USE OF IL-1 ANTAGONISTS TO TREAT GOUT AND PSEUDOGOUT

BACKGROUND

Field of the Invention

[0001] The invention relates to methods of using interleukin-1 (IL-1) antagonists to treat metabolic rheumatic disorders associated with hyperuricemia, including gout, and chronic active (refractory) gout. Further, the invention encompasses treatment of conditions such as pseudogout.

Description of Related Art

[0002] Metabolic rheumatic disorders associated with hyperuricemia, such as gout, are characterized by perversion of the purine metabolism resulting in hyperuricemia, i.e. an excess of uric acid in the blood, attacks of acute arthritis, and formation of chalky deposits in the cartilages of the joints. These deposits are made up chiefly of urates, or uric acid.

[0003] Known methods for treating gout include the use of uric acid synthesis inhibitors to inhibit the accumulation of uric acid in the body, and use of uric acid excretion promoters to accelerate the rapid excretion of uric acid accumulated in the body. Allopurinol is an example of a uric acid synthesis inhibitor. Probenecid, sulfinpyrazone and benzbromarone are examples of uric acid excretion promoters, lnterleukin-6 (IL-6) has been proposed for use in the treatment of gout as a serum uric acid decreasing agent (see US Patent 6,007,804).

[0004] Pseudogout is not a hyperuremic disorder, and involves the deposition of calcium pyrophosphate.

BRIEF SUMMARY OF THE INVENTION

[0005] In a first aspect, the invention features a method of treating, inhibiting, or ameliorating metabolic rheumatic disorders associated with hyperuricemia comprising administering to a subject in need an interleukin 1 (IL-1) antagonist to a subject in need thereof. An IL-1 antagonist is a compound capable of blocking or inhibiting the biological action of IL-1 , including fusion proteins capable of trapping IL-1 , such as an IL-1 "trap". In a preferred embodiment, the IL-1 trap is an IL-1- specific fusion protein comprising two IL-1 receptor components and a multimerizing component, for example, an IL-1 trap described in U.S. patent No. 6,927,044. An IL-1 trap fusion protein comprises an IL-1 binding portion of the extracellular domain of human IL-I RAcP, an IL-1 binding portion of the extracellular domain of human IL-1 Rl, and a multimerizing component. In a specific embodiment, the IL-1 trap is the fusion protein shown in SEQ ID NO: 10 (rilonacept) or a protein having at least 95% identity to the protein of SEQ ID NO: 10 and capable of binding and inhibiting IL- 1. Use of the IL-1 trap to treat gout offers unexpected advantages relative to the use of prior art IL- 1 antagonists for several reasons, including allowing alleviation of gout symptoms with reduced frequency of administration, reduced side effects such as, for example, reduced injection site inflammation or reduced immunogenicity.

[0006] In a preferred embodiment, the metabolic rheumatic disorder associated with hyperuricemia is gout. The subject being treated is most preferably a human diagnosed as suffering from gout, for example, chronic acute gout. The method of the invention encompasses preventing or ameliorating gout or hyperuricemia in a human subject suffering therefrom.

[0007] In a second aspect, the invention features a method of treating, inhibiting, or ameliorating pseudogout, comprising administering to a subject in need an interleukin 1 (IL-1) antagonist to a subject in need thereof.

[0008] The methods of the invention includes administration of the IL-1 antagonist by any means known to the art, for example, subcutaneous, intramuscular, intravenous, transdermal administration or oral routes of administration. Preferably, administration is by subcutaneous or intravenous injection or intravenous infusion.

[0009] In specific embodiments of the therapeutic method of the invention, the subject is treated with a combination of an IL-1 trap and a second therapeutic agent. The second therapeutic agent an additional IL-1 antagonist and/or co- therapies such as uric acid synthesis inhibitors to inhibit the accumulation of uric acid in the body, for example, allopurinol, uric acid excretion promoters to accelerate the rapid excretion of uric acid accumulated in the body, for example, probenecid, sulfinpyrazone and/or benzbromarone are examples of uric acid excretion promoters; corticosteroids; non-steroidal anti-inflammatory drugs (NSAIDs); and/or cholchicine.

