Rilonacept (Arcalyst), an Interleukin-1 Trap for the Treatment of Cryopyrin-Associated Periodic Syndromes

Saloni Kapur, PharmD, MPA, and Mary Ellen Bonk, PharmD

INTRODUCTION

Cryopyrin-associated periodic syndromes (CAPS) comprise a group of rare inflammatory diseases that are inherited in an autosomal dominant pattern. Male and female offspring are affected equally with varying degrees of severity.[1] CAPS comprise three syndromes: familial cold auto-inflammatory syndrome (FCAS), Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease (NOMID), also referred to as chronic infantile neurological cutaneous articular syndrome (CINCA).

The incidence of CAPS in the U.S. is estimated at 1 in 1,000,000 people, with a current prevalence of 300 to 500 individuals.[2] Patients share common symptoms such as periodic fever, inflammation, and an urticaria-like skin rash. The diseases appear to represent a continuum, with FCAS the mildest and NOMID/CINCA the most severe.[3,4] Clinical manifestations are listed in Table 1.[1,3–5]

Inflammation in CAPS is associated with autosomal-dominant mutations in the *NLRP3* gene (also known as the *CIAS1* gene) and resultant alterations in the protein cryopyrin, which it encodes. Cryopyrin regulates the activity of caspase-1, which is responsible for converting interleukin-1β (IL-1β) to its active form, resulting in the activation of the immune and inflammatory systems. Mutations in the *NLRP3* gene lead to overproduction of IL-1β, resulting in the inflammatory symptoms associated with CAPS.[2,6]

Dr. Kapur is a Fellow, and Dr. Bonk is Manager of the Drug Information Group, both at the University HealthSystem Consortium in Oakbrook, Illinois. Drug Forecast is a regular column coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi & Associates in New York, New York.

INDICATIONS AND USAGE

On February 27, 2008, the FDA approved rilonacept (Arcalyst, Regeneron Pharmaceuticals) through an accelerated process.[7] Also known as IL-1 Trap, rilonacept was granted orphan drug status. It is the first agent approved for the treatment of CAPS, including FCAS and Muckle–Wells syndrome in adults and children 12 years of age and older.[8]

Rilonacept is not indicated for patients with NOMID or CINCA.[9] It is currently being studied to determine its safety and efficacy in preventing gout attacks.[10]

CLINICAL PHARMACOLOGY

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the IL-1 receptor components (IL-1RI and IL-1 receptor accessory protein) linked to the Fc portion of human immunoglobulin G_1 (IgG_1).[2] Rilonacept blocks IL-1β signaling by acting as a soluble decoy receptor that binds IL-1β and prevents its interaction with cell–surface receptors, thereby reducing the inflammatory process.[2,8]

PHARMACOKINETICS AND PHARMACODYNAMICS

For CAPS patients receiving 160 mg of rilonacept weekly for up to 48 weeks, steady state was reached in six weeks. Average trough levels were 24 mcg/mL, and the circulation half-life *in vivo* was 8.6 days.[8,11] No pharmacokinetic dosing information is currently available for patients with either renal or hepatic impairment, and no studies have been conducted to evaluate the effect of the drug on age, sex, or body weight. However, clinical data suggest that the concentration of the drug at steady state is not affected by the patient's sex. Given that all patients participating in clinical trials were Caucasian, the effects of race were not able to be determined.

Two indicators of inflammatory disease that are elevated in CAPS patients are C-reactive protein (CRP) and serum amyloid A. Elevated serum amyloid A levels have been associated with the development of one of the more serious manifestations of CAPS, systemic amyloidosis. Clinical trials have demonstrated a reduction and normalization of CRP and serum amyloid A compared with baseline values during the trial period.[8]

Disclosure: The authors have no financial relationships or conflicts of interest to report in regard to this article.

