Title: METHODS RELATED TO TREATMENT OF INFLAMMATORY DISEASES AND DISORDERS

Abstract: The present invention provides a method for treating an inflammatory disease or disorder in a patient suffering from said disease, which method comprises administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein said patient is seropositive.
METHODS RELATED TO TREATMENT OF INFLAMMATORY DISEASES AND DISORDERS

FIELD

The present invention concerns methods within the field of treatment of inflammatory diseases and disorders aiming to improve the treatment options and regiments for patients.

BACKGROUND

Inflammatory diseases and disorders and in particular autoimmune diseases such as rheumatoid arthritis severely impact patient's well-being and treatment options are unsatisfactory for a large group of patients.

Rheumatoid arthritis (RA) is a clinically important, chronic systemic autoimmune disease and is an autoimmune disorder of unknown etiology. Most RA patients suffer a chronic course of disease that, even with currently available therapies, often results in progressive joint destruction, deformity, disability and even premature death. Diagnosis of RA typically relies on clinical and laboratory evaluation of a patient's signs and symptoms.

The American College of Rheumatology (ACR) criteria are the standards used for diagnosis and determination of severity. In July 2010, the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria were introduced. These new classification criteria include ACPA testing, and overruled the "old" ACR criteria of 1987 and are adapted for early RA diagnosis (Aletaha D. et al., Arthritis & Rheumatism, 62(9), 2569-2581 (2010)).

As described in those criteria, laboratory evaluation of a patient suspected of having RA may include determination of the level of certain antibodies in serum known as rheumatoid factor (RF) and antibodies to cyclic citrullinated peptide (anti-CCP). While these antibodies are often found in the serum of RA patients (when both antibodies are found in the serum, the termed used is "seropositive"), not all RA patients have them (Wilson D., Can Fam Current treatments, such as treatment with anti-TNF agents or anti-CD20 agents are not always providing a safe and efficacious treatment for all patients and many patients do not respond well to specific treatments while others do. It is still unclear what is behind this and information on how to predict which patients will respond well is scarce. The underlying reason for the improved rates of ACR responses in anti-CD20 therapy (in particular with Rituximab) seems to be in rituximab's depletion of B lymphocytes. Rituximab has a markedly improved effect in seropositive patients (Edwards JCW et al., N Engl J Med 350, 2572-2581 (2004), Pyrpasopoulou A et al., MolDiagnTher. 14(1), 43-8 (2010)). Also the classic RA drug,
methotrexate (MTX), has an improved profile in seropositive patients (van Dongen H et al., Arthritis Rheum. 56(5), 1424-32 (2007)).

Attempts have been made to improve diagnosis and prognosis based on biomarkers, and recently, methods for subgrouping RA patients and identification of patients groups which demonstrate a higher responsiveness to anti-CD20 therapy based on particular molecular profiles have been presented (WO2011028945). However, no clinically validated diagnostic or prognostic markers, have been identified that enable clinicians or others to accurately define pathophysiological aspects of rheumatoid arthritis, clinical activity, response to therapy, prognosis, or risk of developing the disease.

Accordingly, as RA patients seek treatment, there is considerable trial and error involved in the search for therapeutic agent(s) effective for a particular patient. Such trial and error often involves considerable risk and discomfort to the patient in order to find the most effective therapy. Thus, there is a need for more effective means for determining which patients will respond to which treatment and for incorporating such determinations into more effective treatment regimens for RA patients.

SUMMARY OF THE INVENTION

The present invention relates to a method for treatment of an inflammatory disease or disorder in a patient suffering from said disease, which method comprises administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein said patient is RF-positive and/or anti-CCP-positive. In one embodiment, the patient is seropositive.

In one embodiment, the inflammatory disease or disorder is an autoimmune disease or disorder. In one embodiment, the inflammatory disease or disorder is rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, or psoriatic arthritis. In one embodiment, the inflammatory disease or disorder is rheumatoid arthritis.

In one embodiment, the anti-inflammatory agent is an antagonist of IL-20 or the IL-20 receptor. In one embodiment, the anti-inflammatory agent is an antagonistic anti-hIL-20 antibody. In one embodiment, the antibody is a monoclonal anti-IL-20 antibody. In one embodiment, the antibody is an anti-IL-20 antibody such as the anti-IL-20 antibodies described in WO 2010/000721, WO1 9990271 03, US71 15714 or US7151 166.

In one embodiment, the anti-inflammatory agent is administered to patients, who are also being treated with methotrexate.
DESCRIPTION

As described in the background section the treatments presently available for treatment of inflammatory disease or disorders, such as autoimmune diseases or disorders, such as rheumatoid arthritis, have, at least to some extent, a low success rate and treatment frequently involves some degree of trial and error. This invention provides a method for identification of a patient subgroup that have a high treatment success rate whereby a large number of patients can avoid the risk and discomfort associated with the difficulties in finding an effective therapy.

The inventors of the present inventions have found that patients with a high probability of a successful treatment can be identified based on examination of their level of RF and/or anti-CCP. The present invention is based on data obtained as described in the example section. The patient according to the invention typically suffers from an inflammatory diseases or disorder and in particular an autoimmune disease or disorder, in particular rheumatoid arthritis. Based on the obtained data the information can be used in various methods, as patients with an enhanced probability of responding to therapy can be selected. Using the level of RF and anti-CCF antibodies in serum for predicting clinical success of an anti-inflammatory agent subsequently provides a method of treatment of such patients.

The present invention provides a method for treatment of an inflammatory disease or disorder in a patient suffering from said disease, which method comprises administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein said patient is RF-positive and/or anti-CCP-positive.

The term "rheumatoid factor," or "RF," refers to autoantibodies that are frequently detected in the blood of rheumatoid arthritis patients. RF is directed against the Fc portion of IgG, which is itself an antibody. RF and IgG join to form immune complexes that contribute to the disease process. Rheumatoid factor can also be a cryoglobulin (antibody that precipitates on cooling of a blood sample); it can be either type 2 (monoclonal IgM to polyclonal IgG) or type 3 (polyclonal IgM to polyclonal IgG) cryoglobulin. High levels of rheumatoid factor (in general, above 20 IU/mL, 1:40, or over the 95th percentile; there is some variation among labs and assays) occur in rheumatoid arthritis (present in 80%) and Sjogren's syndrome (present in 70%).

The term "positive for RF" refers to a result of an assay for RF, e.g., an ELISA assay, where the result is above a threshold or cut-off value for that assay for samples that
are considered to reproducibly contain detectable levels of RF as described in Aletaha D. et al., Arthritis & Rheumatism, 62(9), 2569-2581 (2010).

The term "negative for RF" refers to a result of an assay for RF, e.g., an ELISA assay, where the result is at or below a threshold or cut-off value for that assay for samples that are considered to reproducibly contain undetectable levels of RF.

The term "anti-CCP" (antibodies to cyclic citrullinated peptide) refers to autoantibodies that are frequently detected in the blood of rheumatoid arthritis patients. The main epitope for these antibodies is filaggrin and there is cross-reactivity between ACPA and anti-keratin and anti-perinuclear factor (Detrick, B., Manual of molecular and clinical laboratory immunology. Washington D.C.: ASM Press, pp. 1037 (2006) ISBN 1-55581-364-X and Schellekens GA et al., J. Clin. Invest. 101(1), 273-81 (1998)). During inflammation, arginine residues in proteins such as vimentin can be enzymatically converted into citrulline ones (a process called citrullination), and, if their shapes are significantly altered, the proteins may be seen as antigens by the immune system, thereby generating an immune response.

anti-CCPs have proved to be powerful biomarkers that allow the diagnosis of rheumatoid arthritis (RA) to be made at a very early stage.

