Publication Experience in Orphan Diseases: Case Study with Cryopyrin-Associated Periodic Syndromes (CAPS)

Carol Hudson, Hadi Moini, Linda Williams, Rebecca Gall, S. Bala Dass, Scott Mellis, Beate Stych
Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA.

ABSTRACT

Objective: Few medical communication reports discuss the planning and execution of clinical publications that describe treatment options for rare or "orphan" diseases. While orphan-designated drugs follow the same development pathway as other pharmaceutical products, key challenges are the limited resources and small patient pools available for research, thus often restricting the number of scientific studies and associated publications. Physician-driven disease-state/educational publications therefore increasingly become important in highlighting the unmet needs of such patient populations. This report describes publication activity in support of rilonacept, an orphan-designated drug for a rare disorder, Cryopyrin-Associated Periodic Syndromes (CAPS).

Research and Design Methods: We examined completed, ongoing and planned rilonacept publication activities across several areas of research and development in CAPS. In addition, we assessed disease-state/educational publications highlighting unmet therapeutic needs for the CAPS population.

Results: About a dozen reports, including a number of clinical and disease-state/educational manuscripts have been published in peer-reviewed journals such as *Journal of Clinical Pharmacology* and *Arthritis & Rheumatism*. Importantly, we supported a publication on the development of a new patient-reported outcome instrument to measure disease activity in CAPS patients' baseline and treated states.

Conclusions: Our experience demonstrates that publications reporting pivotal trials and physician-driven disease-state/educational publications are both integral to an orphan-disease publication plan.

BACKGROUND

Cryopyrin-Associated Periodic Syndromes (CAPS)

- CAPS are auto-inflammatory disorders associated with autosomal dominant mutations in a gene that encodes a pyrin-related protein called "cryopyrin"[1,2,3]
- Cryopyrin is a component of the inflammasome, a protein complex that includes caspase-1 and controls activation of the proinflammatory cytokine, IL-1β[4]. CAPS are associated with increased production of IL-1β[3,5]
- CAPS are associated with localized and systemic inflammation, and comprise a spectrum of diseases of increasing severity, ranging from Familial Cold Autoinflammatory Syndrome (FCAS) which is associated with lesser severity, to Muckle-Wells Syndrome (MWS), and then to Neonatal-Onset Multisystem Inflammatory Disease (NOMID) as most severe[6]. Rilonacept has not been studied and is not approved for patients with NOMID
- CAPS are chronic illnesses with substantial negative impact on patients' quality of life
- CAPS have common features such as spontaneous generalized painful or pruritic erythematous rash, fever, and flulike symptoms of headache, fatigue, myalgia, arthralgia, and leukocytosis consistent with systemic inflammation[6]; patients with MWS can experience hearing loss and systemic amyloidosis which can progress to end-stage renal disease[2]; patients with NOMID suffer central nervous system inflammation, which can lead to seizures, developmental delay, and visual impairment[6]

Development of Orphan Drugs

- CAPS are designated as a rare disease by the Office of Rare Diseases Research of the National Center for Advancing Translational Sciences, National Institutes of Health, US Department of Health and Human Services[8] and the European Medicines Agency[9]
- The number of studies registered in ClinicalTrials.gov for CAPS, compared to other IL-1 mediated diseases, reflects the key challenges in the development of orphan drugs, such as (Table 1):
  - Limited research interest and resources
  - Small patient pools available for research, which restrict the number of scientific studies that can be conducted

Publications for Orphan Drugs

- With the limitations on clinical trial development for orphan drugs, publications for these conditions also lag behind those with greater prevalence (Table 1)

Table 1. Comparative Number of Clinical Trial Registrations and Publications for IL-1-Mediated Diseases*

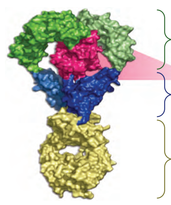
Interleukin-1 Mediated Diseases[10,11]	Study Records in ClinicalTrials.gov[12] (as of March 26, 2013)	Publications Reported in PubMed[13] Since 2002 (as of March 26, 2013)
Cryopyrin-associated Periodic Syndrome	17	221
Systemic Juvenile Idiopathic Arthritis	39	1054
Gout	492	4065
Type 2 Diabetes	5304	68709

*Rilonacept has not been approved for use in Systemic Juvenile Idiopathic Arthritis, Gout, or Type 2 Diabetes, and other cytokines may also play a role in these disease states. Type 2 diabetes is mediated by other processes in addition to IL-1.

