Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Washington Pharmacy Advisory Committee Meeting

June 17th, 2020

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Agenda Topics

- Overview of Disease State
- Indications
- Dosage & Formulations
- Guideline Updates

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Magellan Medicaid Administration

Oncology: Oral- Hematologic

Overview of Disease State – Oncology, Oral- Hematological

- **Acute Myeloid Leukemia (AML)**
  - Most common form of acute leukemia among adults estimated 5,930 cases diagnosed and 1,500 deaths in the US in 2019
  - In patients who obtain a CR, 3 year survival is 45%, remission rates are inversely proportional to age
  - Cytogenetics plays a large role in determining prognosis and treatment options
  - Acute Promyelocytic Leukemia (APL) is a subtype of AML with distinct features and treatment
- **Chronic Myeloid Leukemia (CML)**
  - Comprises 15% of all adult leukemias although does occur in all age groups, including pediatrics with an estimated 8,990 diagnosed cases and 1,140 deaths
  - 3 phases of disease-chronic, accelerated and blast
  - Gene mutation called the Philadelphia chromosome has been identified which involves a translocation t(9;22), also known as BCR-ABL translocation
  - The discovery of tyrosine kinases that inhibit BCR-ABL has revolutionized the treatment of CML making long-term remission a reality
- **Multiple Myeloma**
  - Accounts for > 15% of all hematologic malignancies with 32,110 projected diagnoses and 12,960 deaths projected in 2019
  - Usually responds to initial chemotherapy but responses are often transient and patients often receive re-treatment with multiple different agents
  - Malignant neoplasm of plasma cells resulting in accumulation of plasma cells in the bone marrow
  - Constellation of symptoms associated with multiple myeloma; often an indicator of more severe disease is known as “CRAB”- hypercalcemia, renal insufficiency, anemia and lytic bone lesions

Overview of Disease State – Oncology, Oral- Hematological

- **Non-Hodgkin's Lymphomas (NHL)**
  - Lymphomas are a heterogeneous group of malignancies that originate in the immune cells (predominantly B-cells and T-cells) of the lymphoid tissue
  - Leukemias and lymphomas are similar diseases with overlapping characteristics
  - Most lymphomas involve tumor invasion of the lymph nodes and other tissues, while the malignant clone in most leukemias predominates in the bone marrow
  - The most common presentation is that of a solid tumor, but NHL can also present as circulating tumor cells in the peripheral blood
- ***Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)***
  - Most prevalent adult leukemia with a median age at diagnosis of 72 years
  - Treatment is individualized as some patients may have indolent disease while others require treatment; a small percentage of patients undergo Richter's transformation to a more aggressive non-Hodgkin's lymphoma
  - Cytogenetic abnormalities are of prognostic significance and can help to drive treatment options
- ***Mantle Cell Lymphoma (MCL)***
  - Possesses characteristics of both indolent and aggressive NHLs. Median OS is 3 years but no evidence of a survival plateau, similar to indolent leukemias
  - Chromosomal translocation t(11;14) is usually present

Background & Guidelines – Oncology, Oral- Hematological

- **Graft versus Host Disease (GVHD)**
  - Although the exact cause is unknown, graft versus host disease (GVHD) is an immune-mediated disease that can result following complications of hematopoietic cell transplant in which the transplanted cells (graft) recognize the recipient's body as foreign
  - Chronic GVHD (cGVHD) is generally an extension of acute GVHD that often develops more than 100 days after transplant, but it can also occur in those without acute GVHD
  - Symptoms include ocular manifestations (e.g., burning, irritation, photophobia, pain), oral or gastrointestinal (GI) manifestations (e.g., food sensitivity, oral dryness, pain, weight loss), respiratory manifestations (e.g., wheezing, dyspnea, cough), and neuromuscular manifestations (weakness, neuropathic pain, muscle cramps)
  - The American Society for Blood and Marrow Transplantation has a clinical practice guideline around the first- and second-line treatment of acute GVHD
    - These guidelines state that corticosteroids are the standard of care for the initial treatment of acute GVHD (aGVHD) and note that the literature does not support the choice of any specific agent for secondary therapy of aGVHD
    - These guidelines were published prior to the May 2019 FDA approval of ruxolitinib (Jakafi) for the treatment of corticosteroid-refractory aGVHD in adult and pediatric patients ≥ 12 years of age

Guidelines – Oncology, Oral- Hematological

- **Acute Myeloid Leukemia (AML)- NCCN Guidelines, 2020**
  - Standard Induction:
    - Include oral midostaurin (Rydapt) in combination with cytarabine, with and without daunorubicin, as part of standard induction, consolidation, and post-remission therapies for patients with FLT3-mutated AML
  - Intensive Remission Induction Therapy:
    - Adult patients who are candidates for intensive remission induction therapy with unfavorable risk cytogenetics may receive venetoclax (Venclexta) in combination with hypomethylating agents (decitabine, azacitidine) or cytarabine (all category 2A), while patients aged ≥ 60 years who are not candidates for intensive remission induction or who decline intensive remission and are without actionable mutations may be treated with venetoclax or glasdegib (Daurismo) among other options (category 2A)
    - Venetoclax is also listed as an option along with enasidenib (Idhifa) or ivosidenib (Tibsovo) for IDH2-mutated or IDH1-mutated AML, respectively (all category 2A)
  - Post-induction Therapy:
    - For post-induction therapy in patients who have a response to lower intensity therapy, the lower intensity regimen should be continued, including enasidenib (IDH2-mutated), ivosidenib (IDH1-mutated), venetoclax with either a hypomethylating agent or cytarabine, or glasdegib with low-dose cytarabine (all category 2A)
  - Relapsed/Refractory AML:
    - For patients with relapsed/refractory AML who have IDH1 or IDH2 mutations, therapy with enasidenib or ivosidenib respectively may be utilized (category 2A), and for patients with FLT3-ITD or FLT3-TKD mutations, gilteritinib (Xospata) is a category 1 recommendation
    - The guidelines note that these drugs increase the risk for differentiation syndrome and hyperleukocytosis which may require treatment with hydroxyurea and corticosteroids to mitigate
  - The NCCN guidelines note that in the event of relapsed/refractory disease after completion of consolidation, targeted therapies may be retried if the drugs were not administered continuously and not stopped due to the development of clinical resistance

Overview of Disease State – Oncology, Oral- Hematological

- ONCOLOGY AGENTS : ALKYLATING AGENTS – ORAL
  - Myleran
- ONCOLOGY AGENTS : ANTIMETABOLITES – ORAL
  - Xeloda
  - Capecitabine
  - Mercaptopurine
  - Purixan
  - Tabloid
- ONCOLOGY AGENTS : ANTINEOPLASTICS MISC – ORAL
  - Hydrea
  - Hydroxyurea
  - Matulane
- ONCOLOGY AGENTS : BCL-2 INHIBITORS – ORAL
  - **Venclexta**
- ONCOLOGY AGENTS : HISTONE DEACETYLASE INHIBITORS – ORAL
  - Farydak
  - Zolinza
- ONCOLOGY AGENTS : IMMUNOMODULATORS – ORAL
  - Pomalyst
- ONCOLOGY AGENTS : ISOCITRATE DEHYDROGENASE-1 (IDH1) INHIBITORS – ORAL
  - Tibsovo
- ONCOLOGY AGENTS : ISOCITRATE DEHYDROGENASE-2 (IDH2) INHIBITORS – ORAL
  - Idhifa
- ONCOLOGY AGENTS : JANUS ASSOCIATED KINASE (JAK) INHIBITORS – ORAL
  - **Inrebic**
  - **Jakafi**
- ONCOLOGY AGENTS : PHOSPHATIDYLINOSITOL 3-KINASE (PI3K) INHIBITORS – ORAL
  - Piqray
  - Copiktra
  - Zydelig
- ONCOLOGY AGENTS : PROTEASOME INHIBITORS – ORAL
  - Ninlaro
- ONCOLOGY AGENTS : XPO1 INHIBITORS – ORAL
  - **Xpovio**
- IMMUNE MODULATORS: MYELODYSPLASTIC SYNDROMES
  - **Revlimid**

Overview of Disease State – Oncology, Oral- Hematological

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Oncology, Oral- Hematological

- venetoclax (Venclexta)
  - **August 2019: FDA is alerting the public of risk associated with the investigational use of venetoclax (Venclexta) in patients with multiple myeloma (MM) (off-label use) based on data from the BELLINI clinical trial, which reported after a median follow-up of 17.9 months, an increased risk of death with venetoclax (21.1%) compared to placebo (11.3%) when used in combination with bortezomib and dexamethasone in patients with Multiple Myeloma.**
  - **Indication**
    - For the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
    - In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy
    - This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
  - **Warnings and Precautions**
    - Tumor Lysis Syndrome: Anticipate TLS; assess risk in all patients. Premedicate with anti-hyperuricemics and ensure adequate hydration
    - Neutropenia: Monitor blood counts and for signs of infection; manage as medically appropriate
    - Infections: Monitor for signs and symptoms of infection and treat promptly
      - Withhold treatment for Grade 3 and higher infection until resolution
    - Immunization: Do not administer live attenuated vaccines prior to, during, or after treatment
  - **Dosage**
    - See Full Prescribing Information or TCR for recommended starting and ramp-up dosages
  - **Availability**
    - Tablets: 10, 50, 100 mg

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Overview of Disease State – Oncology, Oral- Hematological

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  - Tibsovo
- ONCOLOGY AGENTS : ISOCITRATE DEHYDROGENASE-2 (IDH2) INHIBITORS – ORAL**– NO UPDATES**
  - Idhifa
- ONCOLOGY AGENTS : JANUS ASSOCIATED KINASE (JAK) INHIBITORS – ORAL
  - **Inrebic**
  - **Jakafi**
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  - Zydelig
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  - **Revlimid**