CLINICAL TRIALS

The safety and efficacy of rilonacept were demonstrated in a series of two randomized, placebo-controlled, double-blind studies conducted in the same group of patients with either FCAS or Muckle–Wells syndrome.[12]

In the first study, a six-week, parallel-group trial, 23 patients received rilonacept at an initial loading dose of 320 mg, then 160 mg weekly; 24 patients received placebo. The second study, which followed immediately afterward, consisted of two parts: a nine-week patient-blind period during which subjects received rilonacept 160 mg weekly, followed by a nine-week, double-blind withdrawal period in which patients were randomly assigned to either continue with the weekly doses (n = 22) or to receive placebo (n = 23). At the conclusion of the second study, patients were given the option to participate in a 24-week, open-label treatment extension study in which all patients received rilonacept 160 mg weekly.[12]

Symptoms of CAPS disorders, including joint pain, rash, sensations of fever or chills, eye redness with pain, and fatigue, were evaluated. Using a daily diary questionnaire, patients rated each symptom on a scale of 0 (none, no severity) to 10 (very severe). The investigators then assessed the change in mean symptom

Table I **Cryopyrin-Associated Periodic Syndromes**

Syndrome	Severity	Disease Onset	Attack Duration	Clinical Manifestations
Familial cold auto-inflammatory syndrome	Mild	First six months of life	< 24 hours	Cold temperature–induced fever, urticaria, rash, headache, nausea, sweating, drowsiness, extreme thirst, conjunctivitis, blurred vision, ocular pain, polyarthralgia
Muckle–Wells syndrome	Moderate	Childhood	24–48 hours	Urticaria, fever, arthralgia, conjunctivitis, abdominal pain, progressive hearing loss, nephropathy, renal amyloidosis
Neonatal-onset multisystemic inflammatory disease	Severe	Neonatum period or early in infancy	Continuous, with episodes of worsening	Nonpruritic urticaria-like rash, central nervous system involvement (headache, macrocephaly, cerebral atrophy, chronic aseptic meningitis, high-frequency hearing loss, ocular changes, developmental delay), lymphadenopathy, hepatosplenomegaly

Adapted from references 1 and 3–5.

scores from baseline to the end of treatment.

Patients receiving rilonacept improved within several days of initiating therapy. The mean change in symptom scores from the baseline evaluation to the endpoint in the first study was –0.5 in placebo patients and –2.4 in rilonacept patients, with a 95% confidence interval (CI) for a between-group difference of –2.4 to –1.3. The study demonstrated that patients receiving treatment experienced a larger reduction in mean symptom scores.

In the second study, mean symptom scores of patients who switched to placebo increased (0.9), compared with patients who continued with rilonacept (0.1), for a 95% CI for a between-group difference of –1.3 to –0.4.[8] These figures (0.9 and 0.1) represent the least-square mean change from baseline to endpoint (for the mean symptom score).

The first study also evaluated serum amyloid A levels (normal range, 0.7–6.4 mg/L) and CRP levels (normal range, 0 to–8.4 mg/L). Both serum amyloid A and CRP are usually elevated during active disease. At the end of six weeks of rilonacept therapy, both mean serum amyloid A levels (pre-treatment baseline value = 60 mg/L, week six = 4 mg/L) and CRP levels (pre-treatment baseline value = 22 mg/L, week six = 2 mg/L) were reduced when compared with the baseline level. Conversely, the placebo patients showed relatively no change in mean serum amyloid A levels (pre-treatment baseline value = 110 mg/L, week six = 110 mg/L) or CRP levels (pre-treatment baseline value = 30 mg/L, week six = 28 mg/L) compared with the baseline value.[8]

The most common adverse effects associated with rilonacept in these trials, from most to least frequent, were injection-site reactions, upper respiratory tract infections, sinusitis, cough, hypoesthesia, nausea, diarrhea, stomach discomfort, and urinary tract infections.[12] The product information for rilonacept mentions six serious adverse effects during the trials, which were reported by four patients, as follows: *Mycobacterium* intracellular infection, gastrointestinal bleeding, colitis, sinusitis, bronchitis, and *Streptococcus pneumoniae* meningitis.[8]

