

Supplemental Appendix

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I. Supplemental Methods

Inclusion criteria

1. Pediatric and adult subjects with mutation positive *IL1RN* indicating DIRA. For the first five patients enrolled, they must have been on a stable dose of anakinra during the 2-week period prior to screening visit. If the subject is on other medications such as NSAIDs, methotrexate and/or oral steroids, it is a requirement that these doses have been stable during the 2-week period prior to screening visit.
2. Subjects > or equal to 3 months of age (however the first 5 patients enrolled will be over 2 years of age). Subjects 3 months old or older will be enrolled after SMC data review of the first 5 enrolled patients.
3. Participation in NIH study #03-AR-0173 (“Studies of the Natural History, Pathogenesis and Outcome of Autoinflammatory Diseases (NOMID/CAPS, DIRA, CRMO, Still’s Disease, Behcet’s Disease, and other Undifferentiated Autoinflammatory Diseases”)
4. Subjects currently treated with anakinra may be enrolled in this study even though their DIRA may be quiescent. For these subjects, a history of active DIRA prior to treatment with anakinra will be sufficient. Subjects will not take anakinra 24 hours before initiation of drug treatment. Treatment naïve patients will also be enrolled after **safety monitoring committee** (SMC) data review of the first 5 enrolled patients.
5. Females of childbearing potential (young women who have had at least one menstrual period regardless of age) must have a negative serum pregnancy test at screening and a urine pregnancy test prior to administration of study medication.
6. Females of childbearing age and men able to father a child and who are sexually active, who agree to use two forms of effective birth control, including abstinence.
7. Negative Purified Protein Derivative (PPD) test using 5 T.U. intradermal testing or the QuantiFERON® - TB Gold test per the Centers for Disease Control and

Prevention (CDC) guidelines, and no evidence of active tuberculosis (TB) on chest X-ray.

8. Guardian/parent able to understand, and complete study-related questionnaires.
9. Guardian/parent able and willing to give informed consent and abide with the study procedures.

