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(54) Titre : UTILISATION D'UN INHIBITEUR DU TNF ALPHA POUR LE TRAITEMENT DE LA POLYARTHRITE EROSIVE
(54) Title: USE OF TNFA INHIBITOR FOR TREATMENT OF EROSIVE POLYARTHRITIS

(57) Abrégé/Abstract:
The invention describes methods of treating erosive polyarthritis comprising administering a TNFα antibody, or antigen-binding portion thereof. The invention also describes a method for testing the efficacy of a TNFo; antibody, or antigen- binding portion thereof, for the treatment of erosive polyarthritis.

Abstract

The invention describes methods of treating erosive polyarthritis comprising administering a TNF.alpha. antibody, or antigen-binding portion thereof. The invention also describes a method for testing the efficacy of a TNFo; antibody, or antigen-binding portion thereof, for the treatment of erosive polyarthritis.

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THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

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USE OF TNFα INHIBITOR FOR TREATMENT OF EROSIVE POLYARTHRITIS

RELATED APPLICATIONS

This application claims priority to U.S. Publication No. US 2007-0071747 A1 , which was filed on May 16, 2005.

This application is related to U.S. Patent Nos. 6,090,382, 6,258,562, and 6,509,015. This application is also related to U.S. Patent Publication No. US 2003-0092059 A1 filed March 7, 2001; U.S. Patent Publication No. US 2003-0235585 A1 , filed June 5, 2002; and U.S. Patent Publication No. US 2004-0009172 A1 , filed April 26, 2002; U.S. Patent Publication No. US 2006-0153846 A1, filed August 16, 2002; U.S. Patent Publication No. US 2004-0166111 A1 , filed October 24, 2003; U.S. Patent Publication No. US 2004-0126372 A1 , filed July 18, 2003; U.S. Patent Publication No. US 2004-0126372 A1 , filed July 18, 2003; U.S. Patent Publication No. US 2004-0131614 A1, filed July 18, 2003; U.S. Patent Publication No. US 2004-0126373 A1, filed July 18, 2003; U.S. Patent Publication No. US 2004-0151722 A1, filed July 18, 2003; U.S. Patent Publication No. US 2004-0136991 A1, filed July 18, 2003; U.S. Patent Publication No. US 2004-0136990 A1, filed July 18, 2003; U.S. Patent Publication No. US 2004-0219142 A1, filed July 18, 2003; U.S. Patent Publication No. US 2004-0136989 A1, filed July 18, 2003.

This application is also related to PCT/US05/12007 (WO 05/110452), filed April 11, 2005, and U.S.Publication No. US 2006-0083741 A1, filed October 6, 2005.

BACKGROUND OF THE INVENTION

Polyarthritis may be erosive or non-erosive. In the erosive form, the underlying disease process erodes the cartilage; in the non-erosive form, the cartilage is not affected. Erosive polyarthritis is an inflammatory disease of joints that results in tissue destruction and erosion within the affected joint. Erosive polyarthritis occurs in many patients having inflammatory disorders, including psoriatic arthritis, spondylarthropathies, such as ankylosing spondylitis, and juvenile rheumatoid arthritis. Many of the current treatments of disorders in which erosive polyarthritis is a manifestation fail to focus on decreasing radiographic progression of joint disease.

SUMMARY OF THE INVENTION

There is a need to treat erosive polyarthritis in a safe and effective manner. While traditional treatments of erosive polyarthritis, such as administration of DMARDs, may

delay disease progression, traditional treatments may be slow to become effective, may lose efficacy with time, and may be associated with potentially serious toxic effects. The present invention provides a safe and effective means for treating erosive polyarthritis and slowing the progression of joint disease.

The present invention includes methods of treating erosive polyarthritis comprising administering TNF inhibitors. The invention also provides a method for treating a human subject suffering from erosive polyarthritis, comprising administering to the subject an anti-TNFα antibody, such that erosive polyarthritis is treated. Kits and articles of manufacture comprising a TNFα inhibitor are also included in the invention.

In one embodiment, the TNFα inhibitor is selected from the group consisting of an anti-TNFα antibody, or an antigen-binding portion thereof, a TNF fusion protein, or a recombinant TNF binding protein. In one embodiment, the TNF fusion protein is etanercept. In another embodiment, the anti-TNFα antibody, or antigen-binding portion thereof, is an antibody selected from the group consisting of a humanized antibody, a chimeric antibody, and a multivalent antibody. In one embodiment, the anti-TNFα antibody, or antigen-binding portion thereof, is infliximab, golimumab, or adalimumab. In still another embodiment, the anti-TNFα antibody, or antigen-binding portion thereof, is a human antibody.

The invention provides a method for treating a human subject suffering from erosive polyarthritis, comprising administering to the subject a TNFα antibody, or antigen-binding portion thereof, such that erosive polyarthritis is treated.

In one embodiment, the TNFα antibody, or antigen-binding portion thereof, is an antibody selected from the group consisting of a humanized antibody, a chimeric antibody, and a multivalent antibody. In another embodiment, the TNFα antibody, or antigen-binding portion thereof, is infliximab or golimumab.

In one embodiment, the TNFα antibody, or antigen-binding portion thereof, is a human antibody. In one embodiment, the human antibody, or an antigen-binding portion thereof, dissociates from human TNFα with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of 1×10^{-3} s^{-1} or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less. In another embodiment, the human antibody, or an antigen-binding portion thereof, has the following characteristics:

a) dissociates from human TNFα with a K_{off} rate constant of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12. In still another embodiment, the human antibody, or an antigen-binding portion thereof, comprises a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8, and comprises a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11. In yet another embodiment, the human antibody, or an antigen-binding portion thereof, comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2. In one embodiment, the human antibody, or an antigen-binding portion thereof, is adalimumab.

In one embodiment, the TNFα antibody, or antigen-binding portion thereof, is administered to the subject on a biweekly dosing regimen.

In one embodiment, the subject has a disorder in which TNFα activity is detrimental. In one embodiment, the disorder in which TNFα activity is detrimental is selected from the group consisting of psoriatic arthritis, ankylosing spondylitis, and juvenile rheumatoid arthritis. In another embodiment, the disorder in which TNFα activity is detrimental is psoriatic arthritis. In still another embodiment, the disorder in which TNFα activity is detrimental is rheumatoid arthritis.

In one embodiment, the invention includes further comprising administering an additional therapeutic agent to the subject. In one embodiment, the additional therapeutic agent is methotrexate. In another embodiment, the additional therapeutic agent is a Disease Modifying Anti-Rheumatic Drug (DMARD) or a Nonsteroidal Antiinflammatory Drug (NSAID) or a steroid, or any combination thereof.

The invention includes a method for testing the efficacy of a TNFα antibody, or antigen-binding portion thereof, for decreasing radiographic progression of joint disease associated with erosive polyarthritis. In one embodiment, the method for testing the efficacy of a TNFα antibody, or antigen-binding portion thereof, comprises determining the efficacy of the TNFα antibody, or antigen-binding portion thereof, using a modified Total Sharp Score (mTSS) of a patient population having joint disease associated with erosive polyarthritis and a mTSS of the patient population following administration of the TNFα antibody, or antigen-binding portion thereof, wherein no change or a decrease in the mTSS indicates that the TNFα antibody, or antigen-binding portion thereof, is

efficacious for decreasing radiographic progression of joint disease associated with erosive polyarthritis. In one embodiment, the decrease in the mTSS is about -0.2.

In one embodiment, the patient population also has a disorder in which TNFα is detrimental. In one embodiment, the disorder in which TNFα activity is detrimental is selected from the group consisting of psoriatic arthritis, ankylosing spondylitis, and juvenile rheumatoid arthritis.

In one embodiment, the TNFα antibody, or antigen-binding portion thereof, is an antibody selected from the group consisting of a humanized antibody, a chimeric antibody, and a multivalent antibody. In one embodiment, the TNFα antibody, or antigen-binding portion thereof, is infliximab or golimumab. In another embodiment, the TNFα antibody, or antigen-binding portion thereof, is a human antibody. In one embodiment, the human antibody, or an antigen-binding portion thereof, dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and a K_{off} rate constant of 1 x 10^{-3} s^{-1} or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-7} M or less.

In another embodiment, the human antibody, or an antigen-binding portion thereof, has the following characteristics:

a) dissociates from human TNFα with a K_{off} rate constant of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12. In still another embodiment, the human antibody, or an antigen-binding portion thereof, comprises a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8, and comprises a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11.

In another embodiment, the human antibody, or an antigen-binding portion thereof, comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the

amino acid sequence of SEQ ID NO: 2. In still another embodiment of the invention, the human antibody, or an antigen-binding portion thereof, is adalimumab.

In one embodiment of the invention, the TNFα antibody, or antigen-binding portion thereof, is administered to the subject on a biweekly dosing regimen. In one embodiment, antibody, or antigen-binding portion thereof, is administered in combination with an additional therapeutic agent, including, for example methotrexate

The invention describes a method for monitoring the effectiveness of a TNFα antibody, or antigen-binding portion thereof, for the treatment of erosive polyarthritis in a human subject comprising determining the effectiveness of the TNFα antibody, or antigen-binding portion thereof, using a baseline modified Total Sharp Score (mTSS) of a patient population having erosive polyarthritis and a mTSS score of a patient population following administration of the TNFα antibody, or antigen-binding portion thereof, wherein a result selected from the group consisting of a decrease in the mTSS in about 9-27% of the patient population; no change in the mTSS in about 65-73% of the patient population; and an increase in the mTSS in about 9-28% of the patient population, indicates that the TNFα antibody, or antigen-binding portion thereof, is effective at treating erosive polyarthritis.

In one embodiment of the invention, the TNFα antibody, or antigen-binding portion thereof, is an antibody selected from the group consisting of a humanized antibody, a chimeric antibody, and a multivalent antibody. In one embodiment, the TNFα antibody, or antigen-binding portion thereof, is infliximab or golimumab. In another embodiment, the TNFα antibody, or antigen-binding portion thereof, is a human antibody.

In another embodiment, the human antibody, or an antigen-binding portion thereof, dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and a K_{off} rate constant of 1 x 10^{-3} s^{-1} or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-7} M or less. In still another embodiment, the human antibody, or an antigen-binding portion thereof, is adalimumab.

The invention also includes a method for testing the efficacy of a TNFα antibody, or antigen-binding portion thereof, to treat erosive polyarthritis associated with psoriatic arthritis, comprising determining the efficacy of the TNFα antibody, or antigen-binding portion thereof, using a baseline modified Total Sharp Score (mTSS) and either a baseline Psoriasis Area and Severity Index (PASI) score or a baseline ACR score of a patient population having erosive polyarthritis in comparison with the mTSS and either the PASI or the ACR score of the patient population following administration of the NFα antibody, or antigen-binding portion thereof, wherein no change or a decrease in the mTSS and either an ACR20 response achieved in at least about 57% or a

PASI 50 response achieved in at least about 75% of the patient population, indicates that the TNFα antibody, or antigen-binding portion thereof, is efficacious for the treatment of erosive polyarthritis associated with psoriatic arthritis. In one embodiment, an ACR50 response is achieved in at least about 39% of the patient population. In another embodiment, an ACR70 response is achieved in at least about 23% of the patient population. In still another embodiment, a PASI75 response is achieved in at least about 59% of the patient population. In yet another embodiment, a PASI90 response is achieved in at least about 42% of the patient population. In one embodiment, the TNFα antibody, or antigen-binding portion thereof, is adalimumab.

The invention describes a method for treating erosive polyarthritis comprising administering to a subject having erosive polyarthritis, adalimumab on a biweekly dosing regimen. In one embodiment, the dose of adalimumab is about 40 mg.

The invention also includes a kit comprising a pharmaceutical composition comprising a TNFα antibody, or an antigen-binding portion thereof, and a pharmaceutically acceptable carrier, and instructions for administration of the pharmaceutical composition for the treatment of erosive polyarthritis. In one embodiment, the pharmaceutical composition comprises the TNFα antibody, or antigen-binding portion thereof, adalimumab. In one embodiment, pharmaceutical composition comprises about 40 mg of adalimumab. In another embodiment, the kit further comprises an additional therapeutic agent. In one embodiment, the additional therapeutic agent is methotrexate.

The invention describes an article of manufacture comprising a packaging material; a TNFα antibody, or antigen-binding portion thereof; and a label or package insert contained within the packaging material indicating that the TNFα antibody, or antigen-binding portion thereof, can be used for the treatment of erosive polyarthritis.

The invention also includes an article of manufacture comprising a packaging material; a TNFα antibody, or antigen-binding portion thereof,; and a label or package insert contained within the packaging material indicating that the TNFα antibody, or antigen-binding portion thereof, can be used for to inhibit radiographic progression of joint disease.

In one embodiment, the article of manufacture comprises an antibody selected from the group consisting of a humanized antibody, a chimeric antibody, and a multivalent antibody.

In one embodiment, the TNFα antibody, or antigen-binding portion thereof, is infliximab or golimumab. In another embodiment, the TNFα antibody, or antigen-binding portion thereof, is a human antibody. In one embodiment, the human antibody, or an antigen-binding portion thereof, dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and a K_{off} rate constant of 1 x 10^{-3} s^{-1} or less, both determined by surface

plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less. In another embodiment, the human antibody, or an antigen-binding portion thereof, is adalimumab.

FIGURES

Figures 1a and 1b show a diagram of the modified total sharp score (mTSS) (Figure 1a) and radiographic findings associated with PsA (Figure 1b).

Figure 2 shows a cumulative distribution function plot of modified Total Sharps Score (mTSS). The graph shows the change in baseline to Week 24 for subjects with both baseline and Week 24 radiographic films.

Figures 3a and 3b show cumulative distribution function plots of mTSS of subjects with (Figure 3a) and without (Figure 3b) methotrexate (mtx).

Figure 4 shows a graph of the mean change in mTSS at Week 48.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

In order that the present invention may be more readily understood, certain terms are first defined.

The term "human TNFα" (abbreviated herein as hTNFα, or simply hTNF), as used herein, is intended to refer to a human cytokine that exists as a 17 kD secreted form and a 26 kD membrane associated form, the biologically active form of which is composed of a trimer of noncovalently bound 17 kD molecules. The structure of hTNFα is described further in, for example, Pennica, D., *et al.* (1984) *Nature* 312:724-729; Davis, J.M., *et al.* (1987) *Biochemistry* 26:1322-1326; and Jones, E.Y., *et al.* (1989) *Nature* 338:225-228. The term human TNFα is intended to include recombinant human TNFα (rhTNFα), which can be prepared by standard recombinant expression methods or purchased commercially (R & D Systems, Catalog No. 210-TA, Minneapolis, MN). TNFα is also referred to as TNF.

The term "TNFα inhibitor" refers to an agent which interferes with TNFα activity. The term also includes each of the anti-TNFα human antibodies and antibody portions described herein as well as those described in U.S. Patent Nos. 6,090,382; 6,258,562; 6,509,015, and in U.S. Patent Application Serial Nos. 09/801185 and 10/302356. In one embodiment, the TNFα inhibitor used in the invention is an anti-TNFα antibody, or a fragment thereof, including infliximab (Remicade®, Johnson and Johnson; described in U.S. Patent No. 5,656,272),
CDP571 (a humanized monoclonal anti-TNF-alpha IgG4 antibody), CDP 870 (a humanized monoclonal anti-TNF-alpha antibody fragment), an anti-TNF dAb (Peptech),

CNTO 148 (golimumab; Medarex and Centocor, see WO 02/12502), and adalimumab (Humira® Abbott Laboratories, a human anti-TNF mAb, described in US 6,090,382 as D2E7). Additional TNF antibodies which can be used in the invention are described in U.S. Patent Nos. 6,593,458; 6,498,237; 6,451,983; and 6,448,380..

