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Tildrakizumab-asmn for Moderate-to-Severe Plaque Psoriasis

By: Bethany Lane, Pharm.D.

Background: Plaque psoriasis is a chronic inflammatory skin disease characterized by well-demarcated, red, scaly plaques involving the scalp, elbows, and knees.¹ Multiple cytokines have been implicated in plaque psoriasis including tumor necrosis factor-alpha (TNF α), interleukin (IL)-23, and IL-12.² Severity of disease is determined by the extent of body surface area (BSA) involved with <3% BSA as mild, 3-10% as moderate, and >10% as severe disease.¹ The Psoriasis Area and Severity Index Score (PASI) accounts for BSA involvement and characteristics of plaques (e.g., redness, scaling, and thickness); it is commonly utilized in clinical trials to determine the efficacy of potential agents.¹ The gold standard assessment tool in clinical trials is the PASI-75 or the proportion of patients achieving at least 75% improvement in baseline scores.³ Topical medications

or phototherapy often control mild-to-moderate disease, while those with severe disease may require additional therapy with biologics to obtain adequate control.¹ Tildrakizumab-asmn (Ilumya™; Sun Pharmaceuticals) was approved by the Food and Drug Administration in March 2018 for the treatment of moderate-to-severe plaque psoriasis in those who are candidates for systemic therapy.⁴

Mechanism of Action: Tildrakizumab, a humanized IgG1/k monoclonal antibody, acts as an IL-23 antagonist.⁴ It selectively binds to the p19 subunit of the IL-23 receptor inhibiting the inflammatory response and subsequent release of other cytokines.

Clinical Trials: Two three-part, double-blind, randomized, placebo-controlled, parallel-group studies, re-

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Crizanlizumab-tmca for Sickle Cell Disease-Related Pain Crises

By: Jessica A. Ward, Pharm.D.

Background: Sickle cell disease (SCD) is a heritable hematologic disorder affecting more than 100,000 Americans.¹ Characteristic erythrocyte malformation, or sickling, results from a single-point amino acid substitution in the beta globulin subunit of hemoglobin. Sickled erythrocytes have impaired oxygen-carrying capacity and ability to pass through the vasculature. This leads to acute and chronic complications, such as anemia, asplenia-related infections, and vaso-occlusive crises (VOCs), including silent cerebral infarctions,

priapism, acute chest syndrome, and pain crises.² The hallmark VOCs, pain crises, are a major cause of hospitalization and morbidity in SCD.^{2,3} The Food and Drug Administration (FDA) approved crizanlizumab-tmca (Adakveo®; Novartis) in November 2019 to reduce VOCs in SCD with or without concomitant hydroxyurea therapy. Prior to this, only hydroxyurea and L-glutamine were FDA-approved for SCD.¹ Hydroxyurea remains a mainstay of therapy, however use may be limited

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SURFACE 1 and reSURFACE 2, assessed the efficacy of tildrakizumab compared with placebo and etanercept.³ Patients enrolled in reSURFACE 1 were randomly assigned (2:2:1) during part one to tildrakizumab 200 mg, 100 mg, or placebo. During part two of reSURFACE 1, those receiving placebo were re-randomized (1:1) to either tildrakizumab 200 mg or 100 mg. Patients enrolled in reSURFACE 2 were randomly assigned (2:2:1:2) during part one to tildrakizumab 200 mg, 100 mg, placebo, or etanercept 50 mg. During part two of reSURFACE 2, those receiving placebo were re-randomized (1:1) to tildrakizumab 200 mg or 100 mg. Upon entering part three of both studies, responders (PASI \geq 75) and partial responders (PASI $<$ 75 and PASI \geq 50) to tildrakizumab 200- and 100-mg were re-randomized at week 28 to continue the same treatment, a different dose of tildrakizumab, or placebo. Assigned medications were administered at weeks 0 and 4 during part one and at week 16 during part two (weeks 12 and 16 if re-randomized from placebo to tildrakizumab); etanercept was administered twice weekly in part one and once weekly during part two. Co-primary endpoints included the proportion of patients achieving PASI-75 and a Physician's Global Assessment (PGA) score of "clear" or "minimal," with at least a two-grade reduction from baseline at week 12. The PASI-75 was achieved by week 12 in 192 patients (62%) receiving tildrakizumab 200 mg and 197 patients (64%) receiving 100 mg compared to nine patients (6%) receiving placebo ($p < 0.0001$ for comparisons of both tildrakizumab groups vs. placebo). The PGA co-primary endpoint was achieved in 182 patients (59%) receiving tildrakizumab 200 mg and 179 patients (58%) receiving 100 mg compared to 11 patients (7%) receiving placebo ($p < 0.0001$ for comparisons of both tildrakizumab groups vs. placebo). In reSURFACE 2, PASI-75 was achieved by week 12 in 206 patients (66%) receiving tildrakizumab 200 mg, 188 patients (61%) receiving 100 mg compared to nine patients (6%) receiving placebo and 151 patients (48%) receiving etanercept ($p < 0.0001$ for comparisons of both tildrakizumab groups to placebo; $p < 0.0001$ for tildrakizumab 200 mg vs. etanercept and $p = 0.0010$ for tildrakizumab 100 mg vs. etanercept). The PGA co-primary endpoint was achieved in 186 patients (59%) receiving tildrakizumab 200 mg and 168 patients (55%) receiving tildrakizumab 100 mg compared with seven patients (4%) receiving placebo and 149 patients (48%) receiving etanercept ($p < 0.0001$ for comparisons of both tildrakizumab groups vs. placebo; $p = 0.0031$ for tildrakizumab 200 mg vs. etanercept and $p = 0.0663$ for tildrakizumab 100 mg vs. etanercept). From the results, the authors concluded both tildrakizumab 200 mg and 100 mg were efficacious compared with placebo and etanercept and were well tolerated for the treatment of moderate-to-severe plaque psoriasis.

