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Review

# Analysis of Anakinra Therapy for the Deficiency of Interleukin-1 Receptor Antagonist through Clinical Evidence

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**Abstract:** Deficiency of interleukin-1 receptor antagonist (DIRA) is a rare life-threatening autosomal recessive autoinflammatory disease with symptoms including but not limited to osteomyelitis, periostitis, and systemic inflammation. DIRA is developed from the loss-of-function mutations of *IL1RN* gene that encodes IL-1 receptor antagonist (IL-1RA), leading to the unchecked pro-inflammatory signaling and subsequent systemic inflammation. Thus, Anakinra as the recombinant IL-1RA has become the primary drug to treat DIRA. Although Anakinra has been effective for complete remission of DIRA, it also showed various side effects. To further address its efficacy and safety in treating DIRA, a review of literature was conducted in this study. We have identified 15 papers with 25 patients studied, making it possible to conduct reliable statistical analyses. The literature review found that continual treatment with Anakinra is effective to cause clinical remission of DIRA. Statistical analyses found that after the treatment with Anakinra, patients had improved Hemoglobin, Erythrocyte Sedimentation Rate, and C-reactive Protein levels. All known cytogenetic abnormalities were also analyzed to inform clinicians for genetic screening and rapid diagnosis of DIRA. The results from this study provide a comprehensive view for further improving the treatment of DIRA by Anakinra.

**Keywords:** autoimmune diseases; deficiency of interleukin-1 receptor antagonist (DIRA); Anakinra; IL-1RA; IL-1RN

## 1. Introduction

The interleukin-1 (IL-1) family is a group of 11 cytokines and 10 receptors that regulate inflammatory responses with various roles. Some of them, such as IL-1 $\alpha$ , IL-33, IL-36, and IL-1 $\beta$ , mediate a pro-inflammatory response [1], whereas others like IL-37 and IL-38 are anti-inflammatory [1]. When the pro-inflammatory cytokines of the IL-1 family bind to the cognate receptor IL-1R1, they recruit the secondary receptor IL-1RacP [2], thus initiating IL-1 signaling through two mediators, myeloid differentiation primary response 88 (MyD88) and interleukin-1 receptor associated kinases 4 (IRAK 4), to eventually activate nuclear factor  $\kappa$ B (NF $\kappa$ B) and activator protein 1 (AP1). Both transcription factors will regulate target gene expression to mediate IL-1 functions. From the given signal transduction pathway, tight regulation is required to prevent detrimental effects that could lead to chronic inflammatory disorders.

Among IL-1 family, IL-1 $\alpha$  plays pleiotropic roles in both inflammation and hematopoiesis; it is widely expressed in various cells including epithelial, endothelial, stromal cells, neutrophils, and activated macrophages [3]. Under the condition of cellular damage, necrotic cells release IL-1 $\alpha$  into the extracellular environment as an alarmin [4]. In addition, IL-1 $\alpha$  is also induced in hematopoietic and non-hematopoietic cells in response to inflammatory stimuli. There exists IL-1RA as an antagonist to compete with IL-1 for binding to IL-1R1. The balance between IL-1RA and IL-1 becomes

very crucial for the development of a variety of inflammatory diseases such as Deficiency of IL-1 Receptor Antagonist (DIRA), Rheumatoid Arthritis (RA), Gastric Cancer, and Osteoporosis.

DIRA is a rare autoinflammatory disorder characterized by marked skin and bone involvement, and elevation of acute phase reactants. DIRA is caused by a loss-of-function mutation occurring in the *IL1RN* gene that prevents the expression of active IL-1RA, causing unchecked pro-inflammatory signaling and subsequent systemic inflammation [5]. DIRA has a challenging feature with very early onset. As early as the first week of life, DIRA manifesting symptoms can be developed, including pustular rash, widening of ribs, periosteal reaction, multifocal osteolytic reactions, cervical vertebral fusion, hepatosplenomegaly, multifocal osteomyelitis [5]. The primary drug choice for DIRA is Anakinra.

