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Annual Update 2003 Musculoskeletal Drugs

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CONTENTS

Abstract

The Annual Update 2003 of Musculoskeletal Drugs is comprised of a Compendium of drug R&D in the areas of musculoskeletal and connective tissue diseases, including 86 drugs for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, scleroderma and Sjögren's syndrome, and Monograph Updates on the following drugs that have been published in previous issues of the journal: abetimus sodium, adalimumab, etoricoxib, iguratimod, licofelone, lumiracoxib, prasterone, tacrolimus and valdecoxib. The Annual Update also includes a comprehensive table listing the drugs, their manufacturers, indications and developmental phases.

Introduction

This month's Annual Update features a Compendium of drug R&D in the areas of musculoskeletal and connective tissue diseases. As can be seen in the following table, 69 drugs are under development for the treatment of rheumatoid arthritis, 5 for juvenile rheumatoid arthritis, 12 for osteoarthritis, 4 for psoriatic arthritis, 3 for ankylosing spondylitis, 6 for systemic lupus erythematosus, 2 for scleroderma, 1 for Sjögren's syndrome and 1 for acute gouty arthritis. The Monograph Updates section offers updated information on the following musculoskeletal drugs that have been published in previous issues of the journal: abetimus sodium, adalimumab, etoricoxib, iguratimod, licofelone, lumiracoxib, prasterone, tacrolimus and valdecoxib.

According to IMS Health Drug Monitor, worldwide sales of drugs for musculoskeletal disorders totaled USD 16,600 million in the 12-month period from November 2001 to November 2002, a 6% increase over the previous 12 months, underlining the importance of this particular therapeutic category.

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Drug	Source	Indication	Phase
Abetimus Sodium[2]	La Jolla Pharmaceutical	Systemic lupus erythematosus	III
ABT-963	Abbott	Osteoarthritis	I
AD-121	Arakis/Penwest	Rheumatoid arthritis	II
AD-452	Arakis/KS Biomedix	Rheumatoid arthritis	I
Adalimumab[2]	Abbott	Juvenile rheumatoid arthritis	III
	Abbott/Eisai	Rheumatoid arthritis	Approved
AGIX-4207	AtheroGenics	Rheumatoid arthritis	II
A-IFN-Gamma	Advanced Biotherapy	Rheumatoid arthritis	II
Amelubant	Boehringer Ingelheim	Rheumatoid arthritis	II
Anakinra	Amgen	Rheumatoid arthritis	L-2001
AnergiX-RA	Corixa/Organon	Rheumatoid arthritis	II
AnervaX.RA	Corixa	Rheumatoid arthritis	II
APT-070C	AdProTech	Rheumatoid arthritis	II
AZD-2315	AstraZeneca	Rheumatoid arthritis	II
AZD-9056	AstraZeneca	Rheumatoid arthritis	I
BMS-188667	Bristol-Myers Squibb	Juvenile rheumatoid arthritis	II
Clenoliximab	IDEC	Rheumatoid arthritis	II
Clodronate Disodium	Abiogen	Osteoarthritis	II
CLX-0921	Calyx Therapeutics	Rheumatoid arthritis	I
CPA-926	Kureha/Sankyo	Osteoarthritis	II
CPD-870	Celltech/Pharmacia	Rheumatoid arthritis	III
CS-502	Sankyo	Rheumatoid arthritis	II
Doramapimod	Boehringer Ingelheim	Rheumatoid arthritis	II
Dronabinol/Cannabinol	GW Pharmaceuticals	Rheumatoid arthritis	II
E21R	BresaGen	Rheumatoid arthritis	II
E-6087	Esteve	Osteoarthritis	I
Eculizumab	Alexion	Rheumatoid arthritis	II
	Alexion	Systemic lupus erythematosus	II
Efalizumab[2]	Xoma/Genentech	Rheumatoid arthritis	II
Etanercept[1]	Amgen	Ankylosing spondylitis	Pend. Appr.
	Immunex/Wyeth/Amgen	Psoriatic arthritis	Approved
ETI-104	EluSys	Systemic lupus erythematosus	II
Etoricoxib	Merck & Co.	Acute gouty arthritis	L-2002
	Merck & Co.	Ankylosing spondylitis	III
	Merck & Co.	Osteoarthritis	L-2002
	Merck & Co.	Rheumatoid arthritis	L-2002
Everolimus[2]	Novartis	Rheumatoid arthritis	II
Fluasterone	Hollis-Eden/Aeson Therapeutics	Rheumatoid arthritis	I
HE-2200	Hollis-Eden	Rheumatoid arthritis	I
HuMax-IL-15	Genmab/Amgen	Rheumatoid arthritis	I/II
IC-485	Icos	Rheumatoid arthritis	I
IgPO	Protein Therapeutics	Juvenile rheumatoid arthritis	II
	Protein Therapeutics	Rheumatoid arthritis	II
Iguratimod[2]	Toyama/Eisai	Rheumatoid arthritis	III
IL-1 Receptor Type II	Amgen	Rheumatoid arthritis	I
IL-1 Trap	Regeneron	Rheumatoid arthritis	II
Ilodecakin	Schering-Plough	Rheumatoid arthritis	II
Infliximab[1]	Schering-Plough	Ankylosing spondylitis	Prereg
	Schering-Plough	Juvenile rheumatoid arthritis	III
	Schering-Plough	Psoriatic arthritis	III
Interferon Alfa[1]	Amarillo Biosciences	Sjögren's syndrome	III
IPL-512602	InflaZyme	Rheumatoid arthritis	I
IPL-550260	InflaZyme	Rheumatoid arthritis	I
ISAtx-247	Isotechnika/Roche	Rheumatoid arthritis	I
ISIS-104838	Isis Pharmaceuticals/Elan/OraSense	Rheumatoid arthritis	II
J-695	Abbott/Genetics Institute	Rheumatoid arthritis	II
LAS-34475	Almirall Prodesfarma	Osteoarthritis	II
	Almirall Prodesfarma	Rheumatoid arthritis	II
Licofelone[2]	Merckle/EuroAlliance	Osteoarthritis	III

Continuation

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Drug	Source	Indication	Phase
Lumiracoxib[2]	Novartis	Rheumatoid arthritis	Pend. Appr.
LymphoStat-B	Human Genome Sciences/Cambridge Antibody Technology	Systemic lupus erythematosus	I
Metelimumab	Genzyme General/Cambridge Antibody Technology	Scleroderma	II
Milican[1]	Dong-Wha	Rheumatoid arthritis	II
MLN-1202	Millennium	Rheumatoid arthritis	I
MRA	Chugai	Juvenile idiopathic arthritis	II
	Chugai	Rheumatoid arthritis	II
	Chugai	Systemic lupus erythematosus	I
MX-1094	Medinox	Rheumatoid arthritis	I
NGD-2000-1	Neurogen	Rheumatoid arthritis	I
Onercept	Serono	Psoriatic arthritis	II
Ono-4817	Ono	Osteoarthritis	I
Org-37663	Organon	Rheumatoid arthritis	I
Org-39141	Organon	Rheumatoid arthritis	II
Paclitaxel[1,2]	Angiotech	Rheumatoid arthritis	II
Pegsunercept	Amgen	Rheumatoid arthritis	II
Pralnacasan	Vertex/Aventis Pharma	Osteoarthritis	II
	Vertex/Aventis Pharma	Rheumatoid arthritis	II
Prasterone[2]	Genelabs/Watson	Systemic lupus erythematosus	Rec. Appr.
R-1487	Roche	Rheumatoid arthritis	I
RAVAX	Immune Response	Rheumatoid arthritis	II
Reumacon	ConPharm/Meda	Rheumatoid arthritis	III
rhIL-18bp	Serono	Psoriatic arthritis	I
	Serono	Rheumatoid arthritis	I
Rituximab[1]	Roche	Rheumatoid arthritis	II
SB-462795	GlaxoSmithKline/Human Genome Sciences	Osteoarthritis	I
SCIO-323	Scios	Rheumatoid arthritis	I
	Scios	Rheumatoid arthritis	I
SCIO-469	Scios	Rheumatoid arthritis	II
SI-6601D	Seikagaku	Rheumatoid arthritis	II
SMP-114	Sumitomo Pharmaceuticals	Rheumatoid arthritis	I
SVT-2016	Salvat	Rheumatoid arthritis	I
T-487	Tularik/ChemoCentryx	Rheumatoid arthritis	I
Tacrolimus[1,2]	Fujisawa	Rheumatoid arthritis	III
Tilmacoxib[2]	Japan Tobacco	Osteoarthritis	II
	Japan Tobacco	Rheumatoid arthritis	II
TR-14035	Tanabe Seiyaku/GlaxoSmithKline	Rheumatoid arthritis	I
TRX-1	TolerRx	Rheumatoid arthritis	I
Valdecoxib[2]	Pharmacia/Pfizer	Osteoarthritis	L-2002
	Pharmacia/Pfizer	Rheumatoid arthritis	L-2002
Vitaxin	MedImmune/Applied Molecular Evolution	Rheumatoid arthritis	I
VX-702	Vertex/Kissei	Rheumatoid arthritis	I
Zoledronic Acid Monohydrate[1,2]	Novartis	Rheumatoid arthritis	II

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, debilitating disease of unknown etiology characterized by persistent intense autoimmune activity, symmetrical joint pain and inflammation, local destruction of bone and cartilage and pannus formation. According to the American College of Rheumatology, RA affects 1.0% of all Americans; some estimates suggest that this figure may be as high as 7% worldwide. Arthritis and related conditions incur annual costs of USD 65 billion in the U.S. alone, according to the Centers for Disease Control and Prevention (CDC).