Oncology, Oral- Hematological

- fedratinib (Inrebic)
  - **August 2019: FDA approved fedratinib (Inrebic), a kinase inhibitor, for the treatment of adults with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis**
  - **Indication**
    - **Treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)**
  - **Warnings and Precautions**
    - **Black Box Warning: Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated treated with Inrebic. Wernicke's encephalopathy is a neurologic emergency. Assess thiamine levels in all patients prior to starting Inrebic, periodically during treatment, and as clinically indicated**
    - **Anemia and Thrombocytopenia: Manage by dose reduction, interruption, or transfusion**
    - **Gastrointestinal Toxicity: Manage by dose reduction or interruption if patient develops severe diarrhea, nausea, or vomiting. Prophylaxis with anti-emetics and treatment with anti-diarrhea medications are recommended**
    - **Hepatic Toxicity: Manage by dose reduction or interruption**
    - **Amylase and Lipase Elevation: Manage by dose reduction or interruption**
    - **Avoid in patients with severe hepatic impairment, patients who are breast-feeding, or strong CYP3A4 Inducers**
  - **Dosage**
    - **400 mg orally once daily with or without food for patients with a baseline platelet count of greater than or equal to 50 x 109 /L**
  - **Availability**
    - **Capsules: 100 mg**

Oncology, Oral- Hematological

- ruxolitinib (Jakafi)
  - **May 2019: FDA approved an expanded indication for steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients ≥ 12 years of age**
  - **Indication**
    - **Intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults**
    - **Polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea**
    - **Steroid-refractory acute graft-versus-host disease in adult and pediatric patients 12 years and older**
  - **Warnings and Precautions**
    - **Thrombocytopenia, Anemia and Neutropenia: Manage by dose reduction, or interruption, or transfusion**
    - **Risk of Infection: Assess patients for signs and symptoms of infection and initiate appropriate treatment promptly. Serious infections should have resolved before starting therapy with Jakafi**
    - **Symptom Exacerbation Following Interruption or Discontinuation: Manage with supportive care and consider resuming treatment with Jakafi**
    - **Risk of Non-Melanoma Skin Cancer: Perform periodic skin examinations**
    - **Lipid Elevations: Assess lipid levels 8-12 weeks from start of therapy and treat as needed**
  - **Dosage**
    - **Doses should be individualized based on safety and efficacy. Starting doses per indication are noted in TCR**
  - **Availability**
    - **Tablets: 5, 10, 15, 20, 25 mg**

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Oncology, Oral- Hematological

- selinexor (Xpovio)
  - **July 2019: FDA approved selinexor (Xpovio) a nuclear export inhibitor indicated in combination with dexamethasone to treat adults with relapsed or refractory multiple myeloma (RRMM) who have received ≥ 4 prior therapies and whose disease is refractory to ≥ 2 proteasome inhibitors, ≥ 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody**
  - **Indication**
    - **Treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody**
  - **Warnings and Precautions**
    - **Thrombocytopenia: Monitor platelet counts at baseline, during treatment, and as clinically indicated. Manage with dose interruption, reduction, and supportive care**
    - **Neutropenia: Monitor neutrophil counts at baseline, during treatment, and as clinically indicated. Manage with dose interruption and/or reduction and granulocyte colony-stimulating factors (G-CSFs)**
    - **Gastrointestinal Adverse Reactions: Nausea, vomiting, diarrhea, anorexia, and weight loss may occur. Provide antiemetic prophylaxis. Manage with dose interruption and/or reduction, antiemetics, and supportive care**
  - **Dosage**
    - **Recommended starting dosage of XPOVIO is 80 mg in combination with dexamethasone taken orally on Days 1 and 3 of each week**
  - **Availability**
    - **Tablets: 20 mg**

Overview of Disease State – Oncology, Oral- Hematological

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Oncology, Oral- Hematological

- lenalidomide (Revlimid)
  - **October 2019: FDA approved lenalidomide (Revlimid) in combination with a rituximab product for previously treated follicular lymphoma (FL) and previously treated marginal zone lymphoma (MZL)**
  - **Indication**
    - Multiple myeloma (MM), in combination with dexamethasone
    - MM, as maintenance following autologous hematopoietic stem cell transplantation (auto-HSCT)
    - Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities
    - Mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib
    - **Previously treated follicular lymphoma (FL), in combination with a rituximab product**
    - **Previously treated marginal zone lymphoma (MZL), in combination with a rituximab product**
  - **Warnings and Precautions**
    - **Black Box Warning: Embryo-fetal toxicity**
    - **Black Box Warning: Hematologic Toxicity (Neutropenia and Thrombocytopenia)**
    - **Black Box Warning: Venous and Arterial Thromboembolism**
  - **Dosage**
    - **Doses should be individualized based on indication. Starting doses per indication are noted in TCR**
  - **Availability**
    - **Capsules: 2.5, 5, 10, 15, 20, and 25 mg**

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Cytokine and CAM Antagonists

Cytokine & CAM Antagonist - Disease State Description

- Cytokines and cell-adhesion molecules (CAMs) are chemical mediators involved in inflammatory processes throughout the body

Cytokines

- Small proteins secreted in response to an immune stimulus for the purpose of mediating and regulating immunity, inflammation, and hematopoiesis
- Derived from monocytes and macrophages and induce gene expression of a number of proteins that contribute to the inflammatory response
- The actions of the individual cytokines are widely varied and they contribute to fibrosis and tissue degeneration associated with chronic inflammation, primarily by inducing the proliferation of fibroblasts and collagenase
- The pro-inflammatory cytokines, tumor necrosis factor (TNF), and interleukin (IL)-1, are involved in tissue destruction in many chronic inflammatory diseases affecting various organs
  - TNFα also has a role in Crohn's disease in stimulation of inflammation

European Respiratory Journal, 2003

Cytokine & CAM Antagonist - Disease State Description

Cell Adhesion Molecules (CAM)

- Cell surface proteins involved in the binding of cells, usually leukocytes, to each other, endothelial cells, or the extracellular matrix
- Specific signals produced in response to wounds and infection control the expression and activation of these molecules
- Most of the CAMs characterized fall into 3 general families of proteins:
  - The immunoglobulin (Ig) superfamily
    - The adhesion molecules that bind to integrins on leukocytes and mediate their flattening onto the blood vessel wall
  - The integrin family
    - Consists of an α chain and a ß chain that mediate cell-to-cell interactions, such as leukocyte adherence to the vascular endothelium
  - The selectin family
    - Involved in the adhesion of leukocytes to activated endothelium followed by extravasation through the blood vessel walls into lymphoid tissues and sites of inflammation
  - Other proteins that are functionally classified as CAMs are involved in strengthening the association of T cells with antigen-presenting cells or target cells, in T cell activation, and in recirculating lymphocytes back to the circulation via the lymphatic system
- Different CAMs have been implicated in inflammatory, fibrotic, and autoimmune diseases

European Respiratory Journal, 2003

Ulcerative Colitis - Disease State Description

- Ulcerative colitis (UC) is a chronic inflammatory disease primarily affecting the colon and rectum
- UC affects approximately 1,000,000 people in the United States (US) and the incidence continues to increase worldwide. The Center for Disease Control and Prevention (CDC) estimates the current prevalence of UC at 238 per 100,000 adults
  - UC may present at any age, but onset typically peaks between 15 and 30 years of age
- The disease is characterized by superficial infiltration of the bowel wall by inflammatory white cells, resulting in multiple mucosal ulcerations and crypt abscesses
- The predominant symptom of UC is diarrhea, which is usually associated with blood in the stool
  - Additional symptoms may include pain in the lower quadrant or rectum along with systemic features, including fever, malaise, and weight loss (which are more common if a greater portion of the colon is affected)
  - The initial attack of UC may be fulminant with bloody diarrhea, but the disease more commonly begins indolently, with non-bloody diarrhea progressing to bloody diarrhea
  - UC can present initially with any extent of anatomic involvement ranging from disease confined to the rectum to the entire large intestine (pancolitis)
  - Most commonly, UC follows a chronic intermittent course with long periods of quiescence interspersed with acute attacks lasting weeks to months. However, a significant percentage of patients suffer a chronic continuous course

Centers for Disease Control and Prevention, 2015

Ulcerative Colitis - Treatment Guidelines

American Gastroenterological Association (AGA), 2019

- Agents in this class are not addressed in their recommendations for induction and maintenance of mildly active disease
- For induction of remission in moderately to severely active UC,
  - The group recommends oral systemic corticosteroids
  - TNF antagonists (adalimumab, golimumab, infliximab) and vedolizumab are also recommended, and if infliximab is used, it should be used with a thiopurine
    - Notably, the ACG states that robust data on combining TNF antagonists and immunomodulator therapy in moderately to severely active UC exist only for infliximab and thiopurines
  - Vedolizumab or tofacitinib is recommended in patients who have previously failed TNF antagonist therapy
  - In patients who were previously TNF antagonist responders but are subsequently having an inadequate response, the group recommends monitoring of serum drug levels
  - In addition, the group states that patients who are primary nonresponders to TNF antagonists should be considered for an alternative mechanism of diseases control rather than a switch to another TNF antagonist; however, for secondary failure (initial response to TNF antagonist with later loss of efficacy), another TNF antagonist may be used
- To maintain remission (in patients with previously moderately to severely active UC), recommend:
  - (1) Against the addition of 5-aminosalicylic acid (5-ASA) in patients on TNF antagonists in those who had previously failed 5-ASA
  - (2) Continuing adalimumab, golimumab, or infliximab if used to achieve remission
  - (3) Continuing vedolizumab if used to achieve remission
  - (4) Continuing tofacitinib if used to achieve remission
- Several other specific recommendations are detailed in the guidelines, including the role of medications not within this class and nonpharmacologic guidance