Anakinra is a recombinant form of the human IL-1RA protein. The primary difference between the recombinant and human form is that the recombinant contains an additional methionine residue in the amino terminus [5]. Anakinra was approved by the U.S. Food and Drug Administration (FDA) in December 2020 for the treatment of DIRA, but had been previously approved and utilized for other disorders such as RA and Cryopyrin Associated Periodic Syndromes [6]. Currently, Anakinra is the primary IL-1 therapeutic due to its short half-life, safety records, and subcutaneous route of delivery.

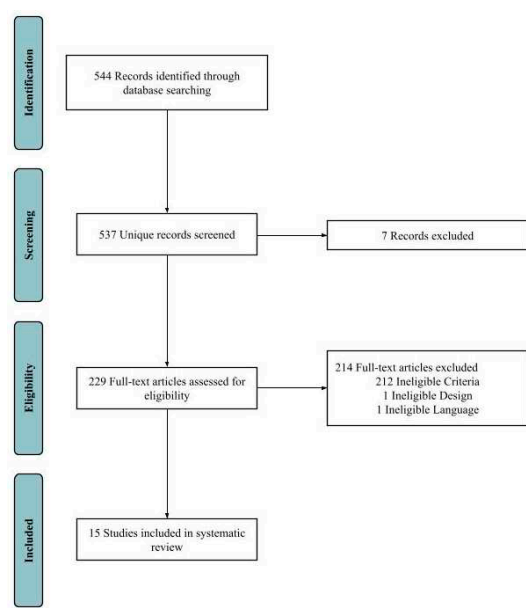
Even though Anakinra has been approved by the FDA for DIRA therapy, there is no previous review to evaluate Anakinra’s clinical efficacy and safety as a recombinant analog of IL-1RA in treatment of this autoinflammatory disease. Here, through review of current literature, we identified that Anakinra decreased acute phase reactants levels and improved anemia of patients in treatment of this autoimmune disease.

2. Materials and Methods

2.1. Literature Search Strategy

A literature search was conducted through PubMed, EMBASE, and Google Scholar, including articles from inception: keywords “DIRA” or “Deficiency of IL-1RA” and “Anakinra” were used to filter the studies evaluating the efficacy of Anakinra in DIRA therapy. Language was restricted to English only.

Gray literature was not included in the literature search. We included clinical trials, clinical studies, case reports, comparative study, original articles, meta-analysis, observational studies, and twin studies in the literature search. The detailed literature search and screening process was depicted below (Figure 1).



**Figure 2.** Literature search and screening process for this review. 544 studies were retrieved from all databases. All studies were screened. 7 duplicate articles were identified and removed. Full-text

articles were assessed for eligibility and 214 studies were removed due to ineligible language, design, or criteria. 15 studies were finally selected for this review.

2.2. Study Selection and Eligibility Criteria

Two paired reviewers independently conducted a title and abstract screening. We assessed the abstracts to identify articles that discussed Anakinra as the main treatment for DIRA and removed duplicate articles. Abstracts were also assessed to see if the efficacy of Anakinra was discussed with laboratory values or other means. Side effects of Anakinra were also considered. Abstracts that discussed Anakinra for the treatment of other rheumatological diseases but not DIRA were excluded from this study. Following screening, both reviewers independently evaluated the full-text of papers for eligibility.

2.3. Data Extraction

The data were extracted from the selected papers on age of presentation of DIRA symptoms, sex, region of origin, reported cytogenetic abnormalities, all previous treatments, consanguinity status, side effects from anakinra treatment, and the reported common clinical presentation. Hemoglobin (HB), C-Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR) were also extracted from these papers. These markers were included to comprehensively assess DIRA as an autoinflammatory disease. The efficacy of Anakinra for the treatment of DIRA has been evaluated with the CRP and ESR laboratory values pre- and post-treatment. HB laboratory values have also reported pre- and post-treatment to evaluate anemia associated with chronic diseases.

2.4. Statistical Analysis

Statistical analysis in this work was performed using GraphPad Prism (version 9.5.1) with its embedded algorithms. The Wilcoxon rank-sum test and the Student’s t-test (two-tailed, paired) were applied to evaluate the significance of laboratory results pre- and post- treatment. Data unavailable either due to patient confidentiality or other reasons were excluded.

