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(54) **Title:** JOINT DESTRUCTION BIOMARKERS FOR ANTI-IL-17A THERAPY OF INFLAMMATORY JOINT DISEASE

(57) **Abstract:** Novel methods and drug products for treating inflammatory joint diseases such as rheumatoid arthritis and associated arthritides are disclosed. The methods and products employ various serum markers of bone and cartilage metabolism or destruction, including cartilage oligomer matrix protein (COMP) and Receptor activator of NFB ligand (RANKL), as biomarkers to assess the effect of IL-17A antagonists on joint destruction in inflammatory joint diseases.

JOINT DESTRUCTION BIOMARKERS FOR ANTI-IL-17A THERAPY OF INFLAMMATORY JOINT DISEASE

The present application claims the benefit of U.S. Provisional Patent Application 60/945239, filed 20 June 2007.

FIELD OF THE INVENTION

The present invention relates generally to the treatment of inflammatory joint diseases with antagonists of interleukin-17A (IL-17A). More specifically, the invention relates to biomarkers that are correlated with the efficacy of IL-17A antagonists for inhibiting joint destruction in rheumatoid arthritis and associated arthritides.

BACKGROUND OF THE INVENTION

Rheumatoid arthritis (RA) is an inflammatory disease caused by the dys-regulation of the immune system resulting in joint inflammation, causing joint pain, discomfort, swelling and stiffness, with progressive bone and cartilage erosion. The combination of inflammation and structural joint damage results in loss of function which can lead to permanent disability.

IL-17A, which was originally named cytotoxic T-Lymphocyte-associated antigen 8 (CTLA8) is a homodimeric cytokine that binds to IL-17RA (also known as IL17R) and IL-17RC. The functional receptor for IL-17A is believed to be a multimeric receptor complex comprising one or both of IL-17RA and IL-17RC (e.g., an IL-17RA homodimer, an IL-17RC homodimer, or an IL-17RA/IL-17RC heterodimer) and possibly a third, as yet unknown, protein (Toy, D. et al., (2006) *J. of Immunol.* 177(1):36-39; unpublished data).

IL-17A is produced by a subset of T cells known as Th17 cells, whose differentiation is initiated by TGF-beta signaling in the context of proinflammatory cytokines, particularly IL-6, IL-1-beta and TNF-alpha, and whose maintenance and survival are dependent on interleukin-23 (IL-23) (Langrish, C.L. et al. (2005), J. Exp. Med 201:233-240; Harrington, L.E., et al., (2005), *Nat. Immunol.* 6:1123-1132; Veldhoen, M. et al., (2006) *Immunity* 24:179-189). IL-23 is a heterodimeric cytokine comprised of two subunits: p19, which is unique to IL-23; and p40, which is shared with IL-12. IL-23 mediates signaling by binding to a heterodimeric receptor, comprised of IL-23R and IL-12Rbeta1 (IL12RB1), which is shared by the IL-12 receptor. Studies in murine disease models suggest that IL-23-dependent Th17 cells

play a pathogenic role in autoimmune and chronic inflammatory diseases (Langrish et al., *supra*, Park, H., et al. (2005), *Nat. Immunol.* 6:1133-1141).

IL-17A is present in RA synovial fluid at the earliest stages of the disease along with other known inflammatory mediators such as TNF and IL-1β. Dys-regulated IL-17A expression within an inflamed joint singly, and in synergy with TNF and IL-1β, stimulates multiple downstream proteases, chemokines and pro-inflammatory cytokines that collectively contribute to cartilage and bone erosion. A variety of IL-17A biological antagonists used in multiple rodent arthritis models have demonstrated that IL-17A blockade inhibits arthritis progression and the resulting joint destruction that occurs with a special emphasis on bone sparing (*see, e.g.*, Koenders MI, et al., (2006) *Ann. Rheum. Dis.* 65 (Suppl. 3):29-33). At least one anti-IL-17A antibody is being tested in clinical trials of human RA patients.

Currently, assessing the effect of anti-rheumatic drugs on the progression of joint destruction relies mainly on radiographic evaluation. However, how to use radiographic data in clinical trials is controversial (van der Heijde, D. et al, (2002) *Arthritis Rheum* 47;215-218). In addition to being time consuming, radiography is impractical in early stages of RA in which symptoms reflecting the inflammatory process often predominate over symptoms related to joint destruction (Morozzi, G., et al, (2007) *Clin Rheumatol.*) Indeed, nonsteroidal anti-inflammatory drugs (NSAIDs), which have traditionally been used as first line therapies for RA, are reasonably effective at ameliorating the signs and symptoms of inflammation, but have little efficacy in retarding joint destruction, leading to speculation that inflammation and subsequent joint destruction can be uncoupled (van den Berg, WB (2001), *Semin Arthritis Rheum.* 30:7-16; Geusens, P.P., et al. (2006), Arthritis & Rheumatism 54 (6):1772-1777). Thus, there is a well-established clinical need for better tools to predict the effect of anti-rheumatic drugs on structural joint damage, with recent development efforts focused on various markers of cartilage and/or bone metabolism that are elevated in the serum or urine of RA patients compared to normal subjects (Crnkic, M. et al., (2003) *Arthritis Res. Ther.* 5:R181-R185; Valleala, H., et al. (2003) *Eur. J. Endocrinol.* 148:527-530); Ziolkowska, M., et al. (2002) *Arthritis & Rheumatism* 46(7):1744-1753).