Antirheumatic drugs fall into two broad classifications: nonsteroidal antiinflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs). Other potential therapeutic strategies under investigation include gene therapy and cell therapy, although these strategies are currently in the earliest stages of investigation and thus do not fall within the scope of this review.

Nonsteroidal antiinflammatory drugs

The synthesis more than 100 years ago of acetylsalicylic acid (aspirin), the first nonsteroidal antiinflammatory drug (NSAID), led to the widespread use of this drug in the treatment of painful and inflammatory symptoms of arthritis. Some 20 other NSAIDs have reached the market for the RA indication since that time.

Only one new NSAID is known to be in development for the treatment of RA at this time: Medinox's **MX-1094**. This drug, a prodrug of naproxen, entered phase I testing in the Netherlands in June 2002. In December 2002, Medinox completed the trial, which was designed to evaluate the initial safety profile, tolerability and pharmacokinetics of MX-1094 in healthy volunteers. Because a good safety profile was observed in this study, the company plans to advance development to a small-scale phase II trial in Europe beginning in early 2003.

COX-2 inhibitors

Designed to circumvent the adverse effects of NSAIDs while maintaining their therapeutic efficacy, selective inhibitors of the cyclooxygenase type-2 enzyme (COX-2) have been actively investigated in the last decade for the treatment of RA, osteoarthritis (OA) and pain. Five COX-2 inhibitors have reached the market to date, and several others are in the pipeline for the treatment of RA, as shown in Table I.

Table I: COX-2 inhibitors recently marketed and in development for the treatment of rheumatoid arthritis.

Drug Name	Source	Status
Etoricoxib	Merck & Co.	L-2002
Valdecoxib	Pharmacia/Pfizer	L-2002
Lumiracoxib	Novartis	Prereg
CS-502	Sankyo	Phase II
LAS-34475	Almirall Prodesfarma	Phase II
Tilmacoxib	Japan Tobacco	Phase II
SVT-2016	Salvat	Phase I

Two new COX-2-specific inhibitors reached the market in 2002, increasing the NSAID options for the treatment of rheumatic disorders. The first, **valdecoxib** (Bextra®), was launched by Pharmacia and marketing partner Pfizer in the U.S. It is indicated for the treatment of signs and symptoms of OA and RA in adults, and for the treatment of primary dysmenorrhea. The second new COX-2 inhibitor, Merck & Co.'s **etoricoxib** (Arcoxia™), was launched for the first time in the U.K. last May. Etoricoxib is indicated for the symptomatic relief of OA and RA, the treatment of acute gouty arthritis, the relief of chronic musculoskeletal pain including low back pain, the relief of acute pain associated with dental surgery and the treatment of primary dysmenorrhea.

Miscellaneous antiinflammatory/analgesic agents

Although a great majority of the antiinflammatory drugs in development for RA target the inhibition of cyclooxygenase, a few other mechanisms of antiinflammatory and/or analgesic activity are being explored, as shown in Table II.

Disease-modifying antirheumatic drugs

Disease-modifying antirheumatic drugs (DMARDs) may be used in combination with NSAIDs and, when necessary, glucocorticoids. Often two or three DMARDs are

Table II: Miscellaneous antiinflammatory/analgesic agents in development for rheumatoid arthritis.

Drug Name	Source	Mechanism of Action/Description	Status
Amelubant	Boehringer Ingelheim	Leukotriene B_4 antagonist	Phase II
E21R	BresaGen	Antagonist of GM-CSF activity	Phase II
SI-6601D	Seikagaku	Ultra-purified sodium hyaluronate	Phase II
THC-CBD	GW Pharmaceuticals	Cannabinoid	Phase II
IC-485	Icos	Phosphodiesterase 4 inhibitor	Phase I
IPL-512602	InflaZyme	Leukocyte-selective antiinflammatory drug	Phase I
IPL-550260	InflaZyme	Leukocyte-selective antiinflammatory drug	Phase I

prescribed together. Commonly used DMARDs include methotrexate, gold salts (oral and intramuscular), the antimalarial agent hydroxychloroquine, sulfasalazine and penicillamine. Drugs in this broad therapeutic class have diverse mechanisms of action; in the case of some older DMARDs, the mechanism of action is still not clearly defined. Their major inconveniences are a slow onset of action and sometimes serious adverse effects.

Anti-TNF-α strategies

Tumor necrosis factor-α (TNF-α) is a naturally occurring proinflammatory cytokine involved in the development and progression of many inflammatory and autoimmune diseases, including RA. The presence of various infectious or inflammatory stimuli can stimulate the biosynthesis of TNF-α by activated phagocytic and non-phagocytic cells. TNF-α plays a major role in the pathology of joints: it stimulates the resorption of bone and cartilage, facilitates inflammation and prevents bone formation by inhibiting bone collagen synthesis. It may also produce many of the systemic symptoms of RA such as fatigue, malaise, fever, anemia and cachexia. The presence of detectable TNF-α in RA patients has been directly correlated to more severe disease. In light of these findings, neutralization of the detrimental effects of this cytokine, either by blocking its interaction with receptors or by inhibiting its production, is a major area of research in RA.

Adalimumab (Humira™) was launched by Abbott in January 2003 in the U.S., its first market. The product is a monoclonal antibody (MAb) that binds to human TNF-α. The only other such product available at this time for the RA indication is Centocor/Schering-Plough's **infliximab** (Remicade®). Specifically, adalimumab is indicated for reducing the signs and symptoms and inhibiting the progression of structural damage in adults with moderately or severely active RA. Eisai is conducting phase I trials of adalimumab in Japan.

Table III presents antirheumatic drugs that act by blocking the production and/or the deleterious effects of TNF-α.

Other strategies targeting proinflammatory cytokines

Although TNF-α is the most frequently targeted proinflammatory cytokine at the present time, it is not the only one. The inhibition of interleukin-1 (IL-1), IL-6, IL-8, IL-12, IL-15, interferon-γ and various other proinflammatory cytokines is also under investigation in the ongoing search for effective new treatments for RA, as reflected in Table IV.

By some estimates, IL-1 is second in importance only to TNF-α in the pathogenesis of RA. Whereas TNF-α is a mediator of inflammation, IL-1 mediates the destruction of bone and cartilage. As such, inhibition of IL-1 has become a goal for investigators searching for new treatments for RA. Amgen's **anakinra** (Kineret™), a recombinant version of human IL-1 receptor antagonist (IL-1RA), was launched for the first time in the U.S. in 2001 for the treatment of moderately to severely active RA in patients failing to respond to DMARDs. IL-1RA is a naturally occurring cytokine that balances the detrimental effects of IL-1. In healthy individuals the endogenous cytokine

Table III: Antirheumatic drugs acting via TNF-α blockade.

Drug Name	Source	Mechanism of Action/Description	Status
Adalimumab	Abbott	Anti-TNF-α monoclonal antibody	L-2003
CDP-870	Celltech/Pharmacia	Pegylated recombinant human anti-TNF-α antibody fragment	Phase III
AGIX-4207	AtheroGenics	Selective modulator of TNF-α-induced inflammatory genes	Phase II
ISIS-104838	Isis Pharm/ Elan/OraSense	Antisense oligonucleotide, TNF-α production inhibitor	Phase II
Pegsunercept	Amgen	Pegylated soluble tumor necrosis factor receptor type I	Phase II
CLX-0921	Calyx Therapeutics	TNF-α production inhibitor	Phase I

Table IV: Other strategies targeting proinflammatory cytokines in development for the treatment of rheumatoid arthritis.

Drug Name	Source	Mechanism of Action/ Description	Status
Anakinra	Amgen	Recombinant human IL-1 receptor antagonist	L-2001
Anti-IFN-γ	Advanced Biotherapy	Anti-interferon-γ antibody	Phase II
HuMax-IL-15	Genmab/Amgen	Human anti-IL-15 MAb	Phase II
IL-1 Cytokine Trap	Regeneron	IL-1 receptor antagonist	Phase II
J-695	Abbott/Genetics Institute	Anti-IL-12 MAb	Phase II
Pralnacasan	Vertex/Aventis Pharma	IL-1β converting enzyme inhibitor	Phase II
AD-452	Arakis/KS Biomedix	Cytokine modulator	Phase I
IL-1 receptor type II	Amgen	IL-1 receptor type II	Phase I
MRA	Chugai	Anti-IL-6 receptor MAb	Phase I
rhIL-18bp	Serono	Recombinant IL-18 binding protein	Phase I

antagonist is sufficient; however, in RA patients endogenous IL-1RA is not sufficient to counteract the overactive and overabundant IL-1α and IL-1β.