The term "positive for anti-CCP" refers to a result of an assay for anti-CCP, e.g., an ELISA assay, where the result is above a threshold or cut-off value for that assay for samples that are considered to reproducibly contain detectable levels of anti-CCP as described in Aletaha D. et al., Arthritis & Rheumatism, 62(9), 2569-2581 (2010).

The term "negative for anti-CCP" refers to a result of an assay for anti-CCP, e.g., an ELISA assay, where the result is at or below a threshold or cut-off value for that assay for samples that are considered to reproducibly contain undetectable levels of anti-CCP.

Generally, quantitative determination of RF and anti-CCP are done in serum, lithium heparin or EDTA plasma. The values of a subjects sample may vary depending on the testing procedure used. Assays for quantitative determination of RF and anti-CCP are generally known in the art, for instance as described in Aletaha D. et al., Arthritis & Rheumatism, 62(9), 2569-2581 (2010). Specific examples are the N Latex RF kit as provided by Siemens Healthcare Diagnostics Products GmbH, Marburg Germany and the anti-CCP electrochemiluminescence immunoassay (ECLA, ref. 05031656) as provided by Roche Diagnostics GmbH, Mannheim, Germany. Physician.52, 180-1 (2006), Pincus T., Bull HospJt Dis. 64(1-2), 32-9 (2006)).

There are many other different assays available for determining if a person/patient is seropositive or not, including numerous ones approved by the US Food and Drug
Administration (FDA). Table 1 discloses a non-limited listing of some of the FDA approved assays for identifying seropositivity.

Table 1

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Table 1. Examples of FDA approved assays for indication of seropositivity.

The term "seropositive patient" refers to a patient who is positive for rheumatoid factor (RF) and also for positive for anti-CCP (antibodies to cyclic citrullinated peptide). While being seropositive is a strong marker for having an inflammatory disease or disorder, in particular RA, as described for instance the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria, it may be negative in patients diagnosed with rheumatoid disease, and consequently, there are patients suffering from RA, which patients are not seropositive. Some patients are seronegative to begin with but 80% becomes seropositive with progression of the disease (they are said to "seroconvert"). Disease severity is often worse in those who are seropositive.

As used herein, "treatment" refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed before or during the course of clinical pathology. In the context of this specification, desirable effects of treatment include preventing the recurrence of a disease or a condition or symptom thereof, alleviating a condition or symptom of the disease, diminishing any direct or indirect pathological consequences of the disease, decreasing the rate of disease progression, ameliorating or palliating the disease state, and/or achieving remission or improved prognosis. In some embodiments, methods and compositions of the invention are useful in attempts to delay development of a disease or disorder.

A "therapeutic amount" or "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A "therapeutically effective amount" of an anti-inflammatory agent may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the anti-inflammatory agent to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the anti-inflammatory agent are outweighed by the therapeutically beneficial effects.

The terms "individual," "subject" or "patient", as used herein generally refers to a vertebrate. In certain embodiments, the vertebrate is a mammal. Mammals include, but are not limited to, primates (including human and non-human primates) and rodents (e.g., mice and rats). In certain embodiments, the mammal is a human. The term "patient" further indicates that the subject or individual is not a healthy subject. In one embodiment a "patient"
is an individual diagnosed or suffering from sign(s) or symptom(s) associated with inflammatory diseases or disorders. In one embodiment the "patient" is suffering from an autoimmune disease or disorders, such as RA.

A "medicament" is an active drug to treat a disease, disorder, and/or condition. In one embodiment, the disease, disorder, and/or condition is RA or its symptoms or side effects.

An "anti-inflammatory agent" is a compound, medicament or agent, which can, or is expected to; decrease an inflammatory response or symptom(s) of inflammatory diseases or disorders.

An "antagonist" refers to a molecule capable of neutralizing, blocking, inhibiting, abrogating, reducing or interfering with the activities of a particular or specified protein, including its binding to one or more receptors in the case of a ligand or binding to one or more ligands in case of a receptor. Antagonists include antibodies and antigen-binding fragments thereof, proteins, peptides, glycoproteins, glycopeptides, glycolipids, polysaccharides, oligosaccharides, nucleic acids, bioorganic molecules, peptidomimetics, pharmacological agents and their metabolites, transcriptional and translation control sequences, and the like. Antagonists also include small molecule inhibitors of the protein, and fusion proteins, receptor molecules and derivatives which bind specifically to the protein thereby sequestering its binding to its target, antagonist variants of the protein, antisense molecules directed to the protein, RNA aptamers, and ribozymes against the protein.

As described herein, the present invention relates to treatment of a variety of diseases, particular including autoimmune and inflammatory diseases or disorders, in which at least some patients become RF-positive and/or anti-CCP-positive over the cause of the disease.

Accordingly, the present invention provides a method for treating an inflammatory disease or disorder in a patient suffering from said disease, which method comprises administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein said patient is RF positive and/or anti-CCP positive.

Examples of such diseases or disorders may be selected from the list consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, Sjogren's syndrome, multiple sclerosis, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, systemic lupus erythematosus, or lupus nephritis, and any combination thereof, as well as co-morbidities associated with these diseases, with cardiovascular disease being a non-limiting example of said comorbidities. Other exemplary diseases or disorders include, but are not limited to, juvenile chronic arthritis, osteoarthritis,
other spondyloarthropathies than ankylosing spondylitis, systemic sclerosis (scleroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), vasculitis, systemic vasculitis, temporal arteritis, atherosclerosis, sarcoidosis, myasthenia gravis, autoimmune hemolytic anemia, autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lupus erythematosus, atrophic thyroiditis), diabetes mellitus, Type 2 diabetes, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis, autoimmune oophoritis), pancreatitis, autoimmune orchitis, autoimmune uveitis, anti-phospholipid syndrome, demyelinating diseases of the central and peripheral nervous systems in addition to multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barre syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, viral hepatitis, primary biliary cirrhosis, granulomatous hepatitis, Wegener's granulomatosis, Behcet's disease, and sclerosing cholangitis, inflammatory bowel diseases such as celiac disease, gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, atopic dermatitis, dermitis herpetiformis, pemphigus vulgaris, vitiligo (leukoderma), allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, sepsis, endotoxemia, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, chronic obstructive pulmonary disease, and organ or bone marrow transplantation associated diseases including graft rejection and graft-versus-host disease, insofar as at least some patients become RF-positive and/or anti-CCP-positive over the cause of the disease.

The causes of inflammatory diseases are multiple and multiple pathways and components are involved. Inflammation is a cascade of events involving multiple components, including the vasculature (e.g., endothelial cells, pericytes, smooth muscle cells), cells of the immune system (e.g., T and B lymphocytes; polymorphonuclear leukocytes or granulocytes, such as monocytes and neutrophils; dendritic cells, macrophages, and NK cells), cell-derived soluble mediators (cytokines, chemokines) and also resident cells in the targeted tissue (e.g., epithelial cells, synovial fibroblasts, neuronal cells). Each of these elements including regulators hereof may have roles in disease development and may subsequently also be a target of therapy for the above mentioned diseases and disorders.

