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The RAndomized Placebo Phase Study Of Rilonacept in the Treatment of Systemic Juvenile Idiopathic Arthritis (RAPPORT)

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Abstract

Background—Interleukin-1 plays a pivotal role in in the pathogenesis of systemic juvenile idiopathic arthritis (sJIA). We assessed the efficacy and safety of rilonacept (IL-1 trap), an IL-1 inhibitor, in a randomized, double-blind, placebo-controlled trial.

Methods—An initial 4-week double-blind placebo phase was incorporated into a 24-week randomized multi-center design, followed by an open label phase. We randomized 71 children with at least 2 active joints 1:1 to 2 arms of the study. Patients in the rilonacept arm received rilonacept (4.4mg/kg loading dose followed by 2.2mg/kg weekly, subcutaneously) from day 0; patients in the placebo arm received placebo for 4 weeks followed by a loading dose of rilonacept at week 4 followed by weekly maintenance doses. The primary endpoint was time to response, using adapted JIA ACR30 response criteria coupled with absence of fever and taper of systemic corticosteroids using pre-specified criteria.

Results: Time to response was shorter in the rilonacept arm than in the placebo arm (Chi-square 7.235, P=.007). Secondary analysis showed 20/35 (57%) of patients in the rilonacept arm responded at week 4 compared to 9/33 (27%) in the placebo arm (P=.016) using the same response criteria. Exacerbation of sJIA (4) was the most common SAE. More patients in the rilonacept arm had elevated liver transaminases, including more than three times the upper limits of normal, as compared to those in the placebo arm. Adverse events were similar in the two arms of the study.

Conclusions—Rilonacept was generally well tolerated and demonstrated efficacy in active sJIA.

Introduction

Systemic juvenile idiopathic arthritis (sJIA) is distinguished from other forms of JIA by its distinctive systemic features at onset, including high spiking fever, characteristic rash, hepatosplenomegaly, polyserositis, lymphadenopathy, anemia, leukocytosis and thrombocytosis and rarely macrophage activation syndrome[1]. More than 50% of children with sJIA have a polyphasic or chronic persistent disease course [2] and more than half suffer poor outcomes [3] and seldom death[4] in the absence of highly active biologic treatment. Predictors of joint damage and poor functional outcome include young age at diagnosis, longer disease duration, persistent systemic long-term corticosteroid therapy thrombocytosis and high inflammatory markers [5,6].

This randomized controlled trial was designed to determine the safety and effectiveness of rilonacept in sJIA, and to confirm and extend findings from a number of anecdotal studies and trials showing effectiveness of IL-1 inhibition[7-15]. Rilonacept is a fusion protein consisting of human cytokine receptor extracellular domains of both receptor components required for IL-1 signaling (IL-1 Type I receptor and the IL-1 receptor accessory protein) with the Fc portion of human IgG1. It binds IL-1α and IL-1β with picomolar affinity but potentially can bind to IL-1 receptor antagonist[16]. Although the primary efficacy endpoint was not met in a pilot, double-blind placebo-controlled study, rilonacept appeared to be well tolerated and efficacious enabling corticosteroid dose reduction in the open label long-term extension phase[17].

Methods

Patients

The study was conducted in compliance with principles of the International Conference on Harmonization and Good Clinical Practice. The study was approved by the Institutional Review Boards of each study site. All patients or parents/guardians provided written informed consent. An independent Data Safety Monitoring Board, appointed by NIH/NIAMS, met every 6 months to evaluate study conduct and safety. Twenty Childhood Arthritis and Rheumatology Research Alliance (CARRA) centers in the US enrolled patients from 11/2008 to 5/2012. Key Inclusion criteria included: International League against Rheumatism criteria for sJIA [18]; age ≥18 months to ≤19 years; ≥2 active joints; stable methotrexate dose for ≥4 weeks; stable corticosteroids ≥2 weeks; ≤ 2mg/kg or 60mg prednisone or equivalent. If previously treated with biologics, the following lengths of discontinuation were required: anakinra ≥4 days, etanercept ≥4 weeks, adalimumab ≥6 weeks, tocilizumab ≥6 weeks, abatacept ≥6 weeks, and infliximab ≥8 weeks. Key exclusion criteria included current treatment with disease modifying anti-rheumatic drug other than methotrexate; intra-articular corticosteroids or pulse steroids within 4 weeks; leflunomide without cholestyramine wash out; cyclophosphamide within 3 months; IVIG within 4 weeks; treatment in the past with an IL-1 inhibitor other than anakinra; renal insufficiency as defined as an elevated serum creatinine; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal; thrombo-, leuko-, or neutro-penia; prolonged PT or PTT; positive PPD without treatment documentation; live virus vaccine within 1 month; pregnancy or sexual activity without contraception.

Study Design

RAPPORT incorporated an initial 4-week double-blind placebo phase within a 24-week randomized multi-center design. As such, patients were randomized 1:1 to treatment with (a) 4 weeks of placebo followed by 20 weeks of rilonacept or (b) 24 weeks of rilonacept, resulting in a double-blind phase (weeks 0-4) and an all active treatment phase (weeks 4-24). This was followed by an open label Long Term Extension (LTE) phase (24 weeks-21 months). The randomized placebo phase study design is based on the assumption that if treatment is effective, patients who receive active drug earlier will respond sooner, on average, than patients who receive active drug later [19]. This design is especially useful when testing highly effective therapies with rapid onset of action of several weeks, and when minimizing time on placebo or safety issues are important [19]. IL-1 inhibition appears to have an onset of action of 2 weeks, based on data in sJIA subjects in the Amgen-sponsored study of anakinra in polyarticular-JIA that included subjects with sJIA [12]. Randomization was performed using a Web-based randomization and drug supply management system (WebEZ, Almac, Durham, North Carolina). The central randomization scheme used a fixed-block size, stratified according to baseline corticosteroid use. Rilonacept and matching placebo were provided by Regeneron Pharmaceuticals, Inc. (New York).