[0010] In a third aspect, the invention features the use of an interleukin 1 (IL-1) antagonist in the manufacture of a medicament for treating, inhibiting or ameliorating a metabolic rheumatic disorder associated with hyperuricemia, wherein the IL-1 antagonist is a fusion protein comprising an IL-1 binding portion of the extracellular domain of human IL-I RAcP, an IL-1 binding portion of the extraceullar domain of human IL-1 R1 , and a multimerizing component, and the metabolic rheumatic disorder is gout or hyperuricemia. Preferably, the IL-1 antagonist is the fusion protein show in the amino acid sequence of SEQ ID NO: 10 (rilonacept). In a preferred embodiment, the metabolic rheumatic disorder is chronic acute (refractory) gout. More specifically, in a preferred embodiment, rilonacept is administered subcutaneously as an initial dose of between about 250-500 mg, followed by one or more doses of 125-250 mg administered subcutaneously.

[0011] In a fourth aspect, the invention provides the use of an IL-1 antagonist as defined above as a first therapeutic agent, and of one or more further therapeutic agents selected from another IL-1 antagonist, a corticosteroid, a non-steroidal anti-inflammatory drug (NSAID) and colchicine, in the manufacture of a medicament for treating, inhibiting, or ameliorating a metabolic rheumatic disorder associated with hyperuricemia. Administration of the first and second therapeutic agents may be separately, simultaneously, or sequentially.

[0012] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION

[0013] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0014] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus for example, a reference to "a method" includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0015] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

Metabolic Rheumatic Disorders Associated with Hyperuricemia

[0016] Gout is a group of metabolic rheumatic disorders associated with hyperuricemia and is the most common cause of an inflammatory arthropathy in middle-aged men. Gout is essentially a disorder of urate metabolism. Deposition of urate crystals in hyperuricemic individuals results in acute gout, characterized by agonizing pain and inflammation of rapid onset, most frequently affecting the first metatarsophalangeal joint. Hyperuricemia is associated with an increased risk of developing gout and this increases with the degree and duration of the hyperuricemia.

[0017] Treatment of gout aims to relieve pain and inflammation of the acute attack, and reduce the incidence of recurrent attacks. Dietary and pharmacological urate-lowering therapies principally aim to prevent clinical joint damage. Common approaches to the treatment of acute gout are corticosteroids, non-steroidal anti-inflammatory drugs $(NSAIDs)_1$ and colchicine. The side effects of these drugs, particularly in the frail, elderly population who experience the highest incidence of acute gout, can be serious. An approach to the prevention of recurrent gout is the use of a xanthine oxidase inhibitor, allopurinol. However, allopurinol can have serious side effects such as allopurinol hypersensitivity syndrome (see, for example, Arellano et al. (1993) Ann Pharmacother 27:337-343).

[0018] Alternative drugs for preventing gout include the uricosuric agent sulphinpyrazone, limited by its side-effect profile, and benzbromarone and probenecid. Fenofibrate, a drug well known in the treatment of various forms of hyperlipidemia, has been proposed for the treatment of hyperuricemia.

Pseudogout

[0019] Pseudogout is a type of arthritis that, as the name implies, can cause symptoms similar to gout, but in reaction to a different type of crystal deposit. Pseudogout, sometimes referred to as calcium pyrophosphate deposition disease, can cause severe episodes of localized pain and swelling resulting in incapacitation for days or weeks. It also can cause more chronic arthritis that mimics osteoarthritis or rheumatoid arthritis. Knees are most often involved but wrists, shoulders, ankles, elbows or hands can be affected. Pseudogout is caused when deposits of calcium pyrophosphate crystals accumulate in a joint.

