

Treatment of Rheumatoid Arthritis With Anakinra: A Systematic Review

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Objective: To perform a systematic review for evaluating efficacy and safety of anakinra in the treatment of rheumatoid arthritis (RA).

Material and method: The MedLine, Embase, and Cochrane Library databases were searched from January 2000 to February 2006 by using a high sensitive search that included every randomised controlled trial (RCTs) or controlled trial (CTs) that evaluated either efficacy or safety of Anakinra for the treatment of RA.

Results: The search identified four relevant studies to evaluate efficacy. Patients treated with anakinra achieved significantly better clinical responses than those treated with placebo. Anakinra combined with methotrexate provided significantly greater clinical benefit than methotrexate alone. Combination therapy with etanercept and anakinra provides no added benefit and an increased safety risk compared with etanercept alone.

Results from a large, placebo-controlled safety study demonstrate that anakinra is safe and well tolerated. The most common adverse effect was a mild local inflammation over the puncture area.

Conclusions: This review confirmed both the efficacy and the safety of anakinra in the short term for the treatment of RA. Anakinra provides adequate clinical responses without major safety problems. This systematic review does not allow us to conclude on Anakinra responses in the long term.

Key words: Anakinra. Interleukin-1 receptor antagonist. Rheumatoid arthritis. Pharmacologic treatment. Systematic review.

Tratamiento de la artritis reumatoide con anakinra: revisión sistemática

Objetivo: Evaluar la eficacia y la seguridad del anakinra en el tratamiento de la artritis reumatoide (AR) mediante una revisión sistemática de la evidencia científica.

Material y método: Búsqueda en MEDLINE, EMBASE y el registro de estudios Cochrane desde el año 2000 hasta febrero de 2006 según una estrategia prediseñada de perfil sensible que incluyó todos los estudios controlados y aleatorizados (ECA) que evaluaron la eficacia o la seguridad del anakinra en el tratamiento de la AR.

Resultados: Se incluyó 4 estudios para evaluar la eficacia del anakinra y un estudio para evaluar su seguridad. En todas las mediciones de eficacia analizadas, se observó un efecto beneficioso del anakinra respecto a placebo y del anakinra + metotrexato (MTX) respecto a la monoterapia con MTX. La combinación de anakinra y etanercept no fue más eficaz que el etanercept en monoterapia y, en cambio, incrementó la incidencia de infecciones graves. La tasa de suspensiones por reacciones adversas al anakinra fue discretamente superior a la del placebo, si bien se puede considerar que el anakinra es un fármaco bien tolerado y seguro a corto plazo cuyo efecto adverso más frecuente es la inflamación local en el punto de inyección.

Conclusiones: El anakinra es una alternativa eficaz y segura para tratar a corto plazo la AR. Esta revisión no permite extraer conclusiones sobre la eficacia y la seguridad de este fármaco a largo plazo.

Palabras clave: Anakinra. Antagonista del receptor de la interleucina 1. Artritis reumatoide. Tratamiento farmacológico. Revisión sistemática.

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Introduction

Biologic therapies have radically modified the spectrum of possible therapeutics in rheumatoid arthritis (RA), and have noticeably increased the efficacy without apparently

increasing toxicity. The antagonist of the receptor for interleukin 1 (IL-1Ra) is a glycoprotein that is naturally secreted by monocytes and tissue macrophages that selectively binds to the receptor of IL-1 and modulates its activity. The blockage of IL-1 leads to the inhibition of inflammation and of joint osteoclast activation in animal models of RA. Human recombinant IL-1Ra is known as anakinra and has been employed in the treatment of RA since 1998. The objective of this study is to analyze the scientific evidence on the efficacy and security of anakinra in the treatment of RA with the intention of establishing its place in the current panorama of treatment of this disease.

Material and Method

A MEDLINE search was done from 1999 to February 2006 and in EMBASE and the Cochrane study registry from the year 2000 to February 2006. A predesigned strategy was employed in the search for high sensitivity descriptors. Only the studies with the highest quality were considered for analysis; therefore, all of the controlled and randomized trials (CRT) in which the efficacy or security of anakinra was compared (in monotherapy or in combination) with placebo or other disease modifying drugs (DMARD) for RA were considered. Unmasked studies were included and, in consequence, open studies or open extensions of the previously studied CRT. We also excluded redundant studies or studies not published in English (Table 1).