DRUG INTERACTIONS

To date, drug-interaction studies have not been performed for rilonacept; however, an increased incidence of serious infections has been associated with the use of IL-1 blockers in combination with tumor necrosis factor (TNF) inhibitors. Concomitant administration of rilonacept with TNF inhibitors is therefore not recommended. In addition, based on the potential pharmacological interaction of rilonacept with drugs that block IL-1 or its receptors, the concomitant administration of these agents is not recommended. Cytochrome P450 enzyme formation is suppressed by increased levels of IL-1 during chronic inflammation. Because rilonacept binds to IL-1, it has the potential of normalizing low CYP 450 enzyme levels. Therefore, therapeutic drug monitoring should be initiated when rilonacept is given with CYP 450 substrates that have narrow therapeutic indexes, such as warfarin (Coumadin, Bristol-Myers Squibb); doses of those medications may need to be adjusted.[8]

PRECAUTIONS AND WARNINGS

Rilonacept may interfere with the body's immune response to infection; therefore, treatment should not be instituted in patients with active or chronic infections. Therapy should be discontinued if a serious infection develops.

Although the impact of the drug on the development of malignancies has not been studied, treatment with rilonacept may increase this risk. No data are available on the concomitant administration of live or inactivated vaccines and rilonacept. Live vaccines should not be given to patients who are being treated with rilonacept; it is recommended that patients receive all necessary vaccinations before starting treatment, including pneumococcal and inactivated influenza vaccines.

If a hypersensitivity reaction occurs when rilonacept is given, therapy should be discontinued.[8]

MONITORING REQUIREMENTS

Patients with chronic inflammation, as in the case of CAPS, may have reduced cholesterol and lipid levels. Rilonacept decreases the inflammatory response; as a result, patients may have increases in total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and triglyceride levels.[8] Physicians should monitor patients' lipid profiles two to three months after therapy has been started.

Lipid-lowering agents should be considered, as needed, according to patients' cardiovascular risk factors and current guidelines.[8]

DOSAGE AND ADMINISTRATION

Rilonacept is being distributed through two specialty pharmacies, which plan to mail patients a monthly shipment of the drug and the supplies needed for self-injection. The pharmacies will also provide access to self-injection training and adherence counseling to patients who need those services. Information is available to patients and physicians toll-free at 1-877-REGN-777 (1-877-734-6777).

Rilonacept injections should be administered via subcutaneous (SQ) injection. After reconstitution, the final concentration is 80 mg/mL with a volume of 2 mL. The recommended dose, up to 2 mL (160 mg), should be drawn using a 3-mL syringe for SQ injection. Each vial should be used for a single dose only and should be discarded after withdrawal of the drug. Before reconstitution, rilonacept should be refrigerated at 36° to 46°F and stored in the original carton to protect the product from light. After the drug is reconstituted, it may be kept at room temperature. It should be protected from light, and it must be used within three hours.[8]

In patients 18 years of age and older, rilonacept therapy should be started with a loading dose of 320 mg, delivered as two separate 2-mL (160-mg) injections. These SQ injections are given on the same day at two different injection sites. Dosing should then be continued with SQ once-weekly injections of 2 mL (160 mg). No dosage adjustments are necessary based on the patient's sex or advanced age.

In pediatric patients 12 to 17 years of age, rilonacept should be started with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two SQ injections. If the loading dose is given as two injections, they should be given on the same day at different injection sites. Dosing should be continued with a once-weekly SQ injection of 2.2 mg/kg, up to a maximum of 160 mg (2 mL).

