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Effectiveness and adverse effects of anakinra in treatment of rheumatoid arthritis: a systematic review

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Abstract. – OBJECTIVE: Rheumatoid arthritis (RA) can be described as a chronic, inflammatory, progressive, autoimmune disorder characterized by generalized inflammation of the synovial joints, which hereby triggers the progressive erosion of both cartilage and bone. Anakinra is a recombinant form of human IL-1 receptor antagonist which targets the type I IL-1 receptor. In the present systematic review, we intend to evaluate the effectiveness and adverse effects of interleukin-1 antagonists in the treatment of rheumatoid arthritis.

MATERIALS AND METHODS: The database search was carried out using PubMed (Medline), Web of Science (Clarivate), Embase, Scopus, and Cochrane Library for the existing studies. A total of 3912 relevant articles were identified as per the search strategy. Out of them, 854 duplicate records and further 3024 records were excluded after going through their titles and abstracts. Further, out of 42 articles left, we excluded 32 more articles matching our inclusion criteria and excluding the reviews and case studies. Finally, we included 10 relevant studies that focused on both the effectiveness and adverse effects of interleukin-1 antagonists during the treatment of adult patients with rheumatoid arthritis in the present analysis. Nine out of 10 included studies are randomized trials (RCT) except for 1 study, which was an extension study.

RESULTS: The results showed an ACR20 response at week 12 and were the most common primary outcome measure in the present review. Various secondary outcome measures studied were changed from baseline at week 24 in individual ACR components. ACR50 and ACR70 responses at subsequent weeks (12 and 24), ESR components, HAQ score, CRP levels, and ESR. Notably, more improvement was observed with anakinra in comparison to placebo for achieving ACR50 and ACR70 responses at 24 weeks. Premature withdrawal of participants was observed in almost all the studies. Adverse drug reactions were attributed to be the most common reason followed by loss of efficacy for withdrawal of patients from the treatment. The infectious episode was another common adverse effect observed in both anakinra and placebo groups. Some malignancies were also documented in the included researches of this systematic analysis. We observed a lower overall incidence of malignancies for the studies screened compared with that of the general population.

CONCLUSIONS: This review demonstrated that anakinra is safe, effective, and well-tolerated, with no significant difference in adverse effects compared to placebo in rheumatoid arthritis patients.

Key Words:
Interleukin-1 antagonist, Anakinra, Efficacy, Adverse effects.

Introduction

Rheumatoid arthritis (RA) can be described as a chronic, inflammatory, progressive, autoimmune disease illustrated as generalized inflammation of the synovial joints, which hereby triggers the progressive erosion of both cartilage and bone. The clinical course of the disease may range from a self-limiting disease to progressive disease with a chronic course and leading to serious joint destruction and structural deformities[1].

Although the causative factors of RA are still uncertain, it is thought to be an autoimmune disease with multiple associated genetic and exogenous factors associated with inflammatory processes. Both innate and adaptive immunity are involved, and macrophages and T-cells play an important role in its pathogenesis. The initiation starts with CD4+ T lymphocytes targeting the arthritogenic antigens within the joints, which in turn stimulates inflammatory cells along with synovial fibroblasts. Chemical mediators like cytokines and chemokines play an important role in modulating the environment within the synovium. In full-blown RA cases, the synovial tissue

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is congested with numerous inflammatory cell types, which release matrix metalloproteinases (MMPs), leading to erosion and degradation of cartilage and bone[2,3].

Untreated RA cases progress towards irreversible joint damage within a short period of time. Treatment goals for RA primarily focus on reducing joint damage, maintain function, and avoid disability. Therefore, in order to manage such patients effectively, a multidisciplinary approach has been suggested according to the American College of Rheumatology (ACR) guidelines. The role of IL-1 produced by the inflammatory cells like monocytes and macrophages has been well allocated in RA patients[4].

Anakinra, also known as an interleukin-1 receptor antagonist, functions by blocking the inflammatory protein interleukin-1 by targeting the type I IL-1 receptor. Anakinra is an approved and recommended drug given to adult patients with active RA. It can be self-administered through subcutaneous injection in a recommended dose of 100mg/d. It can be used alone or in combination with other RA-related drugs like methotrexate and other concomitant drugs. Previous animal studies have demonstrated decreased inflammatory episodes leading to decreased destruction of joints and cartilage[5].