All of the participants analyzed should have an RA of more than 6 months and less than 12 years. As an intervention group we considered: anakinra with or without DMARD (classic or biologic). The control group could be placebo or DMARD (classic or biologic). To analyze the clinical efficacy we employed the ACR criteria (compound index, ACR 20, ACR 50, ACR 70) or the Paulus criteria. To analyze the radiologic efficacy we employed the Larsen criteria. Anakinra security was determined through the total suspension rate recount due to adverse events, serious drug reactions, infections, and death. The results of trial efficacy were combined through random effect models to calculate the difference of means of quantitative variables (MD), or the risk ratio for the qualitative variables (RR), with their 95% confidence intervals (CI). In studies that employed different doses of Anakinra, the efficacy analysis was done using the most similar dose to the one employed in daily clinical practice (100 mg/day). Methodologic quality was evaluated by a random designation, an adequate masking of the designation, the degree of masking, the use of intention-to-treat analysis, and the description of treatment dropouts. To evaluate the quality of each study we employed the instrument

TABLE 1. Excluded Studies and Causes for Exclusion*

Study	Cause for Exclusion
Bresnihan et al, ² 2004	Open extension of CRT of Bresnihan, 1998
Campion et al, ³ 1996	Not CRT
Clark et al, ⁴ 2004	Not CRT. Systematic review that includes CRT independently and evaluated in this study and 1 unpublished pilot study
Cohen et al, ⁸ 2003	Same CRT as Cohen 2002, with another outcome measure
Cohen et al, ⁷ 2004	Not CRT. Metaanalysis with an outcome measure that is not related to anakinra efficacy or security
Dayer et al, ⁹ 2002	Not CRT. Editorial comment
Fleischmann et al, ¹² 2006	Open extension of CRT of Fleischmann, 2003
Fleischmann, ¹⁰ 2003	Not CRT
Jiang et al, ¹⁴ 2000	Open extension of CRT of Bresnihan, 1998
Nuki et al, ¹⁵ 2002	52 week open extension of CRT of Bresnihan, 1998
Schiff et al, ¹⁶ 2004	Same CRT as Fleischmann, 2003
Tesser et al, ¹⁷ 2004	Extension of CRT of Fleischmann, 2003

*CRT indicates controlled randomized trial.

validated by Jadad (Jadad, 1996), whose score varies between 0 (worse) and 5 (best).

Results

The search identified 17 potentially relevant studies; 5 CRT complied with the inclusion criteria (Bresnihan, 1998; Cohen, 2002; Fleischmann, 2003; Cohen, 2004, and Genovese, 2004) (Table 2). In the oldest one, the efficacy of different doses of anakinra when compared to placebo was analyzed (Bresnihan, 1998). In another 3, the efficacy of the combination of anakinra and methotrexate (MTX) (Cohen, 2002, and Cohen, 2004), or etanercept (Genovese, 2004) was evaluated. Only 1 CRT regarding security was found (Fleischmann, 2003). All of them had the same duration and where evaluated upon conclusion (24 weeks). Only 1 included data on radiographic efficacy (Bresnihan, 1998). All of the patients had established RA (over 3 years), had been already treated with DMARD (except biologics), and all of them allowed the concomitant use of corticosteroids. In the efficacy CRT, the outcome criteria proposed by ACR were employed, with ACR 20 being the main outcome measure