Juvenile Idiopathic Arthritis - Treatment Guidelines

ACR/Arthritis Foundation, 2019

- The organization recommends nonsteroidal anti-inflammatory drugs (NSAIDs) conditionally as adjunctive therapy (very low level of evidence)
- Regarding traditional DMARDs for polyarthritis
  - **Methotrexate is conditionally recommended over leflunomide or sulfasalazine** (moderate and very low evidence, respectively)
  - **Subcutaneous (SC) methotrexate is conditionally recommended over oral methotrexate** (very low evidence)
- For biologic DMARDs in patients with polyarthritis
  - **Combination therapy with a DMARD is conditionally recommended over biologic monotherapy when initiating treatment with a biologic** (etanercept [very low evidence], adalimumab [moderate evidence], golimumab [very low evidence], abatacept [low evidence], or tocilizumab [low evidence])
- Combination therapy with a DMARD is strongly recommended for infliximab (low evidence)
- Intraarticular glucocorticoids are conditionally recommended as adjunct therapy (very low evidence), and oral corticosteroids as a bridge therapy are conditionally recommended in patients with moderate or high disease activity (very low evidence); however, bridge therapy is not recommended in patients with low disease activity (very low evidence)
- In addition, the group strongly recommends against adding chronic low-dose glucocorticoids, regardless of disease activity (very low evidence) in polyarthritis patients

Juvenile Idiopathic Arthritis - Treatment Guidelines

ACR/Arthritis Foundation, 2019

- For initial therapy in polyarthritis patients
  - The group strongly recommends **all patients have initial therapy with DMARD over NSAID monotherapy** (moderate evidence), with methotrexate monotherapy conditionally recommended over triple DMARD therapy (low evidence)
- In patients without risk factors (e.g., positive anti-cyclic citrullinated peptide antibodies, positive rheumatoid factor, or presence of joint damage)
  - The group recommends **initial therapy with a DMARD conditionally over a biologic** (low evidence); however, in those with risk factors, the group recognizes that there are situations in which a biologic may be preferred (low evidence; e.g., involvement of high risk joints [cervical spine, wrist, or hip], high disease activity, and or those judged to be high risk of disabling joint damage)
- For subsequent therapy in low disease activity patients, defined as clinical Juvenile Disease Activity Score based on 10 joints (cJADAS-10) ≤ 2.5 and ≥ 1 active joint
  - **Escalation of therapy** (e.g., intraarticular glucocorticoid injection, DMARD dose optimization, methotrexate trial, and adding or changing biologic) is recommended over no escalation (very low evidence)
  - For **subsequent therapy in moderate or high disease activity** (cJADAS-10 > 2.5) **patients receiving DMARD monotherapy**, the group conditionally recommends **adding a biologic to the original DMARD over changing to a second DMARD** (low evidence) or **triple DMARD therapy** (low evidence)
  - For **subsequent therapy in moderate or high disease activity polyarthritis patients receiving a TNF antagonist with or without a DMARD**, the group conditionally recommends **switching to a non-TNF antagonist** (e.g., tocilizumab, abatacept) over switching to a second TNF antagonist (very low evidence); **however, a second TNF antagonist may be appropriate in patients with good initial response to a TNF antagonist who have experienced secondary failure**
  - If the patient is receiving their second biologic, **use of a TNF antagonist, abatacept, or tocilizumab is conditionally recommended over rituximab** (very low evidence)

Juvenile Idiopathic Arthritis - Treatment Guidelines

ACR/Arthritis Foundation, 2019

- For patients with JIA and sacroiliitis
  - Guidelines strongly recommends treatment with an **NSAID over no NSAID treatment** (very low evidence)
  - In those who are **already on NSAIDs with continued active disease, the group strongly recommends a TNF antagonist over NSAID monotherapy** (low evidence), with a conditional recommendation (low evidence) for sulfasalazine in those who have contraindications or have failed a TNF antagonist
  - The group strongly **recommends against the use of methotrexate monotherapy** (very low evidence)
  - **Bridging therapy with a limited duration oral corticosteroid in select conditions and adjunct use of intraarticular glucocorticoid are conditionally recommended** (both very low evidence)
  - For those with **JIA and enthesitis**, the group strongly recommends **NSAID treatment over no NSAID treatment** (very low evidence), **with a TNF antagonist conditionally recommended over methotrexate or sulfasalazine** if disease activity continues (low evidence)
  - Bridging therapy with a **limited duration oral corticosteroid** in select conditions also is conditionally recommended (very low evidence)
  - The group provides additional recommendations on specific glucocorticoids

Pediatric Psoriasis - Treatment Guidelines

American Academy of Dermatology and National Psoriasis Foundation, 2019

- Published guidelines for management and treatment of psoriasis (PSO) in pediatrics
  - Recommend ongoing assessment for psoriatic arthritis (PsA), uveitis, obesity, CV risk factors, dyslipidemia, insulin resistance/diabetes, mental health conditions
  - Body surface area (BSA) plus Children's Dermatology Life Quality Index should be used to assess disease severity

- Treatment:
  - Recommended topical treatments for PSO include:
    - Topical corticosteroids (off-label), tacrolimus 0.1% ointment (off-label) for PSO of face and genital region, calcipotriene/calcipotriol, calcipotriol/betamethasone dipropionate (ages ≥ 12 yo), tazarotene (off-label) + topical corticosteroids, topical anthralin, coal tar, phototherapy/photochemotherapy
  - Recommended systemic treatments for PSO include:
    - Systemic treatments include methotrexate, cyclosporine, systemic retinoids, and biologics, etanercept, infliximab, adalimumab, and ustekinumab
  - Lastly, guidelines recommend treatment of physical and psychosocial wellness (quality of life) in pediatric patients with PSO

Ankylosing Spondylitis – Background and Guidelines

Background:

- Axial spondyloarthritis (axSpA) is an inflammatory condition generally affecting the spine and can be furthered subdivided into ankylosing spondylitis (AS; radiographic axSpA) and nonradiographic axSpA (nr-axSpA

American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network

- Published a 2019 update on the treatment of ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (SpA)
- In general, recommendations for AS and nonradiographic axial SpA are similar
- TNF antagonists (but not a specific one) are recommended as first biologic (over Cosentyx or Tremfya, which are then recommended over a second TNF antagonist if first does not produce a response)
- All the prior mentioned agents are recommended over Xeljanz
- Concurrent low-dose methotrexate with TNF antagonist is not recommended
- Recommend against a strict treat-to-target strategy
- If a patient's disease is stable, guidelines recommend against discontinuing or tapering of biologics
- Sulfasalazine provides a viable option for select patients who cannot take a TNF antagonist

Periodic Fever Syndrome - Background and Guidelines

Background:

- These rare, hereditary syndromes are characterized by short and recurrent severe localized inflammation and fever “attacks” that are not otherwise explained by routine childhood (or adult) infections
- Periodic fever syndrome is defined as 3 or more episodes of unexplained fever in a 6-month period, occurring at least 7 days apart
    - These can occur periodically or irregularly and undergo spontaneous remission
- Cryopyrin-associated periodic syndromes (CAPS) is a family of syndromes associated with mutations in cryopyrin, now known as nucleotide-binding domain and leucine-rich repeat containing family, pyrin domain-containing 3 (NLRP2)
    - CAPS includes Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), and chronic infantile neurologic cutaneous articular syndrome (CINCA), which is also known as neonatal-onset multisystem inflammatory disease (NOMID)

Treatment:

- Anakinra (Kineret), canakinumab (Ilaris), and rilonacept (Arcalyst) are approved for the treatment of CAPS in select ages
- Kineret is only approved for patients with CAPS associated with NOMID
- Arcalyst and Ilaris are approved more generally for patients with CAPS, including FCAS and MWS
    - Ilaris is also approved for the following other periodic fever syndromes:
        - Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF)

Giant Cell Arteritis (GCA) - Background and Guidelines

- Background:
  - GCA, or temporal arteritis, is a systemic inflammatory vasculitis of unknown etiology that is classified as a large-vessel vasculitis, but typically also involves small and medium arteries
  - Most commonly, it affects the occipital, ophthalmic, posterior ciliary, proximal vertebral, and vertebral arteries
    - While the incidence of GCA ranges from 0.5 to 27 cases per 100,000 people in those ≥ 50 years old, the incidence is higher in the northern areas of the U.S
    - It occurs in older persons and can result in a wide variety of neurologic, ophthalmologic, and systemic complications

- Treatment:
  - High-dose corticosteroids, although clinical studies on various dosing protocols are limited
  - Steroids are generally continued until the resolution of symptoms and then may be tapered slowly to the lowest dose that adequately suppresses symptoms
  - Actemra is the only non-corticosteroid drug FDA approved for the treatment of GCA

Hidradenitis Suppurativa - Background and Guidelines

Hidradenitis Suppurativa (HS)

- HS is a chronic condition that affects the terminal follicular epithelium in apocrine gland-bearing skin, such as the armpits or perianal area
- It typically occurs in adolescents (generally after puberty) and adults, is generally diagnosed clinically, and affects approximately 1% to 2% of the U.S. population
- Select signs and symptoms include erythema, raised bumps or lesions, painful lesions, and local arthritis or arthralgia
- In addition to nonpharmacologic treatments, pharmacologic treatment includes anti-inflammatories, antibiotics, antiandrogens, and biologics, such as infliximab (Remicade)
    - Surgery may also be considered in some patients

- **European Dermatology Forum, 2015**
    - Guidelines for treatment are limited, but guidelines from the European Dermatology Forum recommend either adalimumab or infliximab in severe or refractory disease, stating adalimumab appears to be better tolerated; however, only adalimumab is approved by the FDA for this use

Uveitis

- Non-infectious intermediate and posterior uveitis is inflammation of the intermediate and posterior uvea, while panuveitis is inflammation of the anterior chamber, vitreous humor, and choroid or retina simultaneously
- Together, these represent the most severe and highly recurrent forms of uveitis
- The incidence of all cases of uveitis is approximately 15 cases per 100,000 patients per year, and anterior uveitis is the most common form of uveitis

Uveitis – Guidelines

Uveitis (Treatment)