To optimize statistical testing, a quantile-quantile (QQ) plot was first plotted on all laboratory test data to evaluate skewness, central tendency, and dispersion of the data. This determined whether the data were in normal Gaussian distribution, and if further non-parametric tests were needed. Then, all laboratory data were plotted as a Violin plot using GraphPad Prism software to visualize the full distribution of the data. All data presented in this study were listed as the mean differences with 95% confidence intervals. Unless stated otherwise, a *P*-value less than 0.05 was considered significant.

3. Results

3.1. Overall Population

Of the 15 studies included in this review, a total of 25 patients were treated with Anakinra for DIRA [7–21]. 19 patients (*n* = 19, 76%) were 4 weeks old or younger, and a total of 23 patients (*n* = 23, 92%) were under 17 weeks old (Table 1). The sex of all patients was primarily male, making up 16 total (*n* = 16, 64%) as shown in Table 2. The most common ethnicity of patients was Dutch (*n* = 6, 24%), Lebanese (*n* = 3, 12%), Puerto Rican (*n* = 4, 16%), and Brazilian (*n* = 3, 12%) (Table 3). 13 patients (*n* = 13, 52%) were non-consanguineous and 9 patients (*n* = 9, 36%) were consanguineous as shown in Table 4.

**Table 1.** Ages of DIRA Presentations. Data was extracted from the selected studies [7–21]. Percentages were calculated from the given sample size, *n*.

Age (weeks)	<i>n</i> = 25	Percentages (%)
0-4	19	76
5-8	3	12

9-12	0	0
13-16	1	4
17-20	0	0
21-24	0	0
25-28	0	0
29-32	0	0
33-36	0	0
37-40	0	0
41-44	0	0
45-48	0	0
49-52	1	4
53-56	1	4
57-60	0	0

**Table 2.** Sex of patients. Data was extracted from the selected studies [7–21]. Percentages were calculated from the given sample size, *n*.

Sex	<i>n</i> = 25	Percentages (%)
Male	16	64
Female	9	36

**Table 3.** Origins of the studies. Data was extracted from the selected studies [7–21]. Percentages were calculated from the given sample size, *n*.

Ethnicity	<i>n</i> = 25	Percentages (%)
Asian Indian	1	5
Brazilian	3	12
Puerto Rican	4	16
Turkish	1	4
Iranian-Persian	1	4
Lebanese	3	12
Portuguese and French	1	4
Canadian (Newfoundland)	1	4
Dutch	6	24
Not Known	3	12

**Table 4.** Sex of patients. Data was extracted from the selected studies [7–21]. Percentages were calculated from the given sample size, *n*.

Consanguinity	<i>n</i> = 25	Percentages (%)
Non-consanguineous	13	52
Consanguineous	9	36
Not known	3	12

### 3.2. Clinical Presentation and Cytogenetic Abnormalities

The common clinical manifestations of DIRA were pustular rashes (*n* = 21, 84%), multifocal osteolytic lesions (*n* = 17, 68%), widening of ribs (*n* = 15, 60%), periosteal reaction (*n* = 13, 52%), and multifocal osteomyelitis (*n* = 12, 48%). All other clinical symptoms have been reported in Table 5. The most prevalent nucleotide abnormalities leading to the clinical presentation of DIRA was c.229G→T (*n* = 5, 20%), which led to a nonsense mutation on the amino acid found at position 77 (E77X). A 175-kb deletion mutation on chromosome 2q13 (*n* = 5, 20%) was equally prevalent. All other mutations are listed in Table 6.

**Table 5.** Clinical Presentation of DIRA. Data was extracted from the selected studies [7–21]. Percentages were calculated from the given sample size, *n*.

Clinical Presentation	<i>n</i> = 25	Percentages (%)
Pustular Rash	21	84
Widening of Ribs	15	60
Periosteal Reaction	13	52
Multifocal Osteolytic Lesions	17	68
Cervical Vertebral Fusion	4	16
Hepatosplenomegaly	6	24
Multifocal Osteomyelitis	12	48
Hepatomegaly	1	4

**Table 6.** Cytogenetic Abnormalities. Data was extracted from the selected studies [7–21]. Percentages were calculated from the given sample size, *n*.