Nuclear factor κB activation inhibitors

Nuclear factor κB (NFκB) is an ubiquitously expressed protein transcription factor and intracellular mediator of the inflammatory cascade involved in generation of certain adhesion molecules (ICAM-1), iNO synthase, COX-2, cytokines (*i.e.*, IL-1β, TNF-α, IL-6, IL-17) and chemokines (IL-8). It has been implicated in a variety of pulmonary diseases including asthma, cystic fibrosis and adult respiratory distress syndrome. More recently, it has been identified as a target for RA. **Iguratimod** (T-614), a NFκB activation inhibitor from Toyama, is in phase III trials in Japan as a novel antirheumatic agent. Development is being carried out in collaboration with Eisai.

Antiinflammatory cytokines

Schering-Plough is investigating the therapeutic potential of the antiinflammatory cytokine, recombinant human IL-10 (**ilodecakin**, Tenovil®), for the treatment of RA. IL-10 inhibits the synthesis and release of proinflammatory cytokines produced by stimulated monocytes and macrophages, and inhibits matrix metalloproteinases. The product is in phase II for RA and is also in clinical development for psoriasis and inflammatory bowel disease (IBD).

Chemokine inhibitors

Proinflammatory cytokines potentiate the inflammatory response by activating chemokines and other inflammatory mediators. IL-8, macrophage inflammatory protein (MIP)-1α and RANTES are just a few of the chemokines that have been implicated in RA pathogenesis. Compounds targeting the detrimental effects of chemokines in RA include **T-487**, in phase I testing at Tularik. T-487 is a small-molecule compound that binds to a single chemokine receptor without impairing other important immune system functions. It is expected to reduce inflammation in conditions such as RA, IBD and psoriasis. T-487 was originally discovered by ChemoCentryx and licensed to Tularik for codevelopment.

A phase I clinical trial of **MLN-1202**, a humanized MAb that blocks the chemokine receptor CCR2, was initiated by Millennium in late 2002. The antibody is in development as a potential treatment for RA and possibly other inflammatory diseases. The CCR2 receptor is found on the surface of monocytes and some T-cells and binds hormone-like chemokines known as monocyte chemoattractant proteins (MCPs). Using the CCR2 receptor, the MCPs signal these cells to migrate to sites of injury as part of the inflammatory process. MLN-1202 is designed to specifically block the MCP-CCR2 chemokine pathway and prevent the infiltration of immune cells in inflammatory sites, such as arthritic joints.

Anti-T-cell therapies

A direct link has been established between RA arthritis and T-cells, the largest population of cells infiltrating the rheumatoid synovium. An immense body of evidence exists to support the theory that $CD4^+$ T-cells in particular play a pivotal role in the development and progression of RA, and CD4 cells are considered to be an especially interesting target for MAb therapeutics.

IDEC's **clenoliximab** is a second-generation primatized anti-CD4 antibody with potential for the long-term immunotherapy of RA and other chronic diseases. Clenoliximab binds to the CD4 receptor on helper T-cells, where it is believed to regulate helper T-cell function without depleting T-cells or affecting other immune system functions. Clenoliximab is being evaluated in phase II studies in combination with methotrexate.

TRX1, a humanized MAb targeting CD4 receptors being developed by TolerRx in collaboration with Genentech, is designed to induce immunological tolerance in autoimmune disease settings. TolerRx is conducting a single-dose, placebo-controlled, double-blind, dose-escalating phase I study with TRX1 in the U.K.

Cell adhesion molecule inhibitors

In addition to their other proinflammatory effects, cytokines can modulate the expression of cell adhesion molecules (CAMs) on endothelial cell surface membranes, resident tissue cells and trafficking inflammatory cells. Several studies have confirmed the presence of high levels of ICAM-1 in the rheumatoid synovium, indicating that this CAM may contribute to the pathogenesis of RA. The production and expression of ICAM-1 are stimulated by TNF-α *in vitro* in synovial fibroblasts. Other CAMs that have been identified in RA synovial tissue include β_1 (VLA4) and β_2 (CD11a, CD11b and CD18) integrins, E- and P-selectins, VCAM-1 and PECAM.

Efalizumab, a humanized anti-CD11a MAb from Genentech, is being evaluated by licensees Serono and Xoma in phase II trials for RA. Its potential in treating other inflammatory autoimmune disorders such as psoriasis is also being explored.

Tanabe Seiyaku's **TR-14035**, an orally active dual inhibitor of the integrins $\alpha_4\beta_7$ (LPAM-1) and $\alpha_4\beta_1$ (VLA4), is in phase I testing for RA as well as other indications. The product has been licensed to GlaxoSmithKline for development in the U.S. and Europe.

Table V: Immunomodulating agents in development for rheumatoid arthritis.

Drug Name	Source	Status
Tacrolimus	Fujisawa	Phase III
Everolimus	Novartis	Phase II
IgPO	Protein Therapeutics	Phase II
Fluasterone	Hollis-Eden	Phase I
HE-2200	Hollis-Eden	Phase I
ISAtx-247	Isotechnika/Roche	Phase I

Immunomodulatory agents

Nonspecific forms of immunosuppression affect the immune response in a more global fashion. This may have both benefits and disadvantages. While generalized immunosuppression does attenuate rheumatoid inflammation, it can also increase the patient's susceptibility to infection and neoplasia.

Immunomodulating agents in development for the treatment of RA are shown in Table V.

Angiogenesis regulators

Angiogenesis, the formation of new blood vessels from a preexisting vasculature, in the invasive hypertrophic rheumatoid synovium contributes to the characteristic inflammation and pain and may furthermore contribute to synovitis, pannus growth, bone and cartilage destruction and osteophyte formation in RA. Angiogenesis is also present in early synovitis, and may trigger the progression from acute to chronic inflammation by upsetting the delicate balance between synovial perfusion and metabolic demand.

Together with the company's research collaborators, scientists from Angiotech have demonstrated in preclinical studies that **paclitaxel** inhibits angiogenesis and other processes involved in the development of chronic inflammation. This activity was later shown to be due, in part, to the drug's ability to inhibit the protein complex AP-1. AP-1 is a key regulator of various important genes, including those that involve the production of enzymes that cause tissue destruction, cytokines associated with chronic inflammation, and proteins necessary for cell proliferation. Based on the hypothesis that paclitaxel interrupts the AP-1 pathway, Angiotech is exploring its potential in treating chronic inflammatory diseases including RA. The company is conducting phase II studies in the RA indication.

Integrin $\alpha_v\beta_3$ is expressed on synovial endothelial cells and blood vessels within the invasive pannus and may contribute to angiogenesis within the hypertrophic synovium. It is also known to mediate the process of bone resorption. Given that both angiogenesis and bone resorption are characteristic features of RA, small-molecule $\alpha_v\beta_3$ (vitronectin) receptor antagonists have been proposed as a potential approach to the treatment of rheumatoid arthritis. MedImmune's **Vitaxin™**, a MAb directed to $\alpha_v\beta_3$, is in phase I trials for the treatment of rheumatoid arthritis.

Protein kinase inhibitors

Mitogen-activated protein kinases (MAPK) such as ERK, p38 and JNK have been implicated in the pathogenesis of RA. p38 is a modulator of proinflammatory factors including TNF-α, IL-1 and COX-2, and has been studied as a potential target for RA therapy.

Potential new antirheumatic agents with this mechanism of action are presented in Table VI.

Complement inhibitors

Complement activation results in a unidirectional sequence of enzymatic and biochemical reactions known as the complement cascade. In this cascade, a specific complement protein, C5, forms two highly active, inflammatory by-products, C5a and C5b-9, which jointly activate white blood cells. This in turn evokes a number of other inflammatory by-products, including injurious cytokines, inflammatory enzymes and cell adhesion molecules. Together, these byproducts can lead to the destruction of tissue seen in RA and many other inflammatory diseases.

Alexion's lead compound in development, the humanized MAb C5 complement inhibitor **eculizumab** (5G1.1), is in phase II trials for the treatment of RA. Another complement inhibitor, AdProTech's **APT-070C**, is also in phase II for this indication.

NGD-2000-1, an orally active C5a antagonist from Neurogen, is in phase I testing in the U.S. as a potential treatment for RA.

Table VI: Protein kinase inhibitors in development for rheumatoid arthritis.

Drug Name	Source	Mechanism of Action	Status
Doramapimod	Boehringer Ingelheim	p38 protein kinase inhibitor/ TNF-α production inhibitor	Phase II
SCIO-469	Scios	p38 protein kinase inhibitor	Phase II
R-1487	Roche	Protein kinase inhibitor	Phase I
SCIO-323	Scios	p38 protein kinase inhibitor	Phase I
VX-702	Vertex/Kissei	p38 protein kinase inhibitor	Phase I

Table VII: Other DMARDs in active development for rheumatoid arthritis.