- ACR and Arthritis Foundation, 2019
  - Published guidelines on the treatment of uveitis associated with JIA, one of the most common extraarticular manifestation of JIA
  - The group recommends select topical glucocorticoids in patients with JIA and active chronic anterior uveitis for short-term control, but for those who are unable to control symptoms with short-term therapy, they recommend adding systemic therapy in order to taper topical glucocorticoids
    - Changing or escalating systemic therapy is recommended after ≥ 3 months if control is not achieved
  - For JIA patients who develop new chronic anterior uveitis despite stable systemic therapy, they recommend topical glucocorticoids prior to changing or escalating systemic therapy right away
  - Regarding specific agents, they group recommends SC methotrexate conditionally over oral methotrexate; however, use of a TNF antagonist with methotrexate in severe active disease and sight-threatening complications is conditionally recommended over methotrexate monotherapy
  - If starting a TNF antagonist, they conditionally recommend a monoclonal antibody over etanercept
    - Dose or frequency of the TNF antagonist should be escalated for an inadequate response prior to trying another biologic agent
    - Likewise, if a patient has failed a TNF antagonist following an escalated dose/frequency, changing to a different TNF antagonist is conditionally recommended over another biologic
  - Abatacept or tocilizumab as biologics and mycophenolate, leflunomide, or cyclosporine as nonbiologic options are conditionally recommended in patients who have failed methotrexate and 2 monoclonal antibody TNF antagonists
  - The disease should be well-controlled for 2 years on a DMARD and/or biologic therapy prior to tapering
  - For pediatric patients with spondyloarthritis who develop acute anterior uveitis, the group conditionally recommends topical glucocorticoids prior to a change in systemic therapy
  - Notably, the only agent approved for uveitis in this class is adalimumab

Cytokine & CAM Antagonist - Background and Guidelines

Cytokine Release Syndrome (CRS)

- CRS can occur following select immunotherapies and can result in a large, rapid release of cytokines into the blood
- This can manifest as fever, nausea, headache, rash, tachycardia, hypotension, and dyspnea and can be life-threatening
- Tocilizumab (Actemra) is approved for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening CRS in adults and pediatric patients 2 years of age and older

Role of Biosimilars

- In 2017, the ACR published a white paper regarding the use of biosimilars in the treatment of rheumatic diseases and provides a comprehensive overview of the scientific, clinical, economic, and prescribing issues pertaining to biosimilar use, including efficacy and competition
- They note that available real-world studies have demonstrated efficacy for extrapolated indications and state that health care providers should incorporate biosimilars, where appropriate, into treatment for patients with rheumatologic diseases
- An international multidisciplinary task force issued consensus-based recommendations on the use of biosimilars for rheumatologic diseases, focusing on multiple factors, including extrapolation of indications, and switching between originator products and biosimilars
- They state treatment is a shared decision between the patient and clinician, and patients and providers must be educated on biosimilars
- In addition, biosimilars are not considered superior or inferior to the originator product, and biosimilars should be considered safe and effective for all the originator product's approved indications
- Notably, ACR cautions against interchangeability without consultation with a prescriber

Cytokine & CAM Antagonist

- certolizumab pegol (Cimzia)
  - **March 2019: FDA approved expanded indication of Cimzia for the treatment of adults with non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation for the treatment of adults with active ankylosing spondylitis**
  - **Indications:**
    - Indicated for: Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy; **treatment of adults with moderately to severely active rheumatoid arthritis; treatment of adult patients with active psoriatic arthritis; treatment of adults with active ankylosing spondylitis; treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation; treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy**
  - **Limitations**
    - Live vaccines should not be given with Cimzia
    - Black Box Warnings:
      - Serious Infections: Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens
      - Malignancies: Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers
    - Tuberculosis (TB): Evaluate for TB prior to initiating treatment
  - **Dosage**
    - **Dosing stratified by indications and weight- found in TCR**
  - **Availability**
    - For injection: 200 mg lyophilized powder in a single-dose vial and single-dose prefilled syringe

Cytokine & CAM Antagonist

- risankizumab-rzaa (Skyrizi)
  - **April 2019: FDA approved Skyrizi for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy**
  - **Indication:**
    - **Treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy**
  - **Limitations**
    - **Live vaccines should not be given with Skyrizi**
    - **Additional specific contraindications have not been determined**
  - **Dosage**
    - **150 mg (two 75 mg injections) administered by subcutaneous injection at Week 0, Week 4 and every 12 weeks thereafter**
  - **Availability**
    - **Injection: 75 mg/0.83 mL in each single-dose prefilled syringe**

Cytokine & CAM Antagonist

- infliximab-dyyb (Inflectra)
  - **June 2019: FDA approved expanded indication of Inflectra for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients ≥ 6 years old with moderately to severely active UC who have had an inadequate response to conventional therapy**
  - **Indications**
    - **Crohn's Disease, Ulcerative Colitis, Rheumatoid Arthritis in combination with methotrexate, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis**
  - **Limitations**
    - Warnings:
      - Increased risk of an infection (i.e. TB, invasive fungal infections, bacterial, viral, and those caused by opportunistic infections)
      - Lymphoma and other malignancies have been reported in children and adolescent patients
      - Post marketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL)
    - Serious infections – do not give during an active infection
      - If an infection develops, monitor carefully and stop treatment if infection becomes serious
  - **Dosage**
    - **Dosing stratified by indications and weight- found in TCR**
  - **Availability**
    - For injection: 100 mg lyophilized powder in a 20 mL vial for IV infusion

Cytokine & CAM Antagonist

- infliximab-abda (Renflexis)
  - **June 2019: FDA approved expanded indication for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients ≥ 6 years old with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy**
  - **Indication**
    - **Renflexis is a tumor necrosis factor (TNF) blocker indicated for the treatment of: Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis, Rheumatoid Arthritis (in combination with Methotrexate), Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis**
  - **Limitations**
    - No available data for pregnancy
    - Warnings:
      - Increased risk of an infection (i.e. TB, invasive fungal infections, bacterial, viral, and those caused by opportunistic infections)
      - Lymphoma and other malignancies have been reported in children and adolescent patients
      - Post marketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL)
    - Serious infections – do not give Renflexis during an active infection
      - If an infection develops, monitor carefully and stop Renflexis if infection becomes serious
  - **Dosage**
    - **Dosing stratified by indication and found in TCR**
  - **Availability**
    - For injection: 100 mg of lyophilized infliximab-abda in a 20 mL vial for intravenous infusion

Cytokine & CAM Antagonist

- apremilast (Otezla)
  - **July 2019: FDA approved a new indication to treat adults with oral ulcers associated with Behçet's disease. Dosage for this indication is consistent with PSO and PSA indications**
  - **Indication**
    - Treatment of: Adult patients with active psoriatic arthritis, patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, **adult patients with oral ulcers associated with Behçet's Disease**
  - **Limitations**
    - Diarrhea, Nausea, and Vomiting: Consider dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting
    - Depression: Advise patients, their caregivers, and families to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes and if such changes occur to contact their healthcare provider
      - Carefully weigh risks and benefits of treatment in patients with a history of depression and/or suicidal thoughts or behavior
    - Weight Decrease: Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation
  - **Dosage**
    - **Dosing stratified by indication and found in TCR**
  - **Availability**
    - Tablets: 10 mg, 20 mg, 30 mg

Cytokine & CAM Antagonist

- adalimumab-bwwd (Hadlima)
  - **July 2019: FDA approved adalimumab-bwwd (Hadlima), a biosimilar to Humira, for the treatment of RA, juvenile idiopathic arthritis (JIA), plaque psoriasis (PSO), psoriatic arthritis (PSA), ankylosing spondylitis (AS), adult Crohn's disease (CD), and ulcerative colitis (UC); launch is expected on/after June 30, 2023**
  - **Indication**
    - **Treatment of RA, juvenile idiopathic arthritis (JIA), plaque psoriasis (PSO), psoriatic arthritis (PSA), ankylosing spondylitis (AS), adult Crohn's disease (CD), and ulcerative colitis (UC)**
  - **Limitations**
    - **Black Box Warnings:**
      - **Serious Infections: Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens**
      - **Malignancies: Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including etanercept products**
        - **Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including adalimumab products**
    - **Serious infections: Do not start during an active infection**
      - **If an infection develops, monitor carefully, and stop Hadlima if infection becomes serious**
  - **Dosage**
    - **Dosing stratified by indication/weight and found in TCR**
  - **Availability**
    - **Injection: 40 mg/0.8 mL in a single-dose prefilled autoinjector; 40 mg/0.8 mL in a single-dose prefilled glass syringe**

Cytokine & CAM Antagonist

- upadacitinib (Rinvoq)
  - August 2019: FDA approved Rinvoq, a Janus kinase (JAK) inhibitor
  - Indications
    - Treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate
    - Limitation of Use: Use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended
  - Limitations
    - Black Box Warnings:
      - Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients
      - Lymphoma and other malignancies have been observed in patients treated with RINVOQ
      - Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions
      - Prior to starting, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting Rinvoq
  - Dosage
    - The recommended dose is 15 mg once daily
      - May be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs
      - Avoid initiation or interrupt Rinvoq if absolute lymphocyte count is less than 500 cells/mm3 , absolute neutrophil count is less than 1000 cells/mm3 , or hemoglobin level is less than 8 g/dL
  - Availability
    - Extended-release tablets: 15 mg

Cytokine & CAM Antagonist

- baricitinib (Olumiant)
  - **October 2019: FDA approved new formulation of Olumiant 1 mg tablet for dose adjustment in patients with moderate renal impairment or patients taking strong OAT3 inhibitors**
  - **Indications:**
    - **Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies**
    - Limitation of Use: Use of Olumiant in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended
  - **Limitations**
    - Black Box Warnings:
      - Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients
      - Lymphoma and other malignancies have been observed in patients
      - Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions
      - Prior to starting, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting treatment
    - Live vaccines should not be given with Olumiant
  - **Dosage**
    - 2 mg once daily
    - **Moderate Renal Impairment: 1mg once daily**
  - **Availability**
    - **Tablets: 2 mg, 1 mg**

Cytokine & CAM Antagonist

- etanercept-szzs (Erelzi)
  - **October 2019: FDA approved new indication for the treatment of PSA and PSO in adults; was already approved for RA, AS, and polyarticular JIA**
  - **Indications:**
    - Treatment of RA, polyarticular JIA in patients 2 years of age and older, **PsA**, AS, and **PsO in adults**
  - **Limitations**
    - Live vaccines should not be given with Erelzi
    - Black Box Warnings:
      - Serious Infections: Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens
      - Malignancies: Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including etanercept products
  - **Dosage**
    - **Adult RA and PsA: 50 mg once weekly with or without Methotrexate**
    - AS: 50 mg once weekly
    - **Adult PsO: 50 my twice weekly for 3 months, followed by 50 mg once weekly**
    - JIA (patients who weigh >63 kg): 50 mg once weekly
  - **Availability**
    - Injection: 25 mg/0.5 mL and 50 mg/mL solution in a single-dose prefilled syringe with BD UltraSafe Passive Needle Guard
    - Injection: 50 mg/mL solution in single-dose prefilled Sensoready Pen