In another embodiment, the TNFα inhibitor is a TNF fusion protein, e.g., etanercept (Enbrel®, Amgen; described in WO 91/03553 and WO 09/406476.). In another embodiment, the TNFα inhibitor is a recombinant TNF binding protein (r-TBP-I) (Serono).

The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The antibodies of the invention are described in further detail in U.S. Patent Nos. 6,090,382; 6,258,562; and 6,509,015.

The term "antigen-binding portion" of an antibody (or simply "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (*e.g.*, hTNFα). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.* (1989) *Nature* 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules

(known as single chain Fv (scFv); see *e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883) . Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. Other forms of single chain antibodies, such as diabodies are also encompassed. Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see *e.g.*, Holliger *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Poljak *et al.* (1994) *Structure* 2:1121-1123). The antibody portions of the invention are described in further detail in U.S. Patent Nos. 6,090,382, 6,258,562, 6,509,015.

Binding fragments are produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins. Binding fragments include Fab, Fab', $F(ab')_2$, Fabc, Fv, single chains, and single-chain antibodies. Other than "bispecific" or "bifunctional" immunoglobulins or antibodies, an immunoglobulin or antibody is understood to have each of its binding sites identical. A "bispecific" or "bifunctional antibody" is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, *e.g.*, Songsivilai & Lachmann, *Clin. Exp. Immunol.* 79:315-321 (1990); Kostelny *et al.*, *J. Immunol.* 148, 1547-1553 (1992).

A "conservative amino acid substitution", as used herein, is one in which one amino acid residue is replaced with another amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine).

The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from

the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic for human immunoglobulin genes (see *e.g.*, Taylor *et al.* (1992) *Nucl. Acids Res.* 20:6287) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds hTNFα is substantially free of antibodies that specifically bind antigens other than hTNFα). An isolated antibody that specifically binds hTNFα may, however, have cross-reactivity to other antigens, such as TNFα molecules from other species (discussed in further detail below). Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

A "neutralizing antibody", as used herein (or an "antibody that neutralized hTNFα activity"), is intended to refer to an antibody whose binding to hTNFα results in inhibition of the biological activity of hTNFα. This inhibition of the biological activity of hTNFα can be assessed by measuring one or more indicators of hTNFα biological activity, such as hTNFα-induced cytotoxicity (either *in vitro* or *in vivo*), hTNFα-induced cellular activation and hTNFα binding to hTNFα receptors. These indicators of hTNFα biological activity can be assessed by one or more of several standard *in vitro* or *in vivo* assays known in the art (see U.S. Patent No. 6,090,382). Preferably, the ability of an antibody to neutralize hTNFα activity is assessed by inhibition of hTNFα-induced cytotoxicity of L929 cells. As an additional or alternative parameter of hTNFα activity, the ability of an antibody to inhibit hTNFα-induced expression of ELAM-1 on HUVEC, as a measure of hTNFα-induced cellular activation, can be assessed.

The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, NJ). For further descriptions, see Example 1 of U.S. Patent 6,258,562 and Jönsson *et al.* (1993) *Ann. Biol. Clin.* 51:19; Jönsson *et al.* (1991) *Biotechniques* 11:620-627; Johnsson *et al.* (1995) *J. Mol. Recognit.* 8:125; and Johnnson *et al.* (1991) *Anal.Biochem.*198:268.

The term "K_{off}", as used herein, is intended to refer to the off rate constant for dissociation of an antibody from the antibody/antigen complex.

The term "K_d", as used herein, is intended to refer to the dissociation constant of a particular antibody-antigen interaction.

The term "IC_{50}" as used herein, is intended to refer to the concentration of the inhibitor required to inhibit the biological endpoint of interest, *e.g.*, neutralize cytotoxicity activity.

The term "nucleic acid molecule", as used herein, is intended to include DNA molecules and RNA molecules. A nucleic acid molecule may be single-stranded or double-stranded, but preferably is double-stranded DNA.

The term "isolated nucleic acid molecule", as used herein in reference to nucleic acids encoding antibodies or antibody portions (*e.g.*, VH, VL, CDR3) that bind hTNFα, is intended to refer to a nucleic acid molecule in which the nucleotide sequences encoding the antibody or antibody portion are free of other nucleotide sequences encoding antibodies or antibody portions that bind antigens other than hTNFα, which other sequences may naturally flank the nucleic acid in human genomic DNA. Thus, for example, an isolated nucleic acid of the invention encoding a VH region of an anti-hTNFα antibody contains no other sequences encoding other VH regions that bind antigens other than hTNFα.

The term "vector", as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In

general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

The term "dose," as used herein, refers to an amount of TNFα inhibitor which is administered to a subject.

The term "multiple-variable dose" includes different doses of a TNFα inhibitor which are administered to a subject for therapeutic treatment. "Multiple-variable dose regimen" or "multiple-variable dose therapy" describe a treatment schedule which is based on administering different amounts of TNFα inhibitor at various time points throughout the course of treatment. In one embodiment, the invention describes a multiple-variable dose method of treatment of erosive polyarthritis comprising an induction phase and a treatment phase, wherein a TNFα inhibitor is administered at a higher dose during the induction phase than the treatment phase. Multiple-variable dose regimens are described in WIPO Publication No. WO 2005/110452 .

The term "dosing", as used herein, refers to the administration of a substance (*e.g.*, an anti-TNFα antibody) to achieve a therapeutic objective (*e.g.*, the treatment of erosive polyarthritis).

The terms "biweekly dosing regimen", "biweekly dosing", and "biweekly administration", as used herein, refer to the time course of administering a substance (*e.g.*, an anti-TNFα antibody) to a subject to achieve a therapeutic objective (*e.g.*, the treatment of erosive polyarthritis). The biweekly dosing regimen is not intended to include a weekly dosing regimen. Preferably, the substance is administered every 9-19 days, more preferably, every 11-17 days, even more preferably, every 13-15 days, and most preferably, every 14 days.

The term "combination" as in the phrase "a first agent in combination with a second agent" includes co-administration of a first agent and a second agent, which for example may be dissolved or intermixed in the same pharmaceutically acceptable carrier, or administration of a first agent, followed by the second agent, or administration

of the second agent, followed by the first agent. The present invention, therefore, includes methods of combination therapeutic treatment and combination pharmaceutical compositions. In one embodiment, the invention provides a combination therapy for treating erosive polyarthritis comprising administering an anti-TNF antibody.

The term "concomitant" as in the phrase "concomitant therapeutic treatment" includes administering an agent in the presence of a second agent. A concomitant therapeutic treatment method includes methods in which the first, second, third, or additional agents are co-administered. A concomitant therapeutic treatment method also includes methods in which the first or additional agents are administered in the presence of a second or additional agents, wherein the second or additional agents, for example, may have been previously administered. A concomitant therapeutic treatment method may be executed step-wise by different actors. For example, one actor may administer to a subject a first agent and a second actor may to administer to the subject a second agent, and the administering steps may be executed at the same time, or nearly the same time, or at distant times, so long as the first agent (and additional agents) are after administration in the presence of the second agent (and additional agents). The actor and the subject may be the same entity (*e.g.*, human).

The term "combination therapy", as used herein, refers to the administration of two or more therapeutic substances, *e.g.*, an anti-TNFα antibody and another drug. The other drug(s) may be administered concomitant with, prior to, or following the administration of an anti-TNFα antibody.

The term "kit" as used herein refers to a packaged product or article of manufacture comprising components. The kit preferably comprises a box or container that holds the components of the kit. The box or container is affixed with a label or a Food and Drug Administration approved protocol. The box or container holds components of the invention which are preferably contained within plastic, polyethylene, polypropylene, ethylene, or propylene vessels. The vessels can be capped-tubes or bottles. The kit can also include instructions for administering the TNFα antibody, or antigen-binding portion thereof. In one embodiment the kit of the invention includes the formulation comprising the human antibody D2E7, as described in WIPO Publication No. WO/2004/016286 and U.S. Publication No. US 2004-0033228 A1.

Various aspects of the invention are described in further detail herein.

II. <u>TNFα Inhibitors</u>

This invention provides a method of treating erosive polyarthritis in which the administration of a TNFα inhibitor *e.g.*, a TNFα antibody, or antigen-binding portion thereof, is beneficial. In one embodiment, these methods include administration of isolated human antibodies, or antigen-binding portions thereof, that bind to human

TNFα with high affinity and a low off rate, and have a high neutralizing capacity. Preferably, the human antibodies of the invention are recombinant, neutralizing human anti-hTNFα antibodies.

In one embodiment, the TNFα inhibitor used in the invention is an anti-TNFα antibody, or a fragment thereof, including infliximab (Remicade®, Johnson and Johnson; described in U.S. Patent No. 5,656,272). CDP571 (a humanized monoclonal anti-TNF-alpha IgG4 antibody), CDP 870 (a humanized monoclonal anti-TNF-alpha antibody fragment), an anti-TNF dAb (Peptech), CNTO 148 (golimumab; Medarex and Centocor, see WO 02/12502), and adalimumab (Humira® Abbott Laboratories, a human anti-TNF mAb, described in US 6,090,382 as D2E7). Additional TNF antibodies which can be used in the invention are described in U.S. Patent Nos. 6,593,458; 6,498,237; 6,451,983; and 6,448,380.

The most preferred recombinant, neutralizing antibody used in the invention is referred to herein as D2E7, also referred to as HUMIRA® and adalimumab (the amino acid sequence of the D2E7 VL region is shown in SEQ ID NO: 1; the amino acid sequence of the D2E7 VH region is shown in SEQ ID NO: 2). The properties of D2E7 (HUMIRA®) have been described in Salfeld *et al.*, U.S. Patent Nos. 6,090,382, 6,258,562, and 6,509,015. Other examples of TNFα inhibitors include chimeric and humanized murine anti-hTNFα antibodies which have undergone clinical testing for treatment of rheumatoid arthritis (see *e.g.*, Elliott *et al.* (1994) *Lancet* 344:1125-1127; Elliot *et al.* (1994) *Lancet* 344:1105-1110; Rankin *et al.* (1995) *Br. J. Rheumatol.* 34:334-342). In another embodiment, the anti-TNFα antibody is multivalent.

In one embodiment, the method of treating erosive polyarthritis of the invention includes the administration of D2E7 antibodies and antibody portions, D2E7-related antibodies and antibody portions, and other human antibodies and antibody portions with equivalent properties to D2E7, such as high affinity binding to hTNFα with low dissociation kinetics and high neutralizing capacity. In one embodiment, the invention provides a method for treating erosive polyarthritis with an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and a K_{off} rate constant of 1 x 10^{-3} s^{-1} or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-7} M or less. More preferably, the isolated human antibody, or antigen-binding portion thereof, dissociates from human TNFα with a K_{off} of 5 x 10^{-4} s^{-1} or less, or even more preferably, with a K_{off} of 1 x 10^{-4} s^{-1} or less. More preferably, the isolated human antibody, or antigen-binding portion thereof, neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of

1×10^{-8} M or less, even more preferably with an IC_{50} of 1×10^{-9} M or less and still more preferably with an IC_{50} of 1×10^{-10} M or less. In a preferred embodiment, the antibody is an isolated human recombinant antibody, or an antigen-binding portion thereof.

It is well known in the art that antibody heavy and light chain CDR3 domains play an important role in the binding specificity/affinity of an antibody for an antigen. Accordingly, in another aspect, the invention pertains to methods of treating erosive polyarthritis by administering human antibodies that have slow dissociation kinetics for association with hTNFα and that have light and heavy chain CDR3 domains that structurally are identical to or related to those of D2E7. Position 9 of the D2E7 VL CDR3 can be occupied by Ala or Thr without substantially affecting the K_{off}. Accordingly, a consensus motif for the D2E7 VL CDR3 comprises the amino acid sequence: Q-R-Y-N-R-A-P-Y-(T/A) (SEQ ID NO: 3). Additionally, position 12 of the D2E7 VH CDR3 can be occupied by Tyr or Asn, without substantially affecting the K_{off}. Accordingly, a consensus motif for the D2E7 VH CDR3 comprises the amino acid sequence: V-S-Y-L-S-T-A-S-S-L-D-(Y/N) (SEQ ID NO: 4). Moreover, as demonstrated in Example 2 of U.S. Patent No. 6,090,382, the CDR3 domain of the D2E7 heavy and light chains is amenable to substitution with a single alanine residue (at position 1, 4, 5, 7 or 8 within the VL CDR3 or at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 within the VH CDR3) without substantially affecting the K_{off}. Still further, the skilled artisan will appreciate that, given the amenability of the D2E7 VL and VH CDR3 domains to substitutions by alanine, substitution of other amino acids within the CDR3 domains may be possible while still retaining the low off rate constant of the antibody, in particular substitutions with conservative amino acids. Preferably, no more than one to five conservative amino acid substitutions are made within the D2E7 VL and/or VH CDR3 domains. More preferably, no more than one to three conservative amino acid substitutions are made within the D2E7 VL and/or VH CDR3 domains. Additionally, conservative amino acid substitutions should not be made at amino acid positions critical for binding to hTNFα. Positions 2 and 5 of the D2E7 VL CDR3 and positions 1 and 7 of the D2E7 VH CDR3 appear to be critical for interaction with hTNFα and thus, conservative amino acid substitutions preferably are not made at these positions (although an alanine substitution at position 5 of the D2E7 VL CDR3 is acceptable, as described above) (*see* U.S. Patent No. 6,090,382).

Accordingly, in another embodiment, the invention provides methods of treating erosive polyarthritis by the administration of an isolated human antibody, or antigen-binding portion thereof. The antibody or antigen-binding portion thereof preferably contains the following characteristics:

a) dissociates from human TNFα with a K_{off} rate constant of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

More preferably, the antibody, or antigen-binding portion thereof, dissociates from human TNFα with a K_{off} of 5×10^{-4} s^{-1} or less. Even more preferably, the antibody, or antigen-binding portion thereof, dissociates from human TNFα with a K_{off} of 1×10^{-4} s^{-1} or less.

In yet another embodiment, the invention provides a method of treating erosive polyarthritis by administration of an isolated human antibody, or antigen-binding portion thereof. The antibody or antigen-binding portion thereof preferably contains a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8, and with a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11. Preferably, the LCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5 (*i.e.*, the D2E7 VL CDR2) and the HCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6 (*i.e.*, the D2E7 VH CDR2). Even more preferably, the LCVR further has CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7 (*i.e.*, the D2E7 VL CDR1) and the HCVR has a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8 (*i.e.*, the D2E7 VH CDR1). The framework regions for VL preferably are from the $V_{K}I$ human germline family, more preferably from the A20 human germline Vk gene and most preferably from the D2E7 VL framework sequences shown in Figures 1A and 1B of U.S. Patent No. 6,090,382. The framework regions for VH preferably are from the $V_{H}3$ human germline family, more preferably from the DP-31 human germline VH gene and most preferably from the D2E7 VH framework sequences shown in Figures 2A and 2B of U.S. Patent No. 6,090,382.

Accordingly, in another embodiment, the invention provides a method of treating erosive polyarthritis by the administration of an isolated human antibody, or antigen-binding portion thereof. The antibody or antigen-binding portion thereof preferably

contains a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 (*i.e.*, the D2E7 VL) and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2 (*i.e.*, the D2E7 VH). In certain embodiments, the antibody comprises a heavy chain constant region, such as an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region. Preferably, the heavy chain constant region is an IgG1 heavy chain constant region or an IgG4 heavy chain constant region. Furthermore, the antibody can comprise a light chain constant region, either a kappa light chain constant region or a lambda light chain constant region. Preferably, the antibody comprises a kappa light chain constant region. Alternatively, the antibody portion can be, for example, a Fab fragment or a single chain Fv fragment.