Drug Name	Source	Mechanism of Action/ Description	Status
Reumacon	Conpharm/Meda	Mixture of two semisynthetic lignan glycosides from the *Podophyllum* plant	Phase III
AnergiX-RA	Corixa/Organon	MHC-class II molecule loaded with a disease-specific peptide	Phase II
AnervaX.RA	Corixa	Synthetic 20-amino acid peptide vaccine derived from the β chain of the specific MHC-class II molecules (amino acids 57-76)	Phase II
RAVAX™	Immune Response	Arthritis vaccine, combination of three peptides derived from T-cell receptors (Vβ3, Vβ14, Vβ17)	Phase II
Rituximab	Roche	Pan-B anti-CD20 MAb	Phase II
SMP-114	Sumitomo		Phase I

Other DMARDs

Rituximab, a genetically engineered pan-B anti-CD20 MAb that contains both human and murine components, is in phase II testing at Roche for the indication of RA. This biologic has been marketed for the treatment of non-Hodgkin's lymphoma since 1997.

Further information on this and other miscellaneous DMARDs is summarized in Table VII.

Bisphosphonates

Bisphosphonates have established efficacy in the treatment of bone diseases and are considered the gold standard for treatment of Paget's disease; they are also widely used in the prevention and treatment of osteoporosis. New research suggests that bisphosphonates may be useful in preventing bone loss and structural damage to the joints in patients with RA.

Novartis recently announced that the bisphosphonate compound **zoledronic acid monohydrate** (Zometa™), marketed since 2000 for the treatment of tumor-induced hypercalcemia, has entered phase II testing for the treatment of RA.

Other antirheumatic agents

Table VIII presents a list of drugs known to be in development for RA, but for which the mechanism of action is not known or has not yet been revealed. As such, these agents are potentially of interest to readers although they cannot yet be classified as NSAIDs or as DMARDs.

Table VIII: Other drugs in development for the treatment of rheumatoid arthritis.

Drug Name	Source	Status
AD-121	Arakis/Penwest	Phase II
AZD-2315	AstraZeneca	Phase II
Milican™	Dong-Wha	Phase II
Org-39141	Organon	Phase II
AZD-9056	AstraZeneca	Phase I
Org-37663	Organon	Phase I

Juvenile rheumatoid arthritis

Arthritis that causes joint inflammation and stiffness for more than 6 weeks in a child 16 years of age or less can be considered juvenile rheumatoid arthritis (JRA). Any joint can be affected and inflammation may limit the mobility of affected joints. JRA can be classified into three different types by the number of joints involved, symptoms and the presence or absence of certain antibodies. JRA is a serious disease that affects more than 300,000 children in the U.S. alone. The disease may begin as early as the first year of life and typically lasts through childhood and often into adulthood.

JRA is typically treated with NSAIDs (aspirin, ibuprofen or naproxen), DMARDs (methotrexate), corticosteroids and the biological agent etanercept. New drugs for treating JRA are in development, as discussed below.

Anti-TNF-α strategies

Infliximab, a chimeric MAb to TNF-α, is in phase III testing at Schering-Plough for the indication of JRA. Infliximab has been marketed since 1998 for the treatment of IBD, and since 1999 for RA. It is also under clinical investigation for the treatment of psoriatic arthritis, as discussed elsewhere in this review.

Adalimumab, a MAb that binds to human TNF-α, is in phase III clinical trials at Abbott for the treatment of JRA. Adalimumab (Humira™) was launched in the U.S. in early 2003 for rheumatoid arthritis.

Other cytokine modulators

Chugai is conducting phase II trials evaluating the anti-IL-6 receptor MAb **MRA** in patients with JRA.

Anti-T-cell therapies

T-cells are involved in the pathogenesis of RA. In animal models of autoimmune diseases, blockade of costimulatory molecules on antigen-presenting cells has been demonstrated to be effective in preventing or treating this disease by preventing T-cell activation. Blockade of

T-lymphocyte costimulation using Bristol-Myers Squibb's **BMS-188667**, a cytotoxic chimeric fusion protein incorporating T-lymphocyte-associated antigen and 4-immunoglobulin (CTLA4Ig), is being evaluated in phase II studies as a novel approach to the treatment of JRA.

Immunoglobulin

Protein Therapeutics has received orphan drug designation from the FDA for the use of oral human gammaglobulin (**IgPO**) for the treatment of JRA. Protein Therapeutics holds exclusive worldwide rights to patents and applications of the use of oral immunoglobulin for the treatment of a wide variety of autoimmune diseases from Research Corporation Technologies. Oral gammaglobulin is a sterilized immune globulin product prepared from pooled normal human donor plasma that consists primarily of IgG. Phase II clinical trials are currently under way in the JRA indication.

Osteoarthritis

Osteoarthritis (OA) is a joint disease in which the surface layer of cartilage breaks down and wears away, allowing bones to rub together and causing pain, swelling and loss of motion of the joint. It typically strikes the joints that support weight such as the knees, hips and spine. The main symptoms of the disease are joint stiffness, swelling and pain, usually in the morning. Other symptoms include bone spurs and the breaking off of bones and cartilage inside the joint space, which causes more pain and damage. OA affects over 20 million people in the U.S., mostly over the age of 45. The disease is more common in women than in men.

The management of OA includes pharmacological, surgical and other nonpharmacological therapies. Pharmacological intervention typically includes acetaminophen, NSAIDs and COX-2 inhibitors, as well as topical pain-relieving creams, rubs or sprays, mild narcotic pain killers, corticosteroids or hyaluronic acid. OA accounts for more than half of all hip replacements and 85% of all knee replacements done in the U.S. Medical costs for treating OA in the U.S. are estimated to be from USD 15.5 billion to USD 28.6 billion annually.

COX-2 inhibitors

Designed to circumvent the adverse effects of NSAIDs while maintaining their therapeutic efficacy, selective COX-2 inhibitors have been actively investigated in the last decade for the treatment of RA, OA and pain.

Two new COX-2 inhibitors reached the market for OA in 2002. Merck & Co.'s **etoricoxib** (Arcoxia™) was launched in the U.K. for the symptomatic relief of OA and RA, the treatment of acute gouty arthritis, the relief of chronic musculoskeletal pain including low back pain, the relief of acute pain associated with dental surgery and the treatment of primary dysmenorrhea. **Valdecoxib** (Bextra®) was launched by Pharmacia and marketing partner Pfizer in the U.S. for the treatment of signs and symptoms of OA and RA in adults, and for the treatment of primary dysmenorrhea.

Table IX: COX-2 inhibitors recently marketed or in active development for the treatment of osteoarthritis.

Drug Name	Source	Status
Etoricoxib	Merck & Co.	L-2002
Valdecoxib	Pharmacia/Pfizer	L-2002
LAS-34475	Almirall Prodesfarma	Phase II
Tilmacoxib	Japan Tobacco	Phase II
ABT-963	Abbott	Phase I
E-6087	Esteve	Phase I

Table IX presents COX-2 inhibitors recently marketed or in active development for the treatment of OA.

LOX/COX inhibitors

COX-2 inhibitors and conventional NSAIDs exert their analgesic and antiinflammatory actions by reducing production of inflammatory mediators called prostanoids via inhibition of the COX enzyme. However, isolated inhibition of the COX pathway by these agents has been shown to also generate a compensatory increase in the production of proinflammatory mediators called leukotrienes via the 5-lipoxygenase (5-LOX) pathway. Thus, a new strategy has been devised with the objective of achieving balanced inhibition of both COX and 5-LOX to reduce the production of leukotrienes as well as prostanoids.

Licofelone (ML-3000) is the first compound designed to treat patients with OA that balances the inhibition of the 5-LOX and COX pathways. Clinical studies have shown that this combination achieves good antiinflammatory and analgesic activity with excellent gastrointestinal tolerability. Licofelone is currently being evaluated in European phase III clinical trials as a possible new therapeutic for OA. Licofelone was discovered at Merckle and is being developed in conjunction with the company's Euro-Alliance partners Alfa Wassermann and Lacer. In February 2001 it was announced that the drug, in pivotal European studies, did not meet all of the efficacy endpoints required by the FDA for U.S. approval; on the basis of this announcement, former U.S. development partner Forest elected to terminate its license for licofelone.

IL-1β converting enzyme inhibitors

IL-1β converting enzyme (caspase-1) is a key control point in cytokine maturation and signaling pathways.

Therapeutic inhibition of IL-1beta converting enzyme is a potential breakthrough in the long-term management of a number of chronic diseases, including RA and OA.

In January 2003, development partner Aventis initiated a phase II proof-of-concept study evaluating Vertex's IL-1β converting enzyme inhibitor **pralnacasan** in the treatment of OA. The study will evaluate 400 patients treated with pralnacasan or placebo for 12 weeks. The study is intended to enable the companies to evaluate the safety and efficacy of pralnacasan in OA patients. Pralnacasan is also in development for RA.