Exclusion Criteria

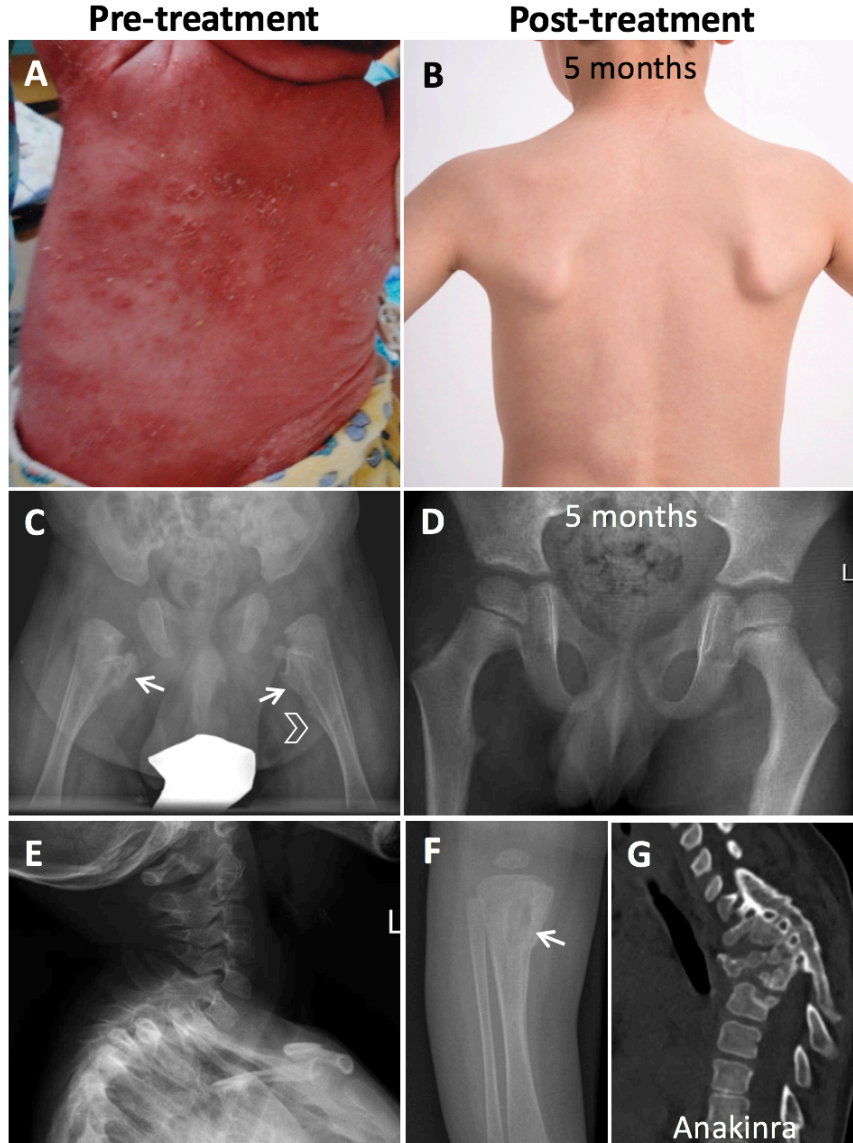
1. Treatment receiving a live virus vaccine (such as the measles, mumps, and rubella vaccine) during the 3 months prior to baseline visit. No live vaccines will be allowed throughout the course of this study.
2. Presence of active infections or a history of pulmonary TB infection without documented adequate therapy. Subjects with current active TB, or recent close exposure to an individual with active TB, are excluded from the study. Exceptions include patients with latent TB treated with adequate therapy for at least one month prior to the first dose of study medication, and patients with history of TB with documentation of adequate treatment.
3. Positive test for, or prior history of, HIV, or Hepatitis B or C.
4. History of malignancy. Subjects deemed cured of superficial malignancies such as cutaneous basal or squamous cell carcinomas, or *in situ* cervical cancer may be enrolled.
5. Known hypersensitivity to Chinese Hamster Ovary cell-derived biological or any components of rilonacept.
6. Presence of any additional rheumatic disease or significant systemic disease. For example, major chronic infectious/ inflammatory/ immunologic disease (such as inflammatory bowel disease, psoriatic arthritis, spondyloarthritis, SLE in addition to autoinflammatory disease).
7. Presence of any of the following laboratory abnormalities at enrollment visit: creatinine > 1.5xULN, WBC < $3.0 \times 10^3/\text{mm}^3$, ANC < 800 cells/ μL ; platelet count < $150,000 \text{ mm}^3$; ALT or AST > 2.0x ULN.
8. Lactating, breastfeeding or pregnant females.

9. Enrollment in any other investigational treatment study or use of an investigational agent, or has not yet completed at least 4 weeks or 5 half-lives, whichever is longer, since ending another investigational device or drug trial.
10. Subjects for whom there is concern about compliance with the protocol procedures.
11. Presence of other severe acute or chronic medical or psychiatric condition, or significant laboratory abnormality requiring further investigation that may cause undue risk for the subject's safety, inhibit protocol participation, or interfere with interpretation of study results, and in the judgment of the Investigator would make the subject inappropriate for entry into this study.
12. Subjects who have received a DMARD (except methotrexate) and or TNF-blocking agent within 4 half-lives prior to study entry.
13. Men able to father a child and who are sexually active, who do not agree to use 2 form of effective birth control, including abstinence during the duration of the study and for at least 28 days following the last dose of riloncept.

Females of childbearing potential (woman > 12 or who have had at least 1 menstrual period regardless of age) who are sexually active and who do not agree to use 2 effective methods of birth control, including abstinence during the duration of the study and for at least 28 days following the last dose of riloncept.