IL-1 Trap Antagonists

[0020] lnterleukin-1 (IL-1) traps are multimers of fusion proteins containing IL-1 receptor components and a multimerizing component capable of interacting with the multimerizing component present in another fusion protein to form a higher order structure, such as a dimer. Cytokine traps are a novel extension of the receptor-Fc fusion concept in that they include two distinct receptor components that bind a single cytokine, resulting in the generation of antagonists with dramatically increased affinity over that offered by single component reagents. In fact, the cytokine traps that are described herein are among the most potent cytokine blockers ever described. Briefly, the cytokine traps called IL-1 traps are comprised of the extracellular domain of human IL-1 R Type I (IL-1 Rl) or Type Il (IL-1 RII) followed by the extracellular domain of human IL-1 Accessory protein (IL-IAcP), followed by a multimerizing component. In a preferred embodiment, the multimerizing component is an immunoglobulin-derived domain, such as, for example, the Fc region of human IgG, including part of the hinge region, the CH2 and CH3 domains. An immunoglobulin-derived domain may be selected from any of the major classes of immunoglobulins, including IgA, IgD, IgE, IgG and IgM, and any subclass or isotype, e.g. IgGI , lgG2, lgG3 and lgG4; lgA-1 and lgA-2. Alternatively, the IL-1 traps are comprised of the extracellular domain of human IL-IAcP, followed by the extracellular domain of human IL-1 Rl or IL- 1 RII, followed by a multimerizing component. For a more detailed description of the IL-1 traps, see WO 00/18932. Preferred IL-1 traps have the amino acid sequence shown in SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26, or a substantially identical protein at least 95% identity to a sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, or 26, and capable of binding and inhibiting ILL Most preferably, the IL-1 antagonist is the protein of SEQ ID NO: 10 (rilonacept).

[0021] In specific embodiments, the IL-1 antagonist comprises an antibody fragment capable of binding IL-1α, IL-1 β, IL-1 R1 and/or IL-1 RAcp, or a fragment thereof. The preferred embodiment would be an antagonist of IL-1 β. One embodiment of an IL-1 antagonist comprising one or more antibody fragments, for example, single chain Fv (scFv), is described in U.S. 6,472,179. In all of the IL-1 antagonist embodiments comprising one or more antibody-derived components specific for IL-1 or an IL-1 receptor, the components may be arranged in a variety of configurations, e.g., a IL-1 receptor component(s)-scFv(s)-multimerizing component; IL-1 receptor component(s)-multimerizing component-

scFv(s); scFv(s)-IL-1 receptor component(s)-multimerizing component, SCFV-SCFV-FC, etc., so long as the molecule or multimer is capable of inhibiting the biological activity of IL-1.

Treatment Population

[0022] The method of the instant invention provides treatment of pseudogout and metabolic rheumatic disorders associated with hyperuricemia to human patients suffering therefrom. The treatment population is thus human subjects diagnosed as suffering from pseudogout, gout or hyperuricemia. The invention encompasses the treatment of a human subject at risk of suffering from a recurrent gout episode or for developing gout or pseudogout.

Methods of Administration

[0023] The invention provides methods of treatment comprising administering to a subject an effective amount of an agent of the invention. In a preferred aspect, the agent is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects).

[0024] Various delivery systems are known and can be used to administer an agent of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction can be enteral or parenteral and include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, epidural, and oral routes. The compounds may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0025] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, e.g., by injection, by means of a catheter, or by means of an implant, said implant being of a porous, non- porous, or gelatinous material, including membranes, such as sialastic membranes, fibers, commercial skin substitutes or angioplasty balloons or stents.

[0026] In another embodiment, the active agent can be delivered in a vesicle, in particular a liposome (see Langer (1990) Science 249:1527-1533). In yet another embodiment, the active agent can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer (1990) supra). In another embodiment, polymeric materials can be used (see Howard et al. (1989) J. Neurosurg. 71 :105). In another embodiment where the active agent of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see, for example, U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see e.g., Joliot et al. 1991 , Proc. Natl. Acad. Sci. USA 88:1864- 1868), etc. Alternatively, a nucleic acid can be introduced intracellular^ and incorporated within host cell DNA for expression, by homologous recombination.

Combination Therapies

[0027] In numerous embodiments, the IL-1 antagonists of the present invention may be administered in combination with one or more additional compounds or therapies. Combination therapy may be separate, simultaneous or sequential. The IL-1 traps of the invention may be combined with, for example, TNF-inhibiting agents such as etanercept (ENBREL®, Amgen), infliximab (REMICADE®, Centocor), HUMIRA® (Abbott). Combination therapy may also include treatment with drugs currently used for the treatment or prevention of gout, including corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs); colchicine; xanthine oxidase inhibitors such as allopurinol; uricosuric agents sulphinpyrazone, benzbromarone and probenecid; and fenofibrate. Preferred co-therapeutics include NSAIDs, steroids and/or cholchicine.

