New advances in interleukin-1 blockade for the treatment of rheumatoid arthritis

Joseph A Markenson
Hospital for Special Surgery, Department of Medicine, Rheumatology, 535 East 70th Street, New York, NY 10021, USA
Tel.: +1 212 606 1261
Fax: +1 212 535 6183
markensonj@hss.edu

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Rheumatoid arthritis is a relatively common systemic inflammatory disease, which has a substantial impact on patient functioning and survival. The etiology of rheumatoid arthritis has not been completely elucidated, but proinflammatory cytokines, such as interleukin-1, have been implicated as important pathogenic players. These cytokines ultimately lead to increased joint cellularity and destruction through immune modulation. The presumed role of interleukin-1 in the pathogenesis of rheumatoid arthritis has lead to the development of interleukin-1 receptor antagonists such as anakinra, which has demonstrated significant efficacy and safety in rheumatoid arthritis clinical trials. Anakinra successfully slows the radiographic progression of joint destruction, reduces disability and improves productivity in patients living with rheumatoid arthritis.

Rheumatoid arthritis (RA) is a chronic and progressive inflammatory disorder that causes marked joint destruction, significant work disability, functional declines and premature mortality. It affects approximately 0.5 to 1% of the population in developed countries, with women being twice as likely as men to be affected [1]. Even in the early stages, RA reduces quality of life, with more than 50% of patients reporting its impact on daily, leisure and social activities [2]. As the disease progresses, work disability becomes increasingly more common, with approximately 40% being disabled after 10 years' follow up [3,4]. Disability is correlated with disease duration, but it shows an even stronger correlation with radiographic measures of joint damage, particularly in patients who have had the disease for at least 5 years [5]. In addition to causing significant morbidity, RA has a substantial economic impact on patients, as well as society. In the USA, total annual costs have been estimated at up to US$32 billion (1998) or more than $20,000 per patient [6]. Direct medical costs, primarily due to hospitalization, account for approximately a third of total costs, whereas indirect costs principally attributed to work disability account for the rest.

Although the exact etiology of RA remains to be fully elucidated, it is generally considered to be an immunologic disorder in which macrophages and T-cells drive chronic joint inflammation and systemic disease manifestations by producing cytokines and other mediators. Cytokines are protein mediators that are involved in many important biological processes, including cell activation, growth and differentiation, inflammation and immune regulation [7]. Under normal conditions, proinflammatory cytokines, notably interleukin (IL)-1, are maintained in balance by several anti-inflammatory cytokines, such as IL-10 and -4 and several natural cytokine inhibitors [7]. Other cytokines may produce either proinflammatory or anti-inflammatory effects depending on the local cytokine environment. However, in the rheumatoid joint, the cytokine balance appears shifted in favor of the proinflammatory cytokines, leading to a state of chronic inflammation [8]. The importance of IL-1 in RA was initially hypothesized based on the abundance of these cytokines in synovial tissue from RA patients [9]. This paper will review recent developments in IL-1 blockade and its effect on clinical outcomes and safety in RA patients.

Molecular pathophysiology of rheumatoid arthritis

The rheumatoid joint is characterized by increased cellularity, particularly in the synovial membrane [10]. During the early stages of RA, this lining layer becomes infiltrated by cells recruited from the blood and increases in thickness from 1-2 to 6-8 cells. These cells consist mostly of activated macrophages, but also include activated fibroblast-like cells, lymphocytes and dendritic cells (DCs). New blood vessel formation in the synovium becomes prominent, with activated endothelial cells lining and lymphoid follicles surrounding the vessels. Joint damage begins when the proliferating synovium or pannus migrates over the cartilage and encroaches into subchondral bone. Proinflammatory cytokines...
play an important role in driving these cellular events. They increase expression of cell-adhesion molecules on endothelial cells, thereby controlling cellular infiltration into the joint as well as interactions between cells. These cytokines activate macrophages and fibroblasts in the synovial membrane to produce additional proinflammatory mediators, including prostaglandin E₂, nitric oxide and other cytokines that contribute to the developing edema and synovial proliferation. They also trigger the release of matrix metalloproteinases and other enzymes that cause cartilage destruction and act on chondrocytes to slow new cartilage matrix synthesis. Finally, proinflammatory cytokines stimulate the differentiation and subsequent activation of osteoclasts, which are responsible for resorption of subchondral bone in RA.