Inflammatory diseases may thus also be characterized by the pathway affected, e.g. as a B
or T-cell mediated disease or disorder, as a cytokine mediated disorder or a receptor mediated disorder etc. etc.

For the present invention the indication may thus be any disorder ameliorated by treatment of an anti-inflammatory agent, such as a disorder mediated by down-regulation of signalling/activity of the IL-10 family e.g. receptors and ligands as described herein below.

Indication which may be treated using modulators of the IL-10 family of cytokines and receptors include autoimmune diseases and disorders, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), inflammatory bowel disease (IBD), psoriasis or psoriatic arthritis (PSA).

Accordingly, in one embodiment, the inflammatory disease or disorder is rheumatoid arthritis, systemic lupus erythematos, multiple sclerosis, or psoriatic arthritis. In one embodiment, the inflammatory disease or disorder is rheumatoid arthritis.

Depending on the indication, diagnosis and clinical response may be determined by a variety of methods. Patients that do not, upon administration of given anti-inflammatory agent, exhibit any or adequate signs of treatment of the disorder for which they are being treated are considered non-responsive. Patients that on the contrary do, upon administration of given anti-inflammatory agent, respond by exhibiting adequate signs of treatment of the disorder for which they are being treated, are considered responsive. Adequate signs of treatment vary from disease to disease and from patient to patient and do not imply that the patient experiences "full" treatment but solely that amelioration of one or more clinical parameters is observed. The responsiveness may be considered a different time point after dosage of the anti-inflammatory agent and patients may respond after one or more dosage, for a short period or for longer periods, but as long as a positive result is obtained, that patient is considered responsive.

The success rate (e.g. the frequency of administering an anti-inflammatory agent to a patient that will respond) may be increased based on the present invention; furthermore the frequency of reaching not only a high success rate but also a strong response in the patient administered may be obtained using the present invention.

The clinical response may be determined by methods known in the art. Official disease scores as approved by governmental authorities are preferably to be used. It is to be said that such disease scores evolve over time, so also future methods for obtaining a clinical score is considered relevant for the present invention.

It is contemplated that a person skilled in the art is able to identify relevant clinical parameters for a given disease or disorder and only few key clinical parameters are therefore included herein. Autoimmune diseases are diagnosed based on variety of criteria.
The methods herein are concerned with indications and predictions of a response of a patient to an anti-inflammatory agent, depending on the indication and symptoms, the expected response may be projected at different time points. In individual embodiment the indication and prediction relates to a response to be obtained within 12 months, within 10 months, within 8 months, within 6 months, within 5 months, within 4 months, within 3 months, or within 2 months.

Rheumatoid arthritis (RA) may be diagnosed based on the criteria defined by the American college of Rheumatology (ACR) or the like. The responsiveness to a treatment may be based on degrees score when applying such criteria. Prevention or retardation of radiographic damage is also a goal for RA treatment. The American College of Rheumatology (ACR) 20% composite criteria for improvement describes patents as "improved" if there is 20% improvement in the tender and swollen joint counts and 20% improvement in at least three of five additional measures (pain, physical function, patient global health assessment, physician global health assessment and acute phase reactant levels). Similarly, the ACR50 and ACR70 represent even higher degrees of improvement for the patient.

The effectiveness of an anti-inflammatory agent as a therapeutic for RA may thus be quantified based on the number of patients or the fraction of patients that obtains ACR20, ACR50 and/or ACR70.

Alternative to the ACR scores, progression of rheumatoid arthritis can also be followed using a Disease Activity Score of 28 joints (DAS28). It is a combined index that has been developed in Nijmegen in the 1980's and has been widely used as an indicator of RA disease activity and response to treatment also in combination with the DAS based European League Against Rheumatism (EULAR) response criteria. The joints included in DAS28 are (bilaterally): proximal interphalangeal joints (10 joints), metacarpophalangeal joints (10), wrists (2), elbows (2), shoulders (2) and knees (2). When looking at these joints, both the number of joints with tenderness upon touching (TJC28) and swelling (SJC28) are counted. Measurements of the level of C-reactive protein (CRP) (in mg/l) may be included and the patient also makes a subjective assessment (SA) of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible". Based herein DAS28 is calculated.

Using the DAS, several thresholds have been developed for high disease activity, low disease activity or even remission. The score can also be used as response criteria, when the DAS of a patient is measured at two time points (e.g. before the start of a treatment and after treatment), the clinical response in the patients can be assessed.
In one aspect, the present invention is concerned with improving the effectiveness of RA treatment. Although several compounds have been approved and are used for treatment of RA treatment outcome is rarely optimal for all patients and involves some aspects of trial and error as no method for predicting the effectiveness of an RA treatment is been applied.

The present invention demonstrates that being RF-positive and/or anti-CCP-positive, or even seropositive, is indicative for a clinical response that is higher than the average clinical response in RA patients, when treated with an anti-inflammatory agent according to the present invention, such as an antagonist of the IL-20 pathway, such as an anti-IL-20 antibody, such as the anti-IL-20 antibodies described in WO 2010/000721, WO1999027103, US71 15714 or US7151 166.

As explained above, being seropositive is a strong marker for having an inflammatory disease or disorder, in particular RA, as described in for instance the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria. Being seropositive is therefore often used as one of many inclusion criteria for patient recruitment during clinical trials for a RA treatment. However, as there patient suffering from RA that are seronegative, this is only usually used as one of many inclusion criteria.

It is also known to use the patients RF-positive and/or anti-CCP-positive status, or even seropositive status, as a stratification tool to positively identify effective responders when treated with anti-CD20 mAbs, such as rituximab, ocrelizumab and ofatumumab.

The link between the treatment with anti-CD20 antibodies and being RF-positive and/or anti-CCP-positive, or even seropositive, is understandable, as anti-CD20 antibodies deplete B cells which are the primary antibody secreting cells. It is therefore logical and not surprising that anti-CD20 therapy resulting in depletion of B cells and lowers serum antibody levels over the treatment period is able to have an effect in seropositive patients as this may support that seropositivity (i.e. the RF and anti-CCP antibodies) plays a role in disease pathogenesis.

However, this logical link does not apply for the present invention wherein the anti-inflammatory agent is an antagonist of the IL-20 pathway, such as an anti-IL-20 antibody, such as the anti-IL-20 antibodies described in WO 2010/000721, WO1 999027103, US71 15714 or US7151 166.

Receptors for IL-20 are not expressed on B cells and there is no evidence that IL-20 directly affects B cells or antibody production. It is therefore not obvious that there is any link between being RF-positive and/or anti-CCP-positive, or even seropositive and being a more
effective responder to a treatment with an anti-inflammatory agent that is an antagonist of the IL-20 pathway compared to a seronegative patient suffering from RA treated with the same IL-20 pathway antagonist. This is a different from the obvious link between treatment where the anti-inflammatory agent is an anti-CD20 antibody that directly affects (depletes) the secreting B cells.

