3844?sec=mondesc&n=Otezla
7. Feuerstein, J.D., Isaacs, K.L., Schneider, Y., et al. (April 2020). AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*,158(5), 1450-1461. doi:10.1053/j.gastro.2020.01.006.
8. Hirten, R.P., Iacucci, M., Shah, S., et al. (Sept 2018). Combining Biologics in Inflammatory Bowel Disease and Other Immune Mediated Inflammatory Disorders. *Clinical Gastroenterology and Hepatology,* 16(9), 1374-1384. Doi: https://doi.org/10.1016/j.cgh.2018.02.024
9. Manis, J.P. (Dec. 2020). *Overview of therapeutic monoclonal antibodies.* UpToDate.com. https://www.uptodate.com/contents/overview-of-therapeutic-monoclonal-antibodies?search=monoclonal%20antibodies&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
10. Menter, A., Strober, B.E., Kaplan, D.H., et al. (Feb 2019). Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol,* 80(4), 1029-1072. doi: 10.1016/j.jaad.2018.11.057
11. National Cancer Institute at the National Institutes of Health. *Biological response modifier therapy.* cancer.gov. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/biological-response-modifier-therapy
12. National Comprehensive Cancer Network. (March 2021). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), B-Cell Lymphomas, Version 3.2021. NCCN.org. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
13. National Comprehensive Cancer Network. (March 2021). Clinical Practice Guidelines in Oncology (NCCN Guidelines), Hodgkin Lymphoma, Version 3.2021. NCCN.org. https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf
14. Olumiant [package insert]. Indianapolis, IN: Eli Lilly and Company; 2020. https://uspl.lilly.com/olumiant/olumiant.html#pi
15. RINVOQ [package insert]. North Chicago, IL: AbbVie Inc. https://www.rxabbvie.com/pdf/rinvoq_pi.pdf
16. Sapkota, B., Makandar, S.N., & Acharya, S. (2020). Biologic Response Modifiers (BRMs). *StatPearls [Internet],* Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK542200/
17. Singh, J.A., Guyatt, G., Ogdie, A., et al. (Nov. 2018). 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis. *Arthritis & Rheumatology,* 1-28. doi: 10.1002/art.40726
18. Rigby, W.F.C, Mease P.J., Olech, E., et al. (May 2013). Safety of Rituximab in Combination with Other Biologic Disease-modifying Antirheumatic Drugs in Rheumatoid Arthritis: An Open-label Study. *The Journal of Rheumatology*, 40 (5), 599-604. DOI: https://doi.org/10.3899/jrheum.120924
19. Rubin, D.T., Ananthakrishnan, A.N., Siegel, C.A., et al. (Feb. 2019). ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*, 114(3), 384-413. Doi: 10.14309/ajg.0000000000000152
20. STELARA® (ustekinumab). (2020). STELARA® (ustekinumab) Has Expanded First-Line Biologic* Access for Your Patients1. Concomitant Therapies. Stelarahcp.com. https://www.stelarahcp.com/psoriatic-arthritis/support
21. U.S. Food & Drug Administration (FDA). Resources for You (Biologics). Fda.gov. https://www.fda.gov/vaccines-blood-biologics/resources-you-biologics
22. U.S. Food & Drug Administration (FDA). (March 2020). *ENTYVIO (vedolizumab) for injection, for intravenous use.* Fda.gov. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125476s025s030lbl.pdf

23. U.S. Food & Drug Administration (FDA). (June 2020). *ORENCIA (abatacept) for injection, for intravenous use. ORENCIA (abatacept) injection, for subcutaneous use.* Packageinserts.bms.com. https://packageinserts.bms.com/pi/pi_orencia.pdf
24. U.S. Food & Drug Administration (FDA). (April 2020). *OTEZLA (apremilast) tablets, for oral use.* FDA.gov. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205437Orig1s008lbl.pdf
25. U.S. Food & Drug Administration (FDA). (May 2020). *REMICADE (infliximab) for injection, for intravenous use.* Fda.gov. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103772s5389s5391s5394lbl.pdf
26. U.S. Food & Drug Administration (FDA). (June 2020). *TYSABRI (natalizumab) injection, for intravenous use.* www.tysabri.com. https://www.tysabri.com/content/dam/commercial/tysabri/pat/en_us/pdf/tysabri_prescribing_information.pdf
27. Yang, E., Panaccione, N., Whitmire, N., et al. (April 2020). Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. *Alimentary Pharmacology and Therapeutics,* 51(11), 1031-1038. https://doi.org/10.1111/apt.15719

Clinical Guideline Revision / History Information

Original Date: 6/24/2021 Reviewed/Revised: 12/01/2021