Role of IL-1 in rheumatoid arthritis

The IL-1 family consists of the proinflammatory molecules IL-1α and IL-1β; the naturally occurring IL-1 inhibitor, termed IL-1 receptor antagonist (IL-1Ra); the related family member IL-18; and a range of new family members including IL-1F5 through -1F10 [10,11]. Although they share a common 3D structure, these molecules are produced by separate genes and have distinct amino acid sequences. IL-1α and β are synthesized as 31 kDα precursors, which are subsequently cleaved by cellular proteases into 17 kDα proteins. Whereas IL-1β is released by cells to exert its biological actions on other cells, IL-1α is primarily membrane bound and is thought to have intracrine mode of action. However, in certain disease states, IL-1α may also be found in the circulation. Secretory IL-1Ra is synthesized directly as a 17 kDα protein, but several structural variants that are retained within the cell have been identified [12].

The members of the IL-1 family bind to two different receptors on target cells. Binding of IL-1 to the Type I receptor (IL-1RI) leads to cell activation and expression of the biological effects of this cytokine, whereas binding of IL-1Ra prevents IL-1 from binding and thereby blocks its biological actions. The Type II receptor (IL-1RII) serves as a decoy, in that it has a short intracellular domain and is unable to transduce an intracellular signal following IL-1 binding. The extracellular domains of these receptors are released by cells in soluble forms (sIL-1R), and they serve to buffer the amounts of IL-1 and IL-1Ra that can reach the IL-1RI. Accordingly, the biological actions of IL-1 are influenced by the levels of its natural inhibitors, including IL-1Ra, sIL-1R and IL-1RII. The biological actions of IL-1 may also be affected by autoantibodies. Autoantibodies may block the effects of cytokine or function as carriers to assist in the delivery of cytokines to tissues [7].

On the basis of studies using cultured synovial cells isolated from RA patients, IL-1Ra production in the rheumatoid joint does not appear sufficient to counteract the amount of IL-1 [13,14]. Studies in cellular systems and animal models showed that IL-1 produces biological actions relevant to the pathophysiology of RA including inflammation and joint erosion as well as inhibition of tissue repair. IL-1 upregulates the expression of cell-adhesion molecules in the vascular endothelium and rheumatoid joint; stimulates the production of other proinflammatory mediators; increases the release of matrix metalloproteinases and other proteolytic enzymes that promote cartilage degradation; and stimulates differentiation of osteoclast precursors and activation of mature osteoclasts, leading to bone resorption. Additionally, IL-1 suppresses joint repair by inhibiting collagen synthesis. Moreover, overexpression of human IL-1β in the rabbit knee joint was associated with augmented cytokine production, synovial hypertrophy and hyperplasia, marked leukocyte infiltration in the joint space, invasive pannus formation, and subsequent erosion of cartilage and subchondral bone [15]. Systemic manifestations of disease were also present, including fever, increased erythrocyte sedimentation rate (ESR) and weight loss.

Blocking the effects of IL-1

Initial efforts to block the effects of IL-1 focused on use of monoclonal antibodies (mAbs) directed against either IL-1α or -β. Administration of a combination of anti-IL-1α and -β completely prevented the onset of collagen-induced arthritis in mice, reduced inflammation, suppressed cartilage destruction and abolished bone erosions when administered to mice with established arthritis [16,17]. The impact of anti-IL-1 on joint destruction has been seen in many other arthritis models induced by a variety of stimuli, including antigen, immune complexes, zymosan and bacterial cell walls [18].

IL-1 can also be blocked by the use of the recombinant IL-1Ra protein. IL-1Ra blocked IL-1-induced mediator production, bone resorption and cartilage degradation in vitro, and it was effective in arthritis models in mice, rats and rabbits when delivered systemically or by gene transfer [12]. Continuous intravenous infusion of
IL-1Ra substantially reduced bone resorption in rats with adjuvant arthritis, and this was accompanied by a significant reduction in the number of osteoclasts [19]. In rats with collagen-induced arthritis, continuous infusion of IL-1Ra, starting at the onset of arthritic signs, significantly reduced histopathologic evidence of bone resorption, pannus formation, cartilage damage and inflammation [19]. In the chronic relapsing streptococcal cell wall arthritis model in rats, gene transfer of IL-1Ra significantly reduced cartilage and subchondral bone erosion in ankle joints expressing the IL-1Ra transgene, but not in contralateral control joints [20]. Similarly, in antigen-induced arthritis in rabbits, gene therapy with IL-1Ra substantially reduced cartilage matrix destruction and restored new matrix synthesis to near-control levels [21].