Safety and Immunogenicity: The commonly observed adverse reactions occurring in $>1\%$ of patients included upper respiratory infections, injection site reactions, and diarrhea.⁴ Approximately 6.5% of patients treated with tildrakizumab 100 mg developed antibodies up to week 64 with 40% classified as neutralizing. Angioedema and urticarial reactions have been reported in trials; if these reactions occur, therapy should be discontinued and appropriate treatment be initiated. Additionally, tildrakizumab was associated with a slightly higher rate of infection; patients with active or recurrent infections should delay therapy until resolution of infection or until adequate treatment is provided.

Dosing and Administration: The recommended dose of tildrakizumab is 100 mg subcutaneously at weeks 0, 4, and every 12 weeks thereafter.⁴ Subcutaneous injections of tildrakizumab must be administered by a healthcare provider. If doses are missed, it is recommended to administer the dose as soon as possible, and resume the regularly scheduled interval.

Cost and Availability: Tildrakizumab, which is available as a 100 mg/mL single-dose prefilled syringe (NDC 47335-177-01), has an average wholesale price of \$16,698.^{4,5} The estimated annual cost of therapy following induction dosing is approximately \$53,316.

Formulary Status: Tildrakizumab is on the CCHS Formulary restricted to the Department of Dermatology for outpatient use only.

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by lack of adherence, unpredictable pharmacokinetics/pharmacodynamics, and side effects.^{4,5} Guidelines for SCD management do not yet include crizanlizumab.⁶

Mechanism of Action: Crizanlizumab is a first-in-class, recombinant humanized IgG2 kappa monoclonal antibody, targeting P-selectin on activated endothelial cells.⁷ P-selectin is thought to facilitate sickled erythrocyte vessel adhesion and VOC development. When bound by crizanlizumab, P-selectin cannot bind to P-selectin glycoprotein ligand 1, which inhibits interactions among endothelial and blood cells in a dose-dependent fashion.

Key Clinical Trial: Crizanlizumab was evaluated in SUSTAIN, a randomized, double-blind, multi-center, placebo-controlled trial including patients aged 16 years and older with SCD of any genotype who experienced two to ten VOCs annually.⁸ Participants were randomized to receive crizanlizumab 5 mg/kg (high-dose n=67) or 2.5 mg/kg (low-dose n=65), or placebo (n=66) administered as loading doses at weeks 0 and 2, followed by maintenance therapy once every 4 weeks. Stable hydroxyurea background therapy was permitted during the 52-week study period. The primary outcome was annualized rate of VOCs; secondary outcomes included median annualized rate of days hospitalized and median times to first and second VOC. Compared to placebo, low-dose crizanlizumab was not associated with significant improvement in primary or secondary outcomes. High-dose therapy was associated with significant reductions in the primary outcome in intention-to-treat (1.63 vs. 2.98; p=0.01) and per-protocol (1.04 vs. 2.18; p=0.02) analyses vs. placebo. Hydroxyurea and crizanlizumab combination therapy was associated with an overall reduction in annual VOCs compared to hydroxyurea alone (2.43 vs 3.58). The median annualized rate of days hospitalized was 41.8% lower in high-dose group vs. placebo (4.00 vs. 6.87; p=0.45). The median times to first and second VOC were significantly longer in the high-dose group vs. placebo (first VOC: 4.07 vs. 1.38 months; p=0.001; second VOC: 10.32 vs. 5.09 months; p=0.02).

Safety and Immunogenicity: Overall incidence of adverse events was 26% in the high-dose treatment group vs. 27% in the placebo group.⁸ Common adverse effects (occurring in >10% of the treatment group) included headache, back pain, nausea, arthralgia, and musculoskeletal pain. Infusion reactions were observed in 3% of patients. Monitoring for associated symptoms is recommended. No development of anti-drug antibodies was observed. Crizanlizumab may cause falsely decreased or uninterpretable automated platelet counts when samples are collected in tubes containing ethylenediaminetetraacetic acid.

Dosing and Administration: The dose of crizanlizumab in patients aged 16 years or older is 5 mg/kg (based on actual body weight) given via intravenous infusion at weeks 0 and 2 and then every 4 weeks thereafter.⁷ The dose should be administered over 30 minutes with a non-pyrogenic 0.2 micron inline filter. No other medications should be mixed with or co-administered through the same line. Following infusion completion, the line should be flushed with at least 25 mL of 0.9% Sodium Chloride or 5% Dextrose. If a dose is missed within 2 weeks of the scheduled dose, it should be given as soon as possible and the original dosing schedule can be maintained. If a dose is missed more than 2 weeks after the scheduled dose, dosing should continue every 4 weeks from the new administration date. No dosing adjustments are recommended for geriatric patients or those with renal or hepatic impairment.

Availability and Cost: Crizanlizumab is available as a single-dose 100 mg/10 mL glass vial (NDC 0078-0883-61) with an average wholesale price of \$2828.57 per vial.⁹ The annual cost of therapy for a 70 kg patient, is approximately \$158,400. Resources for co-pay assistance are available through Patient Assistance Now Oncology (PANO) and the Novartis Universal Co-pay Program.¹⁰

Formular Status: Crizanlizumab is on CCHS Formulary with restrictions to Adult and Pediatric Hematology and Oncology Departments for outpatient use only in patients 16 years of age and older.

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