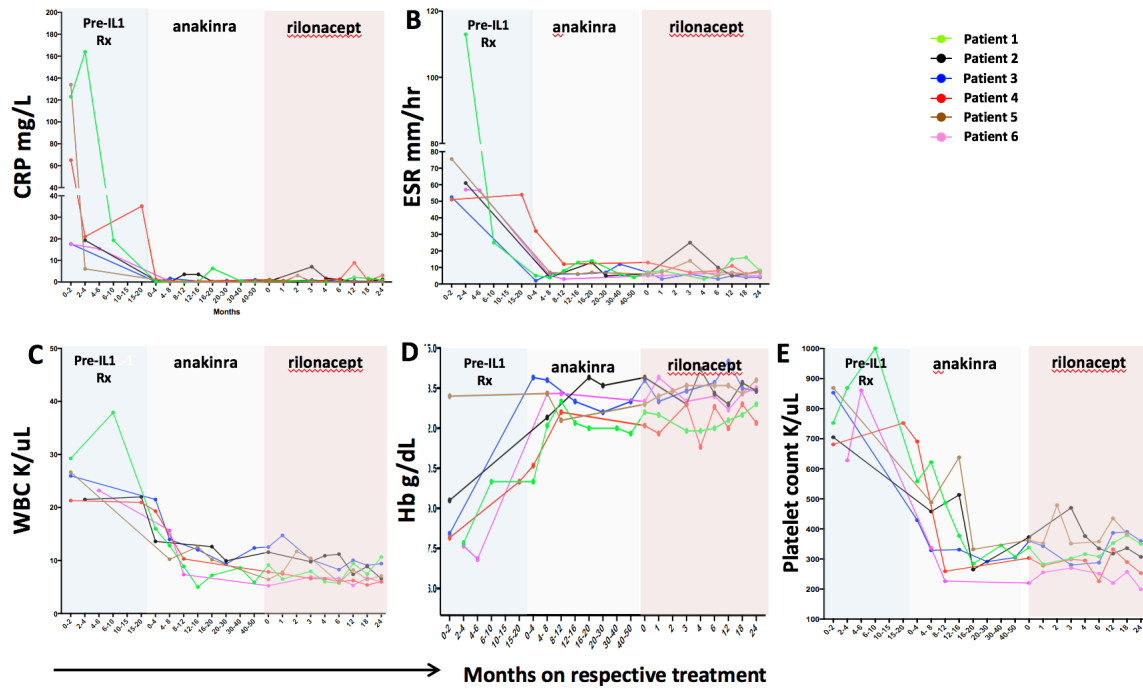
II. Supplemental Figures

Supplemental Figure 1.



Supplemental Figure 1. Improvement in clinical manifestations and maintenance of clinical remission in patients with Deficiency of IL-1 Receptor Antagonist (DIRA) after treatment with anakinra followed by rilonacept. (A) Pre-treatment (patient 1) - Generalized pustular lesions at neonatal onset. **(B)** Post-treatment (patient 1) - Patient continues with absence of generalized pustular lesions 5 months after discontinuation of anakinra, and initiation of rilonacept. **(C)** Pre-treatment (patient 1) - DIRA typical radiographic manifestations, periosteal cloaking of the proximal femoral metaphysis (arrow) and periosteal elevation of the diaphysis (arrowheads). **(D)** Patient 1 - Resolution of femoral lesions, patient did not develop any further bone lesions 5 months after discontinuation of anakinra and initiation of rilonacept. **(E)** Pre-treatment (patient 3) severe anterior kyphotic deformities of the upper thoracic spine with complete destruction and collapse of the T4, T5 and T6 vertebral bodies. **(F)** Pre-treatment (patient 1) - Osteolytic lesion in the proximal tibia that healed on treatment with anakinra. **(G)** Anakinra treatment (patient 3) - Deformity did not progress while on treatment with IL-1 inhibition.

Supplemental Figure 2.