Not being bound to theory, current data suggests that IL-20R is expressed locally in the RA joints and that IL-20 induces chemokines that induce migration of cells to the joint, possibly affecting oedema and this could affect local inflammation and bone metabolism. This proposed mechanism is very distinct from the known mode of action for anti-CD20 antibodies and and therefore it is surprising that being RF-positive and/or anti-CCP-positive, or even seropositive can be used as positive stratification for effective treatment with an anti-inflammatory agent that is an antagonist of the IL-20 pathway, such as an anti-IL-20 antibody, such as the anti-IL-20 antibodies described in WO 2010/000721, W01 9990271 03, US71 15714 or US7151 166.

Due to the similarity in pathways, it is contemplated that this applies mutandis mutandis to other, related inflammatory diseases or disorders, examples of which are described in more detail below.

As for RA, effect of treatment of systemic lupus erythematosus may be based on the basis of the American College of Rheumatology (ACR) classification criteria. These criteria were established mainly for use in scientific research and in clinical trial and not for diagnostic purposes, so not all SLE patients pass the full criteria.

For multiple sclerosis, several subtypes of the disease exist and different prognosis and progression is observed.

The United States National Multiple Sclerosis Society in 1996 standardized four subtype definitions: as 1) relapsing remitting, 2) secondary progressive, 3) primary progressive, and 4) progressive relapsing. Various criteria for diagnosing and evaluation are used which severely complicates testing of drugs potentially effective in treatment of MS.

Based on MS being an autoimmune disease immune-modulators including anti-inflammatory agents may be useful for treatment or management of MS.

Psoriatic arthritis may be diagnosed based on the criteria defined by the American college of Rheumatology (ACR) or the like. The responsiveness to a treatment may be based on degrees score when applying such criteria. Prevention or retardation of radiographic damage is also a goal for PSA treatment. The America college of Rheumatology (ACR) 20%
composite criteria for improvement describes patents as "improved" if there is 20% improvement in the tender and swollen joint counts and 20% improvement in at least three of five additional measures (pain, physical function, patient global health assessment, physician global health assessment and acute phase reactant levels). Similarly, the ACR50 and ACR70 represent even higher degrees of improvement for the patient.

The effectiveness of an anti-inflammatory agent as a therapeutic for PSA may thus be quantified based on the number of patients or the fraction of patients that obtains ACR20, ACR50 and/or ACR70.

Alternative to the ACR scores, progression of psoriatic arthritis can also be followed using a Disease Activity Score of 28 joints (DAS28). It is a combined index that has been developed in Nijmegen in the eighties and is has been widely used as an indicator of PSA disease activity and response to treatment also in combination with the EULAR response criteria. The joints included in DAS28 are (bilaterally): proximal interphalangeal joints (10 joints), metacarpophalangeal joints (10), wrists (2), elbows (2), shoulders (2) and knees (2).

When looking at these joints, both the number of joints with tenderness upon touching (TJC28) and swelling (SJC28) are counted.

Measurements of the level of C-reactive protein (CRP) (in mg/l) may be included and the patient also makes a subjective assessment (SA) of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible". Based herein DAS28 is calculated.

Using the DAS, several thresholds have been developed for high disease activity, low disease activity or even remission. The score can also be used as response criteria, when the DAS of a patient is measured at two time points (e.g. before the start of a treatment and after treatment), the clinical response in the patients can be assessed.

Skin psoriasis is a major aspect of PsA, although the extent of activity in the skin does not necessarily correlate with joint activity. A number of instruments to assess skin psoriasis have been developed. A widely used instrument is the psoriasis area and severity index (PASI). The PASI assesses individual psoriatic lesions for erythema, thickness/induration, and scale, and then uses a formula to account for the overall extent of the body surface area of skin involved, with scores ranging from 0-72.

The Psoriatic Arthritis Response Criteria (PsARC) was specifically developed for PSA clinical trials. The PsARC is composed of four measures: 1) patient global assessment of disease activity (improvement of 1 on a 5 point Likert scale is required for a response), 2) physician global assessment of disease activity (improvement of 1 on a 5 point Likert scale is required for a response), 3) joint pain (reduction of 30% or more in total score, assessing
either 68 or 78 joints, using a 4 point scale is required for a response), and 4) joint swelling (reduction of 30% or more in total score, assessing either 66 or 76 joints using a 4 point scoring scale, is required for a response). In order to be a PsARC responded, patients must achieve improvement in 2 of 4 measures, one of which must be joint pain or swelling, without worsening in any measure.

As for the method of treatment reference is made to the description herein above, including further detailed information of the methods of prediction or identification which is obviously equally relevant to define the characteristics of the anti-inflammatory agent and the medical use hereof.

In one embodiment the subject is a patient e.g. an individual diagnosed or suffering from sign(s) or symptom(s) associated with inflammatory diseases or disorders as described herein. In one embodiment the patient is suffering from an autoimmune disease or disorders. In a specific embodiment the patient is an RA patient or suffering from symptoms of RA.

The patient may be naive for treatment of the inflammatory disease or disorder, meaning that no treatment for the inflammatory disease or disorder has been previously administered to said patient. For the methods according to the present invention, this is likely to be a rare occasion as various treatments, such as treatment with methotrexate (MTX), are usually considered before treatment with anti-inflammatory agents as described in connection with the present invention are considered.

Drugs that are presently used as first line drugs for treatment of the inflammatory disease or disorder will usually be administered to the patient before it is evaluated if a therapy according to the present invention has a high probability of success, but it is also possible to use the method as described herein as first line treatment of a patient suffering from autoimmune disease or disorders, in particular RA.

Drugs that a patient is being treated with or has previously been treated with may include one or more of the following: non-steroidal anti-inflammatory drugs (NSAIDs) like Aspirin™, Ibuprofen™ etc, Corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs) like Plaquenil™, Azulfidine™, Methotrexate™, etc, Copaxone™ (glatirimer acetate), Gilneya™ (fingolimod), antibiotics like Flagyl™, Cipro™, Topical (skin applied) medications including topical corticosteroids, vitamin D analogue creams (Dovonex™), topical retinoids (Tazorac™), moisturizers, topical immunomodulators (tacrolimus and pimecrolimus), coal tar, anthralin, and others, Raptiva™, Ustekinumab™, light therapy like PUVA, UVB and CellCept™ (mycophenolate mofetil). Also including biological anti-inflammatory agents including, but are not limited to, IFN-beta, Orencia™, Humira™, Enbrel™, Remicade™, Simponi™, Cimzia™, Tysabri™, Rituaxan/MabThera™,
Actemra/RoActemra™ and Kineret™ and the like. In one embodiment, this treatment is continued alongside the treatment according to the invention.

In one embodiment of the present invention, the patient is also being treated with methotrexate.

As described herein above multiple pathways are involved in inflammation and each pathway may be targeted at multiple levels. Inhibition of receptor signalling may be obtained by blocking a receptor, by providing a soluble receptor fragment or by preventing the ligand from binding or signalling through the receptor as exemplified by targeted biological therapeutics for treatment of certain autoimmune diseases and/or cancer. For example, patients with cancer may be treated with an antibody against CD20 (anti-CD20); patients with rheumatoid arthritis may be treated with anti-CD20, a TNF antagonist (soluble TNFR or anti-TNF-a); patients with psoriasis may be treated with anti-CD1 1a; patients with multiple sclerosis may be treated with IFN-beta; patients with ulcerative colitis may be treated with anti-TNF-a and patients with Crohn’s disease may be treated with anti-TNF-a or anti-a4 integrin. Unfortunately these treatments are not fully effective.