In the present systematic review, we intend to evaluate the effectiveness and adverse effects of interleukin-1 antagonists in the treatment of rheumatoid arthritis.

Materials and Methods

Search Selection Strategy

In this systematic review, we followed the guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We focused on all the details related to the search methodology, which included the search databases and inclusion criteria. The database search was carried out using PubMed (Medline), Web of Science (Clarivate), Embase, Scopus, and Cochrane Library for the studies existing from the initial records till June 2021 for the clinical trials. This intended search was conducted by two independent reviewers, keeping in observation the structured format of this systematic analysis. Our search included keywords like "interleukin-1 antagonist", "rheumatoid arthritis", 'interleukin-1 receptor antagonist", "IL-1Ra", "interleukin-1 receptor protein", "Kineret" and "Anakinra".

Study Design

In this systematic review, we included Randomized-Controlled Trials (RCT) on adult RA patients using IL-1Ra as a single drug or in combination and primarily focused on the efficacy and side effects of the above-stated intervention. Placebo or other used medications were considered as comparators within the reviewed RCTs.

Eligibility/Inclusion Criteria

In this review, we included all published studies from the last 20 years, i.e., ranging from the year 2001 to the year 2021 (search was conducted on 19/7/2021). Studies published only in English language and published in academic peer-reviewed journals were included. Following the PICOS criteria (population, intervention, comparator, outcomes, study design), the study population and intervention included diagnosed RA patients who were under RCT with using IL-1Ra as a single drug or in combination. Placebo or other used medications were considered as a comparator. Primary outcomes measures of efficacy were the American College of Rheumatology 20% improvement (ACR20) response while adverse drug reactions and treatment-related discontinuation and withdrawals were taken as primary outcomes for safety measures. The secondary outcome measures were evaluated using the ACR50 (50% improvement) and ACR70 (70% improvement), patients Disease Activity Score (DAS or DAS 28), Visual Analog Scale (VAS) scores, Stanford Health Assessment Questionnaire (HAQ) scores, C-reactive protein (CRP) and ESR.

Exclusion Criteria

We excluded all the studies published in a language other than English. Furthermore, studies that used intervention and treatment methods other than the desired one were also excluded from this review.

Study Selection and Processing

All the studies along with the title and abstract were screened for their inclusion in the study by two independent researchers and were shortlisted. We attempted to obtain full-text articles for all these shortlisted studies, and based on the eligibility criteria, studies were finally selected. Any discrepancy related to article selection between the two initial reviewers was sorted through mutual agreement by a third reviewer. For this review, no ethical clearance from the Institutional Ethical Committee was required, as all the obtained data

were extracted from studies that had already been published earlier. We did not receive any outside funding for the execution of this study as well.

The "PRISMA flow chart" was prepared and presented in Figure 1 which clearly represents the screening and selection process of this review.

Data Assessment

The data was carefully and manually extracted from the included studies using a standardized data extraction method. The following information was gathered: authors and year of study, study design, study groups, duration of the study, outcome measures, drug profile of patients, efficacy and adverse effects, and final patient outcome.

Results

After the database search by the reviewers, on the whole, 3912 relevant articles were identified as per the search strategy. Out of them, 854 duplicate records were removed from the search. Among the remaining records, 3024 records were further excluded after going through their titles and abstracts. Further, out of 42 articles left, we excluded 32 more articles matching our inclusion criteria and excluding the reviews and case studies. Finally, we included 10 relevant studies that focused on both the effectiveness and adverse effects of interleukin-1 antagonists during the treatment of adult patients with rheumatoid arthritis in the present analysis. All the included randomized controlled trials were published between the year 2001-2021. Nine out of 10 included studies are randomized trials (RCT)[6-10,12-15], except 1 study which was an extension study[11]. **Supplementary Table I** summarizes the included studies and its baseline characteristics, while **Supplementary Table II** sums up the drug profile of the patients within included studies.