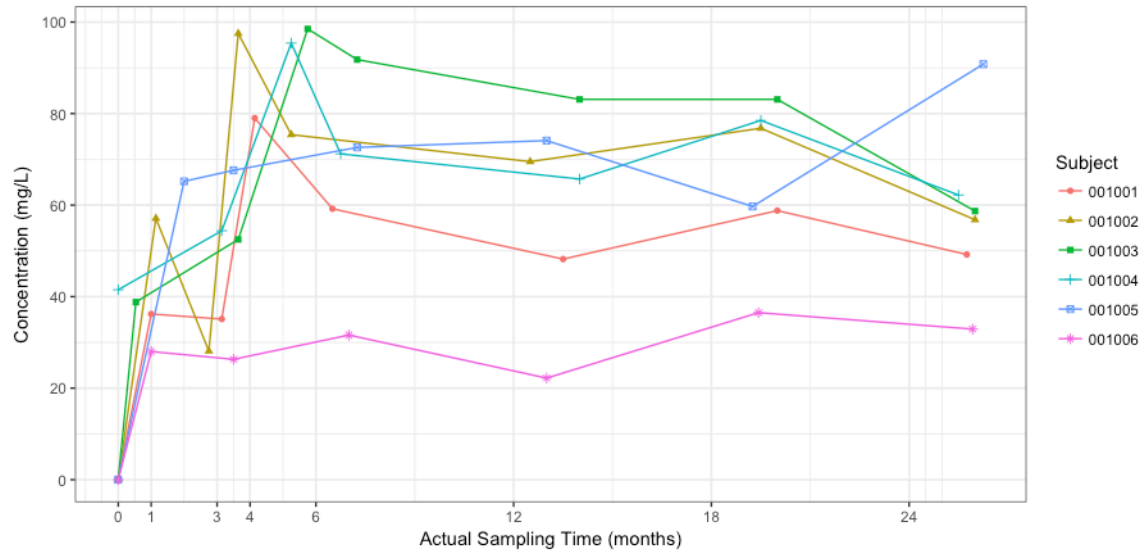
Supplemental Figure 2. Improvement in inflammatory markers in 6 patients with Deficiency of IL-1 Receptor Antagonist (DIRA) after treatment with anakinra followed by rilonacept. (A) C-reactive protein (CRP) level (mg/L). **(B)** Erythrocyte sedimentation rate (ESR) (mm/hr). **(C)** White blood cells count (WBC) (K/uL). **(D)** Hemoglobin (g/dL). **(E)** Platelets (K/uL). P1- Patient 1, P2- Patient 2, P3- Patient 3, P4- Patient 4, P5- Patient 5, P6- Patient 6.

Supplemental Figure 3.



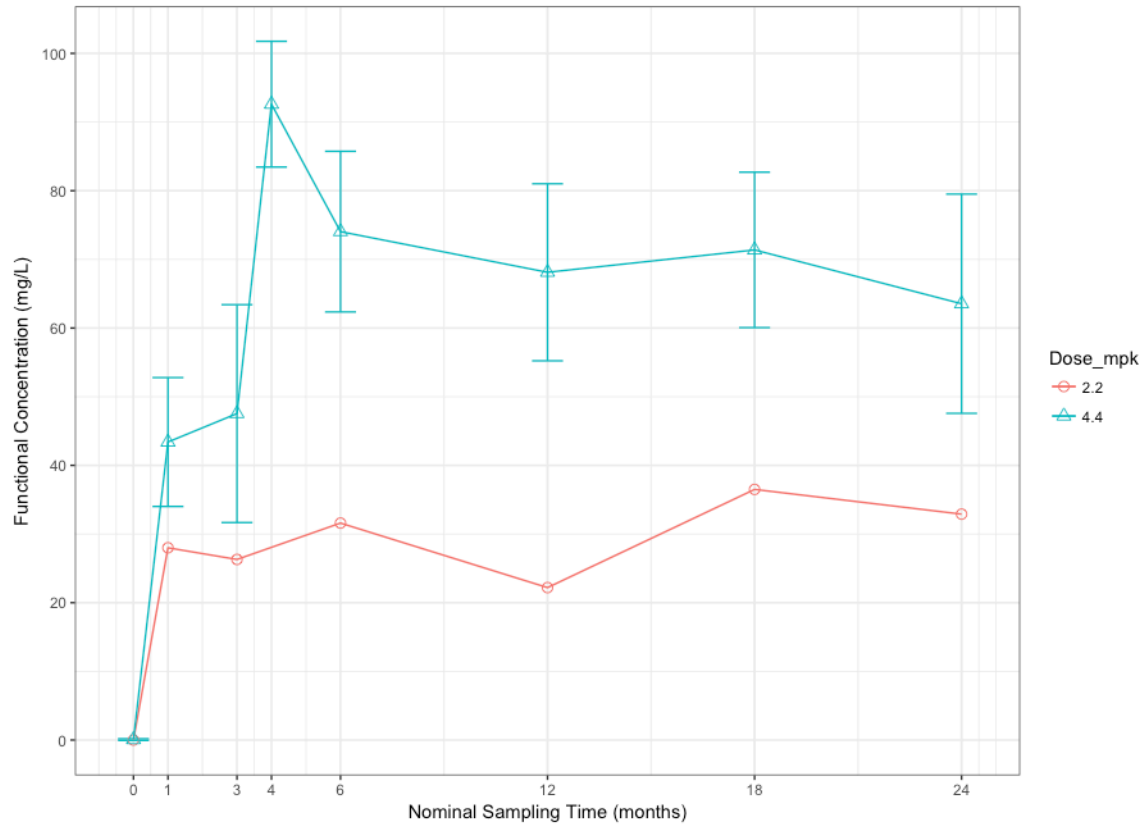
Supplemental Figure 3. Areas of micropustular lesions noted on areas of (A) Previous surgical scars, (B) Cheek, face and (C) Most commonly knees and elbows (not shown).