Cytokine & CAM Antagonist

- ustekinumab (Stelara)
  - **October 2019: FDA approved new indication for the treatment of moderately to severely active UC in adults**
  - **Indications:**
    - Adult patients with:
      - Moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy
      - Active psoriatic arthritis (PsA), alone or in combination with methotrexate
      - Moderately to severely active Crohn's disease (CD)
      - **Moderately to severely active ulcerative colitis**
    - Adolescent patients (12 years or older) with:
      - Moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy
  - **Limitations**
    - Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment
      - Initiate treatment of latent TB before administering
    - Malignancies: Stelara may increase risk of malignancy
      - The safety of Stelara in patients with a history of or a known malignancy has not been evaluated
    - Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL12/IL-23
  - **Dosage**
    - Stratified by indication and age- found in TCR
  - **Availability**
    - Subcutaneous Injection: 45 mg/0.5 mL or 90 mg/mL in a single-dose prefilled syringe; 45 mg/0.5 mL in a single-dose vial
    - Intravenous Infusion: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial

Cytokine & CAM Antagonist

- adalimumab-afzb (Abrilada)
  - **November 2019: FDA approved adalimumab-afzb (Abrilada), a new biosimilar to Humira**
  - **Indications:**
    - **Treatment of RA, juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult Crohn's disease (CD), UC, and plaque psoriasis (Ps)**
  - **Limitations**
    - **Live vaccines should not be given with Abrilada**
    - **Black Box Warnings:**
      - **Serious Infections: Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens**
      - **Malignancies: Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including etanercept products**
    - **Invasive Fungal Infections: For patients who develop a systemic illness on Abrilada, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic**
  - **Dosage**
    - **Dosing stratified by indication and weight- found in TCR**
  - **Availability**
    - **Injection: 40 mg/0.8 mL in a single-dose prefilled pen (Abrilada pen), single-dose prefilled glass syringe, and a single-dose glass vial for institutional use only**
    - **Injection: 20 mg/0.4 mL in a single-dose prefilled glass syringe**
    - **Injection: 10 mg/0.2 mL in a single-dose prefilled glass syringe**

Cytokine & CAM Antagonist

- guselkumab (Tremfya)
  - **November 2019: FDA approved new formulation as a single-dose One-Press patient controlled injector; single-dose prefilled syringe was already approved**
  - **Indications:**
    - Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
  - **Limitations**
    - Live vaccines should not be given with Tremfya
    - Infections: May increase the risk of infection
      - Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur
      - If a serious infection develops, discontinue Tremfya until the infection resolves
    - Tuberculosis (TB): Evaluate for TB prior to initiating treatment
    - Safety and efficacy for patients < 18 years of age have not been established
    - There are no available data on Tremfya use in pregnant women to inform a drug associated risk of adverse developmental outcomes
    - No specific studies have been conducted to determine the effect of renal or hepatic impairment on the PK of Tremfya
  - **Dosage**
    - 100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter
  - **Availability**
    - Injection: 100 mg/mL in a single-dose prefilled syringe or **single-dose OnePress patient-controlled injector**

Cytokine & CAM Antagonist

- infliximab-axxq (Avsola)
  - **December 2019: FDA approved infliximab-axxq (Avsola), a new biosimilar to Remicade**
  - **Indications:**
    - **Treatment of Crohn's disease (CD) in adults and pediatric patients, ulcerative colitis (UC) in adults and pediatric patients, RA in combination with methotrexate, ankylosing spondylitis (AS), psoriatic arthritis (PsA), and plaque psoriasis (PSO)**
  - **Limitations**
    - **Live vaccines should not be given with Abrilada**
    - **Black Box Warnings:**
      - **Serious Infections: Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens**
      - **Malignancies: Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including etanercept products**
    - **Invasive Fungal Infections: For patients who develop a systemic illness on Abrilada, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic**
    - **Hepatotoxicity – severe hepatic reactions, some fatal or necessitating liver transplantation**
      - **Stop Avsola in cases of jaundice and/or marked liver enzyme elevations**
    - **Drug Drug Interaction: Use with anakinra or abatacept – increased risk of serious infections**
  - **Dosage**
    - **Dosing stratified by indication and weight- found in TCR**
  - **Availability**
    - **For injection: 100 mg of lyophilized infliximab-axxq in a 20 mL single-dose vial for intravenous infusion**

Cytokine & CAM Antagonist

- tofacitinib (Xeljanz and Xeljanz XR)
  - **December 2019: FDA issued a safety announcement regarding Xeljanz/Xeljanz XR; an ongoing clinical trial found an increased risk of blood clots in the lungs and death when a 10 mg twice daily dose of tofacitinib was used in patients with RA, which is not an FDA-approved dose for RA. Patients should be monitored for PE and advised to seek medical attention if symptoms of a PE occur**
  - **December 2019: FDA approved a new indication for Xeljanz XR for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have an inadequate response or who are intolerant to TNF blockers**
  - Indication
    - Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA), Ulcerative Colitis
  - Limitations
    - Warnings:
      - Boxed warnings include increased risk of serious and sometimes fatal bacterial, mycobacterial, fungal, and viral infections in patients treated with tofacitinib
      - Thrombosis, including pulmonary embolism, deep venous thrombosis and arterial thrombosis have occurred in patients treated with Xeljanz and other Janus kinase inhibitors. Rheumatoid arthritis patients with at least one cardiovascular (CV) risk factor had a higher rate of all-cause mortality and thrombosis with Xeljanz 10 mg twice daily vs. 5 mg twice daily or TNF blockers
      - Lymphoma and other malignancies have been observed in patients treated with Xeljanz, including an increased rate of Epstein Barr Virus-associated post-transplant lymphoproliferative disorder
  - Dosage
    - **Dosing stratified by indication - found in TCR**
  - Availability
    - Tablets: 5 mg, 10 mg
    - Extended-release tablet: 11 mg , 22 mg

Cytokine & CAM Antagonist

- infliximab-qbtx (Ixifi)
  - **January 2020: FDA approved for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy; previously only indicated for adults with UC**
  - **Indications:**
    - **Crohn's Disease, Ulcerative Colitis, Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, and Plaque Psoriasis**
  - **Limitations**
    - Live vaccines should not be given with Ixifi
    - Infections: Serious infections have occurred
      - Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur
      - If a serious infection develops, discontinue until the infection resolves
    - Tuberculosis (TB): Evaluate for TB prior to initiating treatment
  - **Dosage**
    - **Dosing stratified by weight and indication - found in TCR**
  - **Availability**
    - 100 mg of lyophilized infliximab-qbtx in a 15 mL vial for intravenous infusion

Cytokine & CAM Antagonist

- ixekizumab (Taltz)
  - **August 2019: FDA approved expanded indication of Taltz for the treatment of adults with active ankylosing spondylitis**
  - **March 2020: FDA approved Taltz for use in patients aged ≥ 6 years with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy; previously, this was approved for use in adults only**
  - **Indications:**
    - **Patients aged 6 years or older with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy**
    - Adults with active psoriatic arthritis
    - **Adults with active ankylosing spondylitis**
  - **Limitations**
    - Live vaccines should not be given with Taltz
    - Infections: Serious infections have occurred
      - Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur
      - If a serious infection develops, discontinue until the infection resolves
    - Tuberculosis (TB): Evaluate for TB prior to initiating treatment
    - Inflammatory Bowel Disease: Crohn's disease and ulcerative colitis, including exacerbations, occurred during clinical trials
      - Patients who are treated with Taltz and have inflammatory bowel disease should be monitored closely
  - **Dosage**
    - **Dosing stratified by indication - found in TCR**
  - **Availability**
    - 80 mg/mL solution in a single-dose prefilled autoinjector and in a single-dose prefilled syringe

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Erythropoiesis Stimulating Proteins

Erythropoiesis Stimulating Proteins - Disease State Description

- Anemia
  - A frequent complication, affecting over 3 million Americans
  - Associated with a number of serious diseases, such as chronic kidney disease (CKD), diabetes, heart disease, and cancer, as well as chronic inflammatory conditions like rheumatoid arthritis or inflammatory bowel disease
  - These conditions can cause anemia by interfering with the production of oxygen-carrying red blood cells (RBCs)
  - Sometimes, as in the case of cancer chemotherapy, anemia can be caused by the treatment itself

- Erythropoietin
  - A glycoprotein produced in the kidneys that stimulates RBC production from bone marrow
  - Acts on the erythroid progenitor cells in the bone marrow to cause late differentiation and maturity of the RBCs
  - Endogenous production of erythropoietin by the kidney is normally regulated by the level of tissue oxygenation
  - Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis
  - In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 units/mL and may increase 100- to 1,000-fold during hypoxia or anemia
  - In contrast, patients with CKD have impaired production of erythropoietin, which is the primary cause of their anemia
  - Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents

Erythropoiesis Stimulating Proteins - Disease State Description

- Beta thalassemia
  - A rare inherited blood disorder marked by the reduction of functional hemoglobin levels, has an incidence of approximately 1 in 100,000 individuals in the general population
  - There are 3 subtypes of beta thalassemia, which are characterized by the severity of symptoms – minor, intermedia, and major
  - Individuals with beta thalassemia major require regular blood transfusions, as often as once every 2 to 4 weeks and are dependent on medical care for survival
  - Treatment for beta thalassemia is highly dependent on type of thalassemia, progression and severity of disease, and the presence or absence of certain symptoms
  - Treatment options may include regular blood transfusions, chelation therapy, folic acid treatment, removal of the spleen and/or gallbladder, and bone marrow transplantation
  - **Luspatercept-aamt (Reblozyl)** is the first FDA-approved erythroid maturation agent, which reduces patient transfusion burden by regulating late-stage RBC maturation
  - It is approved for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell transfusions