Articular cartilage in the joints is composed of the proteoglycan aggrecan, collagen (three α-chains form a triple helix), and other non-collagenous proteins (*e.g.*, cartilage oligomer matrix protein (COMP) and human cartilage glycoprotein-39 (HC gp-39), which is also known as YKL-40). Type I collagen is a major component of bone and other tissues; whereas, type II collagen is specifically localized to articular cartilage of the joint. At the ends

of type I and II collagen helixes are short, non-helical N- and C-terminal telopeptides containing covalent cross-links that connect to other α-chains, both within the same trimer and to adjacent trimers. Physiological and pathological cleavage of collagen by MMPs or Cathepsin K results in the generation of degradation products or neo-epitopes (e.g. C2C, C1,2C, C-terminal cross-linking telopeptide of type I collagen (CTX-I), C-terminal cross-linking telopeptide of type II collagen (CTX-II), N-terminal cross-linking telopeptide of type I collagen (NTX-I)), which are released into the synovial fluid, serum, and urine. Cleavage of the collagen triple helix also releases non-collagenous proteins (e.g. COMP, YKL-40, aggrecan) previously incorporated in the collagen fibrils. These molecules are elevated in synovial fluid and serum under conditions of normal remodeling and pathological cartilage destruction.

Cartilage destruction also results in compensatory increased collagen synthesis by chondrocytes. Type I and II collagen is synthesized as a pro-molecule and once outside the cell, cleavage of pro-collagen releases N-terminal and C-terminal pro-peptides. Type II collagen C-terminal pro-peptide (CPII) levels correlate with new type II collagen synthesis. Cartilage destruction also increases aggrecan synthesis and the appearance of the "fetal form" of aggrecan that has the CS846 epitope. Increased CS846 levels in the serum reflect new aggrecan synthesis (versus cleavage of "old" aggrecan).

Bone destruction occurs via the generation of excessive numbers of osteoclasts that resorb the mineralized bone and degrade the organic matrix of the de-mineralized bone. Receptor activator of NFκB (RANK) ligand (RANKL) is a cell-surface molecule expressed by activated T-cells, fibroblast-like synoviocytes (FLS), and osteoblasts that is critical in promoting the differentiation of pre-osteoclasts into mature osteoclasts, which are cells that can erode bone. RANKL can be shed by proteolytic cleavage (both cell surface and soluble RANKL are active), and is elevated in mouse arthritis and human RA serum. Membrane or soluble RANKL binds to RANK on pre-osteoclasts and delivers a differentiation signal. Osteoprotegrin (OPG) is a natural antagonist of this system by binding to RANKL and preventing its interaction with RANK on pre-osteoclasts.

Tartrate-resistant acid phosphatase (TRACP) isoform 5b is released into the serum by bone-resorbing osteoclasts as they transcytose degraded bone proteins from the resorbed bone surface to outside the bone. TRACP isoform 5b serum levels are elevated in bone resorption diseases. The amino acid sequence for TRACP5 is found in Accession No. for NM_001102405, NM_001102404 or NM_007388.

Some of these serum markers of bone and cartilage metabolism (or destruction) are elevated in RA patients and have some prognostic value in identifying patients that are at a higher risk of having more aggressive bone destruction. For example, elevated levels of cartilage oligomeric matrix protein (COMP) have been associated with more aggressive radiographic progression (den Broeder, A. A., et al. (2002) *Ann Rheum Dis* 61(4): 311-318; Wollheim, F. A., et al. (1997) *Br J Rheumatol* 36(8): 847-8499; Skoumal, M., et al. (2003). *Scand J Rheumatol* 32(3):156-161; Mansson, B., et al. (1995), J Clin Invest 95(3):1071-1077; Lindqvist, E., et al. (2005) *Ann Rheum Dis* 64(2):196-201; Forslind, K., et al. (1992) *Br J Rheumatol* 31(9): 593-598; Fex, E., et al. (1997) *Br J Rheumatol* 36(11):1161-1165. Also, a low OPG/RANKL ratio predicted increased five year radiographic progression (Geusens, P. P. et al. (2006) *Arthritis Rheum* 54(6):1772-1777) and elevated CTX-I and CTX-II levels were associated with four year Sharp Score increase in early RA patients (Garnero, P., et al. (2002) *Arthritis Rheum* 46(11):2847-2856).

However, the inventors herein are not aware of any published studies that conclude that blocking IL-17A can inhibit bone erosion and modulate serum levels of any of the above proteins in severely arthritic animals. Thus, a need exists to identify biomarkers that correlate with inhibition of joint destruction by anti-IL-17A therapy.

SUMMARY OF THE INVENTION

The present invention is based on the discovery described herein that COMP, OPG and RANKL serum levels in mice with collagen-induced arthritis (CIA) following treatment with an anti-IL-17A monoclonal antibody (Mab) are modulated by anti-IL-17A therapy. Also, the inventors have discovered that RANKL serum levels in CIA-mice decrease with increasing doses of the anti-IL-17A Mab, and reach normal levels at antibody doses that are effective at inhibiting joint destruction in the CIA mice as measured by traditional histological and μ-CT-based techniques. Based on these results with COMP, OPG and RANKL in the mouse CIA arthritis model, the inventors herein believe that these markers are likely to be useful as surrogate markers, i.e., biomarkers, of the effect of anti-IL-17A therapy on joint destruction in inflammatory joint diseases such as RA and associated athritidies. Also, these data obtained in arthritic mice support the use of other markers of cartilage and bone metabolism that are elevated in human RA patients, including CTX-I, CTX-II, and HC gp-39, as surrogate markers for monitoring the effect of anti-IL-17A therapy on joint destruction in patients with inflammatory joint disease.

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