In the rilonacept arm, a loading dose (4.4mg/kg, maximum dose 320mg) of rilonacept was given on day 0 followed by weekly maintenance doses (2.2mg/kg, to a maximum dose 160mg). In the placebo arm, a loading dose of placebo was given on day 0 followed by 3 maintenance doses of placebo; then a loading dose of rilonacept was given on day 28 followed by weekly maintenance doses of rilonacept. Evaluation of efficacy occurred during the first 12 weeks of the study; safety was assessed in the first 24 weeks and in the LTE. All patients who benefited from rilonacept treatment as judged by the treating physician were eligible for enrollment in the LTE phase. Patients in the LTE were initially offered open label rilonacept for 2 years or until rilonacept was commercially available. These criteria were shortened for some patients because of budgetary issues.

Clinical Assessments

Screening visits could occur up to 4 weeks before randomization. A randomization/baseline visit occurred at week 0 and follow up visits occurred at weeks 2, 4, 6, 8, 10, 12, 14, 18 (by telephone), and 24. Patients were seen every 3 months in the LTE. The 2 week interval between visits in the first 14 weeks was used to maximize the precision of estimation of time to response. Medical history, physical examination, concomitant medications, adverse events, fever (patients' daily diary), blinded joint assessment, physician global assessment, parent/guardian/patient global assessment, clinical laboratory tests, and Childhood Health Assessment Questionnaire (CHAQ) were assessed at every (non-telephone) visit. Fasting lipoprotein profiles and PedsQL questionnaires were assessed at week 0, 12 and 24. Biospecimens (DNA, RNA, whole blood, serum, plasma) were obtained during the trial.

Endpoints

The primary endpoint was time to response during the 12 week efficacy period. Response was defined as a composite of 1)improvement in the JIA ACR30 [20], 2) absence of fever ≥38.5°C in the previous 2 weeks, and 3)at least 10% taper in systemic corticosteroids from

baseline if the patient were taking corticosteroids. The JIA ACR30 algorithm required at least 30% improvement from baseline in at least 3 of 6 core variables, with no more than 1 variable worsening by 30% or more. Corticosteroids were required to be tapered if all of the following criteria developed by consensus among the RAPPORT investigators [21] were met: fever ≤2 days in previous 7 days, absence of poor physical function, and absence of laboratory values associated with impending MAS. The time to response was defined as the visit designation at which the patient first achieved the response criteria and maintained response until the next scheduled visit. Absence of rash was not included in the response criteria.

Corticosteroids were increased or started if one or more of the following criteria developed by consensus of the RAPPORT investigators were met[21]: MAS [22], incomplete MAS, symptomatic anemia with a hemoglobin ≤6.5g/dL, myocarditis, or symptomatic pneumonitis, or serositis unresponsive to NSAIDs. Patients who met criteria for corticosteroid increase/start were deemed non-responders. Patients who met the criteria for non-response and started/increased corticosteroids were no longer eligible for response.

Secondary endpoints included the JIA ACR30, 50, 70, inactive disease [23], presence of fever, serositis, symptomatic anemia, abnormal liver function, rash, MAS, incomplete MAS, corticosteroid dose, CHAQ, and PedsQL Generic Core Modules. Adverse events (AEs) and Serious Adverse Events (SAEs) were collected throughout the study.

Data Analysis

Planned enrollment was 100 patients (50 per arm) to achieve ≥80% power to detect a difference at a 2-sided α level of 0.05. This sample size was determined based on the results from multiple Monte-Carlo simulations conducted under various assumptions for distribution of time to response in the two study arms.The trial was ended before reaching the enrollment goal due to slow enrollment and financial considerations. One pre-specified interim analysis of the primary endpoint to examine early stopping for overwhelming efficacy was performed when data were available for 50 patients. The Lan-DeMets flexible spending function corresponding to the O'Brian-Fleming stopping boundary was used to preserve the overall type I error of 0.05[24]. The stopping boundary P value at the interim analysis was 0.007. After reviewing the efficacy data at the interim analysis, the DSMB recommended to continue the study. The 2-sided P value for rejecting the null hypothesis of no difference between the treatment arms for the primary endpoint at the final analysis was 0.048. A 2-sided α level of 0.05 was considered statistically significant for all other endpoints. P values for the secondary analyses were not adjusted for multiple comparisons. All analyses were performed in SAS version 9.2 (SAS Institute Inc., Cary, NC).

Data were analyzed on an intent-to-treat basis. Descriptive statistics were summarized by treatment arm. The primary endpoint analysis compared time to response between treatment arms using Gehan-Wilcoxon test, which emphasizes early differences. Missing temperatures were imputed as fever free when calculating the response endpoint. A sensitivity analysis was performed treating the response endpoint as missing if the fever criterion could not be determined due to missing temperatures. In both the primary and sensitivity analyses, patients were censored if the response endpoint was missing at two consecutive visits, or if

the patient met criteria for non-response and started/ increased corticosteroids prior to meeting the response criteria. Response rates were calculated using cumulative incidence estimation, treating non-response as a competing event. Comparison of the response to rilonacept vs. placebo at the end of the placebo phase (week 4) was evaluated using Fisher's exact test. Logistic regression was used to adjust for sJIA duration and presence of articular without systemic symptoms and to explore the association between those baseline characteristics and response at week 4.

