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Rilonacept for Recurrent Pericarditis

By: Danielle Powall, Pharm.D.

Background: Pericarditis, an inflammatory condition of the pericardium, is responsible for 0.1% of all hospital admissions and 5% of all emergency room visits.[1] Recurrent pericarditis (RP) is characterized as experiencing a documented first episode of acute pericarditis followed by a symptom-free interval of 4-6 weeks or longer and evidence of another episode of pericarditis. The 2015 European Society for Cardiology guidelines currently recommend aspirin or non-steroidal anti-inflammatory drugs with colchicine as the first-line treatment for RP followed by glucocorticoids as the preferred second-line treatment. Anakinra (Kineret®; Sobi), an interleukin-1 (IL-1) receptor antagonist is recommended off-label as a third-line treatment.[2,3] Rilonacept (Arcalyst®; Kiniksa Pharmaceuticals), an interleukin (IL)-1α and IL-1β cytokine trap, was approved by the Food and Drug Administration in March 2021 for the treatment of RP and reduction in risk of recurrence in adults and children 12 years and older.[4]

Mechanism of Action: Interleukin-1α may contribute to the propagation and maintenance of inflammation which augments the inflammatory response by producing IL-1β in a cascade amplification system.[4] Rilonacept operates as a cytokine receptor trap preventing engagement of IL-1 with the cell-surface receptor inhibiting its activity.

Clinical Trial: Rilonacept was evaluated in RHAPSODY, a double-blind, placebo-controlled, randomized-withdrawal trial.[5,6] Adult and adolescent patients (≥12 years of age) with RP and signs and symptoms of at least a second recurrence despite using standard therapy were recruited. A pain scale

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Aripiprazole Lauroxil for Schizophrenia

By: April Chapman, Pharm.D. , MBA

Background: Non-adherence to antipsychotic therapy can put patients with schizophrenia at risk for exacerbating psychosis, increased outpatient visits, and rehospitalization.[1] A unique treatment option for patients with schizophrenia who struggle with medication adherence includes long-acting injectable antipsychotics which provide medication coverage over weeks to months.[2,3] In a meta-analysis of 16 studies including over 4000 patients, long-acting injectable antipsychotics showed superiority over oral antipsychotic medications in preventing hospitalizations due to psychotic episodes.[4] On October 6, 2015, aripiprazole lauroxil (Aristada®; Alkermes) and aripiprazole lauroxil nanocrystal suspension (Aristada Initio®; Alkermes), two long-acting injectable antipsychotics, received approval from the Food and Drug Administration (FDA) for the treatment of schizophrenia.[5,6] Aristada Initio® and oral aripiprazole are indicated as an initiation regimen for Aristada® therapy.[5] Aristada Initio® has a