Rilonacept (IL-1 Trap)[14]

- A dimeric fusion protein consisting of the extracellular ligand-binding domains of human IL-1 Type I receptor (IL-1RI), the IL-1 receptor accessory protein (IL-1RAcP), and the Fc portion of human IgG13 (Figure 1)
- Blocks interleukin-1 (IL-1) signaling by acting as a soluble decoy receptor that binds IL-1α and IL-β, preventing their interaction with cell surface receptors
- Indicated in the US as a subcutaneous injection for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including FCAS and MWS in adults and children 12 and older
- IL-1 blockade may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking rilonacept; the most common adverse events are injection-site reactions and upper respiratory tract infections

Figure 1. Rilonacept[15,16]

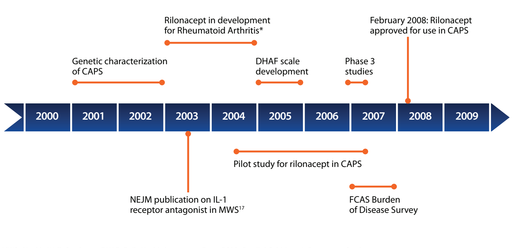


Adapted from Gillespie J et al

Historical Perspectives on the Development of Rilonacept in CAPS (Figure 2)[7]

- Starting in the 1990s, scientists at Regeneron Pharmaceuticals, Inc. were working on cytokine signaling, and in the early 2000s, developed IL-1 Trap, now called rilonacept, for study in models of rheumatoid arthritis
- In the early 2000s, independent research was ongoing to better understand the genetics for CAPS
- A case report publication in the *New England Journal of Medicine* in June of 2003[17] provided impetus for a new direction in the development of rilonacept, with a focus on CAPS as a therapeutic target
- Working with NIH researchers, a proof of concept study was conducted, and patients were followed over the course of 2 years
- Concurrently, scale development was undertaken to ensure a validated end point for measuring impact of treatment in phase 3 trials, in a manner consistent with Food and Drug Administration guidance on patient-reported outcomes
- Completion of the pilot study and development of the Daily Health Assessment Form (DHAF) paved the way for Phase 3 studies
- Prior to the approval of rilonacept for the treatment of CAPS, a survey was conducted to better characterize symptoms and understand the burden of disease for patients with FCAS
- Rilonacept became the first interleukin-1 blocker approved for the treatment of CAPS in the US

Figure 2. Historical Perspectives in the Development of Rilonacept for CAPS



MWS=Muckle-Wells Syndrome; DHAF=Daily Health Assessment Form; FCAS=Familial Cold Auto-Inflammatory Syndrome
*Program suspended in 2004
Dates have been approximated
Adapted from Stahl N et al

OBJECTIVES

- Describe and discuss publication activity in support of rilonacept, an orphan-designated drug for CAPS

METHODS

- Examination of completed and ongoing research and associated publications for rilonacept in CAPS
- Assessment of publications supported by Regeneron research scientists and clinical staff, addressing unmet therapeutic needs of the CAPS population

RESULTS

Publication of a Pilot Study[18]

- In an NIH-led study, rilonacept was investigated in an open-label study of 5 patients with FCAS. Efficacy was assessed 6 and 10 days post-injection, safety was measured for up to 24 months following initiation of rilonacept
- Results of the research were published in *Arthritis & Rheumatism*

Figure 3. Skin Rash During an Attack and After Treatment

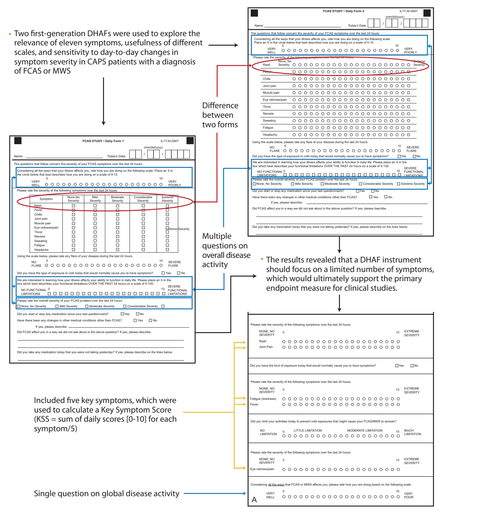
Reprinted with permission from *Arthritis & Rheumatism*

RESULTS

Publication on Developing a New Patient-Reported Outcomes Instrument[19]

- A new questionnaire was developed to capture symptom patterns and severity in patients with CAPS (Figure 4)
- Development and validation of the scale used as primary endpoint in phase 3 trials was published in *Current Medical Research and Opinion*

Figure 4. Development of the Daily Health Assessment Forms (DHAFs)



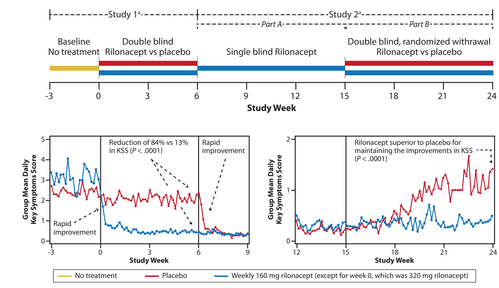
- Mean KSS correlated well with Physician's Global Assessment of Disease Activity ($r = 0.91$; $P < .0001$) and patient-reported limitations of daily activities ($r = 0.68$; $P < .0001$)
- High test-retest reliability (0.93).