The importance of IL-1Ra is also evident from studies of IL-1Ra-deficient mice. Animals lacking the IL-1Ra gene spontaneously developed chronic polyarthritis that was characterized by synovial hyperplasia, leukocytic infiltration and erosive pannus formation [22]. IL-1β levels were ten-times higher in the IL-1Ra-deficient animals than in controls. Interestingly, the incidence of polyarthritis depended on the genetic background, with BALB/c mice being much more prone to develop the disease than C57BL/6j mice. In another study, IL-1Ra-deficient mice developed collagen-induced arthritis, associated with an earlier age of onset and with a more severe course [23].

Recent studies have suggested that IL-1 may play a role in autoinflammatory diseases associated with NALP3 gene mutations, including Muckle-Wells syndrome, neonatal onset multisystem disease, and chronic infantile neurologic, cutaneous, articular syndrome [24]. These findings suggest a broad role for IL-1 blockade.

Clinical studies of IL-1 blockade

Anakinra monotherapy

The presumed role of IL-1 in the pathophysiology of RA and the effectiveness of IL-1Ra in animal models prompted the clinical evaluation of IL-1Ra in patients with active RA. Anakinra, a recombinant human IL-1Ra, is identical to naturally occurring nonglycosylated IL-1Ra, with the exception of a terminal methionine. Monotherapy with anakinra was evaluated in a randomized, controlled trial conducted at 41 centers in 11 European countries [25]. After discontinuing previous disease-modifying antirheumatic drugs (DMARDs), 472 patients with active RA were randomly assigned to receive placebo or anakinra 30, 75 or 150 mg. Treatment was given daily for 24 weeks by subcutaneous injection. Patients had symptoms of RA for 6 months to 8 years, with a mean duration of 3.7–4.3 years in the four treatment groups. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (prednisone ≤10 mg) was allowed – in the different treatment groups NSAID use ranged from 82.4 to 89.3% and corticosteroid use from 40.5 to 48.7%.

The primary therapeutic end point was the American College of Rheumatology (ACR) 20% (ACR20) response [26], which was achieved by 43% of patients receiving anakinra 150 mg, compared with 27% of those receiving placebo (p = 0.014). All ACR clinical parameters were improved significantly by anakinra 150 mg, with patients in this group having significantly fewer swollen joints (p = 0.0009), less disability on the Health Assessment Questionnaire (HAQ) (p = 0.0007), lower ESR (p < 0.0001), and lower C-reactive protein levels (p = 0.0017) compared with placebo. Similarly, patients receiving any one of the three anakinra doses had significant improvements in these individual ACR parameters relative to placebo.
The impact of anakinra on radiographic joint damage was also assessed. Serial hand radiographs were taken at baseline and after 24 and 48 weeks of treatment, and then analyzed by the Larsen and Genant methods. After 24 weeks of treatment, anakinra significantly reduced the total Larsen score by 39% (p = 0.029) and the Larsen erosive joint count by 45% (p = 0.0005), compared with placebo (Figure 1)[27]. Similarly, anakinra significantly reduced the total Genant score by 47% relative to placebo (p = 0.0004), with significant reductions seen in both components of this radiographic score. Joint-space narrowing was reduced by 58% (p = 0.0003) and erosions were reduced by 38% (p = 0.0097). Anakinra significantly slowed radiographic progression in the subset of patients with erosions at baseline [28]. The proportion of patients with no radiographic progression was higher in the 75 and 150 mg dose groups compared with placebo (24 and 31%, respectively vs. 16.7%; p = 0.234 and 0.22, respectively).