TABLE 2. Characteristics of Included Studies*

Study	Methods	Participants	Intervention	Outcome	Conclusions
Bresnihan et al, ¹ 1998	CRT; duration: 24 weeks; sample size: Ak 30: n=119, Ak 75: n=116, Ak 150: n=116 and Pl: n=121	n=472 established RA; mean age, 53 years; 75% women; previous DMARD and steroids: permitted	Ak 30 mg sc, Ak 75 mg sc, Ak 150 mg sc	Clinical efficacy: compound ACR score, Paulus criteria; radiologic efficacy: Larsen method; security: adverse event recount and analytical alterations	Conclusion of study: Ak is efficacious and safe for, treatment of a large cohort of patients with active and severe RA; quality of evidence: Jadad 3, inadequately or poorly described randomization
Cohen et al, ⁶ 2004	CRT: duration: 24 weeks; sample size: Ak + MTX, n=250, Pl + MTX, n=251	n=501 established RA treated for at least 6 consecutive months with MTX; mean age, 56 years; 77% women; previous DMARD: not specified; use of corticosteroids permitted	Ak 100 mg sc + MTX 10-25 mg/week po	Clinical efficacy: ACR 20	Study conclusion: Ak + MTX is an effective and safe treatment for patients with established RA and insufficient response to MTX; quality of the study: Jadad 3, inadequate or poorly described randomization (financed by AMGEN, Thounsy Oaks)
Cohen et al, ⁵ 2002	CRT: duration: 24 weeks; sample size: Ak 0.04 + MTX, n=63; Ak 0.1 + MTX, n=74; Ak 0.4 + MTX, n=77; Ak 1 + MTX, n=59; Ak 2 + MTX, n=72; Pl + MTX, n=74	n=419 established RA treated during at least 6 consecutive months with MTX; mean age, 52.4 years; 73.5% women; 78% FR + DMARD and corticosteroids allowed	Ak 0.04 + MTX; Ak 0.1 + MTX; Ak 0.4 + MTX; Ak 1 + MTX; Ak 2 + MTX; Pl + MTX (Ak: mg/kg/day; MTX 10-25 mg/week)	Clinical efficacy: ACR 20	Study conclusion: Ak + MTX is safe, well tolerated and allows for a larger clinical benefit than MTX monotherapy; quality of evidence: Jadad 3, inadequate or poorly described randomization (financed by AMGEN Inc.; CRT initially designed for 12 weeks)
Fleischmann et al, ¹¹ 2003	CRT: duration: 24 weeks; sample size: Ak, n=1116; Pl, n=283	n=1414, established RA; stable doses of DMARD at least 8 previous weeks; mean age, 55 years; 74.7% women; "real world" conditions: DMARD permitted (except biologics), NSAID and corticosteroids	Ak 100 mg/day sc	Security: adverse event recount, serious medication reactions, infections, and suspensions due to toxicity or death	Conclusions of the study: Ak 100 mg/day is safe and well tolerated by patients with comorbidities or polymedication; slight tendency to serious infections though not by opportunistic germs; quality of evidence: Jadad 5 (financed by AMGEN Inc.)
Genovese et al, ¹³ 2004	CRT: duration: 24 weeks; sample size: ETCPT 2 times/week + Pl, n=80; ETCPT 1 times/week + Ak, n=81; ETCPT twice/week + Ak, n=81	n=242 established RA treated with MTX >16 weeks; mean age, 54.6 years; 77.3% women; 69% FR + previous DMARD permitted; excluded if previously treated with biologics	Ak + ETCPT once/week; Ak + ETCPT 2 times/week (ETCPT 1, 25 mg sc; Ak, 100 mg/day sc)	Clinical efficacy: ACR 20, 50, 70; DAS; security: recount of adverse events	Study conclusion: Ak does not add benefit to ETCPT and does increase the risk of serious infection. Combinations are not recommended; quality of evidence: Jadad 5 (financed by AMGEN Inc.)

*NSAID indicates non steroidal anti-inflammatory drugs; Ak, anakinra; CRT, multicenter study, controlled, randomized and double blind; ETCPT, etanercept; MTX, methotrexate; Pl, placebo.

in most of them. The only CRT that provided radiologic data employed the Larsen method. Four of the 5 CRT where financed by the same pharmaceutical company: AMGEN Inc.

Efficacy Results

Anakinra as monotherapy. The efficacy of anakinra in monotherapy was evaluated in 116 patients with established severe RA (Bresnham, 1998). The efficacy analysis favors anakinra with respect to placebo, both in the compound ACR score (RR=0.61; 95% CI, 0.42-0.88) as well as with the Paulus criteria (RR=0.48; 95% CI, 0.32-0.72). Radiologically, the progression of disease mean is lower in patients treated with anakinra than with placebo (MD=-2.4; 95% CI, -5.25 to 0.45). Therefore, anakinra is a clinically and radiologically effective drug for the treatment of RA. In these patients there are no significant differences in the rates of treatment suspension due to adverse events with respect to placebo.

Anakinra + MTX. The clinically efficacy of anakinra combined with methotrexate was evaluated in 296 patients with established RA (Cohen, 2002; Cohen, 2004). A metaanalysis was not done because the doses of anakinra from both trials were different. For the efficacy analysis of the Cohen, 2002 CRT, a dose of anakinra which was most approximate to the one employed in daily clinical practice was chosen and its effect analyzed in the total number of patients by an intention to treat analysis at the end of the study.

In that CRT, treatment with anakinra 2 mg/kg/day plus MTX 10-25 mg/week (n=46) is more effective than MTX monotherapy (ACR 20, RR=0.66; 95% CI, 0.34-1.27). With respect to dropouts due to adverse events, 11 took place in the combined group, and 3 in the MTX group, with a local reaction at the site of injection of anakinra the most common reason for suspension (n=7). In the Cohen 2004 CRT with anakinra 100 mg/day combined with 10-25 mg/week of MTX (n=250), we also demonstrated a larger efficacy of combined therapy (ACR 20, RR=0.58; 95% CI, 0.43-0.76). Regarding dropouts due to adverse events, the authors described a 14% suspension rate with combined treatment (el 60% due to a local reaction at the injection site) versus 13% with MTX monotherapy. Of the analysis of both studies we can conclude that the combination of anakinra with MTX for 24 weeks is a more effective than MTX monotherapy. This combination, in general was well tolerated and when suspended it is largely due to a local reaction to the injection of anakinra.