In still other embodiments, the invention describes a method of treating erosive polyarthritis in which the administration of an anti-TNFα antibody wherein the antibody is an isolated human antibody, or an antigen-binding portion thereof. The antibody or antigen-binding portion thereof preferably contains D2E7-related VL and VH CDR3 domains, for example, antibodies, or antigen-binding portions thereof, with a light chain variable region (LCVR) having a CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25 and SEQ ID NO: 26 or with a heavy chain variable region (HCVR) having a CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34 and SEQ ID NO: 35.

The TNFα antibody used in the invention can also be modified. In some embodiments, the TNFα antibody or antigen binding fragments thereof, is chemically modified to provide a desired effect. For example, pegylation of antibodies and antibody fragments of the invention may be carried out by any of the pegylation reactions known in the art, as described, for example, in the following references: *Focus on Growth Factors* 3:4-10 (1992); EP 0 154 316; and EP 0 401 384.

Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive polyethylene glycol molecule (or an analogous reactive water-soluble polymer). A preferred water-soluble polymer for pegylation of the antibodies and antibody fragments of the invention is polyethylene glycol (PEG). As used herein, "polyethylene glycol" is meant to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (Cl-ClO) alkoxy- or aryloxy-polyethylene glycol.

Methods for preparing pegylated antibodies and antibody fragments of the invention will generally comprise the steps of (a) reacting the antibody or antibody fragment with polyethylene glycol, such as a reactive ester or aldehyde derivative of PEG, under conditions whereby the antibody or antibody fragment becomes attached to one or more PEG groups, and (b) obtaining the reaction products. It will be apparent to one of ordinary skill in the art to select the optimal reaction conditions or the acylation reactions based on known parameters and the desired result.

Pegylated antibodies and antibody fragments may generally be used to treat erosive polyarthritis and TNFα-related disorders of the invention by administration of the TNFα antibodies and antibody fragments described herein. Generally the pegylated antibodies and antibody fragments have increased half-life, as compared to the nonpegylated antibodies and antibody fragments. The pegylated antibodies and antibody fragments may be employed alone, together, or in combination with other pharmaceutical compositions.

In yet another embodiment of the invention, TNFα antibodies or fragments thereof can be altered wherein the constant region of the antibody is modified to reduce at least one constant region-mediated biological effector function relative to an unmodified antibody. To modify an antibody of the invention such that it exhibits reduced binding to the Fc receptor, the immunoglobulin constant region segment of the antibody can be mutated at particular regions necessary for Fc receptor (FcR) interactions (see *e.g.*, Canfield and Morrison (1991) *J. Exp. Med.* 173:1483-1491; and Lund *et al.* (1991) *J. of Immunol.* 147:2657-2662). Reduction in FcR binding ability of the antibody may also reduce other effector functions which rely on FcR interactions, such as opsonization and phagocytosis and antigen-dependent cellular cytotoxicity.

An antibody or antibody portion of the invention can be derivatized or linked to another functional molecule (*e.g.*, another peptide or protein). Accordingly, the antibodies and antibody portions of the invention are intended to include derivatized and otherwise modified forms of the human anti-hTNFα antibodies described herein, including immunoadhesion molecules. For example, an antibody or antibody portion of the invention can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (*e.g.*, a bispecific antibody or a diabody), a detectable agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate associate of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

One type of derivatized antibody is produced by crosslinking two or more antibodies (of the same type or of different types, *e.g.*, to create bispecific antibodies). Suitable crosslinkers include those that are heterobifunctional, having two distinctly

reactive groups separated by an appropriate spacer (*e.g.*, m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (*e.g.*, disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, IL.

Useful detectable agents with which an antibody or antibody portion of the invention may be derivatized include fluorescent compounds. Exemplary fluorescent detectable agents include fluorescein, fluorescein isothiocyanate, rhodamine, 5-dimethylamine-1-napthalenesulfonyl chloride, phycoerythrin and the like. An antibody may also be derivatized with detectable enzymes, such as alkaline phosphatase, horseradish peroxidase, glucose oxidase and the like. When an antibody is derivatized with a detectable enzyme, it is detected by adding additional reagents that the enzyme uses to produce a detectable reaction product. For example, when the detectable agent horseradish peroxidase is present, the addition of hydrogen peroxide and diaminobenzidine leads to a colored reaction product, which is detectable. An antibody may also be derivatized with biotin, and detected through indirect measurement of avidin or streptavidin binding.

An antibody, or antibody portion, of the invention can be prepared by recombinant expression of immunoglobulin light and heavy chain genes in a host cell. To express an antibody recombinantly, a host cell is transfected with one or more recombinant expression vectors carrying DNA fragments encoding the immunoglobulin light and heavy chains of the antibody such that the light and heavy chains are expressed in the host cell and, preferably, secreted into the medium in which the host cells are cultured, from which medium the antibodies can be recovered. Standard recombinant DNA methodologies are used to obtain antibody heavy and light chain genes, incorporate these genes into recombinant expression vectors and introduce the vectors into host cells, such as those described in Sambrook, Fritsch and Maniatis (eds), *Molecular Cloning; A Laboratory Manual, Second Edition*, Cold Spring Harbor, N.Y., (1989), Ausubel *et al.* (eds.) *Current Protocols in Molecular Biology*, Greene Publishing Associates, (1989) and in U.S. Patent No. 4,816,397 by Boss *et al.*

To express D2E7 or a D2E7-related antibody, DNA fragments encoding the light and heavy chain variable regions are first obtained. These DNAs can be obtained by amplification and modification of germline light and heavy chain variable sequences using the polymerase chain reaction (PCR). Germline DNA sequences for human heavy and light chain variable region genes are known in the art (see *e.g.*, the "Vbase" human germline sequence database; see also Kabat *et al.* (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Tomlinson *et al.* (1992) "The Repertoire of Human Germline V_H Sequences Reveals about Fifty Groups of V_H Segments with Different Hypervariable Loops" *J. Mol. Biol.* 227:776-798; and Cox *et al.* (1994) "A Directory of

Human Germ-line V_{78} Segments Reveals a Strong Bias in their Usage" *Eur. J. Immunol.* 24:827-836.

To obtain a DNA fragment encoding the heavy chain variable region of D2E7, or a D2E7-related antibody, a member of the V_H3 family of human germline VH genes is amplified by standard PCR. Most preferably, the DP-31 VH germline sequence is amplified. To obtain a DNA fragment encoding the light chain variable region of D2E7, or a D2E7-related antibody, a member of the V_KI family of human germline VL genes is amplified by standard PCR. Most preferably, the A20 VL germline sequence is amplified. PCR primers suitable for use in amplifying the DP-31 germline VH and A20 germline VL sequences can be designed based on the nucleotide sequences disclosed in the references cited *supra*, using standard methods.

Once the germline VH and VL fragments are obtained, these sequences can be mutated to encode the D2E7 or D2E7-related amino acid sequences disclosed herein. The amino acid sequences encoded by the germline VH and VL DNA sequences are first compared to the D2E7 or D2E7-related VH and VL amino acid sequences to identify amino acid residues in the D2E7 or D2E7-related sequence that differ from germline. Then, the appropriate nucleotides of the germline DNA sequences are mutated such that the mutated germline sequence encodes the D2E7 or D2E7-related amino acid sequence, using the genetic code to determine which nucleotide changes should be made. Mutagenesis of the germline sequences is carried out by standard methods, such as PCR-mediated mutagenesis (in which the mutated nucleotides are incorporated into the PCR primers such that the PCR product contains the mutations) or site-directed mutagenesis.

Once DNA fragments encoding D2E7 or D2E7-related VH and VL segments are obtained (by amplification and mutagenesis of germline VH and VL genes, as described above), these DNA fragments can be further manipulated by standard recombinant DNA techniques, for example to convert the variable region genes to full-length antibody chain genes, to Fab fragment genes or to a scFv gene. In these manipulations, a VL- or VH-encoding DNA fragment is operatively linked to another DNA fragment encoding another protein, such as an antibody constant region or a flexible linker. The term "operatively linked", as used in this context, is intended to mean that the two DNA fragments are joined such that the amino acid sequences encoded by the two DNA fragments remain in-frame.

The isolated DNA encoding the VH region can be converted to a full-length heavy chain gene by operatively linking the VH-encoding DNA to another DNA molecule encoding heavy chain constant regions (CH1, CH2 and CH3). The sequences of human heavy chain constant region genes are known in the art (see e.g., Kabat *et al.* (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department

of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The heavy chain constant region can be an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region, but most preferably is an IgG1 or IgG4 constant region. For a Fab fragment heavy chain gene, the VH-encoding DNA can be operatively linked to another DNA molecule encoding only the heavy chain CH1 constant region.

The isolated DNA encoding the VL region can be converted to a full-length light chain gene (as well as a Fab light chain gene) by operatively linking the VL-encoding DNA to another DNA molecule encoding the light chain constant region, CL. The sequences of human light chain constant region genes are known in the art (see *e.g.*, Kabat *et al.* (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The light chain constant region can be a kappa or lambda constant region, but most preferably is a kappa constant region.

To create a scFv gene, the VH- and VL-encoding DNA fragments are operatively linked to another fragment encoding a flexible linker, *e.g.*, encoding the amino acid sequence $(Gly_4\text{-}Ser)_3$, such that the VH and VL sequences can be expressed as a contiguous single-chain protein, with the VL and VH regions joined by the flexible linker (see *e.g.*, Bird *et al.* (1988) *Science* 242:423-426; Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883; McCafferty *et al.*, *Nature* (1990) 348:552-554).

To express the antibodies, or antibody portions of the invention, DNAs encoding partial or full-length light and heavy chains, obtained as described above, are inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences. In this context, the term "operatively linked" is intended to mean that an antibody gene is ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the antibody gene. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. The antibody light chain gene and the antibody heavy chain gene can be inserted into separate vector or, more typically, both genes are inserted into the same expression vector. The antibody genes are inserted into the expression vector by standard methods (*e.g.*, ligation of complementary restriction sites on the antibody gene fragment and vector, or blunt end ligation if no restriction sites are present). Prior to insertion of the D2E7 or D2E7-related light or heavy chain sequences, the expression vector may already carry antibody constant region sequences. For example, one approach to converting the D2E7 or D2E7-related VH and VL sequences to full-length antibody genes is to insert them into expression vectors already encoding heavy chain

constant and light chain constant regions, respectively, such that the VH segment is operatively linked to the CH segment(s) within the vector and the VL segment is operatively linked to the CL segment within the vector. Additionally or alternatively, the recombinant expression vector can encode a signal peptide that facilitates secretion of the antibody chain from a host cell. The antibody chain gene can be cloned into the vector such that the signal peptide is linked in-frame to the amino terminus of the antibody chain gene. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (*i.e.*, a signal peptide from a non-immunoglobulin protein).

In addition to the antibody chain genes, the recombinant expression vectors of the invention carry regulatory sequences that control the expression of the antibody chain genes in a host cell. The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals) that control the transcription or translation of the antibody chain genes. Such regulatory sequences are described, for example, in Goeddel; *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). It will be appreciated by those skilled in the art that the design of the expression vector, including the selection of regulatory sequences may depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, *etc.* Preferred regulatory sequences for mammalian host cell expression include viral elements that direct high levels of protein expression in mammalian cells, such as promoters and/or enhancers derived from cytomegalovirus (CMV) (such as the CMV promoter/enhancer), Simian Virus 40 (SV40) (such as the SV40 promoter/enhancer), adenovirus, (*e.g.*, the adenovirus major late promoter (AdMLP)) and polyoma. For further description of viral regulatory elements, and sequences thereof, see *e.g.*, U.S. Patent No. 5,168,062 by Stinski, U.S. Patent No. 4,510,245 by Bell *et al.* and U.S. Patent No. 4,968,615 by Schaffner *et al.*

In addition to the antibody chain genes and regulatory sequences, the recombinant expression vectors of the invention may carry additional sequences, such as sequences that regulate replication of the vector in host cells (*e.g.*, origins of replication) and selectable marker genes. The selectable marker gene facilitates selection of host cells into which the vector has been introduced (see *e.g.*, U.S. Patents Nos. 4,399,216, 4,634,665 and 5,179,017, all by Axel *et al.*). For example, typically the selectable marker gene confers resistance to drugs, such as G418, hygromycin or methotrexate, on a host cell into which the vector has been introduced. Preferred selectable marker genes include the dihydrofolate reductase (DHFR) gene (for use in dhfr$^-$ host cells with methotrexate selection/amplification) and the *neo* gene (for G418 selection).

For expression of the light and heavy chains, the expression vector(s) encoding the heavy and light chains is transfected into a host cell by standard techniques. The

various forms of the term "transfection" are intended to encompass a wide variety of techniques commonly used for the introduction of exogenous DNA into a prokaryotic or eukaryotic host cell, *e.g.*, electroporation, calcium-phosphate precipitation, DEAE-dextran transfection and the like. Although it is theoretically possible to express the antibodies of the invention in either prokaryotic or eukaryotic host cells, expression of antibodies in eukaryotic cells, and most preferably mammalian host cells, is the most preferred because such eukaryotic cells, and in particular mammalian cells, are more likely than prokaryotic cells to assemble and secrete a properly folded and immunologically active antibody. Prokaryotic expression of antibody genes has been reported to be ineffective for production of high yields of active antibody (Boss and Wood (1985) *Immunology Today* 6:12-13).

Preferred mammalian host cells for expressing the recombinant antibodies of the invention include Chinese Hamster Ovary (CHO cells) (including dhfr- CHO cells, described in Urlaub and Chasin, (1980) *Proc. Natl. Acad. Sci. USA* 77:4216-4220, used with a DHFR selectable marker, *e.g.*, as described in Kaufman and Sharp (1982) *Mol. Biol.* 159:601-621), NS0 myeloma cells, COS cells and SP2 cells. When recombinant expression vectors encoding antibody genes are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods.

Host cells can also be used to produce portions of intact antibodies, such as Fab fragments or scFv molecules. It is understood that variations on the above procedure are within the scope of the present invention. For example, it may be desirable to transfect a host cell with DNA encoding either the light chain or the heavy chain (but not both) of an antibody of this invention. Recombinant DNA technology may also be used to remove some or all of the DNA encoding either or both of the light and heavy chains that is not necessary for binding to hTNFα. The molecules expressed from such truncated DNA molecules are also encompassed by the antibodies of the invention. In addition, bifunctional antibodies may be produced in which one heavy and one light chain are an antibody of the invention and the other heavy and light chain are specific for an antigen other than hTNFα by crosslinking an antibody of the invention to a second antibody by standard chemical crosslinking methods.

In a preferred system for recombinant expression of an antibody, or antigen-binding portion thereof, of the invention, a recombinant expression vector encoding both the antibody heavy chain and the antibody light chain is introduced into dhfr-CHO cells by calcium phosphate-mediated transfection. Within the recombinant expression vector, the antibody heavy and light chain genes are each operatively linked to CMV

enhancer/AdMLP promoter regulatory elements to drive high levels of transcription of the genes. The recombinant expression vector also carries a DHFR gene, which allows for selection of CHO cells that have been transfected with the vector using methotrexate selection/amplification. The selected transformant host cells are culture to allow for expression of the antibody heavy and light chains and intact antibody is recovered from the culture medium. Standard molecular biology techniques are used to prepare the recombinant expression vector, transfect the host cells, select for transformants, culture the host cells and recover the antibody from the culture medium.

Recombinant human antibodies of the invention in addition to D2E7 or an antigen binding portion thereof, or D2E7-related antibodies disclosed herein can be isolated by screening of a recombinant combinatorial antibody library, preferably a scFv phage display library, prepared using human VL and VH cDNAs prepared from mRNA derived from human lymphocytes. Methodologies for preparing and screening such libraries are known in the art. In addition to commercially available kits for generating phage display libraries (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, catalog no. 27-9400-01; and the Stratagene *SurfZAP*^{TM} phage display kit, catalog no. 240612), examples of methods and reagents particularly amenable for use in generating and screening antibody display libraries can be found in, for example, Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* PCT Publication No. WO 92/18619; Dower *et al.* PCT Publication No. WO 91/17271; Winter *et al.* PCT Publication No. WO 92/20791; Markland *et al.* PCT Publication No. WO 92/15679; Breitling *et al.* PCT Publication No. WO 93/01288; McCafferty *et al.* PCT Publication No. WO 92/01047; Garrard *et al.* PCT Publication No. WO 92/09690; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum Antibod Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; McCafferty *et al.*, *Nature* (1990) 348:552-554; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J Mol Biol* 226:889-896; Clackson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *PNAS* 89:3576-3580; Garrard *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc Acid Res* 19:4133-4137; and Barbas *et al.* (1991) *PNAS* 88:7978-7982.