Erythropoiesis Stimulating Proteins - Guidelines

- National Comprehensive Cancer Network (NCCN) Guidelines, 2020
  - State that erythropoiesis stimulating agents (ESAs) are associated with an increased risk of thrombosis, decreased survival, and shortened time to tumor
  - Physicians are advised to use the lowest ESA dose possible to maintain hemoglobin (Hb) levels sufficient to avoid blood transfusions, to prescribe according to Food and Drug Administration (FDA) guidelines, and to obtain patient consent
  - ESAs should be discontinued once the course of chemotherapy has been completed and anemia resolves
  - There is not enough evidence to support the use of ESAs for the treatment of anemia related to myelosuppressive chemotherapy with curative intent, patients receiving non-myelosuppressive therapy, or patients with cancer not receiving therapy

National Comprehensive Cancer Network, 2020

- American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH)
  - Updated their 2010 recommendations for use of erythropoiesis-stimulating agents (ESAs) in patients with cancer
  - Guidelines emphasize the intent of treatment be considered when weighing the benefits and risks of these agents (including thromboembolism)
  - ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin level is < 10 g/dL
    - Another option for these patients is a red blood cell transfusion, depending on the severity of the anemia or other clinical circumstances
    - Hemoglobin may be increased to the lowest concentration needed to avoid or reduce the need for red blood cell transfusions, which may vary by patient and condition
    - They can also be used for low-risk myelodysplastic syndrome
  - Regarding biosimilars, they state clinicians should expect similar results among the various formulations (and biosimilars)
  - The goal hemoglobin should be the lowest value that prevents need for transfusion; ESAs should be discontinued if there is a lack of hemoglobin increase by 1 to 2 g/dL by 6 to 8 weeks

ASCO/ASH, 2010

Erythropoiesis Stimulating Proteins – luspatercept-aamt (Reblozyl)

- **Indication**
  - An erythroid maturation agent indicated for the treatment of:
    - Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions
    - Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
  - Limitations of Use: Not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia
- **Contraindications/Warnings**
  - Thrombosis/Thromboembolism: Increased risk in patients with beta thalassemia. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly
  - Hypertension: Monitor blood pressure (BP) during treatment. Initiate anti-hypertensive treatment if necessary
  - Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception
- **Dosage**
  - Recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection
  - Review hemoglobin (Hgb) results prior to each administration
- **Availability**
  - For injection: 25 mg and 75 mg lyophilized powder in single-dose vials for reconstitution

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Colony Stimulating Factors

Colony Stimulating Factors - Disease State Description

- Myelosuppressive chemotherapy can induce neutropenia (< 500 neutrophils/µL or < 1,000 neutrophils/µL and a predicted decline to ≤ 500/µL during the 48 hours after the dose) and febrile neutropenia (≥ 38.3°C orally or ≥ 38°C sustained over 1 hour) which is a dose-limiting toxicity of chemotherapy
- Febrile neutropenia can cause increased diagnostic and treatment costs, prolonged hospitalizations, and broad-spectrum antibiotic use which may necessitate chemotherapy dose reductions, treatment delays, and may ultimately compromise treatment outcomes
- The risk of febrile neutropenia is dependent on treatment and dose intensity, which is often underreported
- Colony stimulating factors (CSF) are hematopoietic growth factors that have been shown to decrease the likelihood of neutropenic complications resulting from chemotherapy and to improve relative chemotherapy dose intensity
  - Colony stimulating factors act on hematopoietic cells and stimulate proliferation, differentiation commitment, and some end-cell functional activation
- Prophylactic CSF use can reduce the severity, risk, and duration of febrile neutropenia and decrease rates of infection and hospitalizations
  - Neupogen, Nivestym, Zarxio, Neulasta, Udenyca, Fulphila, Ziextenzo, and Granix are granulocyte colony-stimulating factors (G-CSF)
  - Leukine is a granulocyte-macrophage colony stimulating factor (GM-CSF)

National Comprehensive Cancer Network, 2020

Colony Stimulating Factors - Guidelines

- **The National Comprehensive Cancer Network (NCCN) v1.2020 Practice Guidelines for Myeloid Growth Factors**
  - Safety data appear similar between Neupogen, Neulasta, and their biosimilars, and the subcutaneous (SC) route is preferred for all agents
    - Subcutaneous filgrastim and its biosimilars, Granix, and pegfilgrastim have a category 1 recommendation stating there is high-level evidence from randomized controlled clinical trials and there is uniform NCCN consensus that they prophylactically reduce the risk of febrile neutropenia
    - Filphila and Udenyca have been designated a category 2A (lower level evidence, there is uniform consensus that the intervention is appropriate)
    - Due to the recent approval, a recommendation for Ziextenzo is not currently provided by NCCN
    - To date, there are insufficient head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs
  - Filgrastim, filgrastim biosimilars, and tbo-filgrastim can be administered the day after chemotherapy, up to 3 to 4 days after chemotherapy, and through post-nadir recovery
  - Based on data from clinical trials, pegfilgrastim and its biosimilars should be administered the day after chemotherapy (category 1); however, administration up to 3 to 4 days after chemotherapy is also reasonable according to the NCCN guidelines
  - For patients unable to return to the clinic the next day for medication administration, a delivery device, (Neulasta Onpro®), is available that allows for the device to be applied to patient the same day as chemotherapy administration, but the device does not release the medication until approximately 27 hours after application
  - There is evidence to support the use of chemotherapy regimens every 3 weeks with pegfilgrastim or its biosimilars (category 1)
  - Efficacy data exist for pegfilgrastim products in chemotherapy regimens given every 2 weeks (category 2A)
  - There are insufficient data to support dose/schedule of weekly chemotherapy regimens; therefore, pegfilgrastim products should not be used
  - Leukine is no longer recommended for prophylactic use in patients with solid tumors receiving myelosuppressive chemotherapy

National Comprehensive Cancer Network, 2020

Colony Stimulating Factors - Guidelines

- **The updated v1.2020 NCCN Hematopoietic Growth Factors Guidelines**
  - The guidelines note that a biosimilar is a biological product that is highly similar to the FDA-approved originator product with very small, clinically inactive differences but no difference in efficacy, safety, or purity
    - The first biosimilar, Zarxio, was approved in March 2015 with a second filgrastim biosimilar, Nivestym, being approved in 2018
    - However, Granix was approved in 2012 as a biologic rather than a biosimilar in the United States; in Europe, Granix is available as a biosimilar to filgrastim
    - The first pegfilgrastim biosimilars, Fulphila and Udenyca, were approved in 2018. Studies have shown these products have similar safety and efficacy profiles as the originator product
  - The guidelines state if overall safety and efficacy are equivalent, biosimilars may be substituted for the originator product
  - However, the guidelines note that current biosimilars are not interchangeable; therefore, alternating between a biosimilar and its originator in not recommended
  - The guidelines also note that the use of biosimilars may provide opportunities for cost containment
  - The panel endorses the use of Zarxio, Nivestym, Granix, Fulphila, and Udenyca for myelosuppressive doses of radiation
  - For mobilization of hematopoietic progenitor cells in the autologous setting, the use of concurrent filgrastim (or 1 of its biosimilars) with sargramostim (category 2B) or single agent filgrastim, Zarxio, Nivestym, or Granix is recommended (category 2A)
  - Filgrastim, Granix, or filgrastim biosimilars (filgrastim-sndz, filgrastim-aafi) are all NCCN category 1 G-CCF options for prophylaxis of febrile neutropenia and maintenance of scheduled dose delivery
  - According to the guidelines, the World Marrow Donor Association (WMDA) recommends filgrastim (NCCN category 2A; preferred) or filgrastim biosimilars (NCCN category 2B) for the mobilization of peripheral blood progenitor cells in healthy donors in the allogeneic setting
  - The NCCN Panel does not recommend Neulasta or its biosimilars for mobilization at this time

National Comprehensive Cancer Network, 2020

Colony Stimulating Factors – pegfilgrastim-bmez (Ziextenzo)

- **Indication**
  - A leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
  - Limitations of Use: Not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation
- **Contraindications/Warnings**
  - Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim products or filgrastim products
  - Fatal splenic rupture have occurred: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture
  - Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue in patients with ARDS
- **Dosage**
  - Patients with cancer receiving myelosuppressive chemotherapy
    - 6 mg administered subcutaneously once per chemotherapy cycle
    - Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy
    - Use weight based dosing for pediatric patients weighing less than 45 kg
- **Availability**
  - Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only

Magellan Rx MANAGEMENT℠

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Sickle Cell Anemia Treatments

Sickle Cell Anemia Treatments - Disease State Description

- Sickle cell disease (SCD) is an inherited red blood cell (RBC) disorder caused by a single gene mutation in the β-globin gene resulting in abnormal hemoglobin (Hb)
  - It affects approximately 100,000 patients in the US and is more common among African Americans, although it is also seen in people of Hispanic ancestry
  - ~1 in 365 African Americans are born with SCD, and 1 in 13 have sickle cell trait (carrier)
  - In Hispanic Americans, SCD occurs in 1 in 16,300 births. People with SCD have a reduced life expectancy by approximately 30 years
    - People with SCD inherit 2 abnormal Hb genes, 1 from each parent

- Sickle cell disease (SCD) comprises several syndromes in which the sickle mutation is inherited along with a mutation at the other beta globin allele that diminishes or eliminates the normal production of beta globin
  - These include sickle cell anemia (homozygous sickle mutation; HbSS), sickle beta thalassemia (HbSβ), and hemoglobin SC disease (HbSC), among others
  - Sickle cell anemia is the most common and most severe form of SCD
  - Sickle cell trait (SCT) is diagnosed when one normal gene and one abnormal gene is inherited
  - Patients with SCT do not have signs or symptoms of SCD, but they can pass the abnormal gene to their children