JIA ACR30, 50, and corticosteroid dose were analyzed using a generalized estimating equation (GEE) repeated measures model. Improvement in JIA ACR70 was analyzed using Fisher's exact test. Adverse events were compared using chi-square test. Infection rates were compared using Poisson regression.

Results

Study Population

Seventy-one patients were randomized (Figure 1). Baseline demographic and disease characteristics were similar between the two arms of the study, except recent fever was more common in the rilonacept group (Table 1). Fourteen patients withdrew from the study prior to week 24: 8 for inadequate response (7 placebo arm, 1 rilonacept arm), 2 withdrew consent (1 in each arm), 1 for a serious adverse event (elevated liver transaminases) in the rilonacept arm, 1 excluded before drug exposure for not meeting inclusion/exclusion criteria, 2 lost to follow up (1 in each arm). Of the 57 completers, 40 enrolled in the LTE; 29 completed the LTE and 11 did not.

Efficacy

The primary endpoint, time to response as defined by time to achieve the composite endpoint of JIA ACR30, absence of fever, and corticosteroid tapering (for patients taking corticosteroids), was shorter in the rilonacept arm (median 4 weeks; 25^{th}, 75^{th} percentiles 2,10 weeks) than in the placebo arm (median 8 weeks; 25^{th} percentile 6 weeks, 75^{th} percentile not estimable from the data) (Figure 2; chi-square 7.235; P=0.007). By week 12, 27 of 35 patients (77%) receiving rilonacept continuously from onset of the trial and 20 of 34 patients (59%) receiving placebo for the initial 4 weeks, met the primary endpoint of response. The sensitivity analysis of time to response without fever imputation also demonstrated shorter time to response in the rilonacept arm as compared to the placebo arm (chi-square = 5.270; P=0.022). Secondary endpoint analysis of the response rate at 4 weeks showed 20 of 35 patients in the rilonacept arm compared to 9 of 33 patients in the placebo arm (57% vs. 27%; P=0.016). The JIA ACR30, 50, and 70 response rates were significantly better in the rilonacept arm at week 4 compared to the placebo arm (Table 2; all $P<0.05$). Twenty-six of 35 (74%) patients in the rilonacept arm compared to 13 of 33 (39%) in the placebo arm met JIA ACR30 response criteria at week 4 (OR=4.54; 95% CI 1.62, 12.72; P=0.004); 21 of 35 (60%) vs. 10 of 33 (30%) in the placebo arm met JIA ACR50 (OR=3.50; 95% CI 1.28, 9.56; P=0.015); 14 of 35 (40%) vs. 4 of 33 (12%) met JIA ACR70 (P=0.013).

A pre-specified logistic regression analysis adjusted for sJIA duration and presence of articular involvement without systemic symptoms showed that the significant rilonacept effect on response at week 4 persisted after adjustment (OR=3.42; 95% CI 1.21, 9.70; P=0.020). We did not observe a statistically significant difference in odds of response at week 4 for patients without systemic manifestations at baseline compared to patients with systemic manifestations (OR=0.87; 95% CI 0.32, 2.40; P=0.794). There was no statistically significant difference in odds of responding at week 4 as a function of longer sJIA duration (OR=0.91; 95% CI 0.75, 1.11; P=0.359). No statistically significant difference in response rates at week 4 was observed for 26 patients unexposed to anakinra (44%) compared to 24 patients previously exposed to anakinra (40%); 8 subjects had missing data regarding anakinra exposure; 2 had missing response data at week 4.

Seventeen of the 50 patients taking corticosteroids at baseline discontinued corticosteroids during the study. Overall, corticosteroid dose decreased more in the rilonacept arm than in the placebo arm during the efficacy period (P=0.036; Figure 3). Laboratory tests reflecting disease activity are reported by treatment arm in Table 2.

Safety

In the double-blind and treatment phases, the rilonacept arm performed at least as well as the placebo arm in terms of safety (Table 3). There was not a higher incidence of infection in the rilonacept arm in either phase. Four patients, all in the rilonacept arm, developed elevations in liver transaminases of ≥2 times the upper limit of normal; 2 patients developed elevations ≥5 times the upper limit of normal (one of these was considered an SAE). There were 14 SAEs: 9 among patients in the rilonacept arm and 5 in the placebo arm with the most common being sJIA flare (4). The AST liver function test was consistently higher in the rilonacept arm.

Discussion

sJIA has proven to be more difficult to treat than other categories of JIA with poor response to methotrexate and TNF inhibitors. This study demonstrates efficacy of rilonacept in active sJIA and confirms the remarkable effectiveness of IL-1 inhibition in sJIA, which is now demonstrated in 3 different IL-1 inhibitors, anakinra[14], canakinumab[10], rilonacept and in one IL-6 inhibitor, tocilizumab[25] . The long-term dependence on corticosteroid therapy for many children with severe systemic manifestations has resulted in significant treatment-related comorbidities, and provided an important impetus to finding an effective no-corticosteroid treatment for sJIA. The remarkable clinical responsiveness to IL-1 inhibition [7-15] suggests that IL-1 plays a pivotal role in the pathogenesis of sJIA [7,26-28] and the lack of HLA association, autoantibodies, and other classical features of autoimmune diseases, suggest the sJIA should be reclassified as an autoinflammatory disease[29].