In a preferred embodiment, to isolate human antibodies with high affinity and a low off rate constant for hTNFα, a murine anti-hTNFα antibody having high affinity and a low off rate constant for hTNFα (*e.g.*, MAK 195, the hybridoma for which has deposit number ECACC 87 050801) is first used to select human heavy and light chain sequences having similar binding activity toward hTNFα, using the epitope imprinting methods described in Hoogenboom *et al.*, PCT Publication No. WO 93/06213. The antibody libraries used in this method are preferably scFv libraries prepared and screened as described in McCafferty *et al.*, PCT Publication No. WO 92/01047, McCafferty *et al.*, *Nature* (1990) 348:552-554; and Griffiths *et al.*, (1993) *EMBO J*

12:725-734. The scFv antibody libraries preferably are screened using recombinant human TNFα as the antigen.

Once initial human VL and VH segments are selected, "mix and match" experiments, in which different pairs of the initially selected VL and VH segments are screened for hTNFα binding, are performed to select preferred VL/VH pair combinations. Additionally, to further improve the affinity and/or lower the off rate constant for hTNFα binding, the VL and VH segments of the preferred VL/VH pair(s) can be randomly mutated, preferably within the CDR3 region of VH and/or VL, in a process analogous to the *in vivo* somatic mutation process responsible for affinity maturation of antibodies during a natural immune response. This *in vitro* affinity maturation can be accomplished by amplifying VH and VL regions using PCR primers complimentary to the VH CDR3 or VL CDR3, respectively, which primers have been "spiked" with a random mixture of the four nucleotide bases at certain positions such that the resultant PCR products encode VH and VL segments into which random mutations have been introduced into the VH and/or VL CDR3 regions. These randomly mutated VH and VL segments can be rescreened for binding to hTNFα and sequences that exhibit high affinity and a low off rate for hTNFα binding can be selected.

Following screening and isolation of an anti-hTNFα antibody of the invention from a recombinant immunoglobulin display library, nucleic acid encoding the selected antibody can be recovered from the display package (*e.g.*, from the phage genome) and subcloned into other expression vectors by standard recombinant DNA techniques. If desired, the nucleic acid can be further manipulated to create other antibody forms of the invention (*e.g.*, linked to nucleic acid encoding additional immunoglobulin domains, such as additional constant regions). To express a recombinant human antibody isolated by screening of a combinatorial library, the DNA encoding the antibody is cloned into a recombinant expression vector and introduced into a mammalian host cells, as described in further detail in above.

Methods of isolating human antibodies with high affinity and a low off rate constant for hTNFα are also described in U.S. Patent Nos. 6,090,382, 6,258,562, and 6,509,015.

The TNFα inhibitor may also be a TNF fusion protein, e.g., etanercept (Enbrel®, Amgen; described in WO 91/03553 and WO 09/406476).

In another embodiment, the TNFα inhibitor is a recombinant TNF binding protein (r-TBP-I) (Serono).

III. Treatment of Erosive Polyarthritis

The invention provides methods of treating erosive polyarthritis comprising administering a TNFα inhibitor, including, for an example, a TNFα antibody, to a

subject having erosive polyarthritis. The invention also describes methods for determining the efficacy of a TNFα inhibitor for the treatment of erosive polyarthritis. Preferably, the TNFα is human TNFα and the subject is a human subject. In one embodiment, the TNFα inhibitor is adalimumab, also referred to as HUMIRA® or D2E7. The use of TNFα inhibitors, including antibodies and antibody portions, in the treatment of erosive polyarthritis, as well as methods for determining the efficacy of a TNFα inhibitor for the treatment of erosive polyarthritis, is discussed further below:

The term "polyarthritis" generally refers to inflammation, *i.e.*, swelling, tenderness, or warmth, at two or more joints of a subject.

As used herein, the term "erosive polyarthritis" refers to a subject who has polyarthritis which is damaging to the joint.

The invention provides a method for treating erosive polyarthritis comprising administration of a TNFα inhibitor, including, for an example, a TNFα antibody. The invention also provides a method for inhibiting radiographic progression of joint disease associated with erosive polyarthritis. Methods for administering a TNFα antibody, or an antigen-binding portion thereof, for the treatment of erosive polyarthritis are described in more detail below.

The invention provides a method for determining the efficacy of an anti-TNFα treatment for erosive polyarthritis. Measures for determining such efficacy include tests which determine whether joint destruction or erosion is improved following treatment. For example, the Total Modified Sharp Score (mTSS) of a subject may be used to determine improvements in erosive polyarthritis in the subject. The mTSS may also be used as an assay to determine the efficacy of a treatment for erosive polyarthritis.

A Sharp score is an X-ray measurement in changes in total joint damage as assessed by bone erosions and joint space narrowing (Sharp *et al.* (1971) *Arthritis & Rheumatism* 14:706; Sharp *et al.* (1985) *Arthritis & Rheumatism* 28:16). The mTSS is a measure of the extent and severity of joint damage based on evaluations of x-rays of patients' hands and feet. Joints are scored for both joint erosions and joint space narrowing. The mTSS is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has, for example, a range of about 0 to about 398, where 0=no damage. The ES is the sum of joint scores collected for 46 joints and has a range, for example, of about 0 to about 230. The JSN is the sum of joint scores collected for 42 joints and has a range, for example, of about 0 to about 168. A score of 0 would indicate no change. In one embodiment of the invention, the mTSS is determined by combining the joint space narrowing score having a range of about 0-192 and an erosion score having a range of about 0-378.

An improved or constant mTSS demonstrates that the TNFα inhibitor is effective for treating erosive polyarthritis. In one embodiment, efficacy of a TNFα inhibitor for

the treatment of erosive polyarthritis is evidenced by a lack of progression of joint disease, *e.g.*, no change in Sharp score, in mTSS over time in a subject having erosive polyarthritis. In another embodiment, efficacy of a TNFα inhibitor for the treatment of erosive polyarthritis is evidenced by a decrease in the radiographic progression of joint disease, *e.g.*, decrease in Sharp score, in mTSS over time in a subject having erosive polyarthritis.

In one embodiment, the overall change in the mTSS between baseline and a time period following treatment with a TNFα inhibitor is between about 0.9 and about- 0.2. In another embodiment, the overall change in the mTSS between baseline and a time period following treatment with a TNFα inhibitor is between about 0.5 and about - 0.2. In still another embodiment, the overall change in the mTSS between baseline and a time period following treatment with a TNFα inhibitor is between about 0.2 and about - 0.2.

It should be noted that ranges intermediate to the above recited scores, *e.g.*, about -0.1 to about 0.3, are also intended to be part of this invention. For example, ranges of values using a combination of any of the above recited values as upper and/or lower limits are intended to be included.

While treatment of an inflammatory disease with an anti-inflammatory agent may result in clinical improvements following treatment, there may still be progressive joint damage resulting from erosive polyarthritis (Gladman *et al.* (1990) *J Rheumatol* 17:809; Hanly *et al.* (1988) *Ann Rheum Dis* 47:386). Thus, it is a feature of this invention to provide a method for treating erosive polyarthritis which may be associated with another disorder. In a preferred embodiment, the invention includes treatment of erosive polyarthritis associated with a disorder in which TNFα activity is detrimental, including, but not limited to, rheumatoid arthritis (including juvenile rheumatoid arthritis), Crohn's disease, psoriasis, psoriatic arthritis, and ankylosing spondylitis. Erosive polyarthritis may also be associated with multicentric reticulohistiocytosis (MRH) (Santilli *et al.* (2002) *Ann Rehum Dis* 61: 485).

As used herein, the term "a disorder in which TNFα activity is detrimental" is intended to include diseases and other disorders in which the presence of TNFα in a subject suffering from the disorder has been shown to be or is suspected of being either responsible for the pathophysiology of the disorder or a factor that contributes to a worsening of the disorder. Accordingly, a disorder in which TNFα activity is detrimental is a disorder in which inhibition of TNFα activity is expected to alleviate the symptoms and/or progression of the disorder. Such disorders may be evidenced, for example, by an increase in the concentration of TNFα in a biological fluid of a subject suffering from the disorder (*e.g.*, an increase in the concentration of TNFα in serum, plasma, synovial fluid, *etc.* of the subject), which can be detected, for example, using an

anti-TNFα antibody as described above. There are numerous examples of disorders in which TNFα activity is detrimental. The use of TNFα inhibitors for the treatment of erosive polyarthritis associated with specific disorders is discussed further below:

A. *Autoimmune Diseases*

In one embodiment, the invention includes treatment of erosive polyarthritis associated with an autoimmune disease. Erosive polyarthritis may be found in patients suffering from autoimmune diseases, including forms of arthritis such as rheumatoid arthritis and juvenile rheumatoid arthritis (Verloes (1998) *Med Genet.* 35:943). TNFα antibodies, such as adalimumab, may be used to treat autoimmune diseases, in particular those associated with erosive polyarthritis. Examples of such autoimmune conditions include rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and gouty arthritis, allergy, multiple sclerosis, autoimmune diabetes, autoimmune uveitis and nephrotic syndrome. Other examples of autoimmune conditions include multisystem autoimmune diseases and autoimmune hearing loss. Other examples of autoimmune disease are described in U.S. Application No. 10/622932.

Juvenile Rheumatoid Arthritis

Tumor necrosis factor has been implicated in the pathophysiology of juvenile arthritis, including juvenile rheumatoid arthritis (Grom et al. (1996) *Arthritis Rheum.* 39:1703; Mangge *et al.* (1995) *Arthritis Rheum.* 8:211). In one embodiment, the TNFα antibody of the invention is used to treat juvenile rheumatoid arthritis.

The term "juvenile rheumatoid arthritis" or "JRA" as used herein refers to a chronic, inflammatory disease which occurs before age 16 that may cause joint or connective tissue damage. JRA is also referred to as juvenile chronic polyarthritis and Still's disease.

JRA causes joint inflammation and stiffness for more than 6 weeks in a child of 16 years of age or less. Inflammation causes redness, swelling, warmth, and soreness in the joints. Any joint can be affected and inflammation may limit the mobility of affected joints. One type of JRA can also affect the internal organs.

JRA is often classified into three types by the number of joints involved, the symptoms, and the presence or absence of certain antibodies found by a blood test. These classifications help the physician determine how the disease will progress and whether the internal organs or skin is affected. The classifications of JRA include the following:

a. Pauciarticular JRA, wherein the patient has four or fewer joints are affected. Pauciarticular is the most common form of JRA, and typically affects large joints, such as the knees.

b. Polyarticular HRA, wherein five or more joints are affected. The small joints, such as those in the hands and feet, are most commonly involved, but the disease may also affect large joints.

c. Systemic JRA is characterized by joint swelling, fever, a light skin rash, and may also affect internal organs such as the heart, liver, spleen, and lymph nodes. Systemic JRA is also referred to as it Still's disease. A small percentage of these children develop arthritis in many joints and can have severe arthritis that continues into adulthood.

B. *Spondyloarthropathies*

In one embodiment, the invention includes treatment of erosive polyarthritis associated with a spondylarthopathy. Erosive polyarthritis may be found in patients suffering from inflammatory diseases, such as spondyloarthopathies, associated with detrimental TNFα activity (see *e.g.*, Moeller *et al.* (1990) *Cytokine* 2:162; U.S. Patent No. 5,231,024; European Patent Publication No. 260 610).

As used herein, the term "spondyloarthropathy" or "spondyloarthropathies" is used to refer to any one of several diseases affecting the joints of the spine, wherein such diseases share common clinical, radiological, and histological features. A number of spondyloarthropathies share genetic characteristics, *i.e.* they are associated with the HLA-B27 allele. In one embodiment, the term spondyloarthropathy is used to refer to any one of several diseases affecting the joints of the spine, excluding ankylosing spondylitis, wherein such diseases share common clinical, radiological, and histological features. Examples of spondyloarthropathies include ankylosing spondylitis, psoriatic arthritis/spondylitis, enteropathic arthritis, reactive arthritis or Reiter's syndrome, and undifferentiated spondyloarthropathies. Examples of animal models used to study spondyloarthropathies include *ank/ank* transgenic mice, HLA-B27 transgenic rats (see Taurog *et al.* (1998) *The Spondylarthritides*. Oxford:Oxford University Press).

Examples of subjects who are at risk of having spondyloarthropathies include humans suffering from arthritis. Spondyloarthropathies can be associated with forms of arthritis, including rheumatoid arthritis. In one embodiment of the invention, a TNFα inhibitor is used to treat a subject who suffers from a spondyloarthropathy associated with erosive polyarthritis.. Examples of spondyloarthropathies which can be treated with a TNFα inhibitor are described below:

Ankylosing Spondylitis (AS)

In one embodiment, the invention includes treatment of erosive polyarthritis associated with ankylosing spondylitis using a TNFα antibody, or antigen-binding portion thereof. Tumor necrosis factor has been implicated in the pathophysiology of ankylosing spondylitis (see Verjans *et al.* (1991) *Arthritis Rheum.* 34:486; Verjans *et al.* (1994) *Clin Exp Immunol.* 97:45; Kaijtzel *et al.* (1999) *Hum Immunol.* 60:140). Ankylosing spondylitis (AS) is an inflammatory disorder involving inflammation of one or more vertebrae. AS is a chronic inflammatory disease that affects the axial skeleton and/or peripheral joints, including joints between the vertebrae of the spine and sacroiliac joints and the joints between the spine and the pelvis. AS can eventually cause the affected vertebrae to fuse or grow together. Spondyarthropathies, including AS, can be associated with psoriatic arthritis (PsA) and/or inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease.

Early manifestations of AS can be determined by radiographic tests, including CT scans and MRI scans. Early manifestations of AS often include scroiliitis and changes in the sacroliac joints as evidenced by the blurring of the cortical margins of the subchrondral bone, followed by erosions and sclerosis. Fatigue has also been noted as a common symptom of AS (Duffy *et al.* (2002) *ACR 66th Annual Scientific Meeting* Abstract).

Psoriatic arthritis

In one embodiment, the invention includes treatment of erosive polyarthritis associated with psoriatic arthritis using a TNFα antibody, or antigen-binding portion thereof. Tumor necrosis factor has been implicated in the pathophysiology of psoriatic arthritis (PsA) (Partsch *et al.* (1998) *Ann Rheum Dis.* 57:691; Ritchlin *et al.* (1998) *J Rheumatol.* 25:1544). As referred to herein, psoriatic TNFα has been implicated in activating tissue inflammation and causing joint destruction in rheumatoid arthritis (see *e.g.*, Moeller, A., *et al.* (1990) *Cytokine* 2:162-169; U.S. Patent No. 5,231,024 to Moeller *et al.*; European Patent Publication No. 260 610 B1 by Moeller, A.; Tracey and Cerami, *supra*; Arend, W.P. and Dayer, J-M. (1995) *Arth. Rheum.* 38:151-160; Fava, R.A., *et al.* (1993) *Clin. Exp. Immunol.* 94:261-266). TNFα also has been implicated in promoting the death of islet cells and in mediating insulin resistance in diabetes (see *e.g.*, Tracey and Cerami, *supra*; PCT Publication No. WO 94/08609). TNFα also has been implicated in mediating cytotoxicity to oligodendrocytes and induction of inflammatory plaques in multiple sclerosis (see *e.g.*, Tracey and Cerami, *supra*). Chimeric and humanized murine anti-hTNFα antibodies have undergone clinical testing for treatment of rheumatoid arthritis (see *e.g.*, Elliott, M.J., *et al.* (1994) *Lancet* 344:1125-1127; Elliot,

M.J., *et al.* (1994) *Lancet* 344:1105-1110; Rankin, E.C., *et al.* (1995) *Br. J. Rheumatol.* 34:334-342).