It has previously been described that member of the IL-10 family are useful targets for treatment of inflammatory diseases or disorders (WO 2001/46261).

The IL-10 family include IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26, which binds to the following receptor heterodimers:

- IL-10: Binds to IL-10R1 / IL-10R2
- IL-19: Binds to IL-20R1 / IL-20R2
- IL-20: Binds to IL-20R1 / IL-20R2 and IL-22R / IL-20R2
- IL-22: Binds to IL-22R / IL-10R2
- IL-24: Binds to IL-20R1 / IL-20R2 and IL-22R / IL-20R2
- IL-26: No known receptor

This receptor overlap suggests that, although some functionalities are specific for each family member there is also some shared effects. The exact role of each ligand and receptor in inflammatory diseases is not yet established but several have been linked to diseases. Examples include IL-20, that may be targeted by antibodies or receptor fragments, for treatment of certain inflammatory diseases (WO 2001/45261, IL-22 and IL-19, IL-17 (WO1 0025369, WO201 0102251), that are all members of the IL-10 family of cytokines.

Interleukin-19 (IL-19), IL-20, and interleukin-24 (IL-24) are members of the interleukin-10 (IL-10) cytokine family. As seen from the above these three interleukins bind and signal through the IL-20R1/IL-20R2 heterodimeric receptor. IL-20 and IL-24 (but not IL-19) are also ligands for the receptor complex composed of IL-20R2 and IL-22R1 (Parrish-
Novak et al., J BiolChem 2002; 277: 47517-47523; Dumoutier et al., J Immunol 2001; 167:3545-3549). It has been proposed that IL-19 and IL-20, along with other IL-10 family members, form a distinct subfamily of helical cytokines where at least IL-19 and IL-20 have similar three-dimensional structures (Chang et al., J BiolChem 2003; 278: 3308-13).

Antagonizing IL-20 activity using receptor fragments or monoclonal antibodies against IL-20 has therefore been described as a promising approach for treatment of various inflammatory conditions. Antigenic epitopes of human IL-20 (hIL-20), as well as rat, murine or human monoclonal antibodies binding hIL-20, have also been described e.g., WO2005052000, US20060142550, WO2007081465, WO1 9990271 03, WO20 10/000721, US71 15714 and US7151 166, which are hereby incorporated by reference as if fully set forth below. Anti-IL-20 monoclonal antibodies that can reduce IL-20-mediated activation of IL-20R1/IL-20R2 and IL-22R1/IL-20R2 receptor complexes in one or more species, including humans, have been described in WO 2010/000721.

The anti-inflammatory agent for use in a method according to the present invention may thus be an antagonist of the IL-20 pathway capable of reducing IL-20 mediated activation of both the IL-20R1/IL-20R2 and the IL-22R1/IL-20 receptor. The anti-inflammatory agent may be specific by not reducing receptor activation through the IL-19 or IL-24 receptor.

Based on an at least shared mode of action targeting of each ligand and receptor may provide a similar biological effect. An anti-inflammatory agent according to the invention may thus be an antagonist of IL-10 family members and their receptors e.g. a compound that regulates signalling of the above mentioned receptors by binding either ligand or receptor, whereby the biological activity of the ligand or the receptor is decreased. Assays for determining antagonistic activity of IL-10 family members are known in the art and also described in WO 201 0/000721.

In one embodiment, the anti-inflammatory agent is directed against a member of the IL-10 family of cytokines. In one embodiment, the anti-inflammatory agent is an antagonist of IL-10 family members and their receptors e.g. a compound that regulates signalling of the above mentioned receptors by binding either ligand or receptor, whereby the biological activity of the ligand or the receptor is decreased. In one embodiment, the anti-inflammatory agent is an antagonist of IL-20 or the IL-20 receptor. In one embodiment, the anti-inflammatory agent is an antagonistic anti-IL-20-antibody. In one embodiment, the anti-inflammatory agent is an antagonistic anti-hIL-20-antibody. In one embodiment, the anti-inflammatory agent is an anti-IL-20 antibody as described in WO1 9990271 03, WO201 0/000721, US71 15714 or US7151 166. In one embodiment, the anti-inflammatory
agent is NNC0109-0012. NNC0109-0012 is a human IgG4 mAb which binds to and neutralises the activity of IL-20. Once-weekly administration of NNC0109-0012 (3 mg/kg s.c.) for 12 weeks significantly reduced disease activity, improved ACR20/50/70 responses in RF- and anti-CCP-positive RA patients as shown herein below.

In one embodiment, the anti-inflammatory agent is an anti-hIL-20 antibody and is administered in an amount of 3 mg/kg subcutaneously once-weekly.

An anti-inflammatory agent for use according to the present invention may be in a pharmaceutical composition e.g. a pharmaceutical composition comprising an anti-inflammatory agent and a pharmaceutically acceptable carrier and a label. The anti-inflammatory agent or pharmaceutical composition may be suitable for oral, intravenous (i.v.) and/or subcutaneous (s.c.) administration. In one embodiment, the pharmaceutical composition comprising an anti-inflammatory agent for use according to the present invention is suitable for subcutaneous use. In one embodiment, the pharmaceutical composition comprising an anti-inflammatory agent for use according to the present invention is a pharmaceutical composition as described in WO201 1/104381. The anti-inflammatory agent, or pharmaceutical composition, may be in an appropriate delivery form, such as an administration device, for repeated administration such as once monthly or once weekly.

The methods herein may also take account of the administration route or regime, as the response may be dependent on the treatment regime applied.

The present invention also provides an article of manufacture comprising, packaged together, (i) a pharmaceutical composition comprising an anti-inflammatory agent and a pharmaceutically acceptable carrier and (ii) a label stating that the pharmaceutical composition can be used for treating a patient suffering from an autoimmune disease or disorder, wherein said patient is RF-positive and/or anti-CCP-positive.

Reference is made to the description herein above, including further detailed information of the method of treatment which is relevant to the article of manufacture of the present invention.

The invention as described herein is summarized, but not limited, in the following list of embodiments.

Embodiment 1. A method for treatment of an inflammatory disease or disorder in a patient suffering from said disease, which method comprises administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein said patient is rheumatoid factor (RF) -positive and/or anti-cyclic citrullinated peptide (CCP)-positive.
Embodiment 2. A method according to embodiment 1, wherein the patient is seropositive.

Embodiment 3. A method according to embodiment 1 or 2, wherein the inflammatory disease or disorder is an autoimmune disease or disorder.

Embodiment 4. A method according to embodiment 3, wherein the inflammatory disease or disorder is rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, or psoriatic arthritis.

Embodiment 5. A method according to embodiment 4, wherein the inflammatory disease or disorder is rheumatoid arthritis.

Embodiment 6. A method according to any of embodiments 1 to 5, wherein the anti-inflammatory agent is directed against a member of the IL-10 family of cytokines.

Embodiment 7. A method according to any of embodiments 1 to 6, wherein the anti-inflammatory agent is an antagonist of one or more members of the IL-10 family.