Matrix metalloproteinase inhibitors

Matrix metalloproteinase (MMP) inhibitors are being developed to directly address the destruction of cartilage during arthritic disease. Although several MMP inhibitors have been studied in the clinic in recent years, only one appears to be in active development at this time: **Ono-4817**, an orally active MMP inhibitor, is in phase I testing at Ono as a potential treatment for OA.

Cathepsin K inhibitors

Cathepsin K is a cysteine protease expressed predominantly in osteoclasts that cleaves important bone matrix proteins and has recently been shown to play a vital role in degrading bone during the process of bone resorption. Several pharmaceutical companies are currently investigating cathepsin K inhibitors as potential agents for the treatment of bone disorders such as osteoporosis, hypercalcemia, Paget's disease, RA and OA.

GlaxoSmithKline's **SB-462795** is in phase I testing and is targeted for the treatment of both OA and osteoporosis. SB-462795 is a genomics-derived compound discovered through a collaboration between GSK and Human Genome Sciences.

Bisphosphonates

Bisphosphonates have been proven to be effective in the treatment of bone diseases, and are considered the gold standard for the treatment of Paget's disease; they are also widely used in the prevention and treatment of osteoporosis. New research suggests that bisphosphonates may be useful in preventing structural damage to the joints, a characteristic of both OA and RA.

Abiogen is conducting phase II testing of **clodronate disodium** as a potential treatment for OA. In OA, hydroxyapatite crystals appear to play an important role in the progression of inflammatory damage. Clodronate, like other bisphosphonates, has high affinity for hydroxyapatite. Furthermore, additional actions on metabolic events in cells involved in the turnover of cartilage, as well as on inflammatory reactions, have been observed. Experimental reports show that clodronate is capable of stimulating the biosynthesis of collagen and proteoglycans and of inhibiting both prostaglandins production and IL-1 synthesis. Moreover, pilot clinical trials have demonstrated the safety and the potential efficacy of clodronate in OA of the knee.

Other drugs for OA

CPA-926, a prodrug of esculetin (dihydroxycoumarin), was discovered by Kureha and is being developed in collaboration with Sankyo. The product is in phase II for the treatment of OA.

Psoriatic arthritis

Psoriatic arthritis is an arthritis associated with psoriasis. The pattern of joint involvement varies widely in people with psoriatic arthritis, although it can affect the wrists, knees, ankles, finger and toe joints, the spine and the sacroiliac joints. The condition affects at least 10% of the 3 million people with psoriasis in the U.S. The exact cause is unknown, but an interplay of immune, genetic and environmental factors are suspected.

At this time, there is no cure for psoriatic arthritis. Therefore, treatment is designed to minimize pain and stiffness. Initial treatment of psoriatic arthritis consists of the use of NSAIDs, but methotrexate may be needed for arthritis that does not respond. The antimalarial drug hydroxychloroquine may be effective, but some patients experience a flare of their psoriasis. Sulfasalazine has been found to be very beneficial for some psoriatic arthritis patients. Azathioprine may be used in severe cases of the disease.

TNF-α antagonists

Last year the FDA approved Immunex's **etanercept** (Enbrel®) for the treatment of psoriatic arthritis. Etanercept is a recombinant fusion protein comprising the soluble human p75 tumor necrosis factor (TNF) receptor linked to the Fc portion of human IgG_1. Immunex and Wyeth-Ayerst have marketed the drug in the U.S. since 1998 as a treatment for RA, and since 1999 for the treatment of polyarticular-course juvenile arthritis. With this new approval, etanercept became the first therapy approved for the reduction of signs and symptoms of active arthritis in patients with psoriatic arthritis. It can be used alone or in conjunction with methotrexate in patients who do not respond adequately to methotrexate alone.

Infliximab is in phase III testing at Schering-Plough for the indication of psoriatic arthritis.

Serono is conducting phase II trials to evaluate the efficacy of **onercept** (recombinant tumor necrosis factor binding protein-1) in the treatment of psoriatic arthritis.

Serono investigators have demonstrated the feasibility of neutralizing IL-18 as an indirect method of inhibiting the secretion of TNF-α by macrophages. The company is evaluating **rhIL-18bp** (recombinant human IL-18 binding protein) in phase I studies for psoriatic arthritis.

Ankylosing spondylitis

Ankylosing spondylitis is a chronic inflammatory form of arthritis that affects the spinal joints. The hallmark feature of the condition is the involvement of the sacroiliac joints, located at the base of the spine where the spine joins the pelvis. The disease course is highly variable, and while some individuals have episodes of transient back pain only, others have more chronic severe back pain that leads to differing degrees of spinal stiffness over time. In almost all cases the disease is characterized by acute painful episodes and remissions. In the most severe cases, the disease causes the spine to fuse solidly in a forward-stooped posture.

According to the Spondylitis Association of America, ankylosing spondylitis affects between 300,000 and 1 million Americans. Men develop it three times more often than women and it usually appears in people between the ages of 15 and 40. Onset after age 40 is uncommon.

While there is no cure, early diagnosis and proper medical management can minimize back pain and stiffness, and help reduce the risk of disability and deformity. Ankylosing spondylitis is typically treated with NSAIDs, DMARDs and, in some cases, corticosteroid injections. In severe cases, surgery may be required.

TNF-α antagonists

Etanercept (Enbrel™) is under FDA review as a potential new treatment for ankylosing spondylitis. It is also available for the treatment of RA and polyarticular-course juvenile arthritis, as well as psoriatic arthritis.

Infliximab has been developed by Centocor and Schering-Plough for the indication of ankylosing spondylitis. It is also marketed for the treatment of IBD and RA. The companies have filed with the U.S. FDA for marketing approval for this new indication.

COX-2 inhibitors

The selective COX-2 inhibitor **etoricoxib** is in phase III trials at Merck & Co. for the treatment of patients with ankylosing spondylitis. As mentioned above, it is already marketed for the symptomatic relief of OA and RA, the treatment of acute gouty arthritis, the relief of chronic musculoskeletal pain including low back pain, the relief of acute pain associated with dental surgery and the treatment of primary dysmenorrhea.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex autoimmune disease. In SLE, autoantibodies are produced that attack the body's own cells and tissues and can result in damage to the joints, skin, kidneys, cardiovascular system and other internal organs.

The prevalence of SLE is estimated to range from 250,000 to more than 1 million people in the U.S., typically women between the ages of 15 and 45. Despite better treatment options, the CDC recently reported a significant increase in deaths from SLE over the last 20 years. SLE is the leading cause of death among women with autoimmune diseases who are in their childbearing years.

Drugs for treating SLE

Prasterone (Prestara™), Genelabs' investigational drug for SLE, is a synthetic form of the human hormone dehydroepiandrosterone (DHEA). DHEA is the most abundant adrenal hormone in humans; lupus patients with active disease generally have low blood levels of DHEA. Following the successful completion of phase III trials, Genelabs has filed for marketing approval of Prestara™ in the U.S. and E.U.

EluSys is evaluating **ETI-104**, a proprietary "antigen-heteropolymer" consisting of a MAb to a receptor on the red blood cell cross-linked to double-stranded DNA, in phase II studies in patients with SLE. ETI-104 is used in conjunction with the company's platform technology, the EluSys Heteropolymer System, which is designed to enable the rapid, safe and efficient removal and destruction of viral particles, bacteria, toxins and autoantibodies from the bloodstream by injecting a therapeutic compound into the patient.

Human Genome Sciences has completed patient enrollment in a multicenter, dose-escalation phase I trial of **LymphoStat-B™** (human MAb to B-lymphocyte stimulator, anti-BLyS) for the treatment of SLE. Study results are scheduled to be reported during the first half of 2003. SLE is characterized by excess antibody production and abnormal B-lymphocyte cell function. LymphoStat-B™ may be able to reduce circulating BLyS levels and autoantibody levels in patients with SLE.

MRA, a humanized anti-human IL-6 receptor MAb from Chugai, is in phase I testing in the U.S. as a potential treatment for SLE.

Treatments for SLE kidney disease

Although many SLE patients may initially develop mild forms of kidney disease, it often progresses over time to become more severe and can lead to renal failure. In SLE, antibodies to double-stranded DNA (dsDNA) are believed to be responsible for kidney disease, a leading cause of sickness and death among SLE patients. La Jolla Pharmaceutical's drug candidate, **abetimus**

sodium (Riquent™), is designed to arrest the production of antibodies to dsDNA in SLE patients and to arrest or delay renal disease without suppressing the healthy functions of the immune system. In December 2002, La Jolla completed a phase III trial evaluating abetimus sodium in 317 patients with a history of SLE renal disease. The company plans to report final results of the study in February 2003.