Psoriatic arthritis refers to chronic inflammatory arthritis which is associated with psoriasis, a common chronic skin condition that causes red patches on the body. About 1 in 20 individuals with psoriasis will develop arthritis along with the skin condition, and in about 75% of cases, psoriasis precedes the arthritis. PsA exhibits itself in a variety of ways, ranging from mild to severe arthritis, wherein the arthritis usually affects the fingers and the spine. When the spine is affected, the symptoms are similar to those of ankylosing spondylitis, as described above. A TNFα antibody, or antigen-binding fragment thereof, can be used for treatment of erosive polyarthritis associated with PsA.

PsA is sometimes associated with arthritis mutilans. Arthritis mutilans refers to a disorder which is characterized by excessive bone erosion resulting in a gross, erosive deformity which mutilates the joint.

Characteristic radiographic features of PsA include joint erosions, joint space narrowing, bony proliferation including periarticular and shaft periostitis, osteolysis including "pencil in cup" deformity and acro-osteolysis, ankylosis, spur formation, and spondylitis (Wassenberg *et al.* (2001) *Z Rheumatol* 60:156). Unlike rheumatoid arthritis (RA), joint involvement in PsA is often asymmetrical and may be oligoarticular; osteoporosis is atypical. Although erosive changes in early PsA are marginal as in RA, they become irregular and ill defined with disease progression because of periosteal bone formation adjacent to the erosions. In severe cases, erosive changes may progress to development of pencil in cup deformity or gross osteolysis (Gold *et al.* (1988) *Radiol Clin North Am* 26:1195; Resnick *et al.* (1977)) *J Can Assoc Radiol* 28:187). Asymmetrical erosions may be visible radiographically in the carpus and in the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints of the hands, but the DIP joints are often the first to be affected. Abnormalities are seen in the phalangeal tufts and at the sites of attachments of tendons and ligaments to the bone. The presence of DIP erosive changes may provide both sensitive and specific radiographic findings to support the diagnosis of PsA. Also, the hands tend to be involved much more frequently than the feet with a ratio of nearly 2:1.

Other examples of spondyloarthropathies are described in U.S. Publication No. US 2004-0126372 A1.

C. *Skin and Nail Disorders*

In one embodiment, the invention includes treatment of erosive polyarthritis associated with skin and nail disorders. As used herein, the term "skin and nail disorder

in which TNFα activity is detrimental" is intended to include skin and/or nail disorders and other disorders in which the presence of TNFα in a subject suffering from the *disorder has been shown to* be or is suspected of being either responsible for the pathophysiology of the disorder or a factor that contributes to a worsening of the disorder, *e.g.*, psoriasis. Accordingly, skin and nail disorders in which TNFα activity is detrimental are disorders in which inhibition of TNFα activity is expected to alleviate the symptoms and/or progression of the disorder. The use of the antibodies, antibody portions, and other TNFα inhibitors for the treatment of specific skin and nail disorders is discussed further below. In certain embodiments, the antibody, antibody portion, or other TNFα inhibitor of the invention is administered to the subject in combination with another therapeutic agent, as described below. In one embodiment, a TNFα antibody is administered to the subject in combination with another therapeutic agent for the treatment of erosive polyarthritis associated with psoriasis and the treatment of psoriasis associated with arthritis.

Psoriasis

Tumor necrosis factor has been implicated in the pathophysiology of psoriasis (Takematsu *et al.* (1989) *Arch Dermatol Res.* 281:398; Victor and Gottlieb (2002) *J Drugs Dermatol.* 1(3):264). Psoriasis is described as a skin inflammation (irritation and redness) characterized by frequent episodes of redness, itching, and thick, dry, silvery scales on the skin. In particular, lesions are formed which involve primary and secondary alterations in epidermal proliferation, inflammatory responses of the skin, and an expression of regulatory molecules such as lymphokines and inflammatory factors. Psoriatic skin is morphologically characterized by an increased turnover of epidermal cells, thickened epidermis, abnormal keratinization, inflammatory cell infiltrates into the epidermis and polymorphonuclear leukocyte and lymphocyte infiltration into the epidermis layer resulting in an increase in the basal cell cycle. Psoriasis often involves the nails, which frequently exhibit pitting, separation of the nail, thickening, and discoloration. Psoriasis is often associated with other inflammatory disorders, for example arthritis, including rheumatoid arthritis, inflammatory bowel disease (IBD), and Crohn's disease.

Evidence of psoriasis is most commonly seen on the trunk, elbows, knees, scalp, skin folds, or fingernails, but it may affect any or all parts of the skin. Normally, it takes about a month for new skin cells to move up from the lower layers to the surface. In psoriasis, this process takes only a few days, resulting in a build-up of dead skin cells and formation of thick scales. Symptoms of psoriasis include: skin patches, that are dry or red, covered with silvery scales, raised patches of skin, accompanied by red borders, that may crack and become painful, and that are usually lovated on the elbows, knees,

trunk, scalp, and hands; skin lesions, including pustules, cracking of the skin, and skin redness; joint pain or aching which may be associated with of arthritis, e.g., psoriatic arthritis.

Treatment for psoriasis often includes a topical corticosteroids, vitamin D analogs, and topical or oral retinoids, or combinations thereof. In one embodiment, the TNFα inhibitor of the invention is administered in combination with or the presence of one of these common treatments. Additional therapeutic agents which can also be combined with the TNFα inhibitor for treatment of psoriasis are described in more detail below.

The diagnosis of psoriasis is usually based on the appearance of the skin. Additionally a skin biopsy, or scraping and culture of skin patches may be needed to rule out other skin disorders. An x-ray may be used to check for psoriatic arthritis if joint pain is present and persistent.

In one embodiment of the invention, a TNFα inhibitor is used to treat psoriasis, including chronic plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, pemphigus vulgaris, erythrodermic psoriasis, psoriasis associated with inflammatory bowel disease (IBD), and psoriasis associated with rheumatoid arthritis (RA). Specific types of psoriasis included in the treatment methods of the invention include chronic plaque psoriasis, guttate psoriasis, inverse psoriasis, and pustular psoriasis. Other examples of psoriasis and other types of skin and nail disorders are described in U.S. Application No. 10/622932.

Methods for determining the efficacy of a TNFα inhibitor for the treatment of erosive polyarthritis in association a disorder in which TNFα activity is detrimental include any assay which measures the degree of joint destruction, including joint space narrowing and/or joint erosion. In one embodiment, joint destruction is measured using radiography. Such assays may be used to examine the efficacy of the TNFα inhibitor by determining whether an improvement occurs in a subject or patient population treated with the TNFα inhibitor. Generally, improvements are determined by comparing a baseline score determined prior to treatment, and a score determined at a time following treatment with the TNFα inhibitor.

Additional improvements in arthritic conditions, such as Ra, PsA, and JRA, may be determined by measuring the ACR response. ACR thresholds, *e.g.*, ACR20, ACR50, ACR70, may be used for defining improvement in RA and PsA, and indicate the percentage improvement in seven disease activity measures. Criteria include percentage improvement in tender and swollen joint count and improvement of at least 3 of the following criteria: patient pain assessment, patient global assessment, physician global assessment, patient self-assessed disability, or laboratory measures of disease activity

(i.e., erythrocyte sedimentation rate or C-reactive protein level) (Felson *et al.* (1993) *Arthritis Rheum.* 36(6):729).

Other assays used to determine improvement for a given therapy for the treatment of RA, JRA, and PsA, include the EULAR response, DAS score, FACIT-F, HAQ score, and SJC and/or TJC counts.

The EULAR criteria uses a DAS for defining response. Response is defined as both: (a) change in disease activity from baseline and (b) the level of disease activity reached during follow-up. Criteria used to define DAS include: Ritchie articular index, swollen joint count (44-joint count), erythrocyte sedimentation rate, and Health Assessment Questionnaire. A modified version of the DAS criteria, DAS28, uses a 28-joint count for swollen and tender joints. Response is defined as a combination of a significant change from baseline and the level of disease activity attained. Good response is defined as a significant decrease in DAS (> 1.2) and a low level of disease activity (< or = 2.4). Non-response is defined as a decrease < or = 0.6, or a decrease > 0.6 and < or = 1.2 with an attained DAS > 3.7. Any other scores are regarded as moderate responses.

The DAS is a score is based on the Ritchie articular index, a 44 swollen joint count, ESR, and a general health assessment on a VAS. Range varies from 1 to 9. Serial measurements of the DAS and DAS28 are strong predictors of physical disability and radiological progression, and both indices are sensitive discriminators between patients with high and low disease activity and between active and placebo treated patient groups.

FACIT-F (Functional Assessment of Chronic Illness Therapy –Fatigue) is a validated questionnaire designed to measure patients' assessment of fatigue-related factors in chronic illness (see Cella and Webster (1997) *Oncology (Huntingt).* 11:232 and Lai *et al.* (2003) *Qual Life Res.* 12(5):485).

The Health Assessment Questionnaire (HAQ) is a validated questionnaire designed to assess patients' ability to perform activities of daily living, particularly in adult arthritics. Instrument consists of the HAQ Disability Index (20 items), Pain Scale (1 item), and Global Health Status (1 item) that measure disability/physical functioning and quality of life (Fries *et al.* (1982) *J Rheumatol.* 9(5):789).

Swollen and tender joints (SJC and TJC) are the most characteristic features of RA, and disease severity is directly related to the number of swollen and tender joints. Counting swollen and tender joints is a key component of the clinical assessment of RA.

Improvements in PsA and psoriasis may also be determined using the PASI response, DLQI, and the BSA score. DLQI (Dermatology Life Quality Index) is a health-related quality of life measure widely used for a variety of dermatological diseases, including PsA and psoriasis. The body Surface Area (BSA) score provides a

measurement of surface area based on height and weight and expressed in m^2. The PASI (Psoriasis Area and Severity Index) is a composite measure of the erythema, induration, desquamation and body surface area that is affected by psoriasis for a particular patient. Patients are evaluated for head, trunk, upper and lower limb involvement. Scores range from 0 (clear) to 72 (maximum severity).

Improvements in treatment for PsA may also be measured using the PsARC (Psoriatic Arthritis Response Criteria), which provides a clinical measure of the change in tender and swollen joint scores, along with a series of global assessments of disease activity.

Improvements in AS may be measured by using any number of instruments to evaluate various AS symptoms. Some of the commonly used scales include the Assessment in Ankylosing Spondylitis (ASAS), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (Garrett *et al.* (1994) *J Rheumatol* 21:2286), the Bath Ankylosing Spondylitis Metrology Index (BASMI) (Jenkinson *et al.* (1994) *J Rheumatol* 21:1694), and the Bath Ankylosing Spondylitis Functional Index (BASFI) (Calin *et al.* (1994) *J Rheumatol* 21:2281).These indices can be used to monitor a patient over time and to determine improvement. Additional description measurements for assessing improvements in AS are described in U.S. Application No. 10/622932.

IV. Pharmaceutical Compositions and Pharmaceutical Administration

A. *Compositions and Administration*

Antibodies, antibody-portions, and other TNFα inhibitors for use in the methods of the invention, may be incorporated into pharmaceutical compositions suitable for administration to a subject having erosive polyarthritis. Typically, the pharmaceutical composition comprises an antibody, antibody portion, or other TNFα inhibitor of the invention and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it is preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody, antibody portion, or other TNFα inhibitor.

The compositions for use in the methods of the invention may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with other antibodies or other TNFα inhibitors. The preferred mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular). In one embodiment, the antibody or other TNFα inhibitor is administered by intravenous infusion or injection. In another embodiment, the antibody or other TNFα inhibitor is administered by intramuscular or subcutaneous injection.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the active compound (*i.e.*, antibody, antibody portion, or other TNFα inhibitor) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

Supplementary active compounds can also be incorporated into the compositions. In certain embodiments, an antibody or antibody portion for use in the methods of the invention is coformulated with and/or coadministered with one or more additional therapeutic agents, including an erosive polyarthritis inhibitor or antagonist. For example, an anti-hTNFα antibody or antibody portion of the invention may be coformulated and/or coadministered with one or more additional antibodies that bind other targets associated with erosive polyarthritis (*e.g.*, antibodies that bind other cytokines or that bind cell surface molecules), one or more cytokines, soluble TNFα receptor (see *e.g.*, PCT Publication No. WO 94/06476) and/or one or more chemical agents that inhibit hTNFα

production or activity (such as cyclohexane-ylidene derivatives as described in PCT Publication No. WO 93/19751) or any combination thereof. Furthermore, one or more antibodies of the invention may be used in combination with two or more of the foregoing therapeutic agents. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible side effects, complications or low level of response by the patient associated with the various monotherapies.

In one embodiment, the invention includes pharmaceutical compositions comprising an effective amount of a TNFα inhibitor and a pharmaceutically acceptable carrier, wherein the effective amount of the TNFα inhibitor may be effective to treat erosive polyarthritis. In one embodiment, the antibody or antibody portion for use in the methods of the invention is incorporated into a pharmaceutical formulation as described in PCT/IB03/04502 and U.S. Appln. No. 10/222140. This formulation includes a concentration 50 mg/ml of the antibody D2E7, wherein one pre-filled syringe contains 40 mg of antibody for subcutaneous injection. In another embodiment, the formulation of the invention includes D2E7.

The antibodies, antibody-portions, and other TNFα inhibitors of the present invention can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is subcutaneous injection. In another embodiment, administration is via intravenous injection or infusion. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, *e.g.*, *Sustained and Controlled Release Drug Delivery Systems*, Robinson, ed., Dekker, Inc., New York, 1978.

TNFα antibodies may also be administered in the form of protein crystal formulations which include a combination of protein crystals encapsulated within a polymeric carrier to form coated particles. The coated particles of the protein crystal formulation may have a spherical morphology and be microspheres of up to 500 micro meters in diameter or they may have some other morphology and be microparticulates. The enhanced concentration of protein crystals allows the antibody of the invention to be delivered subcutaneously. In one embodiment, the TNFα antibodies of the invention are delivered via a protein delivery system, wherein one or more of a protein crystal formulation or composition, is administered to a subject with a TNFα-related disorder.

Compositions and methods of preparing stabilized formulations of whole antibody crystals or antibody fragment crystals are also described in WO 02/072636.

In one embodiment, a formulation comprising the crystallized antibody fragments described in PCT/IB03/04502 and U.S. Appln. No. 10/222140, are used to treat erosive polyarthritis using treatment methods of the invention.

In certain embodiments, an antibody, antibody portion, or other TNFα inhibitor of the invention may be orally administered, for example, with an inert diluent or an assimilable edible carrier. The compound (and other ingredients, if desired) may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer a compound of the invention by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation.

The pharmaceutical compositions of the invention may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody or antibody portion of the invention. A "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 the antibody, antibody portion, or other TNFα inhibitor may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody, antibody portion, other TNFα inhibitor to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody, antibody portion, or other TNFα inhibitor are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

Dosage regimens may be adjusted to provide the optimum desired response (*e.g.*, a therapeutic or prophylactic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound

calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

In one embodiment, the invention provides a single dose method for treating erosive polyarthritis, comprising administering to a subject in need thereof a single dose of a TNFα inhibitor, such as a human antibody. In one embodiment, the TNFα inhibitor is the anti-TNFα antibody adalimumab. The single dose of TNFα inhibitor can be any therapeutically or prophylactically effective amount. In one embodiment, a subject is administered either a 20 mg, a 40 mg, or an 80 mg single dose of adalimumab (also referred to as D2E7). The single dose may be administered through any route, including, for example, subcutaneous administration. Biweekly dosing regimens can be used to treat erosive polyarthritis and are further described in US Appln. No. 10/163657. Multiple variable dose methods of treatment or prevention can also be used to treat erosive polyarthritis, and are further described in PCT appln. no. PCT/US05/012007.