Anakinra + etanercept. The clinical efficacy of anakinra when combined with etanercept was evaluated in 81 patients with established RA treated for 24 weeks

(Genovese, 2004). The efficacy analysis favors etanercept (ACR 20, RR=0.91; 95% CI, 0.73-1.15). No dropouts due to adverse events were recorded among patients receiving only etanercept. On the contrary, combined treatment led to a dropout of approximately 8% of cases, and serious infections were the reason for suspension in 2.5% of them. Therefore, anakinra + etanercept is not more efficient than etanercept in monotherapy and, in addition, it significantly increases the risk of serious infection.

Results Regarding Toxicity

Anakinra security was evaluated in the Fleischmann, 2003 CRT. In this study a total of 1116 patients with established RA, comorbidities and concurrent treatments with DMARD and low dose corticosteroids (<10 mg prednisone) were treated with 100 mg/day of subcutaneous anakinra during 24 weeks. The intervention cohort did not present significant differences at baseline with the control cohort. The general rate of suspension due to adverse events was discreetly higher in patients treated with anakinra (RR=0.68; 95% CI, 0.46-1.02). However, no significant differences in the rates of infection, severe toxicity and death were observed. Patients treated with anakinra had a significant increase of local inflammation at the site of injection (RR=0.45; 95% CI, 0.38-0.53). Therefore, the use of anakinra at 100 mg/day was related to the rate of suspension due to adverse events. A significant increase of local inflammation at the site of injection is observed, but generally does not lead to the suspension of treatment.

It must be pointed out that a slight tendency to present serious infections is observed, though not produced by opportunistic microorganisms. In general, anakinra can be considered safe and well tolerated, even in patients with comorbidities or polymedicated.

Discussion

The conclusions of this review allow us to consider anakinra as an effective and safe drug in the short term for the treatment of RA. Nonetheless, it is important to consider some points on the analyzed evidence because, in some way, it can contribute to define in a more precise manner the profile of this drug. In the first place, if one carefully analyzes the evidence that is available on the efficacy of anakinra, one of the conclusions that can be extracted is that the quality of evidence is weakened by execution bias, mainly defects in randomization or masking, and is penalized by a large degree of sponsorship. To this one must add that the trials reviewed barely provide information or this does not show significant differences on strict clinical measurements, such as ACR 50, ACR 70, or the

remission rate, and, therefore, do not answer the question on whether anakinra could be more effective than is demonstrated.

It would have been desirable to complete an efficacy profile for anakinra, by having long-term data with enough quality evidence. The only data available conclude the same clinical efficacy of anakinra after 1 year than after 6 months.¹⁵ This information comes from open extensions of previous CRT and were excluded from this analysis for considering that they provided weak evidence. The therapeutic blocking of IL-1 in animal models of rheumatoid arthritis, beyond a significant improvement of joint inflammation, produced a noticeable and effective inhibition of subchondral damage. The role of anakinra in the prevention of subchondral erosion, regrettably, was not profiled either in this study. The only information available on the radiologic efficacy, with good quantity and quality of evidence, mentions a follow-up of 6 months, too short for an illness that can delay 3 years in presenting subchondral radiologic changes. This notwithstanding, there is long-term radiologic efficacy data available that points out to a better efficacy of anakinra in prolonged treatments than in shorter ones.^{2,14} However, this data unfortunately, was not masked.

Therefore, the results on the clinical efficacy of anakinra, regarding methodological execution, offer a certain degree of vulnerability and, regarding design, point to a drug with a discreet efficacy profile. The available evidence does not allow us to be clear on its long term clinical and radiological efficacy (more than 6 months), which establishes a reasonable doubt on whether this could be a more effective and useful drug than it appears.

Short-term security is well established in a trial that, by its execution, design and sample size, provides firm evidence that profiles anakinra as a safe drug (Fleischmann,¹⁰ 2003). Data on long-term safety of anakinra come from an unmasked extension at 3 years of the previous CRT (Fleischmann et al,¹² 2006). In this follow-up of 1346 patients treated with anakinra 100 mg/day, a good safety profile is confirmed, though with certain reservations. Even when the principal adverse event and motive of dropout is a local injection site reaction (122.26 cases/100 patient-years), a sensible increase in the incidence of serious infections is observed, one that is double than seen in the control cohort.

In summary, the analyzed evidence permits the consideration of anakinra as an alternative for the treatment of RA that, in the short term, has a discreet profile of safety and an acceptable toxicity profile, and that in the long-term could continue to be safe, though the quality of the evidence in this aspect is not enough to make a definitive judgment neither on its security nor its efficacy. The available evidence on the radiological efficacy of anakinra does not permit us to draw conclusions on its possible benefits. The potential clinical interest of

this information should be analyzed in future clinical trials.

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