Clinical Presentation	<i>n</i> = 25	Percentages (%)
homozygous 22,216 bp deletion	1	4
homozygous stop variant c.62C>G; p. Ser21*	1	4
c.396delC, stop codon c534 position	1	4
p.Asp72_Ile76del; p.Q45* (rs1019766125)	1	4
NM_001318914.2:c.54delC;p. Asn18Lysfs*4,	2	8
c.160C>T; (Q54X)	1	4
15-bpdeletion, (c.213_227delAGATGTGGT ACCCAT; p.Asp72_Ile76del)	2	8
175-kb deletion on chromosome 2q13	5	20
(NM_173841.2:c.364C>T;p.[G ln122Ter])	1	4
E77X, (C140delC;	1	4
p.T47TfsX4; heterozygous (c.156_157delCA);	1	4
N52KfsX25,	1	4
c.229G→T; resultant amino acid mutation, E77X	5	20
c.160C→T; resultant amino acid mutation,Q54X	2	8
Not known	1	4

### 3.3. Previous Treatments and Effects of Anakinra

Before treatment with Anakinra, 16 patients (*n* = 16, 64%) were previously treated with Prednisolone/Methylprednisolone. 17 patients (*n* = 17, 68%) with oral/intravenous antibiotics. Canakinumab, an IL-1 $\beta$  blocker, was also given to patients (*n* = 2, 8%) before the administration of Anakinra. All other previous treatments utilized were listed in Table 7. These previous treatments failed to reach clinical remission. With the treatment of Anakinra, most patients reported no side effects (*n* = 22, 88%). All other side effects (*n* = 3, 12%) we listed in Table 8.

**Table 7.** Previous treatments for DIRA. Data was extracted from the selected studies [7–21]. Percentages were calculated from the given sample size,  $n$ .

Treatments	$n = 25$	Percentages (%)
Prednisone/Prednisolone/Me thylprednisolone	16	64
Canakinumab	2	8
IVIg	2	8
Soriatane (acitretin)	2	8
Etanercept	2	8
Bisphosphonates IV	1	4
Methotrexate	2	8
Azathioprine	1	4
Cyclosporine	2	8
Thalidomide	1	4
Interferon- $\gamma$	1	4
Oral/Intravenous Antibiotics	17	68
Antifungals	2	8

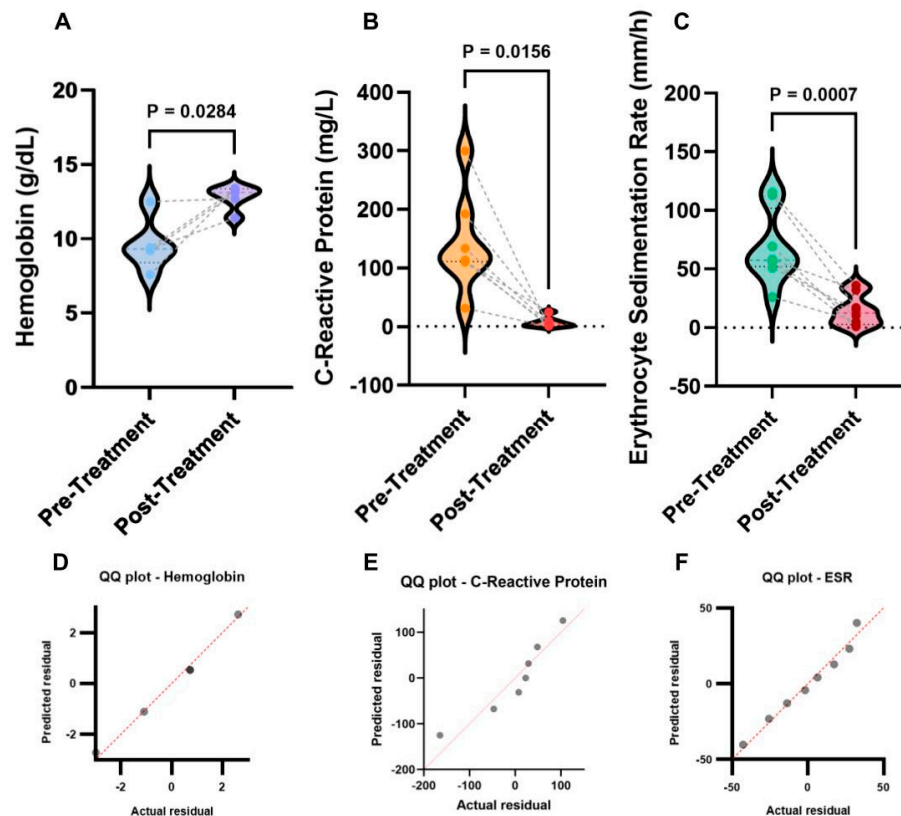
**Table 8.** Known side effects of Anakinra. Data was extracted from the selected studies [7–21]. Percentages were calculated from the given sample size,  $n$ .