It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. It should also be noted that the invention pertains to methods of treatment of erosive polyarthritis including acute management and chronic management of the disease.

The invention also pertains to packaged pharmaceutical compositions or kits for administering the anti-TNF antibodies of the invention for the treatment of erosive polyarthritis. In one embodiment of the invention, the kit comprises a TNFα inhibitor, such as an antibody, a second pharmaceutical composition comprising an additional therapeutic agent, and instructions for administration for treatment of erosive polyarthritis. The instructions may describe how, *e.g.*, subcutaneously, and when, *e.g.*, at week 0 and week 2, the different doses of TNFα inhibitor and/or the additional therapeutic agent shall be administered to a subject for treatment.

Another aspect of the invention pertains to kits containing a pharmaceutical composition comprising an anti-TNFα antibody and a pharmaceutically acceptable carrier and one or more pharmaceutical compositions each comprising a drug useful for treating erosive polyarthritis and a pharmaceutically acceptable carrier. Alternatively,

the kit comprises a single pharmaceutical composition comprising an anti-TNFα antibody, one or more drugs useful for treating erosive polyarthritis and a pharmaceutically acceptable carrier. The kits contain instructions for dosing of the pharmaceutical compositions for the treatment of erosive polyarthritis.

The package or kit alternatively can contain the TNFα inhibitor and it can be promoted for use, either within the package or through accompanying information, for the uses or treatment of the disorders described herein. The packaged pharmaceuticals or kits further can include a second agent (as described herein) packaged with or copromoted with instructions for using the second agent with a first agent (as described herein).

B. *Additional therapeutic agents*

The invention also describes methods of treating erosive polyarthritis comprising administering a TNFα inhibitor in combination with an additional therapeutic agent. The invention also pertains to pharmaceutical compositions and methods of use thereof for the treatment of erosive polyarthritis in combination with an additional therapeutic agent. The pharmaceutical compositions comprise a first agent that treats erosive polyarthritis. The pharmaceutical composition also may comprise a second agent that is an active pharmaceutical ingredient; that is, the second agent is therapeutic and its function is beyond that of an inactive ingredient, such as a pharmaceutical carrier, preservative, diluent, or buffer. In one embodiment, the second agent may be useful in treating or preventing erosive polyarthritis. In another embodiment, the second agent may diminish or treat at least one symptom(s) associated with the disorder which is associated with erosive polyarthritis, *e.g.*, psoriatic arthritis. In yet another embodiment, the additional agent is useful for the treatment of both erosive polyarthritis and the additional disorder. The first and second agents may exert their biological effects by similar or unrelated mechanisms of action; or either one or both of the first and second agents may exert their biological effects by a multiplicity of mechanisms of action. A pharmaceutical composition may also comprise a third compound, or even more yet, wherein the third (and fourth, etc.) compound has the same characteristics of a second agent.

It should be understood that the pharmaceutical compositions described herein may have the first and second, third, or additional agents in the same pharmaceutically acceptable carrier or in a different pharmaceutically acceptable carrier for each described embodiment. It further should be understood that the first, second, third and additional agent may be administered simultaneously or sequentially within described embodiments. Alternatively, a first and second agent may be administered

simultaneously, and a third or additional agent may be administered before or after the first two agents.

The combination of agents used within the methods and pharmaceutical compositions described herein may have a therapeutic additive or synergistic effect on the condition(s) or disease(s) targeted for treatment. The combination of agents used within the methods or pharmaceutical compositions described herein also may reduce a detrimental effect associated with at least one of the agents when administered alone or without the other agent(s) of the particular pharmaceutical composition. For example, the toxicity of side effects of one agent may be attenuated by another agent of the composition, thus allowing a higher dosage, improving patient compliance, and improving therapeutic outcome. The additive or synergistic effects, benefits, and advantages of the compositions apply to classes of therapeutic agents, either structural or functional classes, or to individual compounds themselves.

Supplementary active compounds can also be incorporated into the compositions. In certain embodiments, an antibody or antibody portion of the invention is coformulated with and/or coadministered with one or more additional therapeutic agents that are useful for treating erosive polyarthritis. For example, an anti-hTNFα antibody, antibody portion, or other TNFα inhibitor of the invention may be coformulated and/or coadministered with one or more additional antibodies that bind other targets (*e.g.*, antibodies that bind other cytokines or that bind cell surface molecules), one or more cytokines, soluble TNFα receptor (see *e.g.*, PCT Publication No. WO 94/06476) and/or one or more chemical agents that inhibit hTNFα production or activity (such as cyclohexane-ylidene derivatives as described in PCT Publication No. WO 93/19751). Furthermore, one or more antibodies or other TNFα inhibitors of the invention may be used in combination with two or more of the foregoing therapeutic agents. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

TNFα inhibitors, *e.g.*, a TNFα antibody, or antigen-binding portion thereof, described herein may be used in combination with additional therapeutic agents for the treatment erosive polyarthritis. Preferably the other drug is a Disease Modifying Anti-Rheumatic Drug (DMARD) or a Nonsteroidal Antiinflammatory Drug (NSAID) or a steroid or any combination thereof. Preferred examples of a DMARD are hydroxychloroquine, leflunomide, methotrexate, parenteral gold, oral gold and sulfasalazine.

Nonlimiting additional agents which can also be used in combination with a TNFα inhibitor, *e.g.*, a TNFα antibody, or antigen-binding portion thereof, to treat erosive polyarthritis include, but are not limited to, the following: non-steroidal anti-

inflammatory drug(s) (NSAIDs); cytokine suppressive anti-inflammatory drug(s) (CSAIDs); CDP-571/BAY-10-3356 (humanized anti-TNFα antibody; Celltech/Bayer); cA2/infliximab (chimeric anti-TNFα antibody; Centocor); 75 kdTNFR-IgG/etanercept (75 kD TNF receptor-IgG fusion protein; Immunex; see *e.g.*, *Arthritis & Rheumatism* (1994) Vol. 37, S295; *J. Invest. Med.* (1996) Vol. 44, 235A); 55 kdTNF-IgG (55 kD TNF receptor-IgG fusion protein; Hoffmann-LaRoche); IDEC-CE9.1/SB 210396 (non-depleting primatized anti-CD4 antibody; IDEC/SmithKline; see *e.g.*, *Arthritis & Rheumatism* (1995) Vol. 38, S185); DAB 486-IL-2 and/or DAB 389-IL-2 (IL-2 fusion proteins; Seragen; see *e.g.*, *Arthritis & Rheumatism* (1993) Vol. 36, 1223); Anti-Tac (humanized anti-IL-2Rα; Protein Design Labs/Roche); IL-4 (anti-inflammatory cytokine; DNAX/Schering); IL-10 (SCH 52000; recombinant IL-10, anti-inflammatory cytokine; DNAX/Schering); IL-4; IL-10 and/or IL-4 agonists (*e.g.*, agonist antibodies); IL-1RA (IL-1 receptor antagonist; Synergen/Amgen); anakinra (Kineret®/Amgen); TNF-bp/s-TNF (soluble TNF binding protein; see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S284; *Amer. J. Physiol. - Heart and Circulatory Physiology* (1995) Vol. 268, pp. 37-42); R973401 (phosphodiesterase Type IV inhibitor; see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282); MK-966 (COX-2 Inhibitor; see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S81); Iloprost (see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S82); methotrexate; thalidomide (see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282) and thalidomide-related drugs (*e.g.*, Celgen); leflunomide (anti-inflammatory and cytokine inhibitor; see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S131; *Inflammation Research* (1996) Vol. 45, pp. 103-107); tranexamic acid (inhibitor of plasminogen activation; see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S284); T-614 (cytokine inhibitor; see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282); prostaglandin E1 (see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282); Tenidap (non-steroidal anti-inflammatory drug; see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S280); Naproxen (non-steroidal anti-inflammatory drug; see *e.g.*, *Neuro Report* (1996) Vol. 7, pp. 1209-1213); Meloxicam (non-steroidal anti-inflammatory drug); Ibuprofen (non-steroidal anti-inflammatory drug); Piroxicam (non-steroidal anti-inflammatory drug); Diclofenac (non-steroidal anti-inflammatory drug); Indomethacin (non-steroidal anti-inflammatory drug); Sulfasalazine (see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S281); Azathioprine (see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S281); ICE inhibitor (inhibitor of the enzyme interleukin-1β converting enzyme); zap-70 and/or lck inhibitor (inhibitor of the tyrosine kinase zap-70 or lck); VEGF inhibitor and/or VEGF-R inhibitor (inhibitos of vascular endothelial cell growth factor or vascular endothelial cell growth factor

receptor; inhibitors of angiogenesis); corticosteroid anti-inflammatory drugs (*e.g.*, SB203580); TNF-convertase inhibitors; anti-IL-12 antibodies; anti-IL-18 antibodies; interleukin-11 (see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S296); interleukin-13 (see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S308); interleukin -17 inhibitors (see *e.g.*, *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S120); gold; penicillamine; chloroquine; chlorambucil; hydroxychloroquine; cyclosporine; cyclophosphamide; total lymphoid irradiation; anti-thymocyte globulin; anti-CD4 antibodies; CD5-toxins; orally-administered peptides and collagen; lobenzarit disodium; Cytokine Regulating Agents (CRAs) HP228 and HP466 (Houghten Pharmaceuticals, Inc.); ICAM-1 antisense phosphorothioate oligo-deoxynucleotides (ISIS 2302; Isis Pharmaceuticals, Inc.); soluble complement receptor 1 (TP10; T Cell Sciences, Inc.); prednisone; orgotein; glycosaminoglycan polysulphate; minocycline; anti-IL2R antibodies; marine and botanical lipids (fish and plant seed fatty acids; see *e.g.*, DeLuca *et al.* (1995) *Rheum. Dis. Clin. North Am.* 21:759-777); auranofin; phenylbutazone; meclofenamic acid; flufenamic acid; intravenous immune globulin; zileuton; azaribine; mycophenolic acid (RS-61443); tacrolimus (FK-506); sirolimus (rapamycin); amiprilose (therafectin); cladribine (2-chlorodeoxyadenosine); methotrexate; antivirals; and immune modulating agents. Any of the above-mentioned agents can be administered in combination with the TNFα inhibitor, including a TNFα antibody, to treat erosive polyarthritis or to inhibit radiographic progression of joint disease.

In one embodiment, the TNFα inhibitor, *e.g.*, a TNFα antibody, or antigen-binding portion thereof, is administered in combination with one of the following agents for the treatment of rheumatoid arthritis: small molecule inhibitor of KDR (ABT-123), small molecule inhibitor of Tie-2; methotrexate; prednisone; celecoxib; folic acid; hydroxychloroquine sulfate; rofecoxib; etanercept; infliximab; leflunomide; naproxen; valdecoxib; sulfasalazine; methylprednisolone; ibuprofen; meloxicam; methylprednisolone acetate; gold sodium thiomalate; aspirin; azathioprine; triamcinolone acetonide; propxyphene napsylate/apap; folate; nabumetone; diclofenac; piroxicam; etodolac; diclofenac sodium; oxaprozin; oxycodone hcl; hydrocodone bitartrate/apap; diclofenac sodium/misoprostol; fentanyl; anakinra, human recombinant; tramadol hcl; salsalate; sulindac; cyanocobalamin/fa/pyridoxine; acetaminophen; alendronate sodium; prednisolone; morphine sulfate; lidocaine hydrochloride; indomethacin; glucosamine sulfate/chondroitin; cyclosporine; amitriptyline hcl; sulfadiazine; oxycodone hcl/acetaminophen; olopatadine hcl; misoprostol; naproxen sodium; omeprazole; mycophenolate mofetil; cyclophosphamide; rituximab; IL-1 TRAP; MRA; CTLA4-IG; IL-18 BP; ABT-874; ABT-325 (anti-IL 18); anti-IL 15; BIRB-796; SCIO-469; VX-702; AMG-548; VX-740; Roflumilast; IC-485; CDC-801;

and mesopram. In another embodiment, the TNFα antibody of the invention is administered for the treatment of a TNFα related disorder in combination with one of the above mentioned agents for the treatment of rheumatoid arthritis.

In one embodiment, the TNFα inhibitor, *e.g.*, a TNFα antibody, or antigen-binding portion thereof, is used in combination with a drug used to treat Crohn's disease or a Crohn's-related disorder. Examples of therapeutic agents which can be used to treat Crohn's include mesalamine, prednisone, azathioprine, mercaptopurine, infliximab, budesonide, sulfasalazine, methylprednisolone sod succ, diphenoxylate/atrop sulf, loperamide hydrochloride, methotrexate, omeprazole, folate, ciprofloxacin/dextrose-water, hydrocodone bitartrate/apap, tetracycline hydrochloride, fluocinonide, metronidazole, thimerosal/boric acid, cholestyramine/sucrose, ciprofloxacin hydrochloride, hyoscyamine sulfate, meperidine hydrochloride, midazolam hydrochloride, oxycodone hcl/acetaminophen, promethazine hydrochloride, sodium phosphate, sulfamethoxazole/trimethoprim, celecoxib, polycarbophil, propoxyphene napsylate, hydrocortisone, multivitamins, balsalazide disodium, codeine phosphate/apap, colesevelam hcl, cyanocobalamin, folic acid, levofloxacin, methylprednisolone, natalizumab, and interferon-gamma.

In one embodiment, the TNFα inhibitor, *e.g.*, a TNFα antibody, or antigen-binding portion thereof, is administered in combination with an agent which is commonly used to treat spondyloarthropathies, such as AS. Examples of such agents include nonsteroidal, anti-inflammatory drugs (NSAIDs), COX 2 inhibitors, including Celebrex®, Vioxx®, and Bextra®, aand etoricoxib. Physiotherapy is also commonly used to treat spondyloarthropathies, usually in conjunction with non-steoidal inflammatory drugs.

In one embodiment, the TNFα inhibitor, *e.g.*, a TNFα antibody, or antigen-binding portion thereof, is administered in combination with an additional therapeutic agent to treat ankylosing spondylitis. Examples of agents which can be used to reduce or inhibit the symptoms of ankylosing spondylitis include ibuprofen, diclofenac and misoprostol, naproxen, meloxicam, indomethacin, diclofenac, celecoxib, rofecoxib, sulfasalazine, prednisone, methotrexate, azathioprine, minocyclin, prednisone, etanercept, and infliximab.

In one embodiment, the TNFα inhibitor, *e.g.*, a TNFα antibody, or antigen-binding portion thereof, is administered in combination with an additional therapeutic agent to treat psoriatic arthritis. Examples of agents which can be used to reduce or inhibit the symptoms of psoriatic arthritis include methotrexate; etanercept; rofecoxib; celecoxib; folic acid; sulfasalazine; naproxen; leflunomide; methylprednisolone acetate; indomethacin; hydroxychloroquine sulfate; sulindac; prednisone; betamethasone diprop augmented; infliximab; methotrexate; folate; triamcinolone acetonide; diclofenac;

dimethylsulfoxide; piroxicam; diclofenac sodium; ketoprofen; meloxicam; prednisone; methylprednisolone; nabumetone; tolmetin sodium; calcipotriene; cyclosporine; diclofenac; sodium/misoprostol; fluocinonide; glucosamine sulfate; gold sodium thiomalate; hydrocodone; bitartrate/apap; ibuprofen; risedronate sodium; sulfadiazine; thioguanine; valdecoxib; alefacept; and efalizumab.