Embodiment 8. A method according to embodiment 7, wherein the anti-inflammatory agent is an antagonist of one or more of IL-10, IL19, IL-20, IL-22, IL-24 and IL-26.

Embodiment 9. A method according to embodiment 8, wherein the anti-inflammatory agent is an antagonist of one or more of IL-19, IL-20 and IL-24.

Embodiment 10. A method according to any of embodiments 1 to 9, wherein the anti-inflammatory agent is an antagonist of IL-20 or the IL-20 receptor.

Embodiment 11. A method according to any of embodiments 1 to 10, wherein the anti-inflammatory agent is an antagonist of IL-20.

Embodiment 12. A method according to any of embodiments 1 to 11, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 medicated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors.

Embodiment 13. A method according to any of embodiments 1 to 12, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 medicated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors, but not the IL19 or IL24 mediate receptor activation.

Embodiment 14. A method according to any of embodiments 1 to 11, wherein the anti-inflammatory agent is an antagonistic anti-IL-20-antibody.

Embodiment 15. A method according to embodiment 14, wherein the anti-inflammatory agent is an antagonistic anti-IL-20-antibody.

Embodiment 16. A method according to any of embodiments 1 to 15, wherein the anti-inflammatory agent is an anti-IL-20 antibody as described in W01 9990271 03, WO2010000721, US71 15714 or US7151 166.
Embodiment 17. A method according to any of embodiments 14 to 16, wherein the anti-IL-20 antibody is a human antibody.

Embodiment 18. A method according to any of embodiments 1 to 17, wherein the anti-inflammatory agent is NNC01 09-0012.

Embodiment 19. A method according to any of embodiments 14 to 18, wherein the anti-IL-20 antibody is administered in an amount of 3 mg/kg subcutaneously once-weekly.

Embodiment 20. A method according to any of embodiments 1 to 19, wherein the patient is also being treated with methotrexate.

Embodiment 21. A method according to any of embodiments 1 to 20, wherein the patient is being treated with or has previously been treated with methotrexate.

Embodiment 22. A method according to any of embodiments 1 to 21, wherein the patient is an inadequate responder to methotrexate treatment.

Embodiment 23. Use of an anti-inflammatory agent for treatment of an inflammatory disease or disorder in a patient suffering from said disease, wherein said patient is rheumatoid factor (RF)-positive and/or anti-cyclic citrullinated peptide (anti-CCP)-positive.

Embodiment 24. Use of an anti-inflammatory agent for the preparation of a pharmaceutical product for treatment of an inflammatory disease or disorder in a patient suffering from said disease, wherein said patient is rheumatoid factor (RF)-positive and/or anti-cyclic citrullinated peptide (anti-CCP)-positive.

Embodiment 25. Use according to embodiment 23 or embodiment 24, wherein the patient is seropositive.

Embodiment 26. Use according to any of embodiments 23 or 25, wherein the inflammatory disease or disorder is an autoimmune disease or disorder.

Embodiment 27. Use according to embodiment 26, wherein the inflammatory disease or disorder is rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, or psoriatic arthritis.

Embodiment 28. Use according to embodiment 27, wherein the inflammatory disease or disorder is rheumatoid arthritis.

Embodiment 29. Use according to any of embodiments 23 to 28, wherein the anti-inflammatory agent is directed against a member of the IL-10 family of cytokines.

Embodiment 30. Use according to any of embodiments 23 to 29, wherein the anti-inflammatory agent is an antagonist of one or more members of the IL-10 family.

Embodiment 31. Use according to embodiment 30, wherein the anti-inflammatory agent is an antagonist of one or more of IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26.
Embodiment 32. Use according to embodiment 31, wherein the anti-inflammatory agent is an antagonist of one or more of IL-19, IL-20 and IL-24.

Embodiment 33. Use according to any of embodiments 23 to 32, wherein the anti-inflammatory agent is an antagonist of IL-20 or the IL-20 receptor.

Embodiment 34. Use according to any of embodiments 23 to 33, wherein the anti-inflammatory agent is an antagonist of IL-20.

Embodiment 35. Use according to any of embodiments 23 to 34, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 medicated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors.

Embodiment 36. Use according to any of embodiments 23 to 35, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 medicated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors, but not the IL19 or IL24 medicate receptor activation.

Embodiment 37. Use according to any of embodiments 23 to 34, wherein the anti-inflammatory agent is an antagonistic anti-IL-20-antibody.

Embodiment 38. Use according to embodiment 37, wherein the anti-inflammatory agent is an antagonistic anti-hIL-20-antibody.

Embodiment 39. Use according to any of embodiments 23 to 38, wherein the anti-inflammatory agent is an anti-IL-20 antibody as described in W01 9990271 03.

Embodiment 40. Use according to any of embodiments 37 to 39, wherein the anti-IL-20 antibody is a human antibody.

Embodiment 41. Use according to any of embodiments 23 to 40, wherein the anti-inflammatory agent is NNC0109-0012.

Embodiment 42. Use according to any of embodiments 37 to 41, wherein the anti-IL-20 antibody is administered in an amount of 3 mg/kg subcutaneously once-weekly.

Embodiment 43. Use according to any of embodiments 23 to 42, wherein the patient is also being treated with methotrexate.

Embodiment 44. Use according to any of embodiments 23 to 43, wherein the patient is being treated with or has previously been treated with methotrexate.

Embodiment 45. Use according to any of embodiments 23 to 44, wherein the patient is an inadequate responder to methotrexate (MTX) treatment.

Embodiment 46. An article of manufacture comprising, packaged together, a pharmaceutical composition comprising an anti-inflammatory agent and a pharmaceutically acceptable carrier and a label stating that the pharmaceutical composition is for treating a
patient suffering from an auto-immune disease or disorder, wherein the patient is rheumatoid factor (RF)-positive and/or anti-cyclic citrullinated peptide (anti-CCP)-positive.

Embodiment 47. An article of manufacture according to embodiment 46, wherein said patient is seropositive.

Embodiment 48. An article of manufacture according to embodiment 46 or embodiment 47, wherein the inflammatory disease or disorder is an autoimmune disease or disorder.

Embodiment 49. An article of manufacture according to embodiment 48, wherein the inflammatory disease or disorder is rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, or psoriatic arthritis.

Embodiment 50. An article of manufacture according to embodiment 49, wherein the inflammatory disease or disorder is rheumatoid arthritis.

Embodiment 51. An article of manufacture according to any of embodiments 46 to 50, wherein the anti-inflammatory agent is directed against a member of the IL-10 family of cytokines.

Embodiment 52. An article of manufacture according to any of embodiments 46 to 51, wherein the anti-inflammatory agent is an antagonist of one or more members of the IL-10 family.

Embodiment 53. An article of manufacture according to embodiment 52, wherein the anti-inflammatory agent is an antagonist of one or more of IL-10, IL19, IL-20, IL-22, IL-24 and IL-26.

Embodiment 54. An article of manufacture according to embodiment 53, wherein the anti-inflammatory agent is an antagonist of one or more of IL-19, IL-20 and IL-24.

Embodiment 55. An article of manufacture according to any of embodiments 46 to 54, wherein the anti-inflammatory agent is an antagonist of IL-20 or the IL-20 receptor.