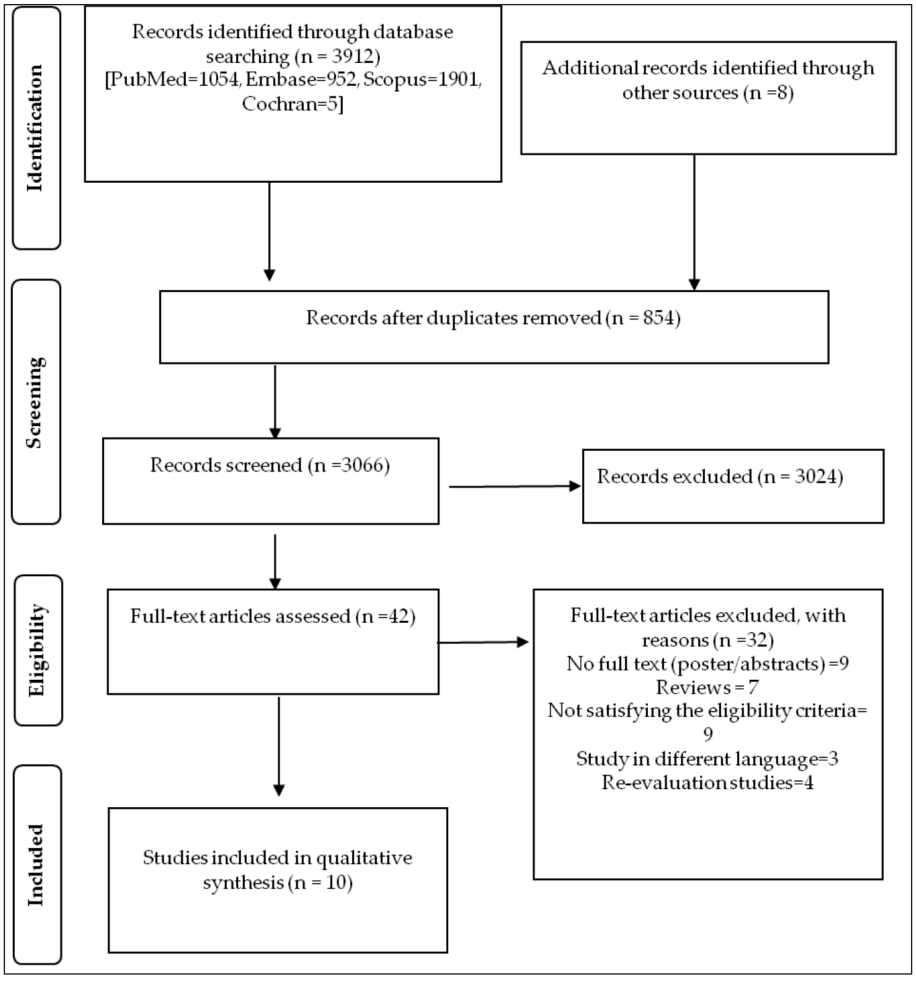

Figure 1. The PRISMA flow chart of the systematic review.

All the included controlled trials included adult patients with female predominance. The follow-up period varied among the studies: 6 trials followed patients for a duration of 24 weeks[7-11,14] among which Cohen 2002 initially followed for 12 weeks, which was extended up to a 24-week study period[7]. Two studies by Fleischman[12] in 2006 and Le Loët[13] in 2008 followed participants up to 3 years, while one trial by Nuki et al[6] in 2002 followed up to 18 months and another one by Ruscitti et al[15] for 6 months.

In most of the studies, placebo was taken as a control in comparison to anakinra[6,8,12-14]. Rest others were as follows: Cohen[7,10] in 2002 and 2004 compared subgroups of anakinra with MTX and placebo with MTX. Further, Genovese et al[11] compared anakinra with etanercept weekly, anakinra with etanercept biweekly and MTX, and placebo with etanercept biweekly and MTX. Le Loët et al[13] compared anakinra and MTX, anakinra and SSZ, and anakinra with HCQ, while a recent study by Ruscitti et al[15] compared the Anakinra group and TNF group.