In one embodiment, the TNFα inhibitor, *e.g.*, a TNFα antibody, or antigen-binding portion thereof, is administered in combination with topical corticosteroids, vitamin D analogs, and topical or oral retinoids, or combinations thereof, for the treatment of psoriasis. In addition, the TNFα antibody of the invention is administered in combination with one of the following agents for the treatment of psoriasis: small molecule inhibitor of KDR (ABT-123), small molecule inhibitor of Tie-2, calcipotriene, clobetasol propionate, triamcinolone acetonide, halobetasol propionate, tazarotene, methotrexate, fluocinonide, betamethasone diprop augmented, fluocinolone, acetonide, acitretin, tar shampoo, betamethasone valerate, mometasone furoate, ketoconazole, pramoxine/fluocinolone, hydrocortisone valerate, flurandrenolide, urea, betamethasone, clobetasol propionate/emoll, fluticasone propionate, azithromycin, hydrocortisone, moisturizing formula, folic acid, desonide, coal tar, diflorasone diacetate, etanercept, folate, lactic acid, methoxsalen, hc/bismuth subgal/znox/resor, methylprednisolone acetate, prednisone, sunscreen, salicylic acid, halcinonide, anthralin, clocortolone pivalate, coal extract, coal tar/salicylic acid, coal tar/salicylic acid/sulfur, desoximetasone, diazepam, emollient, pimecrolimus emollient, fluocinonide/emollient , mineral oil/castor oil/na lact, mineral oil/peanut oil, petroleum/isopropyl myristate, psoralen, salicylic acid, soap/tribromsalan, thimerosal/boric acid, celecoxib, infliximab, alefacept, efalizumab, tacrolimus, pimecrolimus, PUVA, UVB, and sulfasalazine.

An antibody, antibody portion, or other TNFα inhibitor, *e.g.*, a TNFα antibody, or antigen-binding portion thereof, may be used in combination with other agents to treat skin conditions. For example, an antibody, antibody portion, or other TNFα inhibitor of the invention is combined with PUVA therapy. PUVA is a combination of psoralen (P) and long-wave ultraviolet radiation (UVA) that is used to treat many different skin conditions. The antibodies, antibody portions, or other TNFα inhibitors of the invention can also be combined with pimecrolimus. In another embodiment, the antibodies of the invention are used to treat psoriasis, wherein the antibodies are administered in combination with tacrolimus. In a further embodiment, tacrolimus and TNFα inhibitors are administered in combination with methotrexate and/or cyclosporine. In still another embodiment, the TNFα inhibitor of the invention is administered with excimer laser treatment for treating psoriasis.

Nonlimiting examples of other therapeutic agents with which a TNFα inhibitor, *e.g.*, a TNFα antibody, or antigen-binding portion thereof, can be combined to treat a

skin or nail disorder include UVA and UVB phototherapy. Other nonlimiting examples which can be used in combination with a TNFα inhibitor include anti-IL-12 and anti-IL-18 therapeutic agents, including antibodies.

Any one of the above-mentioned therapeutic agents, alone or in combination therewith, can be administered to a subject suffering from erosive polyarthritis, in combination with the TNFα α inhibitor, including a TNFα antibody, or antigen-binding portion thereof. A TNFα antibody, or antigen-binding portion thereof, may be used in combination with additional therapeutic agents known to be effective at acute management of subjects with erosive polyarthritis. A TNFα antibody, or antigen-binding portion thereof, may also be used in combination with additional therapeutic agents known to be effective at management of subjects with erosive polyarthritis.

This invention is further illustrated by the following example which should not be construed as limiting.

EXAMPLE

Treatment of Erosive Polyarthritis in Patients with Psoriatic Arthritis Using a TNF Inhibitor

Erosive polyarthritis occurs in a substantial proportion of patients with psoriatic arthritis (PsA). Traditional, non-biologic DMARDs have not been shown to effectively inhibit the radiographic progression of joint damage in this disease.

The following study was performed to evaluate the efficacy of a TNF inhibitor, more specifically the anti-TNF antibody adalimumab, for the treatment of erosive polyarthritis. The study was performed to evaluate whether adalimumab was effective at inhibiting the radiographic progression of joint disease associated with erosive polyarthritis in patients with moderate to severe PsA.

A 24-week, double-blind, randomized, placebo-controlled trial of adult patients with moderate to severely active PsA (≥3 swollen and ≥3 tender joints) who had failed NSAID therapy was performed. Patients were stratified according to methotrexate (MTX) use (yes/no) and degree of psoriasis (<3% or ≥3% Body Surface Area [BSA]). In addition to having ≥3 swollen and ≥3 tender joints, inclusion criteria included an inadequate response to NSAID therapy, a history of psoriasis, and age ≥ 18 years. Exclusion criteria included the following: prior anti-TNF therapy, alefacept within 12 weeks prior to study entry, other biologics within 6 weeks prior to study entry, systemic therapies for psoriasis within 4 weeks prior to study entry, and phototherapy and topicals within 2 weeks prior to study entry.

Patients were randomized to receive either adalimumab 40 mg or placebo subcutaneously every other week (eow) for 24 weeks. Patients who completed the 24-week trial were eligible to enroll in an open-label extension (OLE) study, in which all patients received adalimumab eow. After 12 weeks of treatment with open label therapy, patients failing to meet pre-specified criteria were eligible to receive 40 mg weekly.

Radiographic assessments were performed during both the blinded portion (Weeks 0 and 24) and the open-label portion (Week 48). Radiographs of the hands and feet were assessed by a modified total Sharp score (mTSS) in which additional joints typically involved in PsA were added, and, to better quantify the significant osteolysis that occurs in PsA, the numerical scales were expanded. The mTSS was determined by combining the joint space narrowing score (0-192) and the erosion score (0-378), as shown in Figure 1a. Clinical findings associated with PsA, *e.g.*, pencil-in-cup changes, were also evaluated. Diagrams of the mTSS and the radiographic findings associated with PsA used in this study are shown in Figures 1a and 1b, respectively.

The radiograph reading procedure included the following. All films were read by two independent readers who were blinded to treatment and film order. Read number 1 was an evaluation of baseline and week 24 films. Read number 2 was an evaluation of baseline, week 24, and week 48 films.

Several sensitivity analyses were utilized to assess the impact of missing radiographs (imputation of zero change, worst rank change, $50^{th}/75^{th}$ percentile change based on patients with similar baseline scores, and linear extrapolation when multiple radiographs were available).

Week 24 analysis included the following: inclusion in the week 24 analysis required both baseline and week 24 films, where at least 50% of the joints were evaluable. Week 48 analysis included the following: All patients from the 24 week analysis were included in the week 48 analysis. If the week 48 film was not available (or <50% of the joints evaluable), then the following imputation was performed: if originally randomized to placebo, a change of 0 was imputed; and if originally randomized to adalimumab, linear extrapolation using first two films was conducted.

Baseline demographics and disease severity characteristics were consistent with moderate to severe PsA and were well-matched between treatment arms (adalimumab N=151, placebo N=162; mean±SD): age 49.0±11.8 yrs; duration of PsA 9.5±8.5 yrs; SJC (76) 14±12; TJC (78) 25±18; HAQ 1.0±0.6; mTSS 20.8±40.9; 51% were taking concomitant methotrexate. Of the total, 296 patients had X-rays at baseline and Week 24, and 265 patients also had X-rays at Week 48.

As reported in previous studies, the ACR20, 50, and 70 responses and the PASI 50, 75, and 90 responses for adalimumab-treated patients at week 24 were significantly

better than placebo. ACR and PASI responses at week 24 are shown below in tables 1 and 2 (all results $p \leq 0.001$ placebo vs. adalimumab):

Table 1: ACR response: % of patients

	ACR20	ACR50	ACR70
Placebo (N=162)	15	6	1
Adalimumab (N=151)	57	39	23

Table 2: PASI response: % of patients

	PASI 50	PASI 75	PASI 90
Placebo (N=69)	12	1	0
Adalimumab (N=69)	75	59	42

During the blinded study period (24 wks), adalimumab patients had significantly less progression in mTSS than placebo patients (mean change in mTSS –0.2 vs. 1.0, $p<0.001$, ranked ANCOVA). Statistical significance was maintained in all sensitivity analyses. Figure 2 shows the distribution of mTSS scores which demonstrates that fewer patients treated with adalimumab had an increase in structural damage during 24 weeks of treatment compared with placebo. The difference in distribution was observed by looking at mean scores at week 24 and the number and percentage of patients who had an increase in Sharp score during the study (see Table 3). Approximately three times as many placebo-treated patients had an increase in mTSS (>0.5 units) than adalimumab-treated patients during the first 24 weeks of treatment.

Table 3: Change in Modified Total Sharp Score at Week 24*

	Placebo N = 152 n (%)	Adalimumab N = 144 n (%)
Decrease in Sharp Score	8 (5.3%)	27 (18.8%)
No change in Sharp Score	100 (65.8%)	104 (72.2%)
Increase in Sharp Score	44 (28.9%)	13 (9.0%)

$p \leq 0.001$ placebo vs. adalimumab using CMH test
* Change defined as >0.5 units in mTSS Score

Statistically significant differences were observed between adalimumab and placebo treated subjects for both erosion scores and joint narrowing scores ($p \leq 0.001$ using a ranked ANACOVA). At Week 24, the change in erosion scores (change from baseline) were 0.6 for placebo patients and 0.0 for adalimumab patients ($p<0.001$, ranked ANCOVA), and the change in joint space narrowing scores (change from baseline) were 0.4 for placebo patients and -0.2 for adalimumab patients ($p<0.001$, ranked ANCOVA).

Sensitivity analyses to account for missing patients films were performed and results maintained statistical significance with all analyses. Post-hoc sensitivity analyses excluding feet and DIPs were as follows: one analysis was run excluding feet and DIPs and a second analysis was run excluding all DIP joints. Statistical significance was maintained in both analyses.

Statistically significant differences were observed between adalimumab and placebo treated subjects regardless of whether concomitant MTX was being used. Mean differences were slightly higher for patients taking concomitant MTX. Patients on monotherapy showed a change from baseline of -0.1 in adalimumab (n=68) vs. 0.9 for placebo (n=74) ($p \leq 0.001$ using a ranked ANACOVA). Patients on concomitant MTX showed a change from baseline of -0.3 in adalimumab (n=76) vs. 1.2 for placebo (n=78) ($p \leq 0.001$ using a ranked ANACOVA). Figures 3a and 3b show cumulative distribution function plots of mTSS of subjects with and without MTX.

Analysis of 48-week radiographs demonstrated that the lack of progression (lack of changes in mTSS) observed at Week 24 was maintained to Week 48 in adalimumab patients (see Figure 4). Patients treated with placebo for 24 weeks did not have radiographic progression of disease during the open-label period. Neither treatment arm demonstrated significant progression in PsA-associated features. The prevalence of PsA-associated findings are shown in Table 4. No significant difference was found

between groups at baseline, and no significant progression was found in either group during the 24-week study.

Table 4: Prevalence of PsA-associated findings

	All patients (N=313) n (%)
Joint space widening	38 (12.1%)
Gross osteolysis	60 (19.2%)
Subluxation	49 (15.7%)
Pencil-in-cup	9 (2.9%)
Juxta-articular periostitis	247 (78.9%)
Shaft periostitis	140 (44.7%)
Phalangeal tuft resorption	224 (71.6%)

Furthermore, adalimumab was generally well-tolerated as reported previously. Adalimumab was more effective compared with placebo in inhibiting radiographic disease progression over a 24-week period. Adalimumab showed differences versus placebo both in patients taking concomitant methotrexate and in those taking adalimumab as monotherapy. The inhibition of structural damage progression observed in adalimumab-treated patients at 24 weeks was maintained at one year. In conclusion, this study demonstrated that adalimumab was effective in treating erosive polyarthritis and radiographic disease progression over one year in patients who also had moderate to severely active PsA.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein.

The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as as a whole.

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2___

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

NOTE: For additional volumes please contact the Canadian Patent Office.

What is claimed is:

1. Use of adalimumab for treating structural damage associated with psoriatic arthritis, wherein adalimumab is for subcutaneous administration at a dose of 40 mg every other week to a human subject having structural damage associated with psoriatic arthritis, such that progression of structural damage in the human subject is inhibited or lessened.

2. The use of claim 1, wherein the change between baseline mTSS of the subject prior to said treating, and mTSS of the subject following said treating, is -0.2.

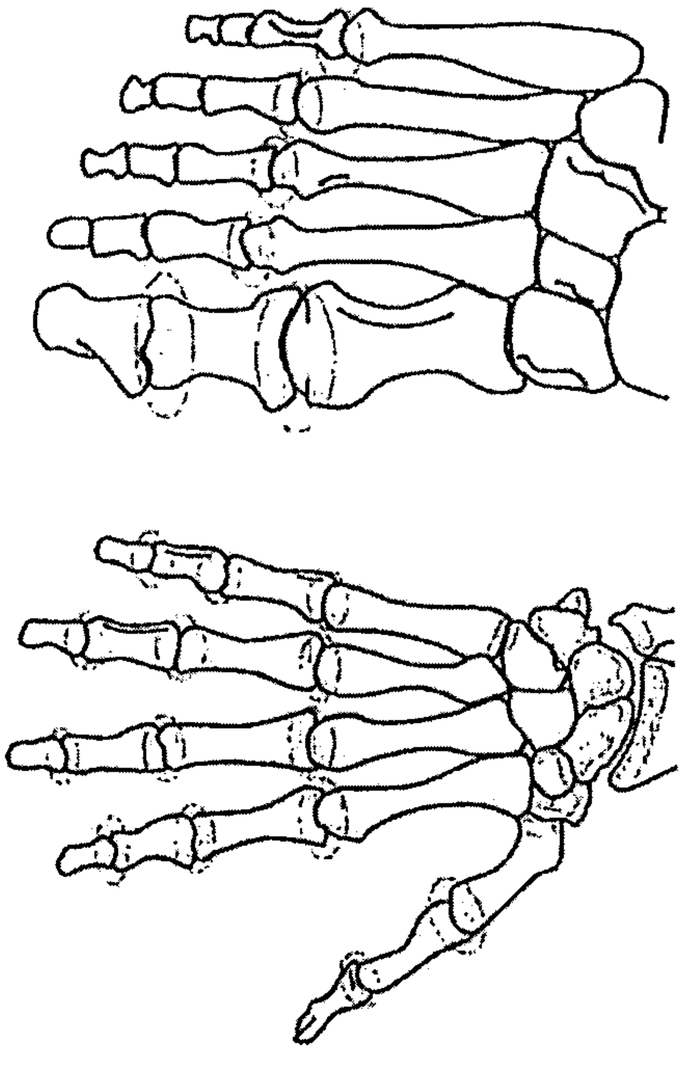
Erosions (0–7): 54 sites
Joint Space Narrowing (0–4): 48 sites
0–192
0–378
0–570
Erosion
Joint Space Narrowing
Modified Total Sharp Score