Side Effects of Anakinra	$n = 25$	Percentages (%)
Elevated Acute Phase Reactant	1	4
No Reported Effects	22	88
Respiratory Distress & Death	1	4
Urticarial Rash	1	4

### 3.4. Analysis of Laboratory Tests

All laboratory testing results were plotted as Violin plots in Figure 2A-C along with the QQ plots shown in Figure 2D-F. From the QQ plots, the distance between the data and the predicted regression line, or the line of identity, displayed whether the laboratory test data was a normal Gaussian distribution. From Figure 2D and 2F, the distribution of HB and ESR was confirmed to be a normal Gaussian distribution. However, the data listed on the QQ plot for CRP (Figure 2E) appeared to be distant from the regression line, and therefore could not be assumed to be a normal Gaussian distribution. Furthermore, Student's  $t$ -test (two-tailed, paired) was utilized to evaluate significance for HB and ESR. Since the distribution of CRP is not normal, the Wilcoxon rank-sum non-parametric test was utilized. The data were then plotted as Violin plots.





**Figure 2.** Statistical Analyses of laboratory results of Anakinra therapy. (A) Comparison of Hemoglobin (HB) levels pre- and post- treatment. (B) Comparison of C-Reactive Protein (CRP) levels pre- and post- treatment. (C) Comparison of Erythrocyte Sedimentation Rate (ESR) pre- and post-treatment. P values are determined from the Student's t-test (two-tailed, paired) or Wilcoxon rank-sum test. (D) Quantile-Quantile (QQ) plot of HB. (E) Quantile-Quantile (QQ) plot of CRP. (F) Quantile-Quantile (QQ) plot of ESR.

From these data analysis, it was found that before the treatment with Anakinra, CRP levels were  $142.17 \pm 62.20$  mg/L, after treatment its levels were reduced to  $6.72 \pm 6.52$  mg/L (Cohen's  $d$  effect sizes = 2.27, Pearson's  $r$  correlations = 0.75). HB levels were increased from  $9.60 \pm 1.56$  g/dL (before the treatment with Anakinra) to  $12.78 \pm 0.71$  g/dL (after the treatment; Cohen's  $d$  effect sizes = 2.25, Pearson's  $r$  correlations = 0.75). For ESR, its levels were reduced from  $68.12 \pm 21.40$  mm/h (before Anakinra treatment) to  $14.72 \pm 9.18$  mm/h (after the treatment; Cohen's  $d$  effect sizes = -2.29, Pearson's  $r$  correlations = -0.75).

#### 4. Discussion

The majority of patients had an eruption of pustular rash within the first eight weeks of life. However, in the case report by Abdwani *et al.* [18] chronic diarrhea was reported as the initial unusual presentation of DIRA. Many patients also exhibited anemia. A small portion of patients also had extramedullary hematopoiesis leading to hepatomegaly and hepatosplenomegaly. With the administration of Anakinra, there was clinical remission of DIRA, however some patients experienced side effects. In the case report by Mendenco *et al.* [11], the patient experienced an urticarial rash within fifteen minutes of administration of Anakinra for the first time. This was well controlled by pre-medication with diphenhydramine, followed by the administration of Anakinra. However, in a case report by Ziaee *et al* [13], a patient showed signs of respiratory distress two weeks after administration of Anakinra. This patient also showed bone and skin complications. Then, Anakinra was discontinued, and Etanercept and prednisolone were started, and an improvement was observed. The patient's respiratory involvement never went back to baseline, and the patient



died eight months later. This may be a word of caution for clinicians who treat DIRA patients with bone, skin, and respiratory complications.