This study utilized a novel design, the randomized placebo phase trial[19] to meet several objectives. First and foremost, we were concerned that the randomized withdrawal study design which was so successful in other JIA trials[30,31] might trigger a life threatening event when rilonacept was abruptly withdrawn in responders. Secondly, our study design directly tested corticosteroid tapering, by allowing inclusion of patients requiring high doses of

corticosteroids, and incorporating a forced corticosteroid taper into the primary endpoint. Lastly, the placebo phase occurring at the beginning of the trial allowed collection of biospecimens for studying the effects of an IL-1 inhibitor on the immunobiology of sJIA in the context of highly curated clinical data. Currently, 4 translational studies are underway.

Previous observational studies suggest that sJIA patients without systemic manifestations, and/or longer disease duration have poorer responses to IL-1 inhibition[11,32]. We did not observe a statistically significant association between response at week 4 and those patient characteristics in our study population. However, a trend was noted with regard to duration of disease: the median disease duration was shorter among patients who responded at week 4 compared to those who didn't (9.6 vs. 15.3 months).

Rilonacept had an acceptable safety profile in this study. There were no opportunistic infections, however elevation in liver transaminases in at least one patient was clearly caused by rilonacept as the adverse event recurred on re-challenge. There was only one episode of MAS which was triggered by EBV infection during the LTE.

Recently, another IL-1 inhibitor – canakinumab – was shown to be effective in treating sJIA patients with systemic symptoms in two separate double-blind, placebo-controlled studies and has been FDA approved for sJIA[10]. Rilonacept could offer an alternative with its circulating half-life of 8.6 days[33] in contrast to the long biologic activity of canakinumab (236 days) which could be a disadvantage in the setting of an SAE. The weekly administration of rilonacept may be preferred by families over anakinra which must be given by painful daily subcutaneous injections[14]. In contrast to all the IL-1 inhibitors tocilizumab, an IL-6 inhibitor which has also been shown to be effective in a double-blind, placebo controlled trial, and is approved by the FDA for sJIA, is given by infusion[25].

Limitations of the study were missing data regarding prior anakinra exposure, difficulty in comparing adverse events between the two arms of the study because of the short placebo phase and not meeting our enrollment goals by the time the study was discontinued by the NIH/NIAMS.

In summary, rilonacept was generally well tolerated and demonstrated efficacy in active sJIA in our study. Rilonacept treatment facilitated corticosteroid tapering similarly to tocilizumab and canakinumab. In addition, the ability to integrate clinical data and biospecimens associated with this study will likely lead to advances in our understanding of this unique and challenging disease.

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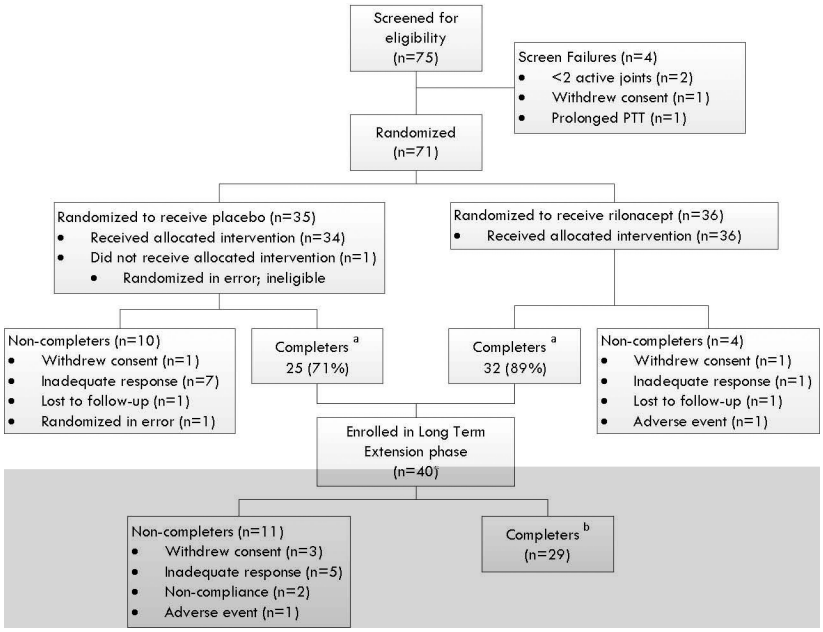

Figure 1. Flow of Patients in RAPPORT Trial

RAPPORT, The RAndomized Placebo Phase Study Of Rilonacept in the Treatment of Systemic Juvenile Idiopathic Arthritis.

[a] Indicates patients who attended the week 24 study visit.

[b] Indicates patients who remained in long term extension until the LTE period ended.