Fig. 1a

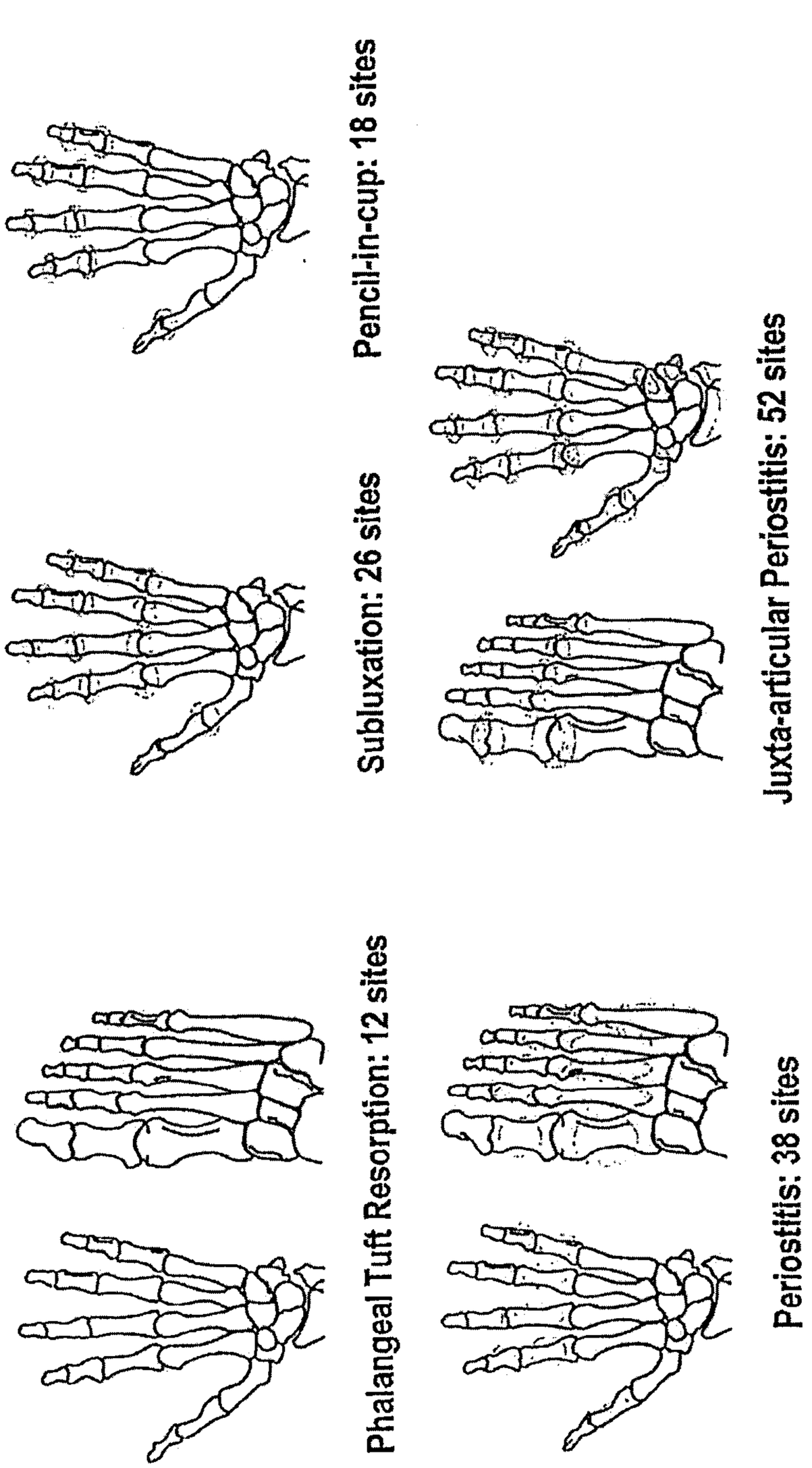
Pencil-in-cup: 18 sites
Subluxation: 26 sites
Juxta-articular Periostitis: 52 sites
Phalangeal Tuft Resorption: 12 sites
Periostitis: 38 sites

Fig. 1b

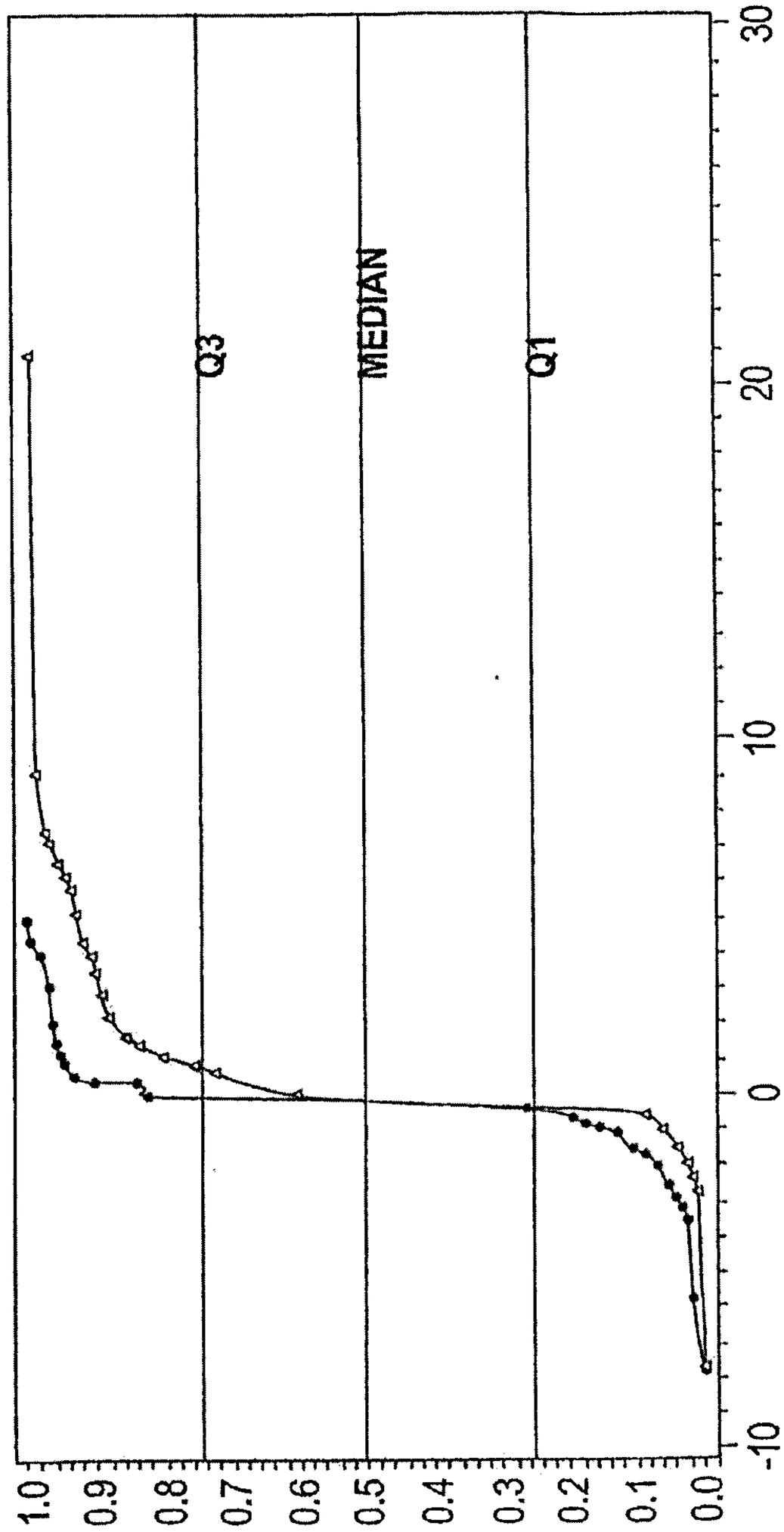
CUMULATIVE PROBABILITY
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-10
0
10
20
30
CHANGE FROM BASELINE TO WEEK 24 IN mTSS
TREATMENT
ADALIMUMAB
PLACEBO
Q1
MEDIAN
Q3

Fig. 2

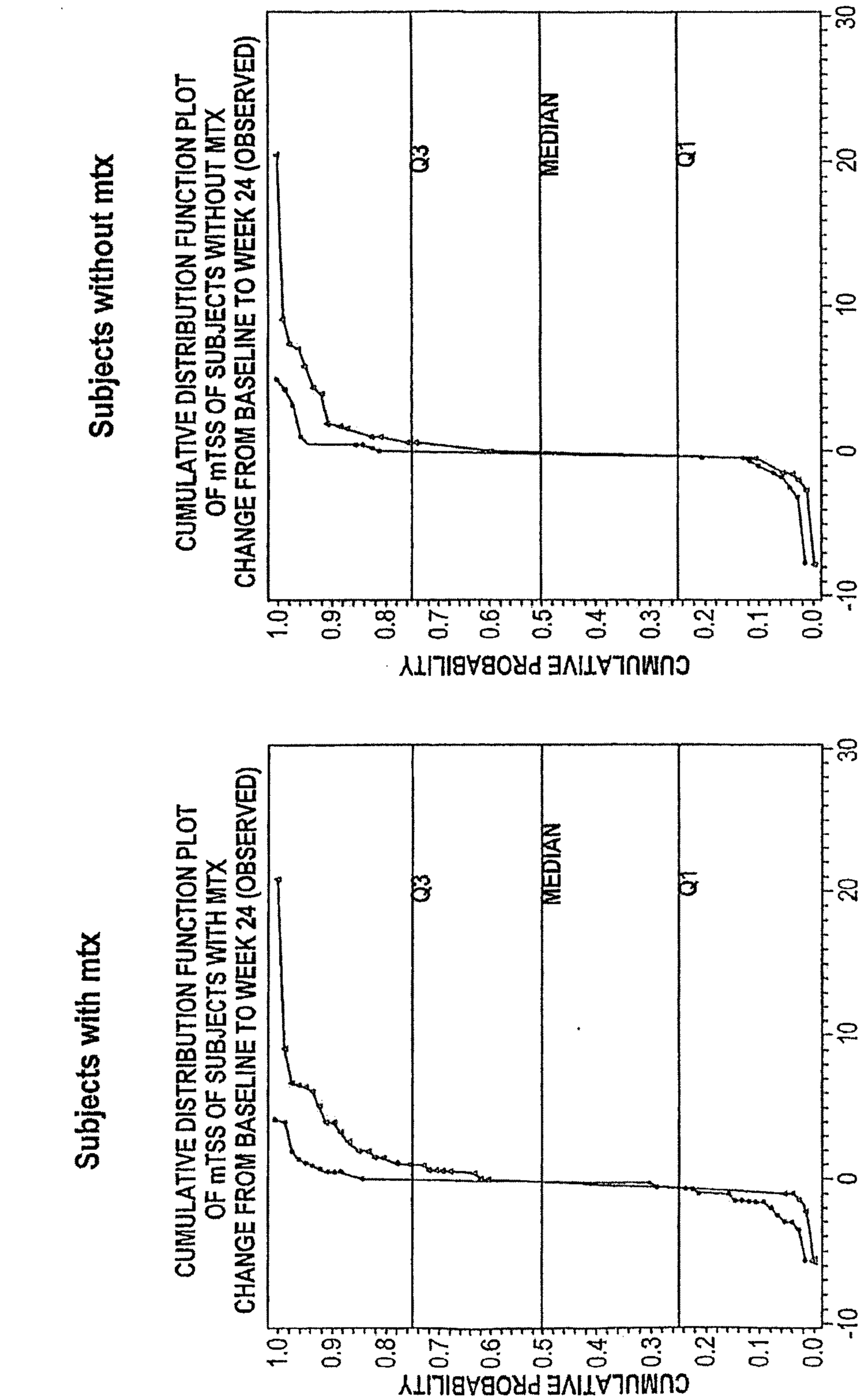
Subjects without mtx
CUMULATIVE DISTRIBUTION FUNCTION PLOT
OF mTSS OF SUBJECTS WITHOUT MTX
CHANGE FROM BASELINE TO WEEK 24 (OBSERVED)
Q3
MEDIAN
Q1
CUMULATIVE PROBABILITY
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-10
0
10
20
30
CHANGE FROM BASELINE TO WEEK 24 IN mTSS

Fig. 3B

Subjects with mtx
CUMULATIVE DISTRIBUTION FUNCTION PLOT
OF mTSS OF SUBJECTS WITH MTX
CHANGE FROM BASELINE TO WEEK 24 (OBSERVED)
Q3
MEDIAN
Q1
CUMULATIVE PROBABILITY
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-10
0
10
20
30
CHANGE FROM BASELINE TO WEEK 24 IN mTSS

Fig. 3a

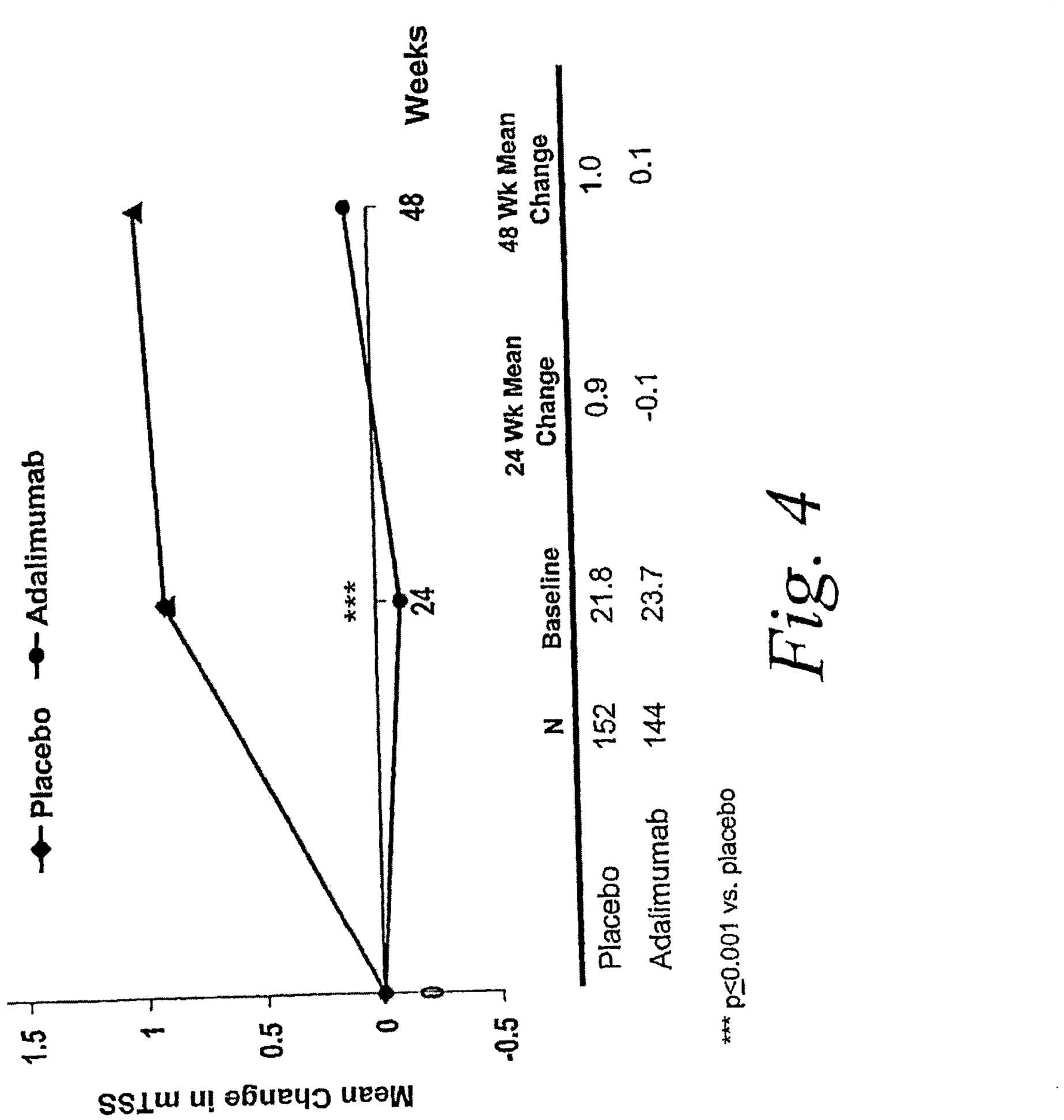
Placebo
Adalimumab
Mean Change in mTSS
1.5
1
0.5
0
-0.5
0
24
48
Weeks
***
N
Baseline
24 Wk Mean Change
48 Wk Mean Change
Placebo
152
21.8
0.9
1.0
Adalimumab
144
23.7
-0.1
0.1
*** p≤0.001 vs. placebo

Fig. 4