Efficacy: Primary Outcome Measure

ACR20 response at week 12 was the most common primary outcome measure in the present review[6-8,10,11,14]. Nuki et al[6] mentioned patients with 51% and 46% ACR20 response after 24 and 48 weeks of treatment, respectively. A similar response was also reported by Cohen et al[7]. They demonstrated ACR20 dose-related response rate of 1.0-mg/kg was 46%, and at 2.0-mg/kg group was 38%.

Further at week 12, anakinra plus MTX groups reported a statistically considerable dose-response relationship in comparison to the placebo plus MTX group. Also, the ACR20 responses observed by 24 weeks were steady in relation to the response observed by 12 weeks. Cohen et al[9] demonstrated ACR20 response at four weeks was twice high in anakinra group. Bresnihan et al[11] mentioned 43% of their study patients on 150 mg/day anakinra dose experienced an ACR 20 response at 24 weeks using 30 mg/day and 75 mg/day anakinra (39% and 34%, respectively). In contrast, Genovese et al[10] studies reported no evidence of an added treatment benefit with etanercept and anakinra combination.

Only two studies by Ruscitti et al[15] and Bao et al[14] reported the DAS28 scores (regarded as a coprimary outcome of this review). Ruscitti et al[15] mentioned DAS28 scores progressively decreased in both the groups (Anakinra group *vs.* TNF group), and this reduction was persistent for at least 6 months. While Bao et al[14] reported a decline in the mean DAS28 score in relation to the anakinra-treated patients when compared to the placebo group.

Efficacy: Secondary Outcome Measure

Various secondary outcome measures studied were as follows: change in individual ACR components after 24 weeks, both ACR50 and ACR70 responses subsequently at 12 and 24 weeks, ESR components, HAQ score, CRP levels, and ESR. Notable progress was observed using anakinra at a dose ranging from 50 to 150 mg/ in comparison to placebo for achieving ACR50 and ACR70 responses at 24 weeks. Nuki et al[6] mentioned ACR50 and ACR70 response in 18% and 3% cases, respectively, on anakinra, by 48 weeks. Bao et al[14] observed an ACR50 response of 38% and an ACR70 response 17% within the Anakinra group. Not any of the patients taking MTX alone attained ACR50 or ACR 70 improvement.

Only two studies focused on EULAR response[13,15], while radiographic evaluation along with ACR 20 was adapted in only one study[11]. At 24 weeks, among patients using anakinra (50 to 150 mg/day), a noticeable improvement was observed in both VAS and HAQ scores as well. Anti-anakinra neutralizing antibodies were observed in 5 of the studies included in this review[7,8,10,12,14]. Fleischmann et al[8] stated that 0.8% of their cases seroconverted and produced neutralizing antibodies, which were detectable either at 3 months or 6 months during follow-ups (**Supplementary Table III**).

Safety and Adverse Effects

The various observed adverse events documented in the included studies are tabulated in **Supplementary Table IV.** Premature withdrawal of participants was observed in almost all the studies except for Genovese et al[10]. Patients treated with anakinra showed a withdrawal of a minimum of 3 cases[14] in contrast to a maximum of 389 cases[12] when compared to placebo groups. No noteworthy difference was observed in the overall discontinuation of ongoing treatment among those undertaking anakinra and other study groups. Likewise, even the difference in treatment withdrawal observed after 24 weeks and after 48 weeks was also insignificant. Adverse drug reactions were attributed to be the most common reason followed by loss of efficacy for withdrawal of patients from the treatment. Furthermore,

among adverse drug reactions, injection site reaction was the most encountered cause. No major difference was seen between the total number of withdrawals among the anakinra and placebo (without MTX) subgroups. Similarly, no variation was detected in the number of discontinuations observed for the anakinra and MTX subgroup *vs.* the placebo and MTX subgroup.