For decades, clinical studies have demonstrated the presence of systemic complement activation in SLE patients undergoing flares. Studies have further shown an abundant deposition of activated complement proteins or localized inflammation in tissue biopsies from kidney or other tissues in SLE patients with active nephritis. Based on this evidence, Alexion is developing **eculizumab** in phase II trials for the treatment of SLE nephritis.

Scleroderma

Scleroderma is an autoimmune rheumatic disorder in which the skin becomes thick and hard. The name scleroderma is derived from the Greek words *skleros*, which means hard, and *derma*, which means skin. The full medical name of the condition is progressive systemic sclerosis. The most characteristic feature of scleroderma is the build-up of tough scar-like fibrous tissue in the skin. Less visible changes include damage to the cells lining the walls of small blood vessels. This may in turn damage major organs.

Localized scleroderma generally affects only the skin on the hands and face. The course of localized scleroderma is very slow and it rarely becomes more widespread or causes severe complications. With generalized scleroderma (sometimes called systemic scleroderma) the organs of the body, widespread areas of the skin or both may be involved. Generalized scleroderma also occurs in two different forms: limited (also called CREST syndrome) and diffuse scleroderma. Both of these are slowly progressive. Diffuse scleroderma is a chronic and life-threatening form of the disorder in which the production of excess collagen leads to scarring of the skin and internal organs. About 40% of all patients with this disorder die within 10 years of diagnosis.

Scleroderma is a relatively rare disease. It affects women 3-5 times more frequently than men. Its incidence occurs increasingly with age but its onset is most commonly between the ages of 30 and 50. However, localized scleroderma is more common in children.

Because scleroderma can be hard to diagnose and it overlaps with or resembles other diseases, scientists can only estimate how many cases there actually are. Estimates for the number of people in the U.S. with systemic sclerosis range from 40,000 to 165,000. The diffuse progressive form of scleroderma is estimated to affect some 300,000 people worldwide.

Currently, there is no treatment that controls or stops the underlying problem, *i.e.*, the overproduction of collagen, in all forms of scleroderma. Thus, treatment and management focus on relieving symptoms and limiting damage.

Drugs for treating scleroderma

Cambridge Antibody Technology and Genzyme General are collaborating on the development of the anti-TGF-beta1 MAb **metelimumab** (CAT-192) for the treatment of diffuse scleroderma. Phase II trials are under way in the U.S. and the U.K. Metelimumab has orphan drug status in both the U.S. and E.U. for the scleroderma indication.

Sjögren's syndrome

Sjögren's syndrome is an autoimmune disorder that is often defined by its two most common symptoms, *i.e.*, dry eyes and a dry mouth. In Sjögren's syndrome the immune system attacks healthy tissue. The mucous membranes or moisture-secreting glands of the eyes and mouth are usually attacked first, decreasing the production of tears and saliva. This can lead to everything from difficulty swallowing and dental cavities to photosensitivity and corneal ulcers. When the disease is limited to the eyes and mouth, it is called primary Sjögren's syndrome. In about 50% of all cases, the disease also causes skin, nose and vaginal dryness, and may affect other organs including the kidneys, blood vessels, lungs, liver, pancreas and brain. In such cases, Sjögren's syndrome typically accompanies other connective tissue disorders such as RA, SLE, scleroderma or polymyositis. This form of the disease is known as secondary Sjögren's syndrome.

Sjögren's syndrome affects an estimated 2-4 million people in the United States, many of whom are undiagnosed. The disease can develop at any age, although most cases develop in people over age 40. The condition is also 9 times more likely to occur in women than in men.

Currently there is no cure for Sjögren's syndrome, but treatments are available to relieve many of the symptoms. Moisture replacement therapies may ease the symptoms of dryness. NSAIDs may be used to treat musculoskeletal symptoms. For individuals with severe complications, corticosteroids or immunosuppressive drugs may be prescribed.

Interferons

Amarillo Biosciences has completed a phase III trial evaluating **low-dose, oral interferon alfa** for the treatment of Sjögren's syndrome.

Abetimus Sodium

Abetimus sodium (LJP-394, Riquent™) is in late-stage clinical evaluation at La Jolla Pharmaceutical for the treatment of lupus renal disease and has been granted orphan drug status for this indication in both the U.S. and the E.U. The compound, a B-cell Toleragen®, is designed to specifically arrest the production of antibodies to double-stranded DNA (dsDNA) which are responsible for lupus kidney disease, without suppressing the immune system (1, 2).

La Jolla Pharmaceutical has completed its phase III trial of abetimus and initial results are expected in early 2003. The randomized, double-blind, placebo-controlled study enrolled 317 patients with a history of lupus renal disease and assessed whether abetimus could significantly delay renal flares and delay the need for treatment with high-dose corticosteroids and/or cyclophosphamide in patients with high-affinity antibodies to abetimus. The primary endpoint of the trial was time to renal flare in patients with high-affinity antibodies to abetimus. Based on data to date, there were 41 renal flares in patients with high-affinity antibodies and 5 renal flares in patients with low-affinity antibodies. However, the company remains blinded as to whether the renal flares occurred in patients receiving abetimus or placebo. To date, 313 patient samples have been analyzed and 94% had high-affinity antibodies to abetimus. All patients completing the trial are eligible to enter an ongoing open-label follow-on trial in which abetimus is given once weekly in order to assess longer term safety. In an earlier phase II/III trial, abetimus-treated patients who had high-affinity antibodies to the drug had fewer renal flares and fewer treatments with high-dose corticosteroids and/or cyclophosphamide than placebo-treated patients and it is believed that patients with high-affinity antibodies to the drug are more likely to benefit from treatment (3, 4).

Abetimus 1, 20 or 50 mg was administered every week, every 2 weeks or every month for 5, 9 or 17 doses in a randomized, double-blind, placebo-controlled study of its effect on serum dsDNA antibodies in 58 patients with systemic lupus erythematosus (SLE). The treatment was safe and reduced sdDNA antibody titers by 29.3% and 37.1% at doses of 10 and 50 mg/week, respectively (5). The results of this study and some that follow are summarized in Table I.

Results from a phase II/III trial evaluating abetimus demonstrated a dose-dependent reduction in renal flares in lupus patients. A dose-dependent response was observed in 89% of patients with high-affinity antibodies

Table I: Clinical studies of abetimus (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Systemic lupus erythematosus	Randomized, double-blind, multicenter	Abetimus, 1 mg iv infusion 1x/wk x 17 wk (n=13) Abetimus, 1 mg iv infusion 2x/wk x 18 wk (n=13) Abetimus, 1 mg iv infusion 1x/mo x 5 mo (n=13) Abetimus, 10 mg iv infusion 1x/wk x 17 wk (n=18) Abetimus, 10 mg iv infusion 2x/wk x 18 wk (n=18) Abetimus, 10 mg iv infusion 1x/mo x 5 mo (n=18) Abetimus, 50 mg iv infusion 1x/wk x 17 wk (n=18) Abetimus, 50 mg iv infusion 2x/wk x 18 wk (n=18) Abetimus, 50 mg iv infusion 1x/mo x 5 mo (n=18) Placebo (n=9)	58	Abetimus was safe and reduced double-strand DNA antibodies in patients with systemic lupus erythematosus	5
Systemic lupus erythematosus	Double-blind	Abetimus, 100 mg iv infusion 1x/wk x 16 wk → 50 mg (intermitent dosing) 1x/wk x 60 wk Placebo	230	Abetimus appeared to provide clinical benefit in patients with systemic lupus erythematosus, impaired renal function and high-affinity antibodies	7
Systemic lupus erythematosus	Randomized, double-blind	Abetimus, 100 mg 1x/wk x 4 mo (n=70) Placebo (n=75)	145	Abetimus reduced antibody affinity in patients with systemic lupus erythematosus and renal failure	8
Systemic lupus erythematosus	Randomized, double-blind	Abetimus, 100 mg iv 1x/wk x 16 wk + High-dose corticosteroids (if considered necessary by the investigator) Placebo + High-dose corticosteroids (if considered necessary by the investigator)	230	Abetimus 100 mg once weekly effectively decreased the levels of anti-dsDNA antibodies in patients with systemic lupus erythematosus	10

to abetimus. Specifically, during the induction phase of the trial, when patients were treated with 100 mg/week for 4 months, there was only 1 renal flare in the drug-treated group *versus* 8 flares in the placebo-treated group. During the maintenance phase, when patients were treated periodically for up to 14 months with 50 mg/week, there were 6 renal flares in the drug-treated group *versus* 13 renal flares in the placebo-treated group. An observable dose-dependent difference in the ratio of renal flares during the induction phase when compared to the maintenance phase of the trial (1:8 *vs*. 1:2) was observed. One paper described that time to renal flare was significantly increased in the drug-treated group compared to the placebo-treated group. Another paper reported that in a group of 27 lupus patients with poor renal function, there were no renal flares in the 11 abetimus-treated patients with high-affinity antibodies to the drug. The same author in another paper reported that abetimus treatment reduced a patient's antibody affinity. When patients with high-affinity antibodies to drug were treated with 100 mg/week for 4 months, their average affinity for drug was reduced by about 60%, whereas the affinity of placebo-treated patients' antibodies was essentially unchanged (6).