Embodiment 56. An article of manufacture according to any of embodiments 46 to 55, wherein the anti-inflammatory agent is an antagonist of IL-20.

Embodiment 57. An article of manufacture according to any of embodiments 46 to 56, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 medicated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors

Embodiment 58. An article of manufacture according to any of embodiments 46 to 57, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 medicated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors, but not the IL19 or IL24 medicate receptor activation.
Embodiment 59. An article of manufacture according to any of embodiments 46 to 56, wherein the anti-inflammatory agent is an antagonistic anti-IL-20-antibody.

Embodiment 60. An article of manufacture according to embodiment 59, wherein the anti-inflammatory agent is an antagonistic anti-hIL-20-antibody.

Embodiment 61. An article of manufacture according to any of embodiments 46 to 60, wherein the anti-inflammatory agent is an anti-IL-20 antibody as described in W01 9990271 03, WO201 0000721, US71 15714 or US7151 166.

Embodiment 62. An article of manufacture according to any of embodiments 59 to 61, wherein the anti-IL-20 antibody is a human antibody.

Embodiment 63. An article of manufacture according to any of embodiments 46 to 62, wherein the anti-inflammatory agent is NNC0109-0012.

Embodiment 64. An anti-inflammatory agent for treatment of an inflammatory disease or disorder in a patient suffering from said disease, wherein said patient is RF-positive and/or anti-CCP-positive.

Embodiment 65. An anti-inflammatory agent according to embodiment 64, wherein the patient is seropositive.

Embodiment 66. An anti-inflammatory agent according to any of embodiments 64 or 65, wherein the inflammatory disease or disorder is an autoimmune disease or disorder.

Embodiment 67. An anti-inflammatory agent according to embodiment 66, wherein the inflammatory disease or disorder is rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, or psoriatic arthritis.

Embodiment 68. An anti-inflammatory agent according to embodiment 67, wherein the inflammatory disease or disorder is rheumatoid arthritis.

Embodiment 69. An anti-inflammatory agent according to any of embodiments 64 to 68, wherein the anti-inflammatory agent is directed against a member of the IL-10 family of cytokines.

Embodiment 70. An anti-inflammatory agent according to any of embodiments 64 to 69, wherein the anti-inflammatory agent is an antagonist of one or more members of the IL-10 family.

Embodiment 71. An anti-inflammatory agent according to embodiment 70, wherein the anti-inflammatory agent is an antagonist of one or more of IL-10, IL19, IL-20, IL-22, IL-24 and IL-26.

Embodiment 72. An anti-inflammatory agent according to embodiment 71, wherein the anti-inflammatory agent is an antagonist of one or more of IL-19, IL-20 and IL-24.
Embodiment 73. An anti-inflammatory agent according to any of embodiments 64 to 72, wherein the anti-inflammatory agent is an antagonist of IL-20 or the IL-20 receptor.

Embodiment 74. An anti-inflammatory agent according to any of embodiments 64 to 73, wherein the anti-inflammatory agent is an antagonist of IL-20.

Embodiment 75. An anti-inflammatory agent according to any of embodiments 64 to 74, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 mediated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors.

Embodiment 76. An anti-inflammatory agent according to any of embodiments 64 to 75, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 mediated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors, but not the IL19 or IL24 medicate receptor activation.

Embodiment 77. An anti-inflammatory agent according to any of embodiments 64 to 76, wherein the anti-inflammatory agent is an antagonistic anti-IL-20-antibody.

Embodiment 78. An anti-inflammatory agent according to embodiment 77, wherein the anti-inflammatory agent is an antagonistic anti-hIL-20-antibody.

Embodiment 79. An anti-inflammatory agent according to any of embodiments 64 to 78, wherein the anti-inflammatory agent is an anti-IL-20 antibody as described in WO1 9990271 03, WO201 0000721 , US71 15714 or US7151 166.

Embodiment 80. An anti-inflammatory agent according to any of embodiments 77 to 79, wherein the anti-IL-20 antibody is a human antibody.

Embodiment 81. An anti-inflammatory agent according to any of embodiments 64 to 80, wherein the anti-inflammatory agent is NNC0109-0012.

Embodiment 82. An anti-inflammatory agent according to any of embodiments 77 to 81, wherein the anti-IL-20 antibody is administered in an amount of 3 mg/kg subcutaneously once-weekly.

Embodiment 83. An anti-inflammatory agent according to any of embodiments 64 to 82, wherein the patient is also being treated with methotrexate.

Embodiment 84. An anti-inflammatory agent according to any of embodiments 64 to 83, wherein the patient is being treated with or has previously been treated with methotrexate.

Embodiment 85. An anti-inflammatory agent according to any of embodiments 64 to 84, wherein the patient is an inadequate responder to methotrexate (MTX) treatment.

Embodiment 86. A pharmaceutical product comprising an anti-inflammatory agent for treatment of an inflammatory disease or disorder in a patient suffering from said disease, wherein said patient is RF-positive and/or anti-CCP-positive.
Embodiment 87. A pharmaceutical product according to embodiment 86, wherein said patient is seropositive.

Embodiment 88. A pharmaceutical product according to embodiment 86 or embodiment 87, wherein the inflammatory disease or disorder is an autoimmune disease or disorder.

Embodiment 89. A pharmaceutical product according to embodiment 88, wherein the inflammatory disease or disorder is rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, or psoriatic arthritis.

Embodiment 90. A pharmaceutical product according to embodiment 89, wherein the inflammatory disease or disorder is rheumatoid arthritis.

Embodiment 91. A pharmaceutical product according to any of embodiments 86 to 90, wherein the anti-inflammatory agent is directed against a member of the IL-10 family of cytokines.

Embodiment 92. A pharmaceutical product according to any of embodiments 86 to 91, wherein the anti-inflammatory agent is an antagonist of one or more members of the IL-10 family.

Embodiment 93. A pharmaceutical product according to embodiment 92, wherein the anti-inflammatory agent is an antagonist of one or more of IL-10, IL19, IL-20, IL-22, IL-24 and IL-26.

Embodiment 94. A pharmaceutical product according to embodiment 93, wherein the anti-inflammatory agent is an antagonist of one or more of IL-19, IL-20 and IL-24.

Embodiment 95. A pharmaceutical product according to any of embodiments 86 to 94, wherein the anti-inflammatory agent is an antagonist of IL-20 or the IL-20 receptor.

Embodiment 96. A pharmaceutical product according to any of embodiments 86 to 95, wherein the anti-inflammatory agent is an antagonist of IL-20.

Embodiment 97. A pharmaceutical product according to any of embodiments 86 to 96, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 mediated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors.

Embodiment 98. A pharmaceutical product according to any of embodiments 86 to 97, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 mediated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors, but not the IL19 or IL24 mediate receptor activation.

Embodiment 99. A pharmaceutical product according to any of embodiments 86 to 96, wherein the anti-inflammatory agent is an antagonistic anti-IL-20-antibody.
Embodiment 100. A pharmaceutical product according to embodiment 99, wherein the anti-inflammatory agent is an antagonistic anti-hIL-20-antibody.

Embodiment 101. A pharmaceutical product according to any of embodiments 86 to 100, wherein the anti-inflammatory agent is an anti-IL-20 antibody as described in WO1 9990271 03, WO201 0000721 , US71 15714 or US7151 166.