Reprinted with permission from *Current Medical Research and Opinion*

Clinical Publications[20]

- Two consecutive, pivotal, phase 3 trials enrolling 47 CAPS patients provided clinical evidence for the efficacy and safety of rilonacept in the treatment of CAPS
- Phase 3 study results were published in *Arthritis & Rheumatism*

Figure 5. Design and Outcomes of Two Pivotal Trials Evaluating Efficacy and Safety of Rilonacept for CAPS

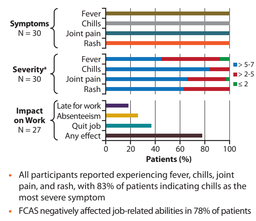


* Of 47 patients randomized into study 1, 44 patients completed study 2
Adapted from Hoffman HM et al

Publication on Disease Awareness[21]

- Results of a survey designed to characterize symptomatology and evaluate the debilitating effects of FCAS on patients' daily lives were published in *Current Medical Research and Opinion*
- Results of a survey encompassing 18% (30/167) of the known FCAS population in the US provided disease awareness among healthcare professionals for accurate and timely diagnosis and improved disease management (Figures 6A and 6B)

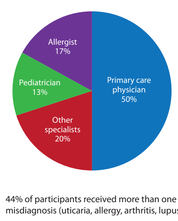
Figure 6A. FCAS Symptoms, Severity of Symptoms, and Impact on Employment



- All participants reported experiencing fever, chills, joint pain, and rash, with 83% of patients indicating chills as the most severe symptom
- FCAS negatively affected job-related abilities in 78% of patients

*Scale of 1 to 7 (most severe)

Figure 6B. Healthcare Professionals Seen for the First Time for FCAS



- 44% of participants received more than one misdiagnosis (uticaria, allergy, arthritis, lupus)

Table 2. Summary of Key Publications Supporting Clinical Development and Application of Rilonacept for CAPS

Year	Title	Key Contribution
2008	A pilot study to evaluate the safety and efficacy of the long-acting interleukin-1 inhibitor rilonacept (interleukin-1 Trap) in patients with familial cold autoinflammatory syndrome[18]	Magnitude of clinical and laboratory responses at different dose levels
2008	Cryopyrin-associated periodic syndromes: development of a patient-reported outcomes instrument to assess the pattern and severity of clinical disease activity[19]	Development of a new patient-reported questionnaire for capturing symptom patterns and severity
2008	Efficacy and safety of rilonacept (interleukin-1 trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies[20]	Pivotal trial of efficacy and safety
2008	Familial cold auto-inflammatory syndrome (FCAS): characterization of symptomatology and impact on patients' lives[21]	Disease symptomatology and burden of disease
2008	Molecule of the month: Rilonacept[22]	Review for industry personnel
2009	Rilonacept: CAPS and beyond[7]	Review for multidisciplinary audience
2009	Rilonacept (Arcalyst®), an interleukin-1 trap for the treatment of cryopyrin-associated periodic syndromes[23]	Review for managed care and hospital formulary management
2009	Rilonacept for the treatment of cryopyrin-associated periodic syndromes (CAPS)[24]	Review in international biotechnology journal
2010	Safety and pharmacokinetics of subcutaneously administered rilonacept in patients with well-controlled end-stage renal disease (ESRD)[25]	Pharmacokinetics in renally compromised patients
2012	Long-term efficacy and safety profile of rilonacept in the treatment of cryopyrin-associated periodic syndromes: results of a 72-week open-label extension study[26]	Long-term trial of safety and efficacy

CONCLUSIONS

- Our experience demonstrates that publications reporting pivotal trials and physician-driven disease-state/educational publications are both integral to an orphan-disease publication plan that leads to increasing awareness of rare diseases and options for their treatment, thus potentially contributing to improved patient care