Centers for Disease Control and Prevention, 2019

Sickle Cell Anemia Treatments – Disease State Description

- In SCD, RBCs become crescent or “sickle”-shaped, sticky, and inflexible
  - The abnormal RBCs are also fragile, with a shortened cell life (a decrease to about 10 to 20 days instead of 90 to 120 days)

- The hallmark of SCD is painful vaso-occlusive crisis (VOCs) that arises when the abnormally shaped RBCs adhere to blood vessel walls, resulting in blockage of small blood vessels, reduced oxygen flow to tissues, and organ damage, including damage to the spleen, brain, eyes, lungs, liver, heart, kidneys, joints, bone, penis, and skin
  - VOCs can have sudden onset, last hours to days, and can lead to chronic disability or death
  - Triggers include hypoxemia, dehydration, and change in body temperature

- Onset of signs and symptoms of SCD typically occurs at 5 to 6 months of age
  - Early symptoms include jaundice, fatigue, and swelling and pain of the hands and feet
  - While anemia associated with SCD is usually mild to moderate, severe anemia can occur, which can be life-threatening

Centers for Disease Control and Prevention, 2019

Sickle Cell Anemia Treatments – Guidelines

- Treatment goals in patients with SCD focus on management of symptoms and disease complications
  - Strategies include management/prevention of VOC, chronic pain (managed with opioid and non-opioid analgesics), chronic hemolytic anemia, organ damage, pulmonary hypertension, and infection
  - For treatment of acute VOCs, intravenous (IV) hydration and analgesia are the mainstay of therapy
- A hematopoietic cell transplant (HCT) is the only cure for SCD, but its use is limited by associated risks and lack of matched donors
  - HCT is typically performed in children with complications such as strokes
- Blood transfusions are often used to treat and prevent complications of SCD, particularly in patients at risk for stroke
  - Regularly administration of transfusions are associated with complications such as iron overload and alloimmunization
- Individuals with SCD are also at increased risk for bacterial and viral infections; therefore, immunization and prophylactic penicillin are important aspects of care during early childhood (ages < 5 years) in patients with SCD

- For decades, oral hydroxyurea (Droxia, Siklos) was the only approved pharmacologic treatment for SCD in the US.[1] Hydroxyurea reduces the frequency of vaso-occlusive events and is indicated to reduce the need for blood transfusion in patients with recurrent VOCs
  - In 2017, the FDA approved Endari to reduce acute complications of SCD
  - This was followed by approval in late 2019 of oral voxelotor (Oxbryta), for the treatment of SCD, and the IV monoclonal antibody crizanlizumab-tmca (Adakveo), to reduce the frequency of VOCs in adults and pediatric patients with SCD

Sickle Cell Anemia Treatments – Guidelines

National Heart, Lung, and Blood Institute's (NHLBI) Guidelines, 2014

- Recommend hydroxyurea in
  - Adults who have had ≥ 3 SCD-associated moderate to severe pain crises in a 12-month period
  - Adults with SCD-related pain or severe chronic anemia, either of which can interfere with activities of daily living (ADLs) and quality of life (QOL)
  - Adults with a history of severe and/or recurrent ACS or severe symptomatic chronic anemia
  - Pediatric patients ages ≥ 9 months regardless of clinical severity to reduce SCD-related complications (strong, high-quality for ages 9 to 42 months; moderate, moderate-quality for ages > 42 months)
  - Children and adults who have had a stroke when implementation of a transfusion program is not possible
    - Endari, Adakveo, and Oxbryta were not FDA-approved at the time these guidelines were developed
- The addition of hydroxyurea to erythropoietin in adults and children with chronic kidney disease (CKD) can improve anemia
- An expert in SCD management should be consulted regarding hydroxyurea therapy for patients with HbSβ+-thalassemia or HbSC who experience recurrent SCD-related pain that interferes with ADLs or QOL and those who are experiencing a clinical response to appropriately prescribed hydroxyurea

Sickle Cell Anemia Treatments – Indications

Drug	Generic	Indication(s)
crizanlizumab-tmca (Adakveo)	---	To reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients ages ≥ 16 years with sickle cell disease (SCD)
hydroxyurea (Droxia)	---	To reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises
hydroxyurea (Siklos)	---	To reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients ages ≥ 2 years with sickle cell anemia with recurrent moderate to severe painful crises
L-glutamine (Endari)	---	To reduce the acute complications of SCD in adult and pediatric patients ages ≥ 5 years
voxelotor (Oxbryta)	---	Treatment of SCD in adults and pediatric patients ages ≥ 12 years

Sickle Cell Anemia Treatments – Dosage & Availability

Drug	Dosage	Availability
crizanlizumab-tmca (Adakveo)	• 5 mg/kg by IV infusion over 30 minutes given by a HCP at week 0 and week 2, followed by maintenance dosing every 4 weeks • May be used as monotherapy or with hydroxyurea	Single-dose vial (SDV): 100 mg/10 mL
hydroxyurea (Droxia)	• Initial dosage is 15 mg/kg orally once daily; if blood counts are in an acceptable range, the dose may be increased by 5 mg/kg/day every 12 weeks; • Maximum daily dose of 35 mg/kg, or the highest dose that does not produce toxic blood counts, over 24 consecutive weeks	Capsules: 200 mg, 300 mg, 400 mg
hydroxyurea (Siklos)	• Initial dosage is 20 mg/kg orally once daily; if blood counts are in an acceptable range, the dose may be increased by 5 mg/kg/day every 8 weeks or if a painful crisis occurs; • Administer until mild myelosuppression (ANC of 2,000 cells/mm3 to 4,000 cells/mm3) is achieved; maximum daily dose of 35 mg/kg	Tablets: 100 mg, 1,000 mg Scored tablets may be split to achieve desired dose
L-glutamine (Endari)	Weight-based dosing: ▪ < 30 kg: administer 5 g orally twice daily ▪ 30 to 65 kg: administer 10 g orally twice daily ▪ > 65 kg: administer 15 g orally twice daily	Powder packets: 5 grams powder
voxelotor (Oxbryta)	• 1,500 mg (3 tablets) orally once daily with or without food • Swallow tablet whole; do not crush, chew, or cut • May be used as monotherapy or with hydroxyurea	Tablet: 500 mg

Appendices

Crohn's Treatment Guidelines- ACG, 2018

- The American College of Gastroenterology (ACG) guidelines for Crohn's Disease
  - Recommend the use of TNF antagonists (e.g., infliximab, certolizumab pegol, adalimumab) for the treatment of moderate to severe disease in patients who have not responded to corticosteroids or immunosuppressive agents or for severely active disease (strong recommendation)
  - Ustekinumab should be given for patients who failed previous treatment with corticosteroids, traditional agents, or TNF antagonists or who are naïve to TNF antagonists (strong recommendation)
  - Further, combination therapy of infliximab with immunomodulators is more effective than treatment with either agent alone in patients who are naïve to those agents (strong recommendation)
  - For patients with objective evidence of active disease and moderate to severe disease, vedolizumab with or without an immunomodulator should be considered for induction of symptomatic remission (strong recommendation)
  - Natalizumab (Tysabri) should be considered for induction of symptomatic response and remission in patients with active disease (strong recommendation)
  - Infliximab may be administered to treat fulminant disease (conditional recommendation)
  - Additional information on diagnosis, treatment of mild to moderate disease/low-risk disease, fistulizing disease, and other treatment agents are further detailed in the guidelines

Crohn's Treatment Guidelines- AGA, 2013

- Inducing Remission
  - Recommends using TNF antagonists to induce remission in patients with moderately severe Crohn's disease (strong recommendation)
  - The TNF antagonists infliximab or adalimumab are more likely than placebo to induce remission in patients with moderately severe Crohn's disease refractory to other therapies, including mesalamine, antibiotics, corticosteroids, and immunomodulators
    - A key feature of these agents is the ability to induce remission in patients who have not responded to treatment with corticosteroids or immune modulators
  - Certolizumab pegol has not been found to be more effective than placebo in inducing remission in patients with moderately severe Crohn's disease and is approved for reducing signs and symptoms and maintaining response only
  - The guideline suggests using TNF antagonists in combination with thiopurines over TNF antagonist monotherapy to induce remission in patients who have moderately severe Crohn's disease (moderate-quality evidence)
    - The combination of infliximab and azathioprine was superior to infliximab alone in inducing remission in patients with moderately severe Crohn's disease who had not previously received either therapy
- Maintaining Remission
  - The TNF antagonists are superior to placebo in maintaining remission among patients with moderately severe Crohn's disease who had remission induced by these drugs
  - The data indicate that infliximab and adalimumab, as well as certolizumab, have substantial and similar benefits in the maintenance setting
  - Following surgically induced remission, the AGA suggests using TNF antagonists and/or thiopurines over other agents
  - In addition, in patients with asymptomatic endoscopic recurrence, the AGA suggests initiating or optimizing TNF antagonists and/or thiopurine therapy over continued monitoring alone

Rheumatoid Arthritis Guidelines- ACR, 2015

The American College of Rheumatology (ACR) guidelines for Rheumatoid Arthritis (RA)

- The guidelines describe the use of agents in early (< 6 months) and established (≥ 6 months) RA and focus on a treat-to-target approach based on mutual determination of a target between the patient and clinician

- **In patients with early symptomatic RA**
  - The guidelines recommend use of a disease modifying antirheumatic drug (DMARD) monotherapy (methotrexate [MTX] preferred) over double or triple therapy in patients who have never taken a DMARD, regardless of disease severity

- **If disease activity remains moderate or high despite DMARD treatment**
  - The use of combination DMARDs, an anti-TNF agent, or a non-TNF biologic (all with or without methotrexate) is preferred over DMARD monotherapy
  - While there is no particular order to this recommendation, they do recommend the use of anti-TNF agents over tofacitinib (Xeljanz, Xeljanz XR), with or without methotrexate
  - Glucocorticoids may be added if disease activity remains moderate or high despite DMARD or biologic therapy and for disease flares

- **In patients with established RA**
  - Recommend use of DMARD monotherapy (methotrexate preferred) over combination therapy or Xeljanz in patients who have never taken a DMARD, regardless of disease severity