Rilonacept should not be given more often than once weekly in either adult or pediatric patients.[8]

Rilonacept is classified as a Pregnancy Category C agent and should be used during pregnancy only if expected benefits outweigh potential risks to the fetus.[8]

ALTERNATIVE THERAPIES

Colchicine, 1 to 2 mg/day orally, and TNF-α blockers, such as SQ etanercept (Enbrel, Amgen/Wyeth) 25 mg twice weekly, have been ineffective for FCAS and Muckle–Wells syndrome.[1] Treatment with high-dose corticosteroids can be beneficial in managing these disorders, but their long-term use is limited by the adverse effects of these agents. Nonsteroidal anti-inflammatory medications (NSAIDs) can be used to alleviate arthralgias associated with FCAS and Muckle–Wells syndrome, but they do not help with other clinical manifestations.[4]

Anakinra (Kineret, Biovitrum; formerly, Amgen), an IL-1 receptor antagonist, has been shown to be effective in preventing and decreasing heightened inflammatory response in studies evaluating patients with FCAS or Muckle–Wells syndrome.[13–16] This use of anakinra is an off-label treatment option for CAPS disorders.[17]

Anakinra is not approved for children younger than 18 years of age. However, in one case study of a pediatric patient with FCAS,[16] a 50-mg/day SQ dose of anakinra was successful in achieving sustained clinical improvement and a reduction in serum amyloid A and CRP levels. In various studies evaluating anakinra in the treatment of FCAS or Muckle–Wells syndrome, adults were given a dose of 100 mg/day subcutaneously (the recommended dose and schedule for rheumatoid arthritis).[13–15] Although anakinra is approved only for rheumatoid arthritis, these studies demonstrated the efficacy of the drug in treating auto-inflammatory diseases. Table 2 shows a cost comparison of rilonacept and anakinra.

IMPLICATIONS FOR MANAGED CARE

Regeneron has created the Arcalyst Resource Center (ARC) program to support patients throughout the entire reimbursement process.[18] Services include finding physicians familiar with diagnosing and treating CAPS, contacting the patient's insurance companies to conduct benefit investigations to determine coverage, working with physicians to obtain and assist with prior authorization requests and appeals, referring patients to foundations that may assist with high copayments, and helping uninsured patients by evaluating their eligibility for the company's assistance program that offers the drug free of charge to qualifying patients or by finding alternative coverage for nonqualifying patients. Patients with Medicare prescription drug coverage or other government insurance may also receive assistance, but coverage is specific for each plan.[18]

Table 2 Cost Comparison of Rilonacept and Anakinra*

Agent	Strength	Recommended Dose	AWP (Unit Price)	Monthly Cost (Adult Dose)
Rilonacept (Arcalyst)	80-mg/mL vial	Adults: 320-mg loading dose, followed by 160 mg/week subcutaneously	$6,000	$30,000
		Pediatric patients: 4.4 mg/kg loading dose, followed by 2.2 mg/kg per week subcutaneously		
Anakinra (Kineret)	100-mg/0.67-mL prefilled syringe	Adults: 100 mg/day subcutaneously	$54	$1,515
		Pediatric patients: not approved in pediatric patients younger than 18 years of age		

AWP = average wholesale price.
* Unlabeled indication; anakinra is not approved for use in cryopyrin-associated periodic syndromes.
Adapted from references 8, 13–16, and 19.

COST

Rilonacept is available as a sterile, single-use, 20-mL glass vial containing 220 mg as a lyophilized powder for reconstitution.[7] The average wholesale price is $6,000 per vial.[8,19]

CONCLUSION

An IL-1 blocker, rilonacept is the only currently FDA-approved treatment option for CAPS, particularly FCAS and Muckle–Wells syndrome, in adults and children older than 12 years of age. Rilonacept is administered as a once-weekly SQ injection. In contrast, treatment options such as anakinra are not approved by the FDA for the treatment of CAPS, and daily SQ injections are required.[13] Additional treatment options are limited by adverse effects or because they are effective in managing only certain symptoms.[4]

The safety and efficacy of rilonacept were evaluated in two, randomized, placebo-controlled studies that subsequently allowed patients to participate in a 24-week open-label study.[12] Study patients who received rilonacept showed a significant decrease in disease-related symptom scores along with reduced serum amyloid A and CRP levels.