Among the Injection Site Reactions (ISR), pain, erythema, pruritus, and rash of mild to moderate severity were observed in 3 studies[6-8], and an urticarial lesion was reported by only one included study by Ruscitti et al[15]. Cohen et al[9] mentioned that the first episode of ISR was observed during the first month of treatment with anakinra only. Worsening or flaring up of RA symptoms due to anakinra was reported by four reviewed studies[6-8,12,13]. Fleischmann et al[11] and Le Loët et al[13] documented 67.80 events/100 patient-years of flaring of RA events and incidence of 4.6% cases respectively related to anakinra treatment in their research. Further, in relation to serious adverse events due to treatment with anakinra, Nuki et al[6] reported hematological changes like decreased blood cell counts, granulocytopenia, and eosinophilia during the first six months of study only. Genovese et al[10] observed 2 cases of neutropenia with the combination therapy of anakinra daily + etanercept. Headache and abdominal pain were reported by Cohen et al[9] and Le Loët et al[13], while Interstitial lung disease accompanied in one patient by pulmonary fibrosis was documented by Cohen et al[9]. Fleischmann et al[8] mentioned 7.7% of adverse events in the anakinra treated group in comparison to 7.8% cases within the placebo group.

The infectious episode was another common adverse effect observed in both anakinra and placebo groups. Overall, the total number of infectious episodes was not appreciably different between the anakinra group (30-150 mg/day) and placebo group patients after 24 weeks in the reviewed studies as reported by Nuki et al[6] and Cohen et al[7] in their studies. Among the infectious episodes, upper respiratory system infections were commonly seen among the studied researches. Others included sinusitis, fractures, urinary tract infections, diarrhea, and pneumonia.

Furthermore, Fleischmann et al[8] reported episodes of serious infections in both the Anakinra group (2.1%) and placebo group (0.4%). While Genovese et al[10] observed 3.7–7.4% cases with episodes of serious infections for combination therapy with anakinra + etanercept, whereas no case was documented with etanercept alone. Talking in relation to specifically anakinra, both pneumonia and cellulitis have been reported by Fleischmann et al[8] and herpes zoster, pneumonitis, and pyelonephritis by Genovese et al[10] in their specific research. In one of our included research, serious episodes of sepsis were seen with 0.10, 0.28, and 0.35 events/100 patient-years for the 0 to 1 year, 0 to 2 years, and 0-to-3-year intervals[12].

Further, some malignancies were also documented in the included research of this systematic analysis. We observed a lower overall incidence of malignancies for the studies screened compared with that of the general population. Cohen et al[7] reported two malignancies, namely large-cell carcinoma of the lung and breast cancer, although the authors mentioned that they were not related to the drug studied. Fleischmann et al[8] also reported 4 malignancies from their cohort, namely diffuse metastatic melanoma, poorly differentiated adenocarcinoma of the caecum, uterine carcinoma, and basal cell carcinoma, but they were also of the same opinion that they were not related to the drug studied. In yet another study, 1 case of malignancy associated with the combination group was reported by Genovese et al[10]. Fleischmann et al[13] mentioned 1.2 events per 100 patient-years of malignancies, while Loët et al[14] reported 1 case of lymphoma in the MTX group and mentioned it to be possibly related to the anakinra treatment group.

Mortality was presented by 4 studies namely Nuki et al[6], Fleischman[8], Fleischman[13] and Loët et al[14]. Overall, no noteworthy difference was observed in the number of deaths related to anakinra (30 to 150 mg/day) and placebo groups.

Discussion

Anakinra is presently FDA approved and is used for the treatment of rheumatoid arthritis patients. The present review aimed at systematically analyzing the effectiveness and adverse events of interleukin-1 antagonists in the treatment of rheumatoid arthritis from ten RCTs of anakinra, involving a total of 6012 patients. Our data depicted that at 24 weeks of therapy with anakinra (30 to 150 mg daily), there was a noteworthy improvement among patients in achieving ACR20 against the placebo. Additional efficacy estimation outcomes included ACR50 and 70, HAQ, VAS, ESR, EULAR response score, and sharp radiographic scores. An improvement in the above-mentioned efficacy data using anakinra was also observed

against the placebo or methotrexate-related treatment modalities.