- **If disease activity remains moderate or high despite DMARD treatment**
  - The use of combination DMARDs, an anti-TNF agent, a non-TNF biologic, or Xeljanz (all with or without methotrexate) is preferred over DMARD monotherapy
  - In addition, if the patient is using an anti-TNF agent and not taking a DMARD and disease activity remains moderate or high, the addition of a DMARD is recommended over anti-TNF agent monotherapy

Rheumatoid Arthritis Guidelines- ACR, 2015

The American College of Rheumatology (ACR) guidelines for Rheumatoid Arthritis (RA)

- **If disease activity remains moderate or high despite anti-TNF monotherapy**
  - Use of a non-TNF biologic (with or without methotrexate) is preferred over another anti-TNF agent or Xeljanz
- **If disease activity remains moderate or high despite non-TNF biologic use**
  - An alternative non-TNF biologic (with or without methotrexate) is preferred over Xeljanz
    - Non-TNF biologics are also preferred over Xeljanz or another anti-TNF agent for sequential anti-TNF agent failures
  - Thus, in general, Xeljanz is an alternative in the case of multiple anti-TNF and non-TNF biologic failures and most treatments are appropriate with or without methotrexate
  - Similar to early RA, short-term glucocorticoids may be used for multiple treatment failures or for disease flares in experienced RA
  - If disease activity is low, it is appropriate to continue treatment; if the disease is in remission, it is appropriate to taper therapy but not discontinue all treatments
- Traditional DMARDS (non-biologics) included in these guidelines are Plaquenil, Arava, methotrexate, and Azulfidine
- Anti-TNF biologics include Humira, Cimzia, Enbrel, Simponi, Simponi Aria, and Remicade
- Non-TNF biologics include Orencia, Rituxan, and Actemra. Kineret was excluded from the guidelines due to infrequent use/limited data
- Baricitinib and sarilumab were not FDA-approved at the time these guidelines were developed
- **An update to these guidelines is anticipated in late 2019/early 2020**

Rheumatoid Arthritis Guidelines

The Medical Letter, 2014

- Recommends that TNF antagonists (etanercept, infliximab, adalimumab, golimumab, infliximab, and certolizumab pegol) are typically the first-line biologic agents prescribed after an inadequate response to a DMARD
  - They may be given as monotherapy or in combination with methotrexate

- For patients who do not respond adequately to a TNF antagonist, switching to another TNF antagonist or a non-TNF biologic agent may be effective

- The combination of a biologic agent with a DMARD (usually methotrexate) offers better disease control without a substantial increase in toxicity and is now commonly used to achieve remission
  - Combinations are used particularly for patients with highly active disease, a long duration of disease, or with clinical features that indicate a poor prognosis
  - Aggressive early therapy with methotrexate and/or a biologic agent results in longer disease-free remissions, less joint destruction, and a better quality of life

Ankylosing Spondylitis- ACR Spondylitis Association of America (SAA) & Spondyloarthritis Research and Treatment Network (SPARTAN), 2015

- Axial spondyloarthritis (axSpA) is an inflammatory condition generally affecting the spine and can be furthered subdivided into ankylosing spondylitis (AS; radiographic axSpA) and nonradiographic axSpA (nr-axSpA)
- Guidelines recommendations for Ankylosing Spondylitis
  - Primary Treatment:
    - Continuous therapy with NSAIDs with TNF antagonists as alternatives in patients with persistent activity despite NSAID treatment
  - If activity still persists
    - Different TNF antagonist should be tried
    - No particular TNF antagonist is preferred over another, except in patients with comorbid inflammatory bowel disease or recurrent iritis, in which monoclonal antibodies should be used (e.g., infliximab or adalimumab) over etanercept
- For nr-axSpA, the group recommends treatment with a TNF antagonist over no TNF antagonist treatment if nr-axSpA remains active despite NSAID treatment
- An update to this guideline is anticipated in 2019

Plaque Psoriasis & Psoriatic Arthritis

The American Academy of Dermatology (AAD), 2011

- The evidence-based clinical practice guidelines of the American Academy of Dermatology (AAD) published in sections from 2008 to 2011 are currently undergoing a gradual update in collaboration with the National Psoriasis Foundation (NPF)
- The first few publications in the series, issued beginning in 2019, include the treatment of psoriasis with biologics and comorbidities (additional topics related to psoriasis, such as phototherapy, topicals, and non-biologics, and special populations, are forthcoming)
- The group recommends adalimumab, etanercept, and infliximab (strength of recommendation A for all) for moderate to severe psoriasis
    - Due to limited evidence, certolizumab does not have a recommendation, but they state that it is likely to have class characteristics similar to other TNF antagonists
    - Treatment response with TNF antagonists is best ascertained at 12 to 16 weeks following initiation (infliximab at 8 to 10 weeks)
- Brodalumab, guselkumab, ixekizumab, secukinumab, tildrakizumab, and ustekinumab, with a response ascertained after 12 weeks, are also recommended for moderate to severe psoriasis (strength of recommendation A for all)
- The group also stated that risankizumab is recommended for moderate to severe psoriasis (response ascertained after 12 weeks); however, they assigned this a strength of recommendation B as this was not FDA-approved at the time of guideline publication
- They also state that while there is no evidence to support combining risankizumab with adjunct topical or systemic therapies, there is no reason that combination therapy should be considered unsafe
- Based on limited data from a retrospective case series, apremilast may be combined with TNF antagonists (adalimumab, etanercept, infliximab) or ustekinumab to augment efficacy to treat moderate-to-severe cases (recommendation C for all)
- In general, the group recommends that efficacy and safety data be discussed with the patient for treatment initiation and switching
- In addition, a quality of life discussion should occur with the patient

Plaque Psoriasis & Psoriatic Arthritis

The American Academy of Dermatology (AAD), 2011

- Other factors affecting patient preference (e.g., dosing, cost, route) should also be discussed
    - Notably, they state that biologics with less frequent dosing (e.g., 8 to 12 weeks) may be preferred in some patients
- Regarding treatment switching, all other biologic therapies for psoriasis may be switched with another with the possibility for improved efficacy, safety, and/or tolerability; however, there are insufficient data to make more specific recommendations
- Primary failure to respond to a TNF antagonist does not prevent a response to an alternative TNF antagonist, although reduced efficacy could occur
- In addition, all products can lose efficacy over time (secondary failure)
    - Rigorous data to guide therapy at that time are limited, but there are various treatment strategies that can be employed on a case-by-case basis
- Augmentation using a combination of a biologic with select small molecule systemic agents, phototherapy, or topical agents is recommended in select patients with continued disease severity
- Extensive recommendations by medication, class, and/or group, including dosing (initial, maintenance, escalation, and optimal intervals), monitoring, treatment discontinuation and reinitiation, antibody development, comorbidities, adverse effects, timeline, and augmentation strategies, are detailed in the guidelines

Plaque Psoriasis & Psoriatic Arthritis

ACR, & National Psoriasis Foundation, 2018

- For initial treatment in treatment-naïve patients with active PsA, the group recommends treatment with a TNF antagonist over an oral small molecule (e.g., methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast), an IL-17 inhibitor (brodalumab, ixekizumab, secukinumab), or an IL-12/23 inhibitor (e.g., ustekinumab)
  - In addition, an oral small molecule is recommended over an IL-17 inhibitor or IL-12/23 inhibitor, and methotrexate, specifically, is recommended over an NSAID
  - Use of an IL-17 antagonist is recommended over an IL-12/23 antagonist
- Patients with active PsA despite treatment with an oral small molecule, recommend switching to a TNF antagonist over a different oral small molecule, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, tofacitinib, or a TNF antagonist in combination with methotrexate
  - Recommend switching to an IL-17 antagonist, over a different oral small molecule, IL-12/23 inhibitor, abatacept, tofacitinib, or an IL-17 antagonist in combination with methotrexate, and to an IL-12/23 inhibitor over a different oral small molecule, abatacept, tofacitinib, or an IL-12/23 inhibitor in combination with methotrexate
  - Adding apremilast to an oral small molecule rather than switching to apremilast and recommend switching to another oral small molecule rather than adding another non-apremilast small molecule

Plaque Psoriasis & Psoriatic Arthritis

ACR, & National Psoriasis Foundation, 2018

- Adults with active PsA despite treatment with TNF antagonist monotherapy, the group recommends switching to a different TNF antagonist over switching to an IL-17 or IL-12/23 inhibitor, abatacept, or tofacitinib, or adding methotrexate, although adding methotrexate to a different TNF antagonist is an option
  - Recommend switching to an IL-17 inhibitor (without methotrexate) over switching to an IL-12/23 inhibitor (without methotrexate), abatacept, or tofacitinib and switching to an IL-12/23 inhibitor over switching to abatacept or tofacitinib
- Adults with active PsA despite treatment with TNF antagonist and methotrexate therapy, the group recommends switching to a different TNF antagonist plus methotrexate over a different TNF antagonist, but recommends switching to IL-17 or -12/23 inhibitor monotherapy (over IL-17 or -12/23 inhibitor in combination with methotrexate)
  - Several other conditional recommendations are included in the guidelines based on patients with active disease despite treatment, and, in general, the recommendations prefer alternative treatments in the following order: TNF antagonist, IL-17 inhibitor, IL-12/23 inhibitor, and addition of methotrexate
- A notably strong recommendation in these guidelines is that in adult patients with active PsA and frequent serious infections who are both oral small molecule- and biologic treatment–naïve, an oral small molecule should be started over a TNF antagonist
- Guidelines also provided recommendations for patients who have PsA and other related disorders, such as active axial disease or inflammatory bowel disease (IBD)
  - Generally, these recommendations are similar to others in order of treatment preference; however, the group did include some notable strong recommendations for patients with active PsA and concomitant active IBD despite treatment with an oral small molecule, including recommendations to switch to a monoclonal antibody TNF antagonist over a TNF soluble receptor biologic (e.g., etanercept) or IL-17 inhibitor and that an IL-12/23 inhibitor is preferred over switching to an IL-17 antagonist
  - A monoclonal antibody TNF antagonist is also preferred over an IL-12/23 inhibitor in this population, but this is a conditional recommendation