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score of at least 4 on a numerical rating scale (NRS) and a C-reactive protein (CRP) level of at least 1 mg/dL within 7 days before the first administration of rilonacept was required for enrollment. Patients were enrolled in a 12-week run-in period where rilonacept was initiated and guideline-directed medications were discontinued. Patients who had a clinical response during the run-in period, defined as pain reduction or normalization of CRP, were randomly assigned 1:1 to receive rilonacept monotherapy or placebo. A total of 86 adult patients with pericarditis pain and an elevated CRP level were enrolled in the run-in period and 61 of those patients participated in the randomized-withdrawal period with 30 in the rilonacept group and 31 in the placebo group. Adults who received rilonacept were given a 320 mg loading dose via subcutaneous (SQ) injection followed by weekly SQ injections of 160 mg. Patients <18 years of age would receive a 4.4 mg/kg loading dose of rilonacept, followed by a weekly maintenance dose of 2.2 mg/kg. The primary efficacy endpoint was time to the first pericarditis recurrence. The major secondary efficacy endpoints included the percentage of patients who had a persistent clinical response at the week 16 assessment, the percentage of days with no or minimal pain through week 16 determined by a NRS score ≤2, and the percentage of patients with absent or minimal pericarditis symptoms with a score according to the patient's global impression of pericarditis severity scale of 0 to 1 (scores range from 0 to 6, with lower scores indicating less severity). During the run-in period, the median time to resolution or near-resolution of pain was 5 days and the median time to normalization of the CRP level was 7 days. In the placebo-controlled randomized–withdrawal period, there were too few occurrences of pericarditis in the rilonacept group to determine a median time of recurrence. However, the median time in the placebo group was 8.6 weeks (95% CI, 4.0-11.7). During this period, only two patients out of 30 treated with rilonacept experienced a recurrence, in contrast to 23 out of 31 patients in the placebo group. Rilonacept led to a lower risk of RP than placebo (HR, 0.04; 95% CI, 0.01-0.18; p<0.001). Persistent clinical response at week 16 occurred in 81% of the rilonacept group vs 20% of the placebo group (HR, 61; 95% Cl, 37-85; p<0.001). The least-squares mean percentage of enrolled patients with no or minimal pain was 97.7 ± 7.5 in the rilonacept group vs 45.9 ± 7.2 in the placebo group (HR, 51.8; 95% CI, 35.3-68.4; p<0.001). The percentage of enrolled patients with absent or minimal pericarditis symptoms was 81% in the rilonacept group vs 25% in the placebo group (HR, 56; 95% CI, 31-81; p<0.001). Based on these results, the authors concluded that among patients with RP, rilonacept led to rapid resolution of pericarditis episodes and a significantly lower risk of RP than placebo.

Safety: The most common adverse events observed in rilonacept group were injection-site reactions (34%) and upper respiratory tract infections (23%).[6] Patients who received rilonacept had higher low-density lipoprotein (LDL) and mean triglyceride (TG) levels. The mean LDL levels were (124.8 ± 33.4 mg/dL vs 111.7 ± 24.4 mg/dL) and the mean TG levels were (198.0 ± 105.8 mg/dL vs 96.7 ± 34.0 mg/dL) for the rilonacept group vs the placebo group, respectively at week 24.

Dosing and Administration: The recommended adult dosing of rilonacept includes a 320 mg SQ loading dose given as two separate 160 mg injections at two different injection sites followed in 1 week by a 160 mg maintenance dose administered weekly, thereafter.[4] A loading dose of 4.4 mg/kg (up to a maximum of 320 mg) given as one or two injections not to exceed 2 mL per injection is recommended for adolescents 12 to 17 years of age followed by a weekly maintenance dose of 2.2 mg/kg (up to a maximum of 160 mg). The first SQ injection of rilonacept must be administered under the supervision of a healthcare professional. If doses are missed, it is recommended to administer the next dose within 7 days from the missed dose and resume the original schedule. If the dose is not administered within 7 days, patients should start a new schedule based on the last date administered. No dosage adjustments are recommended for geriatric patients or those with renal or hepatic impairment.

Cost and Availability: Rilonacept is available as a 220 mg vial (NDC 73604-914-04) and has an average wholesale price of $6000.[4,7] The estimated annual cost of therapy is approximately $315,000.

Formulary Status: Rilonacept is not currently on the CCHS Formulary.

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more rapid onset of action and shorter half-life than Aristada®.[5,6] The two formulations are not interchangeable.

Mechanism of Action: Aripiprazole lauroxil is a prodrug of aripiprazole.[5,6] After the medication is metabolized to its active form, it is believed to exert partial agonist activity at certain dopamine and serotonin receptors and antagonistic activity at different serotonin receptors.