Pharmaceutical Compositions

[**0028]** The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of an active agent, and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the

like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

[0029] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0030] The active agents of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0031] The amount of the active agent of the invention which will be effective in the treatment of delayed-type hypersensitivity can be determined by standard clinical techniques based on the present description. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the condition, and should be decided according to the judgment of the practitioner and each subject's circumstances.

[0032] For systemic administration, a therapeutically effective dose can be estimated initially from in vitro assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Initial dosages can also be estimated from in vivo data, e.g., animal models, using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to humans based on animal data.

EXAMPLES

[0033] The following example is put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts

have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. A Phase I/II, Placebo Controlled Pilot Study of the Safety, Tolerability, and Clinical Activity of Rilonacept for the Treatment of Chronic Active Gout

[0034] Gout is a common disease with increasing incidence. There are approximately 5MM Americans with gout. Medical needs are not fully met; a large number of individuals are either intolerant or not good candidates for current therapeutic or prophylactic strategies. This study explores the activity of rilonacept at one end of the gout spectrum: chronic active (refractory) gout. Results from this study may or may not be indicative of rilonacept's potential utility in acute active gout or in the prevention of gout flares; however, activity in this situation suggests potential benefit. The chronic active (refractory) gout population, while small, represents a true situation of medical need.

[0035] **Primary Objective**: To assess the safety of rilonacept in subjects with chronic, active gout, having at least one joint continuously inflamed.

[0036] **Secondary Objectives**: (1) To compare within subject changes in self-reported pain score (VAS) during the placebo run-in phase with the active treatment phase; (2) to assess the changes in the Subject and Physician Global Assessments during the placebo run-in and active treatment phases; (3) to assess the effect of rilonacept on C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in subjects with chronic active gout.

[0037] **Study Arms and Cohorts**: Subjects are screened at Day -7; a two-week single blind placebo run-in begins at the Baseline visit (2 x 2 ml of placebo for rilonacept SQ); Single blind rilonacept 320 mg is administered subcutaneously at the Week 2 visit and then subjects self-inject 160 mg/week at home. Visits occur every two weeks through Week 8. PPD skin test, CXR, and inclusion/exclusion criteria are assessed at the Screening visit. Self-injection technique is taught at Screening and Baseline. Laboratory sample collections occur at Screening, Baseline, Weeks 2, 4, and 8. A follow- up visit occurs at Week 14.

[0038] **Sample Size and Number of Sites**: N = 5 from up to 5 sites in the U.S.

[0039] **Drug Supply**: Placebo: 5 subjects x 2 vials = 10 vials + 30% overage = 13 vials; Rilonacept: 5 subjects x 8 vials = 48 vials + 30% overage = 66 vials, 3 vials per kit.

[0040] **Subject Eligibility Criteria**. Inclusion Criteria: (1) Male or female ≥ 21 years; (2) Chronis, active monoarticular or polyarticular gout (> 1 continuously inflamed joint due to gout, ± tophi); (3) VAS 10-point pain scale score of ≥ 3 (i.e., moderate or greater) due to joint pain/inflammation; (4) subjects for whom standard therapies are ineffective or associated with risks related to side effects.

[0041] **Exclusion Criteria**: (1) Organ transplant recipient; (2) current active infection; (3) serum creatinine < 2.5 mg/dL; (4) other arthritic condition that could interfere with evaluations.

[0042] **Primary Endpoint**: Tolerability and safety profile of rilonacept.

[0043] **Secondary Endpoints**: (1) The change from Baseline to Week 8 in subject's pain score (10 cm VAS scale); (2) the change from Baseline to Week 8 in the Subject's Global Assessment; (3) the change from Baseline to Week 8 in the Physician's Global Assessment; (4) the change from Baseline to Week 8 in ESR and CRP.

Example 2. Safety of Rilonacept in Subjects with Chronic Active Gouty Arthritis.