Supplemental Figure 4.



Supplemental Figure 4. Individual rilonacept trough concentration-time profiles for patients receiving rilonacept 4.4mg/kg (Patient 1, 2, 3, 4 and 5) or 2.2mg/kg (Patient 6). PK blood samples were drawn before weight appropriate dosing adjustments were made at the respective visit, the actual doses patients received at the time of blood draw may have been lower than 4.4mg/kg or 2.2mg/kg.

Supplemental Figure 5.



Supplemental Figure 5. Trough concentration-time profile for patients receiving riloncept 4.4mg/kg/week (mean SD \pm n=5) or 2.2mg/kg/week (n=1).

III. Supplemental Tables

Supplemental Table 1.

Laboratory Parameters	Pre- treatment	anakinra	rilonacept
ESR (mm/hr)	57.4 ± 13.2	9.2 ± 6.4	7.5 ± 2.1
CRP (mg/L)	45.2 ± 35.7	0.6 ± 0.5	1.3 ± 0.9
Platelets (K/uL)	741.2 ± 99.3	398.9 ± 84.1	329.7 ± 50.9

Supplemental Table 1. Changes in inflammatory markers and platelets between pre-treatment, on anakinra and 24 months on rilonacept. Inflammatory markers (mean ± SD) improved on anakinra and stayed normal on rilonacept.

Supplemental Table 2.

Adverse Event[†]	rilonacept (n=6)
Number of TEAEs ^A	84
Number of subjects with at least one TEAE	6 (100%)
Upper respiratory infection (URI)	6
Otitis media	4
Rash	5
Pharyngitis	3
Rhinorrhea	3
Abdominal Pain	2
Vomiting	2
Viral gastroenteritis	2
Allergic Reaction ^B	2
Fever	2
Headache	2
CPK increased	2

Supplemental Table 2. Summary of Treatment Emergent Adverse Events:

[†]Suspected and Non- suspected TEAEs in more than 1 patient are included.

^ASubject with multiple TEAEs was counted once for the same event term

Other less frequent TEAEs include: hypercholesterolemia, allergic conjunctivitis, arthralgia, dry skin, constipation, muscle soreness, photosensitivity, pneumonia, pruritus, seborrheic dermatitis, sinusitis, thrombocytosis, viral illness, and skin reaction to anakinra. The latter TEAE was reported after discontinuation of rilonacept, and re-initiation of anakinra.

^BFood allergy (n=1), and fixed reaction to acetaminophen (n=1)

TEAEs=Treatment Emergent Adverse Events, n=number of patients