Clinical Trial: The safety and efficacy of aripiprazole lauroxil were evaluated in the ALPINE study, a phase 3b, randomized, double-blind, active-control trial in patients hospitalized with acute schizophrenia.[7] The study included patients aged 18 to 65 years with schizophrenia who were hospitalized with an acute exacerbation or relapse of symptoms. Patients were randomized 1:1 to receive either aripiprazole lauroxil long-acting injection every 8 weeks (n=99) or paliperidone palmitate long-acting injection every 4 weeks (n=101). Patients without prior exposure to aripiprazole were given a 5 mg test dose to establish tolerability. As part of the inpatient initiation phase, the aripiprazole lauroxil group received a gluteal injection of aripiprazole lauroxil nanocrystal suspension along with a placebo deltoid injection on day 1 plus a 30 mg dose of oral aripiprazole. Afterwards, aripiprazole lauroxil 1064 mg was administered on day 8 along with a placebo injection. As part of outpatient treatment, aripiprazole lauroxil was administered every 8 weeks (weeks 9 and 17) with placebo injections administered weeks 5, 13, and 21 to match the timing of the paliperidone palmitate injections. As part of the inpatient initiation phase, the paliperidone palmitate group received a deltoid injection of 234 mg with a placebo gluteal injection and a placebo oral tablet on day 1. On day 8, they received a 156 mg deltoid injection of paliperidone palmitate and a placebo gluteal injection. As part of the outpatient regimen, paliperidone palmitate 156 mg was administered via gluteal injection every 4 weeks after the day 8 (weeks 5, 9, 13, 17, and 21). The primary endpoint was the within-group change in Positive and Negative Syndrome Scale total score ($PANSS_T$) from baseline to week 4. Secondary endpoints included change in $PANSS_T$ from baseline to weeks 9 and 25 in each group and between-group changes in $PANSS_T$ at weeks 4, 9, and 25. The mean $PANSS_T$ in the aripiprazole lauroxil group at baseline was 94.1 and after treatment, the scores were significantly reduced at week 4 (-17.4; $p<0.001$), and were reduced at weeks 9 and 25 (-19.8; $p<0.001$) and (-23.3; $p<0.001$), respectively. The mean $PANSS_T$ in the paliperidone palmitate group at baseline was 94.6 and after treatment, the scores were significantly reduced at week 4 (-20.1; $p<0.001$), and were reduced at weeks 9 and 25 (-22.5; $p<0.001$) and (-21.7; $p<0.001$), respectively. The study was not powered to detect between-group differences. The authors concluded that both antipsychotics were effective and well-tolerated therapies for schizophrenia that may be initiated in the hospital and then continued on an outpatient basis.

Safety: Aristada® and Aristada Initio® carry a black box warning of increased mortality in elderly patients with dementia-related psychosis.[5,6] The most common adverse events occurring during the follow-up period of the ALPINE study were injection site pain (17.2%), increased weight (9.1%), and akathisia (9.1%).[7]

Dosing and Administration: After establishing tolerability with oral aripiprazole, Aristada® can be initiated in one of two ways.[5] The first option is to administer one intramuscular injection of Aristada Initio® 675 mg in the deltoid or gluteal muscle and one dose of oral aripiprazole 30 mg in conjunction with the first Aristada® injection. The second option is to administer oral aripiprazole for 21 consecutive days in conjunction with the first Aristada® injection. The starting Aristada® dose options include 441 mg, 662 mg, or 882 mg monthly, 882 mg every 6 weeks, or 1064 mg every 2 months. The choice of the starting dose is based on the patient's previous oral aripiprazole regimen as outlined in the package insert. Aristada® and Aristada Initio® may only to be administered by a healthcare professional. Aristada® 441 mg may be administered intramuscularly in either the deltoid or gluteal muscle; all other doses are administered in the gluteal muscle.

Cost and Availability: Aristada Initio® is available as a 674 mg/2.4 mL kit (NDC 65757-500-03).[6] Aristada® is available as 441 mg (NDC 65757-401-03), 662 mg, (NDC 65756-402-03), 882 mg (NDC 6575-403-03), and 1064 mg (NDC 65757-404-03) kits.[5] The average annual cost of Aristada® therapy for a patient is approximately $7200, based on a one-day initiation with Aristada Initio® and a maintenance dose of 1064 mg every 2 months.[8]

Formulary Status: Aristada® and Aristada® Initio® were added to the CCHS Adult Formulary restricted to the Department of Psychiatry for initiation of therapy. Continuation of therapy is not restricted.

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