Given that the primary ethnicities of patients were Dutch, Puerto Rican, and Brazilian listed in Table 3, their heterozygous relatives were not identified to exhibit any symptoms of DIRA shown in Table 6. These cytogenetic abnormalities are first generation homozygous mutations and have been characterized in isolated geographical regions. The allele frequencies of the founder mutations in Puerto Rico (Arecibo) and Newfoundland have been estimated by Reddy *et al.* [17] and Aksentijevich *et al.* [21] to be 1.3% and 0.2%, respectively. In such isolated geographic regions, genetic counseling and prenatal screening is recommended for identification.

Recent studies such as Al-Herz *et al.* [26] demonstrate that consanguineous marriages increase the risk of autoimmune diseases in offspring. However, in this study, shown in Table 4, patients were primarily born to non-consanguineous parents. Due to the limited sample size of this review, further studies are required to precisely determine the correlation of consanguinity with DIRA.

In multiple studies, such as Kuemmerle-Deschner *et al.* [8] and Minkis *et al.* [12], DIRA patients were first diagnosed with pustular psoriasis based on skin biopsy and clinical presentation. However, genome-wide sequencing identified mutations in the *IL1RN* gene and the diagnosis of DIRA. Across all studies, Sanger sequencing, SNP array, PCR, *In silico* modeling, and Next-Generation Sequencing were utilized to identify DIRA to accurately differentiate DIRA from other similar systemic autoinflammatory disorders, such as chronic nonbacterial osteomyelitis. Thus, molecular diagnosis with the following genes has been incorporated: *IL1RN*, *MEFV*, *MVK*, *TNFRSF1A*, *NLRP12*, *NLRP3*, *NOD2*, *LPIN2*, *PSMB8*, *PSTPIP1*, provides a rapid and effective genetic screening for early treatment as the delayed treatment can cause major complications such as severe osteomyelitis.

One of the limitations of this study is a lack of clinical trials and animal models. Given the nature of DIRA as an ultra-rare disorder, clinical trials with enough participants would be very challenging. Randomized animal trials could be utilized to solve this problem for the better evaluation of the effectiveness of Anakinra as compared to multiple interventions.

From this review, we obtained more evidence on the effectiveness of Anakinra therapy for the treatment of DIRA. With a dose of 2-3 mg/kg/day Anakinra, complete remission of DIRA is possible. Although most patients have reported no side effects of Anakinra, some patients have reported adverse effects from Anakinra. This could be attributed to the different genetic predisposition of each individual patient. With proper desensitization to Anakinra with diphenhydramine, improvement of treatment and full clinical remission of DIRA can be reached.

## 5. Conclusions

DIRA is a rare autoinflammatory disorder with early onset (1-8 weeks) and poor prognosis (systemic inflammation, mortality, etc). Due to its similarity to other common heterozygous autoinflammatory disorders, it has been difficult to diagnose DIRA. In this review, we evaluated the efficacy of Anakinra in the treatment of DIRA and reported statistical analyses of laboratory data from the selected studies. The results indicated that most patients had no adverse effects to Anakinra. In addition, we also identified a decrease in acute phase reactants and an increase in hemoglobin levels from these laboratory data. In summary, our study further confirms that complete remission of DIRA is possible through Anakinra therapy with minimal or no side effects.

**Supplementary Materials:** The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table S1: Supplementary Data.

**Author Contributions:** Conceptualization, K.P., J.P. and J.L.; methodology, K.P.; software, J.P.; validation, K.P., J.P. and J.L.; formal analysis, K.P. and J.P.; investigation, K.P. and J.P.; resources, K.P. and J.P.; data curation, K.P. and J.P.; writing—original draft preparation, K.P. and J.P.; writing—review and editing, K.P., J.P. and J.L.; visualization, K.P., J.P. and J.L.; supervision, J.L.; project administration, K.P., J.P. and J.L.; funding acquisition, J.L. All authors have read and agreed to the published version of the manuscript.

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