In the extension period, patients continuing on anakinra showed similar changes in joint-space narrowing as in the double-blind study, but they showed a further 52% slowing of erosions (p = 0.0001) (Figure 2)[27]. Patients who switched from placebo to anakinra showed a 65% reduction in joint-space narrowing (p = 0.0195) and a 59% reduction in erosions (p = 0.0001), compared with double-blind placebo treatment. A repeated-measures mixed-model analysis was used to compare patients continuing on anakinra with the control group that was switched from placebo to anakinra [29]. Continuous anakinra therapy for 12 months was effective in slowing radiographic progression and showing significantly smaller changes in erosions (p = 0.006) and modified total Sharp score (p = 0.015) than the control group.

The effect of anakinra monotherapy on the productivity of patients with RA was evaluated using an economic resource survey [30]. The total number of days of work and domestic activity that were gained after starting anakinra or placebo therapy was quantified as productivity. Anakinra 30, 75 and 150 mg produced greater gains in productivity than placebo during each 4-week period of the 24-week monotherapy study. By the end of the 24-week study, patients receiving anakinra gained 13.4 days of productivity, compared with a gain of 3.6 days with placebo (p < 0.05).

Combination therapy with anakinra & methotrexate

The effect of anakinra on the inhibition of joint destruction was assessed in a large, randomized, double-blind, placebo-controlled study. Subjects with active RA (n = 906) despite therapy with methotrexate (10–25 mg/week) were randomized to treatment with daily subcutaneous injections of anakinra 100 mg or placebo (n = 453 per group), in conjunction with methotrexate therapy. All patients were diagnosed with RA by ACR criteria with a mean duration of RA for 10 years. In addition, all subjects demonstrated radiographic evidence of one or more bone erosions, had a minimum of six swollen joints and nine tender or painful joints, as well as an elevated acute-phase reactant. The primary end point was the change from baseline in total modified Sharp score at 52 weeks. Joint destruction was significantly inhibited by anakinra and methotrexate combination therapy, as compared with methotrexate monotherapy (p = 0.002). In addition, patients receiving anakinra who failed to achieve an ACR20 improvement criteria by 24 weeks exhibited a significant reduction in joint destruction (p = 0.006). In conclusion, anakinra has a significant protective effect on bone and cartilage in patients with active RA receiving methotrexate [31].

Figure 2. Anakinra provides further slowing of erosions with extended treatment.

Mean changes in Genant total score, JSN, and erosion score with anakinra therapy during weeks 0 to 24 and weeks 24 to 48.
JSN: Joint space-narrowing score.

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Another 24-week randomized, controlled study enrolled 419 patients who had moderately to severely active RA even though they had been receiving methotrexate (15–25 mg weekly) for at least 6 consecutive months and stable doses for at least 3 months [32]. These patients were randomly assigned to receive anakinra 0.04, 0.1, 0.4, 1.0 or 2.0 mg/kg or placebo once daily in addition to their regular methotrexate therapy. Most patients in all groups were also receiving NSAIDs and low-dose corticosteroids. Patients had RA symptoms for 6 months to 12 years, with a mean duration of 7.8 years in the placebo group and 6.3 to 8.8 years in the anakinra groups. At baseline, the methotrexate dose was 16.3 mg weekly in the placebo group and 16.7 to 17.6 mg in the anakinra groups.

After 24 weeks, the ACR20 response rate was significantly higher with anakinra 1.0 mg/kg than placebo (42 vs. 23%; p = 0.018). Anakinra 1.0 and 2.0 mg/kg significantly reduced many of the components of ACR response. The 1.0-mg/kg dose produced significant improvements in investigator's global assessment (p = 0.037), patient's global assessment (p = 0.014), HAQ score (p = 0.036), and ESR (p = 0.009) as compared with placebo, whereas the 2.0 mg dose improved the investigator's global assessment (p = 0.013), patient's global assessment (p = 0.0001), patient's assessment of pain (p < 0.0001), swollen joint count (p = 0.014), HAQ (p = 0.0005) and ESR (p = 0.002). Moreover, patients treated with anakinra were significantly more likely to achieve ACR responses of greater magnitude, compared with placebo (p = 0.001) (Figure 3).

Addition of anakinra to methotrexate led to significant improvements in functional status as evaluated by the HAQ [33]. Patients treated with anakinra 1.0 or 2.0 mg/kg showed significant improvements in six of the eight scales of the HAQ relative to placebo and also showed a trend for improvement on a seventh scale (Figure 4). More than half of the functional improvement was realized by 4 to 8 weeks of anakinra therapy. By the end of the 24-week treatment period, patients treated with anakinra were more likely to report no impairment in function than those in the placebo group (19 vs. 7%, respectively).