Systemic lupus erythematosus patients were treated with abetimus or placebo in a randomized, double-blind trial. In a subgroup analysis of 28 patients with the greatest impairment of renal function, renal flares were seen in 18% and 55% of patients given abetimus and placebo, respectively. None of the patients treated with abetimus who had high-affinity antibodies to the drug before treatment experienced a renal flare (7).

Analysis of serum samples from patients with SLE enrolled in a double-blind, placebo-controlled trial of treatment with abetimus revealed that those with high-affinity antibodies to the drug prior to treatment (n=70) had significantly reduced affinity after 4 months of weekly treatment with abetimus 100 mg (8).

In a randomized trial lasting 76 weeks, patients with SLE were given placebo or abetimus 100 mg/week i.v. during a 16-week induction period, then alternating periods of 8 weeks off therapy and 12 weeks on with abetimus 50 mg/week i.v. or placebo. Abetimus improved health-related quality of life after induction and after renal flares, whereas those given placebo reported reductions in health-related quality of life (9).

Data from a phase II/III clinical trial indicated that treatment with abetimus appeared to be as effective as current immunosuppressive therapy in reducing antibodies to dsDNA, which are believed to be responsible for lupus renal disease. These data were from over 200 patients with lupus renal disease who were treated for up to 18 months with abetimus or placebo. Patients on placebo who were treated with high doses of corticosteroids and/or cyclophosphamide (HDCC) were compared to patients who received abetimus. Following treatment with HDCC, anti-dsDNA antibody levels in 38 patients receiving placebo were reduced within 4 weeks by a mean of 25%, whereas in 100 patients treated weekly with 100 mg abetimus, but not HDCC, anti-dsDNA antibodies were reduced at this time by a mean of 36%. In patients requiring HDCC, mean levels of anti-dsDNA antibodies decreased 37% in 22 patients receiving abetimus *versus* 25% in 38 patients receiving placebo (10).

Additional data from a phase II/III clinical study of abetimus, which was stopped prior to completion, on outcomes following a renal flare in all patients and in patients with impaired renal function demonstrated the importance of preventing renal flares. In this trial, patients were randomized to receive placebo or abetimus 100 mg weekly for 15 weeks, followed by intermittent dosing at 50 mg for 60 weeks. In all patients, a renal flare was declared only when a predefined, significant, reproducible increase in serum creatinine, proteinuria or hematuria was observed. Of those with a renal flare, 83% required treatment with HDCC and 48% required hospitalization. In patients who entered the trial with impaired renal function and flared, serum creatinine levels significantly increased from an average of 1.9 mg/dl at baseline to 5.0 mg/dl at final visit. In lupus patients, renal flares can lead to a loss of kidney function, kidney failure and the need for long-term dialysis. As previously reported, patients with high-affinity antibodies to the drug (89% of patients) had one-third the number of renal flares on abetimus compared to placebo, and abetimus also prolonged the time to renal flare compared to placebo. Patients receiving abetimus required about half as many courses of HDCC. In the 21 high-affinity patients with impaired renal function, there were no renal flares in the 11 drug-treated patients *versus* 6 (60%) renal flares in the 10 placebo-treated patients (11).

La Jolla Pharmaceutical reported that approximately 90% of patients enrolled in three previous clinical trials had high-affinity antibodies to abetimus prior to treatment. Earlier, the company announced that 89% of the patients in a phase II/III trial had high-affinity antibodies and that drug-treated patients in this group had only one-third as many renal flares and less than one-half as many treatments with HDCC as placebo-treated patients. In two additional studies, 94% and 90% of patients had high-affinity antibodies to abetimus. Patients enrolled in these trials had mild, moderate and severe disease. These initial findings also suggest that a majority of lupus patients have high-affinity antibodies to abetimus regardless of the severity of their disease (12).

1. *LJP expands phase III lupus trial to Europe.* DailyDrugNews.com (Daily Essentials) June 12, 2001.

2. *Lupus kidney disease drug candidate LJP-394 designated an orphan drug in Europe.* DailyDrugNews.com (Daily Essentials) Nov 30, 2001.

3. *La Jolla set to complete LJP-394 phase III enrollment.* DailyDrugNews.com (Daily Essentials) Oct 25, 2002.

4. *Completion of phase III Riquent trial announced.* DailyDrugNews.com (Daily Essentials) Dec 19, 2002.

5. Furie, R.A., Cash, J.M., Cronin, M.E. et al. *Treatment of systemic lupus erythematosus with LJP 394.* J Rheumatol 2001, 28(2): 257.

6. *Dose-dependent response reported by La Jolla for LJP-394 at recent lupus conference.* DailyDrugNews.com (Daily Essentials) April 10, 2001.

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8. Linnik, M.D., McNeeley, P.A., Iverson, G.M. *Affinity of antibodies for LJP 394 influences pharmacodynamic response to LJP 394 in SLE patients*. Lupus 2001, 10(Suppl. 1): S52.

9. Strand, V., Aranow, C., Cardiel, M., Furie, R., Sherrer, Y., Tumlin, J., Wallace, D.J., Crawford, B. *Improvement in health-related quality of life in SLE patients enrolled in a randomized clinical trial comparing LJP 394 treatment with placebo*. 66th Annu Meet Am Coll Rheumatol (Oct 25-29, New Orleans) 2002, Abst 221.

10. Linnik, M.D., Bagin, R.G., Strand, V. *Effect of LJP 394 or high dose corticosteroids and cyclophosphamide on anti-dsDNA antibodies in SLE patients*. Arthritis Rheum 2001, 44(9, Suppl.): S282.

11. Tumlin, J.A., Linnik, M.D., Appel, G.B. *The B-cell Toleragen LJP-394 reduces renal flares in patients with lupus nephritis: A prospective, double-blinded, placebo-controlled trial*. ASN/ISN World Congr Nephrol (Oct 13-17, San Francisco) 2001, Abst A1300.

12. *La Jolla reports that 90% of lupus patients have key antibodies*. DailyDrugNews.com (Daily Essentials) Jan 18, 2001.

Original monograph - Drugs Fut 2001, 26(7): 633.

Adalimumab

Abbott just recently received FDA approval for and began marketing adalimumab (D2E7, Humira™) for reducing the signs and symptoms and inhibiting the progression of structural damage in adults with moderately or severely active rheumatoid arthritis (RA). Adalimumab was discovered through a collaboration between Abbott and Cambridge Antibody Technology using phage display technology, resulting in a fully human antibody that binds to human TNF-α. The antibody is presented in a specially designed prefilled syringe offering convenient every-other-week dosing by s.c. injection alone or in combination with other disease-modifying antirheumatic drugs (DMARDs). Approval for adalimumab in Europe is anticipated in mid-2003. Clinical trials are also under way in juvenile rheumatoid arthritis and Crohn's disease (1-5).

The approval of adalimumab was based on safety and efficacy data obtained from clinical trials involving more than 2,000 patients with RA. The antibody reduced signs and symptoms of RA in over half the patients, with some patients experiencing improvement as early as 1 week. In one study, patients treated with the antibody plus methotrexate for a year demonstrated less joint deterioration than patients receiving methotrexate alone. The antibody has been administered s.c. or i.v. for up to 4.5 years with or without methotrexate and it was concluded that it could be administered safely over the long term without significant loss of efficacy (6). The results of this study and some that follow are summarized in Table II.

Transgenic Tg197 mice were used as a model to compare the efficacy of adalimumab, infliximab and etanercept in the prevention of polyarthritis. Intraperitoneal administration of doses of the drugs ranging from 0.01-10 mg/kg prevented the appearance of arthritis compared to control mice, which developed arthritis at 4 weeks and progressed to severe arthritis by 10 weeks. Treated mice showed lower arthritic scores and less inflammation and joint damage than untreated mice. Adalimumab was reported to be superior to the other drugs as it induced a higher degree of protection against polyarthritis (7).

The pharmacokinetics of a single i.v. injection of adalimumab at doses ranging from 0.25-5 mg/kg were assessed in patients with RA. The drug provided plasma levels that increased with dose, a very low clearance and a dose-independent half-life that ranged from 14.7-19.3 days. No need for dose adjustment based on body weight, sex or age was found, and no interaction with serum methotrexate levels was detected (8).

Patients with RA enrolled in a phase I study (n=50) received either a single dose of adalimumab or placebo. The active treatment demonstrated clinical efficacy and downregulated systemic IL-1β mRNA and rapidly reduced concentrations of IL-1 receptor antagonist (IL-1ra) and IL-6. In immunohistological investigations of synovial biopsies, however, adalimumab did not significantly alter IL-1β or TNF-α levels (9).

A 2-year, double-blind, randomized study examined the long-term use of adalimumab in 54 patients with active RA and a partial response to methotrexate. Repeated s.c. injections of 1 mg/kg of adalimumab in conjunction with methotrexate produced sustained clinical responses and were well tolerated. At 24 months, 78% of patients had a EULAR response, 50% had an ACR20 response and 30% had an ACR50 response (10).