Embodiment 102. A pharmaceutical product according to any of embodiments 99 to 101, wherein the anti-IL-20 antibody is a human antibody.

Embodiment 103. A pharmaceutical product according to any of embodiments 86 to 102, wherein the anti-inflammatory agent is NNC0109-0012.

While certain features of the invention have been illustrated, exemplified and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended embodiments are intended to cover all such modifications and changes as fall within the spirit of the invention.

EXAMPLES

Example 1 - Treatment with anti-hIL-20 antibody (NNC01 09-0012) reduced disease activity primarily in RF-positive and/or anti-CCP-positive patients

A total of 67 patients (51 females: 16 males) with active RA (1987 ACR classification criteria) were randomised in a multicentre, double-blind, multiple-dose, placebo-controlled trial. Patients were dosed once-weekly for 12 weeks and followed for additional 13 weeks. Patients were 18 to 75 years old with active RA (DAS28-CRP >4.5 as well as ≥5 swollen and ≥5 tender joints of the 28 joint count) and on stable methotrexate (MTX) treatment (>7.5 to <25 mg/week) for at least 4 weeks prior to randomisation. Patients were randomised in a 2:1 ratio (45 NNC01 09-001 2: 22 placebo).

At 12 weeks, mean changes in DAS28-CRP were significantly greater for patients treated with NNC0109-0012 compared to placebo (-0.88; p=0.020). Significant reduction of disease activity (-0.5; p=0.011) was observed already after 1 week of treatment and maintained for 5 weeks after end of treatment. The reduction of disease activity was primarily observed in patients, who were RF-positive and/or anti-CCP-positive (p=0.0003) and maintained throughout 25 weeks. NNC0109-0012 also induced a higher proportion of subjects with improved EULAR response compared to placebo after 12 weeks’ treatment (p=0.014). ACR 20/50/70 responses were significantly higher in NNC0109-0012-treated patients being RF-positive and/or anti-CCP-positive, compared to placebo-treated patients (p=0.027, 0.045 and 0.018 respectively), although the trial was not powered to detect
differences in ACR20/50/70 responses. NNC01 09-001 2 also significantly shortened the time to first ACR20/50/70 responses compared to placebo (p=0.004, 0.029 and 0.047 respectively). No changes in CRP, RF, anti-CCP or MMP-3 levels were observed throughout the trial. The NNC01 09-001 2 serum concentrations increased with repeated dosing approaching steady state after administration of the 12th dose.

In this trial, NNC0109-0012 administered at 3 mg/kg s.c. once-weekly for 12 weeks in combination with methotrexate (MTX) significantly reduced disease activity and improved ACR20/50/70 responses in RF- and/or anti-CCP-positive patients. The results are shown in Table 2.

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Mean difference (3 mg/kg – Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF negative</td>
<td>N/Group 13, 0.59, 95% CI [-]</td>
</tr>
<tr>
<td>RF positive</td>
<td>N/Group 32, -1.52, 95% CI [-]</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>N/Group 14, 0.45, 95% CI [-]</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>N/Group 31, -1.45, 95% CI [-]</td>
</tr>
<tr>
<td>Seronegative</td>
<td>N/Group 16, 0.49, 95% CI [-]</td>
</tr>
<tr>
<td>Seropositive</td>
<td>N/Group 29, -1.61, 95% CI [-]</td>
</tr>
</tbody>
</table>

Table 2 shows the interactions between change in DAS28 (CRP) and baseline characteristics.
CLAIMS

1. A pharmaceutical product comprising an anti-inflammatory agent, directed against a member of the IL-10 family of cytokines, for treatment of rheumatoid arthritis (RA) in a patient suffering from RA, wherein said patient is rheumatoid factor (RF)-positive and/or anti-cyclic citrullinated peptide(CCP)-positive.

2. A pharmaceutical product according to claim 1, wherein the anti-inflammatory agent is an antagonist of one or more members of the IL-10 family.

3. A pharmaceutical product according to any of claims 1 to 2, wherein the anti-inflammatory agent is an antagonist of IL-20 or the IL-20 receptor.

4. A pharmaceutical product according to any of claims 1 to 3, wherein the anti-inflammatory agent is an antagonist of IL-20.

5. A pharmaceutical product according to claim 4, wherein the anti-inflammatory agent is an antagonistic anti-IL-20-antibody.

6. A pharmaceutical product according to claim 5, wherein the anti-IL-20 antibody is a human antibody.

7. A pharmaceutical product according to any of claims 1 to 6, wherein the patient is also being treated with methotrexate.

8. Use of an anti-inflammatory agent, directed against a member of the IL-10 family of cytokines, for the preparation of a pharmaceutical product for treatment of an rheumatoid arthritis (RA) in a patient suffering from RA, wherein said patient is rheumatoid factor (RF)-positive and/or anti-cyclic citrullinated peptide(CCP)-positive.

9. Use according to claim 8, wherein the anti-inflammatory agent is an antagonistic anti-IL-20-antibody.

10. Use according to claim 9, wherein the anti-IL-20 antibody is a human antibody.
11. An article of manufacture comprising, packaged together, a pharmaceutical composition comprising an anti-inflammatory agent, directed against a member of the IL-10 family of cytokines, and a pharmaceutically acceptable carrier and a label stating that the pharmaceutical composition is for treating a patient suffering from rheumatoid arthritis (RA), wherein the patient is rheumatoid factor (RF)-positive and/or anti-cyclic citrullinated peptide (CCP)-positive.

12. An anti-inflammatory agent directed against a member of the IL-10 family of cytokines, for treatment of rheumatoid arthritis (RA) in a patient suffering from RA, wherein said patient is rheumatoid factor (RF)-positive and/or anti-cyclic citrullinated peptide (CCP)-positive.

13. A method for treatment of rheumatoid arthritis (RA) in a patient suffering from RA, which method comprises administering a therapeutic amount of an anti-inflammatory agent, directed against a member of the IL-10 family of cytokines, to said patient, wherein said patient is rheumatoid factor (RF)-positive and anti-cyclic citrullinated peptide (CCP)-positive.

14. A method of treatment according to claim 13, wherein the anti-inflammatory agent is an antagonistic anti-IL-20-antibody.

15. A method of treatment according to claim 14, wherein the anti-IL-20 antibody is a human antibody.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K16/28 G01N33/564 A61P19/02

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K G01N A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>X</td>
<td>JÉRÉMI E SELLAM ET AL: &quot;B cell acti vity on biomarkers as predicti ve factors for the response to rituximab in rheumatoid arthritis: A six-month, national, multicenter, open-label study&quot;, ARTHRITIS &amp; RHEUMATISM, vol. 63, no. 4, 1 April 1 2011 (2011-04-01), pages 933-938, XP055030352, ISSN: 0004-3591, DOI: 10.1002/art.30233 e.g. abstract, paragraph 3; the whole document</td>
<td>I-5,7-9, II-14</td>
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<td>X</td>
<td>US 2009/311255 Al (BRUNETTA PAUL G [US] ET AL) 17 December 2009 (2009-12-17) e.g. paragraph 67, 75, 126, 134, 203, 204, 229; claim 10; the whole document</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search

23 May 2013

Date of mailing of the international search report

03/06/2013

Name and mailing address of the ISA

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Gruber, Andreas

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