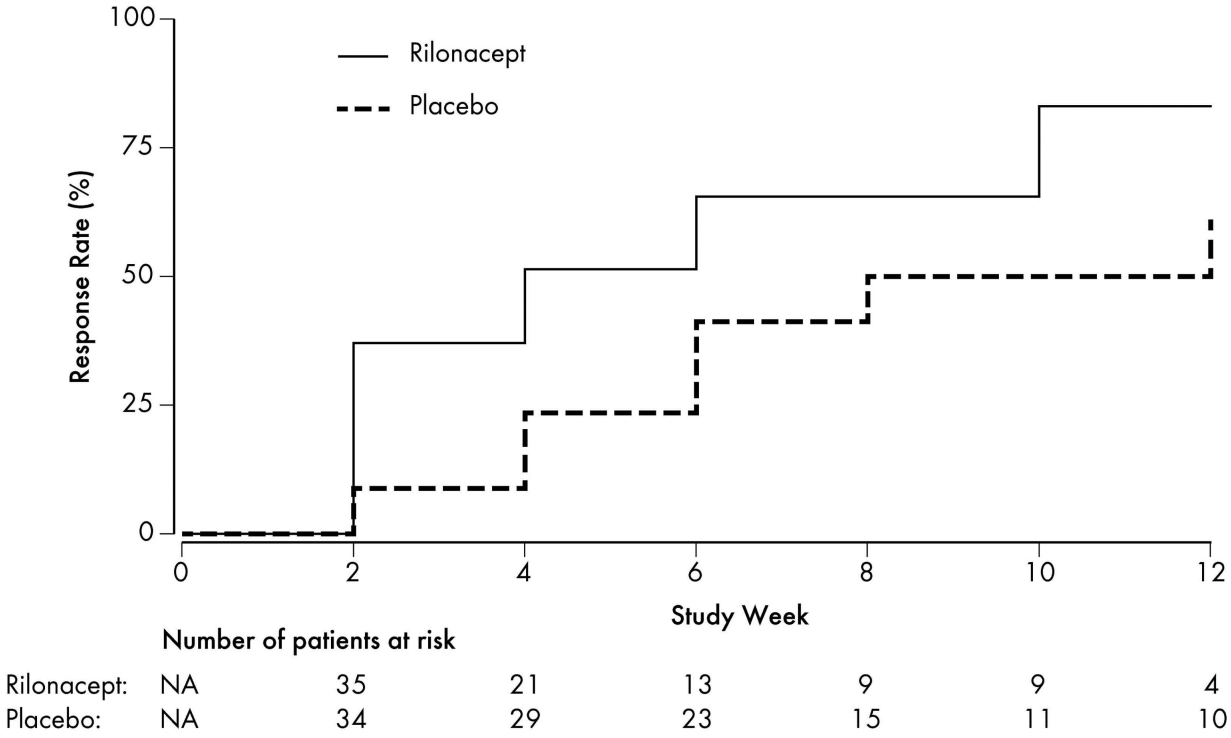

Figure 2. Cumulative Incidence Estimates of Response by Treatment Arm

The cumulative incidence curve shows a higher rate of response in the rilonacept arm compared to the placebo arm. The primary endpoint of response was assessed at bi-weekly study visits during the efficacy period. Response was defined as improvement in the American College of Rheumatology (ACR) Pediatric 30, absence of fevers ≥38.5°C in the previous 2 weeks, and at least 10% taper in systemic corticosteroids from baseline. Missing temperatures were imputed as fever free. Patients were no longer eligible for the primary endpoint if corticosteroids were increased or started based on the non-response algorithm prior to meeting the criteria for response. The cumulative incidence estimation treated non-response as a competing event. The number of patients at risk displayed below the figure shows the number of patients eligible to meet the response designation for the first time at each study week.