Safety of anakinra

Postmarketing reports of serious infections, some associated with fatalities, have led to the inclusion of warnings of serious infections and tuberculosis in the product labeling for the tumor necrosis factor (TNF) inhibitors, adalimumab, infliximab and etanercept [34–36]. Anakinra's labeling includes a warning concerning an increased risk of serious infections, 2% in anakinra-treated patients versus less than 1% in patients receiving placebo [37]. Only one case of tuberculosis has been observed with anakinra [38].

Anakinra is generally well tolerated, with dose-related injection-site reactions being the most common adverse event observed in randomized, controlled trials [25,27,32]. Injection-site reactions were experienced by 50, 73 and 81% of patients treated with anakinra 30, 75 and 150 mg, respectively, in the monotherapy study (vs. 25% with placebo) and by 19, 38, 56, 64 and 63% of patients treated with anakinra 0.04, 0.1, 0.4, 1.0 and 2.0 mg/kg, respectively, in the combination study (vs. 28% with placebo). Injection-site reactions were generally mild and tended to resolve with continued administration; they led to premature study withdrawal in 5% of patients treated with anakinra 150 mg in the combination study (vs. 2% with placebo). Injection-site reactions were generally mild and tended to resolve with continued administration; they led to premature study withdrawal in 5% of patients treated with anakinra 150 mg in the monotherapy study (vs. 2% receiving placebo) and by 19, 38, 56, 64 and 63% of patients treated with anakinra 0.04, 0.1, 0.4, 1.0 and 2.0 mg/kg, respectively, in the combination study (vs. 28% with placebo). Injection-site reactions were generally mild and tended to resolve with continued administration; they led to premature study withdrawal in 5% of patients treated with anakinra 150 mg in the monotherapy study (vs. 2% receiving placebo) and by 19, 38, 56, 64 and 63% of patients treated with anakinra 0.04, 0.1, 0.4, 1.0 and 2.0 mg/kg, respectively, in the combination study (vs. 28% with placebo).
Place of anakinra in clinical treatment

Emerging patterns of clinical utilization suggest that rheumatologists most often use biologic response modifiers to treat patients in whom DMARD therapy with methotrexate or leflunomide has already been initiated [41]. RA DMARD Intervention and Utilization Study (RADIUS 1), is a long-term, prospective, multicenter, observational study designed to collect data on the utilization patterns, safety and effectiveness of DMARD therapy in more than 5000 RA patients. In RADIUS 1, 91% of patients receiving a biologic response modifier (anakinra, etanercept or infliximab) had concurrent or prior treatment with methotrexate or leflunomide, whereas only 6% of patients starting on methotrexate or leflunomide had concomitant or prior therapy with a biologic response modifier. Patients in whom a biologic response modifier was initiated tended to have RA of longer duration (mean: 9.8 vs. 4.3 years), more DMARDs used previously (mean: 2.2 vs. 0.6) and greater disease severity compared with patients starting methotrexate or leflunomide [41].

Of the biologic-response modifiers, anakinra is establishing a position as the agent to which rheumatologists turn when patients have failed therapy on one or more of the anti-TNF agents, due to lack of response or intolerance [42]. These candidates for anakinra therapy constitute a substantial population, given that by the end of 2003 some 55,000 patients were expected to discontinue anti-TNF therapy [42]. In RADIUS 1, 52% (186 out of 358) of patients starting on anakinra therapy had taken an anti-TNF agent previously (etanercept: 72%; infliximab: 54%; both: 25%) [43]. Anakinra-treated patients had RA of long duration (mean: 10.7 years) and considerable severity (moderate: 48%; severe: 49%). Anakinra was discontinued by 33% (61 out of 186) of the patients (lack of efficacy: 57% [35 out of 61]; adverse events: 21% [13 out of 61]), but 70% of patients persisted with anakinra for 6 months (mean time on anakinra: 6.5 months), suggesting satisfactory efficacy. These preliminary data support the use of anakinra as treatment for most patients previously treated with an anti-TNF agent. Theoretically, simultaneous blockade of IL-1 and TNF via combination therapy with anakinra and a TNF inhibitor would seem to be beneficial. However, results from combination therapy studies have been inconsistent. Initially, combination therapy was shown to be no more efficacious than monotherapy, and was also associated with an increased risk of serious infections [38,44]. Subsequent preliminary results from Rooney and colleagues found observed in clinical rheumatology practices [39].