Safety and adverse effects for anakinra have been studied previously by many authors by assessing long-term treatment plans among large and diverse cohorts with rheumatoid arthritis. The included studies in this current review focused on a wide range of patients with varying degrees of disease severity along with associated comorbid conditions and considered the use of concomitant drugs in RA treatment. Rheumatoid arthritis is generally associated with an increased risk of infections, mainly of bones and joints, skin, and even the upper respiratory tract. This has been attributed either due to the basic disease mechanism only or maybe because of the treatment leading to a decrease in immune function, or possibly both.

Our findings revealed that safety data for anakinra was similar to that of placebo groups in terms of patient treatment withdrawals, mortality, adverse effects, and various infections. Studies have concluded that anakinra has been well-tolerated at various doses (30, 75, and 150 mg/day) from 12 to 24 weeks, till a maximum of 76 weeks. Injection site reactions were observed to be the major widespread adverse event during the first 24 weeks of treatment, although the majority of these reactions ranged from mild to moderate and were transient. This considerably increased in patients under treatment with anakinra against the placebo group. Studies with the extension phase have reported some other adverse events leading to treatment withdrawal by the patients. On further analysis, the overall figures of adverse events were noticeably increased within the anakinra+MTX group, hereby questioning the use of both these medications together. Various infectious episodes were another common adverse effect observed in both anakinra and placebo groups. Overall, the total number of infectious episodes was not appreciably different between the anakinra group (30-150 mg/day) and placebo group patients after 24 weeks in the reviewed studies. Further, we observed that those patients who had a prior history of infections like pneumonia or some other predisposing pulmonary infections presented with a slightly augmented risk of developing adverse infectious episodes associated with the respiratory system when being treated with anakinra alone or with MTX and thus should be monitored suitably. The reason behind the increased risk of adverse infections in rheumatoid arthritis cases and undergoing anakinra treatment has not been completely understood. The possible explanation might be an immune suppression caused due to inhibition of IL1. The findings of our review support the safety of anakinra when used over extended periods, although alongside it also recommends continuous monitoring of patients under high risk for infections like those with active infections and those undergoing concomitant corticosteroid treatment.

In the present review, malignancy rates were comparatively quiet less, with no observed noticeable difference between the anakinra treated group and placebo groups. Authors from the included studies have revealed that due to various associated risk factors and the use of confounding medications, an association of anakinra treatment with such malignancies is not yet established. However, evaluation of the risk of malignancy or other rare serious adverse events in association with anakinra could not be ruled out.

The radiographic evaluation also revealed that treatment with anakinra alone or in combination with MTX led to a decreased radiographic progression of the disease in relation to the joint space reduction and increase in erosions.

Mertens et al[16] in their review analyzed five randomized clinical trials related to anakinra use in RA patients. They mentioned a considerable improvement of about a 15% increase in the number of cases achieving ACR20 with anakinra in comparison to placebo. Safety outcomes were almost the same between the anakinra group and placebo. A high incidence of Injection site reactions was also observed treated within anakinra treated group, although the incidence of serious infections was not statistically different between both the groups. In another review, Nikfar et al[17] mentioned that anakinra appreciably improves ACR20, HAQ, DAS28 scores, and ESR at 48 weeks. They confirmed no appreciable difference in relation to safety and harmful events between anakinra and placebo groups. Conversely, anakinra presented with an increased number of treatment-related withdrawals.

This present systematic review has its own limitations; firstly, there were a limited number of studies fulfilling our inclusion criteria, and among them, we observed a wide variability in relation to the specific outcomes measured, which limited the strength of our systematic review. Secondly, we were not able to evaluate specific dose-related differences between individual doses of anakinra due to the limited number of studies. Lastly, the efficacy and adverse effect results were assessed only at specific points in the studies.

Conclusions

This review demonstrated that anakinra is safe, effective, and well-tolerated, with no significant difference in adverse effects compared to placebo in rheumatoid arthritis patients. It can be used as a monotherapy or in combination with other anti rheumatoid arthritis drugs. The combination of anakinra and MTX also proved to be safe and well-tolerated and can be used to achieve greater clinical benefit than MTX alone.

Conflicts of Interest

The authors declare no conflicts of interest.

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