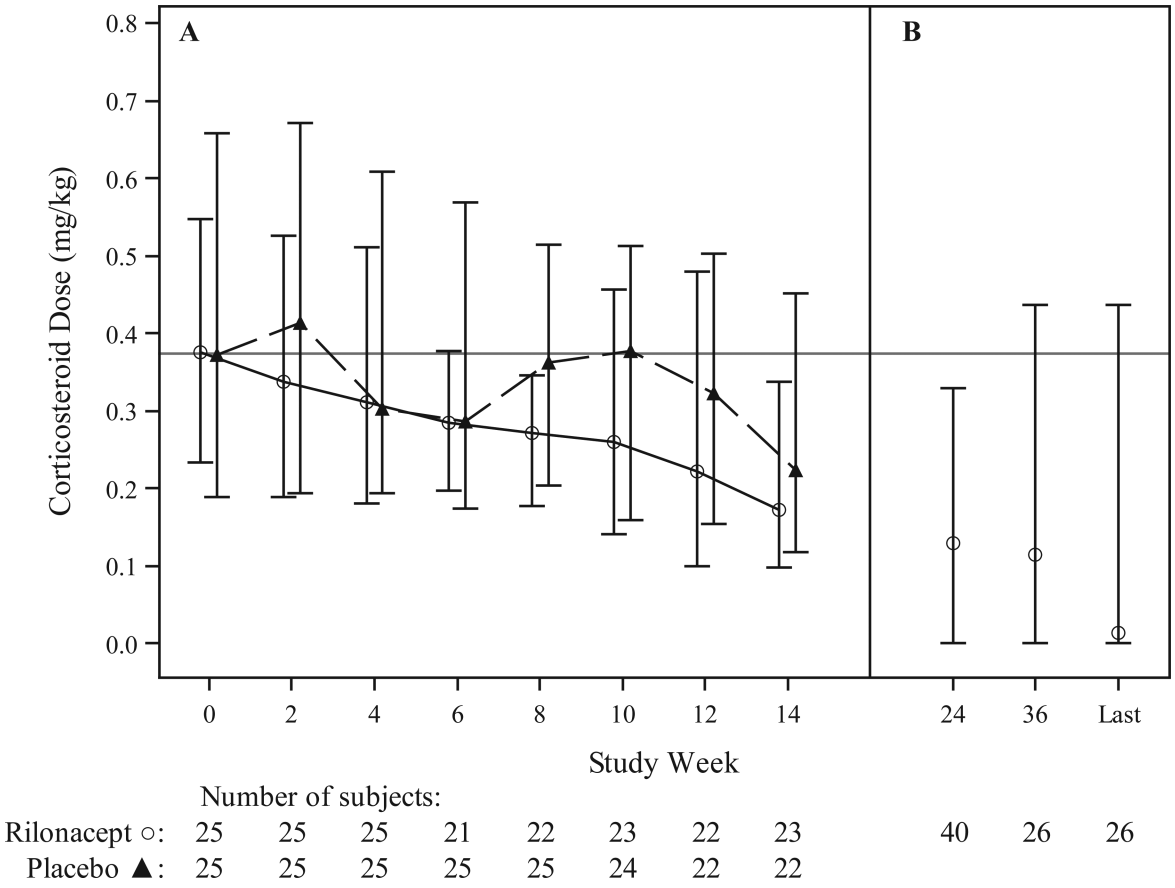

Figure 3. Change Over Time in Corticosteroid Dose

Panel A shows the median corticosteroid dose by treatment group during the efficacy period, with I bars representing interquartile range. Panel B shows the median corticosteroid dose aggregated for all patients during the follow-up safety period, with I bars representing interquartile range. Patients' oral dose at their last visit during the long term extension phase is displayed. The median time on study at the last visit was 16 months, with a range of 8 to 26 months.

Table 1

Baseline Demographics and Disease Characteristics of Study Patients

Characteristic	Rilonacept (N=36)	Placebo (N=35)
Sex–no. (%)		
Male	13 (36)	12 (34)
Female	23 (64)	23 (66)
Race–no. (%)[a]		
Black	5 (14)	7 (20)
White	25 (69)	23 (66)
Other[b]	6 (17)	5 (14)
Ethnicity–no. (%)[c]		
Hispanic	7 (19)	5 (14)
Non–Hispanic	29 (81)	30 (86)
Age–yr		
Mean (SD)	9.5 (4.6)	10.5 (4.4)
Median (25^{th},75^{th})	9.5 (6.0,13.0)	11.0 (6.0,14.0)
Disease duration–yr		
Mean(SD)	2.6 (3.6)	2.6 (3.1)
Median (25^{th},75^{th})	0.7 (0.2, 4.0)	1.4 (0.4, 3.6)
Number of active joints		
Mean(SD)	11.7 (9.6)	10.5 (7.6)
Median (25^{th},75^{th})	7.5 (4.0, 16.0)	9.0 (5.0, 15.0)
Fever past 7 days–no. (%)	10 (28)	6 (17.1)
Articular without systemic symptoms–no. (%)	16 (44)	16 (46)
Prior medication use –no. (%)		
Corticosteroids	30 (83)	33 (94)
Methotrexate	21 (58)	26 (74)
Leflunomide	1 (3)	2 (6)
Infliximab	5 (14)	6 (17)
Etanercept	12 (33)	16 (46)
Abatacept	5 (14)	4 (11)
Anakinra[d]	13 (36)	13 (37)
Baseline medication use–no. (%)	30 (83)	33 (94)
Corticosteroid[e]	25 (69)	22 (63)
Corticosteroid dose[f]	.38(.23,.55)	.37(.19,.66)
Methotrexate	16 (44)	19 (54)
Characteristics in the past–no. (%)		
Incomplete MAS	1 (3)	3 (9)
Complete MAS	1 (3)	1 (3)
Serositis	9 (25)	8 (23)

Characteristic	Rilonacept (N=36)	Placebo (N=35)
sJIA rash	32 (89)	33 (94)

[a] Race was collected via self-report . Categories consisted of American Indian/Alaska Native, Asian, black/African American, Native Hawaiian/other Pacific Islander, and white.

[b] Other includes patients who self-identified as Asian, Native Hawaiian/other Pacific Islander, and multiracial. It also includes 3 patients where race was not reported.

[c] Ethnicity was collected via self-report. Categories consisted of Hispanic/Latino and non-Hispanic/Latino.

[d] Anakinra exposure data were missing in 8 subjects; 4 in each arm.

[e] Corticosteroid includes oral, intravenous, and intramuscular steroids.