[0044] A 14 week, multi-center, non-randomized, single-blind, placebo-controlled, monosequence crossover study of rilonacept in subjects with chronic, active monoarticular or polyarticular gouty arthritis. Subjects receive 2 weeks of single-blind placebo followed by a loading dose of subcutaneous injections of 320 mg rilonacept, followed by weekly subcutaneous injections for 5 weeks of 160 mg rilonacept. Study Population. The study population included adult subjects (at least 18 years of age, male or female) with chronic, active monoarticular or polyarticular gouty arthritis diagnosed by a physician for at least 6 months with at least one continuously inflamed joint (self- reported or otherwise) for > 4 weeks, a diagnosis of gout based on a history of the presence of crystals in the synovial fluid analysis, chronically elevated serum uric acid, and/or tophi; a visual analogue scale increment pain scale score of at least 3 due to joint pain/inflammation at both the Screening and Baseline Visits, and subjects for whom standard therapies for gout are less than effective or are associated with risks related to side effects.

[0045] **Study Design**. This study was a 14-week, multi-center, non-randomized, single-blind, placebo-controlled, monosequence crossover study of IL-1 trap (rilonacept) in subjects with chronic, active monoarticular or polyarticular gouty arthritis. Subjects received 2 weeks of single-blind placebo followed by a loading dose of subcutaneous injections of 320 mg rilonacept, followed by weekly subcutaneous injections for 5 weeks of 160 mg rilonacept. The study was conducted in approximately 12 sites in the U.S. This study includes a monosequence crossover design for the enrolled subjects: Treatment 1 : Placebo injections for two weeks; Treatment 2: Injections of rilonacept for six weeks. Descriptive statistics was used to evaluate safety and efficacy of rilonacept in gout. Approximately 10 subjects were enrolled to receive placebo (2 weeks) and rilonacept (6 weeks) administered subcutaneously. Subjects received a total of two doses of placebo (on study days 0 and 7) and six doses of rilonacept on Days 14, 21 , 28, 35, 42, and 49 during the study. Dose escalation was not allowed. Subjects were evaluated for efficacy and safety on a regular basis with clinical observations and laboratory measurements including anti-rilonacept antibodies, hs-CRP and ESR. The overall structure of the study included the following periods: Screening period: Screening procedures occurred within 7 days of start of study and included obtaining informed consent and evaluations to determine eligibility for study participation. Baseline: At the

baseline visit (day 0), eligibility was confirmed, and the subject enrolled. Baseline assessments were made. The first injection of placebo was administered, and a vial of placebo dispensed. Placebo Treatment period: During the treatment period (Day 0 through Week 2), patients received placebo study medication, efficacy assessments were taken; safety and tolerability assessments were taken, including urine and blood samples for clinical laboratory testing. Active Treatment period: During the treatment period (Week 2 through Week 8), patients received active study medication, efficacy assessments were taken; safety and tolerability assessments were taken, including urine and blood samples for clinical laboratory testing. Blood samples were collected for biomarkers, IL-1 trap (rilonacept) plasma levels, and rilonacept antibodies. Follow-up: At Week 14, vital signs, bodyweight, adverse events, and concomitant medications assessments were taken. Blood samples were collected for biomarkers, rilonacept plasma levels, and rilonacept antibodies. The results are shown in Table 1. The first column lists the parameters assessed; column 2 (placebo response) compares the parameter measurements obtained at Week 2 with those measured at Day 0; column 3 (response of rilonacept) compares the parameter measurements obtained at Week 8 with those of Week 2; and column 4 (effect of withdrawal from treatment with rilonacept) compares the parameter measurements obtained at Week 14 with those obtained at Week 2.

[0046] **Results**. During treatment with placebo, there was no apparent trend toward improvement in any clinical parameter nor in CRP. Also, during treatment with placebo, there is no evidence of improvement. At the end of treatment with rilonacept, the proportion of responders is significantly better than a placebo response of 10%, regardless of how response was defined ($p<0.01$). Also, there was a significant reduction in patient's self-reported pain ($p = 0.02$). When treatment with rilonacept was withdrawn, the trends toward efficacy waned and pain returned. These results suggest that placebo response is minimal, and reduction in pain is not observed until treatment with rilonacept is administered.