Common adverse effects were injection-site reactions and upper respiratory tract infections.[12] Rilonacept should not be administered concomitantly with TNF-blocking agents, other IL-1 antagonists, or vaccines.[8]

Rilonacept is a promising treatment option for the small population of patients with the rare but serious inflammatory disorders associated with CAPS.

REFERENCES

1. Yao Q, Furst DE. Autoinflammatory diseases: An update of clinical and genetic aspects. *Rheumatology* 2008;47(7):946–951.
2. Hoffman HM, Yasothan U, Kirkpatrick P. Fresh from the pipeline: Rilonacept. *Nat Rev Drug Discov* 2008;7(5):385–386.
3. Simon A, van der Meer JWM. Pathogenesis of familial periodic fever syndromes or hereditary auto-inflammatory syndromes. *Am J Physiol Regul Integr Comp Physiol* 2007;292(1):R86–R98.
4. Farasat S, Aksentijevich I, Toro JR. Autoinflammatory diseases: Clinical and genetic advances. *Arch Dermatol* 2008; 143(3):392–402.
5. Stankovic K, Grateau G. Auto inflammatory syndromes: Diagnosis and treatment. *Joint Bone Spine* 2007;74(6):544–550.
6. Tunca M, Ozdogan H. Molecular and genetic characteristics of hereditary autoinflammatory diseases. *Curr Drug Targets Inflamm Allergy* 2005;4(1):77–80.
7. FDA, Center for Drugs and Research. Drug and Biologic Approvals for Calendar Year 2008 (updated through January 31, 2008). Available at: www.fda.gov/CDER/rdmt/InternetNDA08.htm. Updated March 13, 2008. Accessed July 7, 2008.
8. Arcalyst (rilonacept), package insert. Tarrytown, NY: Regeneron, 2008.
9. FDA approves rilonacept for the treatment of rare inflammatory syndromes. Doctor's Guide News, February 28, 2008. Available at: www.docguide.com/news/content.nsf/news/85257102007CCF6852573FD006DCBC1. Accessed July 2, 2008.
10. Study of the safety and effectiveness of rilonacept for the prevention of gout flares. Available at: http://clinicaltrials.gout+rilonacept&rank=1. Updated January 24, 2008. Accessed July 2, 2008.
11. Hoffman HM, Amar NJ, Cartwright RC, et al. Durability of response to rilonacept (IL-1 Trap) in a phase 3 study of patients with cryopyrin-associated periodic syndromes: Familial cold auto-inflammatory syndrome and Muckle–Wells syndrome. Paper presented at the American Academy of Allergy Asthma and Immunology meeting, March 14–18, 2008, Philadelphia.
12. Hoffman HM, Throne ML, Amar NJ, et al. Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: Results from two sequential placebo-controlled studies. *Arthritis Rheum* 2008; 58(8):2443–2452.
13. Hoffman HM, Rosengren S, Boyle DL, et al. Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. *Lancet* 2004;364(9447): 1779–1785.
14. Hawkins PN, Lachmann HJ. Interleukin-1 receptor antagonist in the Muckle–Wells syndrome (letter). *N Engl J Med* 2003;348(25):2583–2584.
15. Metyas SK, Hoffman HM. Anakinra prevents symptoms of familial cold autoinflammatory syndrome and Raynaud's disease. *J Rheumatol* 2006;33(10):2085–2087.
16. O'Connell SM, O'Regan GM, Bolger T, et al. Response to IL-1-receptor antagonist in a child with familial cold autoinflammatory syndrome. *Pediatr Dermatol* 2007;24(1):85–89.
17. FDA. Anakinra, product approval information, licensing action. Available at: www.fda.gov/cder/biologics/products/anakamg111401.htm. Updated November 16, 2001. Accessed July 8, 2008.
18. Arcalyst Resource Center Patient Information Brochure. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2008.
19. *Red Book* (July 2008 update). Montvale, NJ: Thomson PDR; 2008:43(7). ■