[f] Median and inter quartile ranges prednisone equivalents mg/kg/d

Table 2

Change over time in Systemic Features, ACR Variables, and Laboratory Values

	Baseline		Week 4		Week 12		Week 24
Variable	**Rilonacept**	**Placebo**	**Rilonacept**	**Placebo**	**Rilonacept**	**Placebo**	**Rilonacept**
Systemic features							
Fever[a]	10/36 (28%)	6/35 (17%)	3/36 (8%)	5/34 (15%)	4/33 (12%)	1/29 (3%)	--
Rash	15/36 (42%)	15/35 (43%)	3/36 (8%)	8/34 (24%)	3/33 (9%)	1/29 (3%)	4/57 (7%)
JIA ACR 30 response[b,c]	--	--	26/35 (74%)	13/33 (39%)	29/33 (88%)	22/29 (76%)	45/55 (82%)
JIA ACR 50 response[b,d]	--	--	21/35 (60%)	10/33 (30%)	28/33 (85%)	19/29 (66%)	43/55 (78%)
JIA ACR 70 response[b,e]	--	--	14/35 (40%)	4/33 (12%)	23/33 (70%)	17/29 (59%)	35/55 (64%)
Inactive disease[f]	--	--	2/36 (6%)	0/34	4/33 (12%)	3/29 (10%)	11/55 (20%)
JIA ACR core set of variables							
No. of joints with active arthritis							
Median	7.5	9.0	3.0	7.0	2.0	4.0	1.0
Interquartile range	4.0-16.0	5.0-15.0	1.0-7.5	4.0-17.0	0.0-5.0	0.0-10.0	0.0-7.0
Median % change from baseline			70.0	12.5	81.3	63.6	90.0
No. of joints with limited range of motion							
Median	4.0	8.0	2.0	8.0	1.0	2.0	1.0
Interquartile range	2.0-10.5	2.0-11.0	0.0-6.5	2.0-12.0	0.0-8.0	0.0-9.0	0.0-7.0
Median % change from baseline	--	--	50.0	0.0	75.0	47.7	66.7
Score for physician's global assessment of disease activity[g]							
Median	43.0	59.5	12.5	40.5	10.0	18.0	6.0
Interquartile range	26.0-65.0	49.0-68.0	3.0-34.0	25.0-65.0	2.0-19.0	5.0-30.0	1.0-33.0
Median % change from baseline			73.7	27.9	81.7	73.1	85.8
Score for parent's global assessment of overall well-being[h]							
Median	49.5	53.0	12.0	34.0	3.5	8.0	7.0
Interquartile range	33.0-65.0	28.0-68.0	3.0-23.0	15.0-67.0	0.0-17.0	2.0-38.0	1.0-29.0
Median % change from baseline	--	--	60.8	6.2	81.5	66.7	79.4
CHAQ-DI score							

Variable	Baseline		Week 4		Week 12		Week 24
	Rilonacept	Placebo	Rilonacept	Placebo	Rilonacept	Placebo	Rilonacept
Median	1.00	1.25	0.43	0.88	0.25	0.25	0.13
Interquartile range	0.75-1.63	0.50-1.63	0.00-1.13	0.38-1.63	0.00-0.88	0.00-1.25	0.00-1.00
Median % change from baseline	--	--	34.5	16.7	50.0	59.4	80.0
C-reactive protein (mg/dL)[i]							
Median	4.40	4.48	0.40	4.12	0.40	0.40	0.40
Interquartile range	0.40-9.15	0.80-7.23	0.40-1.85	0.87-8.14	0.40-0.92	0.40-2.29	0.40-1.95
Median % change from baseline	--	--	52.4	0.0	72.6	50.0	50.0
Laboratory variables							
Hemoglobin (g/dL)[k]							
Median	11.0	11.8	11.8	11.2	12.0	11.6	12.1
Interquartile range	10.3-11.9	9.8-12.5	10.9-12.6	9.6-12.4	11.4-13.2	11.0-12.4	11.2-13.0
Total neutrophils ($\times 10^9$/L)[l]							
Median	9.76	7.65	5.46	8.71	4.20	4.83	3.94
Interquartile range	5.43-19.07	5.69-12.06	3.07-8.48	6.69-13.14	2.36-6.16	3.51-6.24	2.27-5.74
Platelet count ($\times 10^9$/L)[m]							
Median	449.0	357.0	341.0	376.0	315.0	338.0	312.0
Interquartile range	352.0-534.0	274.0-457.0	279.0-400.0	306.5-546.0	276.5-376.5	275.0-389.0	277.0-409.0
D-dimer (ug/mL)[j,n]							
Median	1.38	1.63	0.52	1.31	0.37	0.59	--
Interquartile range	0.36-3.66	0.30-3.05	0.34-1.58	0.32-3.59	0.25-0.98	0.23-1.86	
Fibrinogen (mg/dL)[o]							
Median	361.0	361.0	243.5	365.0	231.0	258.0	257.0
Interquartile range	283.0-532.0	308.0-487.0	228.0-329.0	272.0-487.0	211.5-292.0	217.0-334.0	213.0-360.5
Ferritin (ng/mL)[j,p]							
Median	112.0	80.0	29.0	52.5	24.0	20.0	--
Interquartile range	52.5-291.0	37.0-207.0	13.0-68.0	25.5-181.5	11.0-44.0	8.0-36.0	
ESR (mm/hr)[q]							
Median	40.0	47.0	12.0	37.0	11.0	15.5	10.5

Variable	Baseline		Week 4		Week 12		Week 24
	Rilonacept	Placebo	Rilonacept	Placebo	Rilonacept	Placebo	Rilonacept
Interquartile range	14.0-69.0	21.0-67.0	7.0-28.0	15.0-70.0	7.0-15.0	8.0-29.0	6.0-22.0
Albumin (g/dL)[r]							
Median	4.1	4.1	4.4	4.1	4.4	4.3	4.4
Interquartile range	3.7-4.4	3.8-4.4	4.2-4.4	3.8-4.2	4.3-4.6	4.2-4.6	4.1-4.6

Abbreviations: ACR, American College of Rheumatology; CHAQ-DI, Childhood Health Assessment Questionnaire–Disability Index

[a] Fever was assessed 7 days prior to baseline based on self-report. Fever (>=38.5° C) was assessed 14 days prior to Week 4 and Week 12 based on patient diaries. Days with missing temperature data were imputed as “fever free.” Fever data was not collected at Week 24.

[b] The core variables for ACR Pediatric response included number of joints with active arthritis, number of joints with limited range of motion, score for physician's global assessment of disease activity, score for parent's global assessment of overall well-being, CHAQ-DI score, and C-reactive protein value. Absence of fever was not included.