Table 1

Assessment	Placebo Response	Rilonacept Response			Effects of Withdrawal from Treatment with Rilonacept
	Change Day 0- week 2	Change Week 2-4	Change Week 2-4	Change Week 2-8	Change Week 8-14
Subject's Assessment of Pain	0.96	0.046	0.07	0.02	0.07
Physician's Global Assessment	0.09	0.4	0.8	0.2	0.02
Subject's Global Assessment	1.0	0.07	0.14	0.06	0.02
Number of Affected Joints	0.3	0.7	0.9	0.099	0.95
Symptom-Adjusted Scores for Affected Joints (maximum of 3 per joint)	0.2	0.7	0.8	0.04	0.3
Severity-and-Symptom-Adjusted Scores for Affected Joints (maximum of 9 per joint)	0.2	0.2	0.8	0.04	0.14
Change from Baseline CRP	0.5	0.002	0.004	0.004	0.04

CLAIMS

1. Use of an interleukin 1 (IL-1) antagonist in the manufacture of a medicament for treating, inhibiting or ameliorating a metabolic rheumatic disorder associated with hyperuricemia, wherein the IL-1 antagonist is a fusion protein comprising an IL-1 binding portion of the extracellular domain of human IL-1RAcP, an IL-1 binding portion of the extraceullar domain of human IL-1R1, and a multimerizing component, and the metabolic rheumatic disorder is gout.

2. Use according to claim 1, wherein the metabolic rheumatic disorder is chronic acute (refractory) gout.

3. Use according to claim 1, wherein the IL-1 antagonist is a fusion protein comprising the amino acid sequence of SEQ ID NO:10.

4. Use according to any one of claim 1 to 3, wherein administration is by subcutaneous or intravenous administration.

5. Use according to claim 4, wherein administration is by single or multiple subcutaneous injections or intravenous infusions.

6. Use according to claim 5, wherein administration comprises an initial dose of between about 250-500 mg of the IL-1 antagonist administered subcutaneously, followed by one or more doses of 125-250 mg administered subcutaneously.

7. Use of an IL-1 antagonist as defined in claim 1 or 3 as a first therapeutic agent,

and of one or more further therapeutic agents selected from another IL-1 antagonist, a corticosteroid, a non-steroidal anti-inflammatory drug (NSAID) and colchicine

in the manufacture of a medicament for treating, inhibiting, or ameliorating a metabolic rheumatic disorder associated with hyperuricemia, where the metabolic rheumatic disorder is gout.

8. An interleukin 1 (IL-1) antagonist for use in a method of treating, inhibiting, or ameliorating pseudogout, the method comprising administering to a subject in need a therapeutic amount of the antagonist, wherein the disorder is treated, inhibited, or ameliorated and wherein the IL-1 antagonist is a fusion protein as defined in claim 1.

9. An interleukin 1 (IL-1) antagonist for use in a method of treating, inhibiting or ameliorating a metabolic rheumatic disorder associated with hyperuricemia, wherein the IL-1 antagonist is a fusion protein as defined in claim 1 or 3 and the metabolic rheumatic disorder is gout.

10. Use of an IL-1 antagonist as defined in claim 1 or 3 in the manufacture of a medicament for the treatment, in combination with one or more further therapeutic agents selected from another IL-1 antagonist, a corticosteroid, a non-steroidal anti-inflammatory drug (NSAID) and colchicine, of a

metabolic rheumatic disorder associated with hyperuricemia, where the metabolic rheumatic disorder is gout.

11. Use of one of more therapeutic agents selected from an IL-1 antagonist other than that defined in claim 1, a corticosteroid, a non-steroidal anti-inflammatory drug (NSAID) and colchicine in the manufacture of a medicament for the treatment, in combination with an IL-1 antagonist as defined in claim 1 or 3, of a metabolic rheumatic disorder associated with hyperuricemia, where the metabolic rheumatic disorder is gout.

12. A product containing an IL-1 antagonist as defined in claim 1 or 3 and one or more further therapeutic agents selected from another IL-1 antagonist, a corticosteroid, a non-steroidal anti-inflammatory drug (NSAID) and colchicine for simultaneous, separate or sequential use in the treatment of a metabolic rheumatic disorder associated with hyperuricemia, where the metabolic rheumatic disorder is gout.