REFERENCES

1. Feldmann J, Prieur AM, Quartier P, Berquin P, Certain S, et al. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. *Am J Hum Genet* 2002;71(1):198-203.
2. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold auto-inflammatory syndrome and Muckle-Wells syndrome. *Nat Genet* 2001;29(3):301-5.
3. Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, et al. De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated auto-inflammatory diseases. *Arthritis Rheum* 2002;46(12):3340-8.
4. Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, et al. NALP3 forms an IL-1β-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. *Immunity* 2004;20(3):319-25.
5. Kastner DL, Janka G, Dinauer MC. Hereditary periodic fever syndromes. *Hematology Am Soc Hematol Educ Program* 2005:74-81.
6. Hoffmann HM. Hereditary Immunologic Disorders Caused by Pyrin and Cryopyrin. *Curr Allergy Asthma Rep* 2007;7:323-330.
7. Stahl N, Radin A, Mellis S. Rilonacept: CAPS and beyond. *Ann NY Acad Sci* 2009;1182:124-34.
8. Genetic and Rare Diseases Information Center, Office of Rare Diseases Research of the National Center for Advancing Translational Sciences, National Institutes of Health, US Department of Health and Human Services http://rarediseases.info.nih.gov/GARD/Condition/10927/Cryopyrinassociated_periodic_syndrome.aspx. Accessed March 26, 2013.
9. European Medicines Agency. EU/3/07/456. Orphan Designation. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2009/11/human_orphan_000164.jsp&mid=WC0b01ac058001d12b. Accessed March 26, 2013.
10. Holzinger D, Becker H, Jacobi AM. Interleukin-1-mediated diseases. *Internist (Berl)* 2013;54(4):408-15.
11. Goldbach-Mansky R. Blocking interleukin-1 in rheumatic diseases. *Ann N Y Acad Sci* 2009;1182:111-23.
12. ClinicalTrials.gov, A Service of the US National Institutes of Health, http://clinicaltrials.gov/. Accessed March 26, 2013.
13. PubMed.gov, US National Library of Medicine, National Institutes of Health. http://www.ncbi.nlm.nih.gov/pubmed/. Accessed March 26, 2013.
14. Arcalyst® Full Prescribing Information. Tarrytown, NY: Regeneron Pharmaceuticals, Inc. 2010.
15. Gillespie J, Mathews R, McDermott MF. Rilonacept in the management of cryopyrin-associated periodic syndromes (CAPS). *J Inflamm Res* 2010;3:1-8.
16. Arcalyst.com. Information for Healthcare Providers, What is Arcalyst® (rilonacept)? http://arcalyst.com/index.php/healthcare-providers-mainmenu-45/ about-arcalyst-mainmenu-147/what-is-arcalyst-mainmenu-148?phpMyAdmin=e9fe09ae33c1fdbbad69fc8883f97963. Accessed March 26, 2013.
17. Hawkins PN, Lachmann HJ, McDermott MF. Interleukin-1-receptor antagonist in the Muckle-Wells syndrome. *N Engl J Med* 2003;348(25):2583-4.
18. Goldbach-Mansky R, Shroff SD, Wilson M, Snyder C, Plehn S, et al. A pilot study to evaluate the safety and efficacy of the long-acting interleukin-1 inhibitor rilonacept (interleukin-1 Trap) in patients with familial cold autoinflammatory syndrome. *Arthritis Rheum* 2008;58(8):2432-42.
19. Hoffman HM, Wolfe F, Belomestnov P, Mellis SJ. Cryopyrin-associated periodic syndromes: development of a patient-reported outcomes instrument to assess the pattern and severity of clinical disease activity. *Curr Med Res Opin* 2008 Sep;24(9):2531-43.
20. Hoffman HM, Throne ML, Amar NJ, Sebai M, Kivitz AJ, 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):2443-52.
21. Stych B, Dobrovolny D. Familial cold auto-inflammatory syndrome (FCAS): characterization of symptomatology and impact on patients' lives. *Curr Med Res Opin* 2008;24(6):1577-82.
22. Molecule of the month. Rilonacept. *Drug News Perspect* 2008;21(4):232.
23. Kapur S, Bonk ME. Rilonacept (Arcalyst®), an interleukin-1 trap for the treatment of cryopyrin-associated periodic syndromes. *PT* 2009;34(3):138-41.
24. Hoffman HM. Rilonacept for the treatment of cryopyrin-associated periodic syndromes CAPS). *Expert Opin Biol Ther* 2009;9(4):519-31.
25. Radin A, Marbury T, Osgood G, Belomestnov P. Safety and pharmacokinetics of subcutaneously administered rilonacept in patients with well-controlled end-stage renal disease (ESRD). *J Clin Pharmacol* 2010;50(7):835-41.
26. Hoffman HM, Throne ML, Amar NJ, Cartwright RC, Kivitz AJ, et al. Long-term efficacy and safety profile of rilonacept in the treatment of cryopyrin-associated periodic syndromes: results of a 72-week open-label extension study. *Clin Ther* 2012;34(10):2091-103.

Research supported by Regeneron Pharmaceuticals, Inc. Presented at the 9th Annual Meeting of the International Society for Medical Publication Professionals (ISMPP) April 29-May 1, 2013, Baltimore, Maryland, USA