[c] The JIA ACR30 algorithm required at least 30% improvement from baseline in at least 3 of 6 core variables, with no more than 1 variable worsening by 30% or more.

[d] The JIA ACR50 algorithm required at least 50% improvement from baseline in at least 3 of 6 core variables, with no more than 1 variable worsening by 50% or more.

[e] The JIA ACR70 algorithm required at least 70% improvement from baseline in at least 3 of 6 core variables, with no more than 1 variable worsening by 70% or more.

[f] Inactive disease was defined as the following: absence of joints with active arthritis, fever, rash, serositis, splenomegaly, or generalized lymphadenopathy; normal erythrocyte sedimentation rate or C-reactive protein; and score ≤1 for physician's global assessment of disease activity.

[g] Physician's global assessment was based on a 100-mm visual-analogue scale. Score ranged from 0 (very well) to 100 (very poor).

[h] Parent's global assessment was based on a 100-mm visual-analogue scale. Score ranged from 0 (not active) to 100 (very active).

[i] The normal range for C-reactive protein was 0 to 0.90 mg/dL.

[j] D-dimer and ferritin were not tested at week 24.

[k] The normal range for Hgb was 11.5-13.5g/dL

[l] The normal range for total neutrophils was 1.8-8.0 X 10^9/L

[m] The normal range for platelets was 130-400 X 10^9/L

[n] The normal range for D-dimer was <0.499ug/ml

[o] The normal range for fibrinogen was 200-400mg/dl

[p] The normal range for ferritin was 10-143ng/ml

[q] The normal range for ESR varied by site

[r] The normal range for albumin was 3.2-5.0g/dl

Table 3

Adverse Events

	Double-Blind Phase (0-4 weeks)		Treatment Phase (4-24 weeks)		LTE Open-Label Phase (24 weeks -21 months)
Variable	**Rilonacept (N=36)**	**Placebo (N=35)**	**Rilonacept (N=35)**	**Placebo (N=33)**	**Rilonacept (N=40)**
Adverse event					
No. of events	17	63	81	123	110
No. of events per patient-year	6.1	23.9	6.2	11.3	3.0
Patients with an event - no. (%)	10 (28%)	19 (54%)	27 (77%)	28 (85%)	28 (70%)
Most frequently reported events - no. of patients (%)[a]					
Abdominal pain upper	1 (3%)	2 (6%)	3 (9%)	1 (3%)	0
Arthralgia	0	1 (3%)	2 (6%)	6 (18%)	1 (3%)
Cough	0	1 (3%)	2 (6%)	3 (9%)	2 (5%)
Headache	1 (3%)	6 (17%)	1 (3%)	4 (12%)	3 (8%)
Nausea	0	1 (3%)	1 (3%)	2 (6%)	3 (8%)
Pharyngitis streptococcal	0	0	2 (6%)	2 (6%)	4 (10%)
Pyrexia	0	1 (3%)	5 (14%)	1 (3%)	1 (3%)
Rash	2 (6%)	1 (3%)	1 (3%)	3 (9%)	1 (3%)
Upper respiratory tract infection	0	1 (3%)	5 (14%)	9 (27%)	2 (5%)
Vomiting	1 (3%)	2 (6%)	1 (3%)	2 (6%)	4 (10%)
Serious adverse events (SAE)					
No. of events	1	1	3	1	8
No. of events per patient-year	0.4	0.4	0.2	0.1	0.2
Patients with an event - no. (%)	1 (3%)	1 (3%)	3 (9%)	1 (3%)	6 (15%)
All reported events - no. of patients (%)					
Gastroenteritis salmonella	0	0	0	0	1 (3%)
Histiocytosis haematophagic[b]	0	0	0	0	1 (3%)
Juvenile arthritis[c]	1 (3%)	1 (3%)	0	1 (3%)	1 (3%)
Liver function test abnormal[d]	0	0	1 (3%)	0	0
Mental status changes	0	0	0	0	1 (3%)
Pericarditis	0	0	0	0	1 (3%)
Pharyngitis streptococcal[e]	0	0	0	0	1 (3%)
Pyrexia	0	0	1 (3%)	0	0
Varicella	0	0	1 (3%)	0	0
Viral upper respiratory tract infection	0	0	0	0	1 (3%)
Infection					
No. of events	2	2	25	29	37
No. of events per patient-year	0.7	0.8	1.9	2.7	1.0

	Double-Blind Phase (0-4 weeks)		Treatment Phase (4-24 weeks)		LTE Open-Label Phase (24 weeks -21 months)
Variable	**Rilonacept (N=36)**	**Placebo (N=35)**	**Rilonacept (N=35)**	**Placebo (N=33)**	**Rilonacept (N=40)**
Patients with an event - no. (%)	2 (6%)	2 (6%)	16 (46%)	20 (61%)	14 (35%)

[a] The most frequently reported events were defined as events that occurred in at least 10% of all patients during the entire study.

[b] One patient developed EBV triggered macrophage activation syndrome (proven by polymerase chain reaction testing) deemed an SAE during the LTE phase.

[c] The juvenile arthritis SAE summarized in the rilonacept arm during the double-blind phase was a pre-treatment event. The onset date occurred after consent but prior to randomization.

[d] One patient had elevations in the liver function tests deemed an SAE during the treatment phase. The elevations subsided when drug was temporarily discontinued but recurred on re-challenge.

[e] One patient had two separate episodes of streptococcal pharyngitis deemed SAEs during the LTE phase.