This was the first study of the safety of any biologic response modifier in such a setting. Patients thus presented with a variety of comorbidities, a wide range of RA disease activity and various background medications. To reflect real-world conditions, patients were allowed to use NSAIDs, corticosteroids and DMARDS, except for TNF inhibitors. Patients were randomized to anakinra 100 mg (n = 1116) or placebo (n = 283). After 6 months, the rate of serious adverse events was similar in each group (anakinra: 7.7% vs. placebo: 7.8%). Serious infections were more frequent in the anakinra group than in the placebo group (2.1 vs. 0.4%), but 74% (17 out of 23) of the anakinra patients with serious infections were able to resume anakinra therapy after the infection resolved. No opportunistic infections were reported. Rates of premature study withdrawal were similar (anakinra: 21.6%; placebo: 18.7%). Injection-site reactions were the most commonly reported adverse event (anakinra: 72.6%; placebo: 32.9%), but most were transient and of mild or moderate severity. The 6-month study was extended to a 3-year, open-label treatment trial, which evaluated the long-term safety of anakinra in 1103 subjects. The overall long-term safety of anakinra observed during this trial was consistent with that seen in earlier studies, demonstrating that anakinra is generally well tolerated [40].

Figure 4. Anakinra reduces disability as assessed by the Health Assessment Questionnaire (HAQ).

Mean changes from baseline through week 24 for the eight scales of the HAQ for patients treated with anakinra 1.0 or 2.0 mg/kg (+methotrexate) or placebo (+methotrexate). Reproduced with permission from Cohen SB, Chan WW, Woolley JM. Interleukin 1 receptor antagonist anakinra improves functional status in patients with rheumatoid arthritis. J. Rheumatol. 30, 225–231 (2003).
Interleukin-1 blockade for rheumatoid arthritis - REVIEW

Highlights

- Rheumatoid arthritis (RA) causes marked joint destruction, significant disability, reduced overall function, and premature mortality.
- Proinflammatory cytokines, such as interleukin (IL)-1, play an essential role in the pathogenesis of RA.
- Anakinra, an IL-1 receptor antagonist, blocks the pathogenic effects of IL-1 in the rheumatoid joint.
- Anakinra alone and in combination with methotrexate is effective and well tolerated in RA clinical trials.
- Anakinra slows radiographic progression of joint destruction, reduces patient disability, and improves productivity.

the combination of anakinra and pegsunecept, a pegylated TNF agent, to be beneficial, with no serious infections observed during the study [45]. Although the concomitant administration of anakinra and a TNF inhibitor is not currently recommended [38], future therapeutic recommendations may be different.

Expert opinion

Early aggressive treatment of RA is required to slow or arrest progressive joint destruction with the expectation that better long-term outcomes will be realized. Clinical evidence continues to emerge showing that proinflammatory cytokines play important roles in the pathogenesis of RA. Anakinra, a recombinant human IL-1Ra, blocks the pathogenic effects of IL-1. In controlled clinical trials, anakinra was effective and well tolerated when used as monotherapy or in combination with methotrexate. Anakinra relieved the signs and symptoms of disease and slowed radiographic progression, as well as showing evidence of reducing disability and improving patient productivity. The clinical effectiveness of anakinra confirms the importance of IL-1 in the pathogenesis of RA.

Other IL-1-blocking agents currently in clinical development include the IL-1-Trap [46]. This system comprises a complex of the cytokine bound to two receptor extracellular domains that binds with high affinity to initiate signal transduction. Collectively, these approaches to IL-1 blockade may provide physicians with new strategies for managing their RA patients.

Outlook

Therapy for RA has progressed from medications that are "anti-inflammatory" in general, to "targeted therapies." Presently, specific mediators that cause inflammation as well as tissue damage (example—bone erosions in RA) that are found to be upregulated in the disease process are isolated (example—cytokines, cell receptors, TNF-α, IL-1 in RA, etc.) and specific inhibitors are designed to neutralize them. Future research trends will more specifically target the mediators discovered to be pathogenic in each disease process.

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