Twenty-four patients failing a mean of 3.5 DMARDs were enrolled in a 12-week, double-blind, placebo-controlled study and continued on open-label adalimumab for up to 2 years. Repeated weekly injections of 0.5 or 1 mg/kg adalimumab as monotherapy were effective and well tolerated. At the end of the study, 74%, 61% and 35% of patients had EULAR, ACR20 and ACR50 responses (11).

In the phase II ARMADA (Anti-TNF Research study program of the Monoclonal Antibody D2E7 in patients with rheumatoid Arthritis) trial, patients with active RA despite concurrent stable doses of methotrexate were enrolled under a double-blind, randomized, placebo-controlled design. All patients had failed up to 4 DMARDs prior to methotrexate therapy and had 6 or more swollen joints and 9 or more tender joints. Participants were randomized to receive placebo or adalimumab at 20, 40 or 80 mg s.c. every other week for 24 weeks in addition to

Table II: Cinical studies of adalimumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Rheumatoid arthritis		Methotrexate Adalimumab sc x 4 y Adalimumab iv Placebo		Adalimumab was well tolerated and effective in treating patients with active rheumatoid arthritis	6
Rheumatoid arthritis	Open, multicenter	Adalimumab, 1 mg/kg sc or iv x 2 over 3 mo → 1 mg/kg sc x 2.5 y → 40 mg sc 1x/2 wk + Methotrexate x 6 mo Placebo x 3 mo → Adalimumab, 1 mg/kg sc x 2.5 y → 40 mg sc 1x/2 wk + Methotrexate x 6 mo	65	Adalimumab combined with a standard dose of methotrexate was well tolerated and effective throughout the study period of 3 years	10, 30, 33
Rheumatoid arthritis	Randomized, double-blind	Adalimumab, 0.5 mg/kg sc 1x/wk x 12 wk (n=15) Adalimumab, 0.5 mg sc 1x/wk x 12 wk → 1 mg s.c. 1x/wk x 2 y (n=3) Placebo → Adalimumab, 1 mg sc 1x/wk x 2 y (n=6)	24	Adalimumab was well tolerated and effective in patients with active rheumatoid arthritis	11
Rheumatoid arthritis	Randomized, double-blind	Adalimumab, 20 mg sc 1x/2wk + Methotrexate, 16.8 (mean) mg/wk x 24 wk Adalimumab, 40 mg sc 1x/2wk + Methotrexate, 16.8 (mean) mg/wk x 24 wk Adalimumab, 80 mg sc 1x/2wk + Methotrexate, 16.8 (mean) mg/wk x 24 wk Placebo x 24 wk + Methotrexate, 16.8 (mean) mg/wk x 24 wk	271	Adalimumab in addition to methotrexate was effective in inducing significant improvements in physical function and health-related quality of life in patients with active refractory rheumatoid arthritis	12, 16
Rheumatoid arthritis	Double-blind, open, multicenter	Adalimumab, 20 mg sc 1x/2 wk x 6 mo → 40 mg sc 1x/2 wk + Methotrexate x 6 mo Adalimumab, 40 mg sc 1x/2 wk x 6 mo → 40 mg sc 1x/2 wk + Methotrexate x 6 mo Adalimumab, 80 mg sc 1x/2 wk x 6 mo → 40 mg sc 1x/2 wk + Methotrexate x 6 mo	250	Adalimumab added to methotrexate was safe and well tolerated, with sustained responses throughout the course of 1 year	17
Rheumatoid arthritis	Randomized, double-blind, multicenter	Adalimumab, 40 mg sc 1x/2 wk + Background therapy x 24 wk (n=318) Placebo + Background therapy x 24 wk (n=318)	636	Adalimumab was effective in improving the signs and symptoms of rheumatoid arthritis when administered to patients with or without additional DMARD therapy. The rate of adverse events, serious adverse events, death, infection or withdrawal due to adverse events was similar to placebo when adalimumab was added to preexisting antirheumatic therapy	18, 32
Rheumatoid arthritis	Randomized, double-blind, multicenter	Adalimumab, 20 mg sc 1x/wk x 12 wk → 40 mg sc 1x/wk x 92 wk Adalimumab, 40 mg sc 1x/wk x 104 wk Adalimumab, 80 mg sc 1x/wk x 12 wk → 40 mg sc 1x/wk x 92 wk Placebo x 12 wk → Adalimumab, 40 mg sc 1x/wk x 92 wk	229	Adalimumab was safe and well tolerated in patients with rheumatoid arthritis being treated with methotrexate, and sustained a high level of efficacy over a period of 2 years	19, 23
Rheumatoid arthritis	Randomized, double-blind, multicenter	Adalimumab, 20 mg sc 1x/2 wk + DMARDs x 26 wk (n=106) Adalimumab, 20 mg sc 1x/wk + DMARDs x 26 wk (n=112) Adalimumab, 40 mg sc 1x/2 wk + DMARDs x 26 wk (n=113) Adalimumab, 40 mg sc 1x/wk + DMARDs x 26 wk (n=103) Placebo + DMARDs x 26 wk (n=110)	544	Adalimumab administered alone was well tolerated at all doses tested, and showed a rapid and consistent effect in improving the physical function, bodily pain, mental health and vitality of rheumatoid arthritis patients	20-22
Rheumatoid arthritis	Randomized, double-blind	Adalimumab, 20 mg sc 1x/wk x 52 wk + Methotrexate x 52 wk (n=212) Adalimumab, 40 mg sc 1x/2 wk x 52 wk + Methotrexate x 52 wk (n=207) Placebo + Methotrexate x 52 wk (n=200)	619	Adalimumab combined with methotrexate was well tolerated and significantly inhibited progression of structural joint damage in patients with rheumatoid arthritis	24

Continuation

Table II (Cont.): Cinical studies of adalimumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Rheumatoid arthritis	Randomized, double-blind, multicenter	Adalimumab, 20 mg sc 1x/wk + Methotrexate x 52 wk (n=212) Adalimumab, 40 mg sc 1x/2 wk + Methotrexate x 52 wk (n=207) Placebo + Methotrexate x 52 wk (n=200)	619	Adalimumab at 20 mg once weekly or 40 mg once every 2 weeks decreased disability, improved physical functioning and reduced fatigue in patients with rheumatoid arthritis treated with methotrexate	25
Rheumatoid arthritis	Pooled/ meta-analysis	Adalimumab, 20 mg sc 1x/wk x 24-52 wk (n=1380) Adalimumab, 20 mg sc 1x/2 wk x 24-52 wk Adalimumab, 40 mg sc 1x/wk x 24-52 wk Adalimumab, 40 mg sc 1x/2 wk x 24-52 wk Adalimumab, 80 mg sc 1x/2 wk x 24-52 wk Placebo (n=690)	2070	Adalimumab induced a low incidence of injection site reactions in a large population of patients with rheumatoid arthritis. Most injection site reactions were mild, did not cause withdrawal from the study and often resolved after a few injections	26
Rheumatoid arthritis	Randomized, double-blind	Adalimumab, 20 mg sc 1x/wk + Methotrexate x 52 wk Adalimumab, 40 mg sc 1x/2 wk + Methotrexate x 52 wk Placebo + Methotrexate x 52 wk	64	Adalimumab administered for 24 weeks did not significantly modify the normal immune function of patients with rheumatoid arthritis on methotrexate treatment	27
Rheumatoid arthritis	Randomized, double-blind, multicenter	Adalimumab, 0.5 mg/kg iv bolus sd (n=17) Adalimumab, 1 mg/kg iv bolus sd (n=18) Adalimumab, 3 mg/kg iv bolus sd (n=18) Adalimumab, 5 mg/kg iv bolus sd (n=18) Adalimumab, 10 mg/kg iv bolus sd (n=18) Placebo (n=31)	120	Intravenous administration of a single dose of adalimumab (0.5-10 mg/kg) was well tolerated and significantly improved the symptoms of rheumatoid arthritis	31

methotrexate. The results demonstrated that all doses of adalimumab were significantly superior to placebo in reducing signs and symptoms of RA. The dose of 40 mg appeared to be the most effective, 65.7% achieving ACR20 criteria *versus* 14.5% on placebo, 53.7% achieving ACR50 criteria *versus* 8.1% on placebo, and 26.9% achieving ACR70 criteria *versus* 4.8% on placebo. The treatment was well tolerated, only injection-site reactions occurring more frequently on adalimumab than on placebo (15.2% *vs.* 3.2%) (12). Further data from the ARMADA trial showed that adalimumab groups had a significant reduction in serum pro-MMP-1 and pro-MMP-3 compared to the placebo group at 12 and 24 weeks. At 24 weeks, the adalimumab groups had a 23.3% decrease in MMP-1 and a 26.6% decrease in MMP-3 *versus* increases of 10.4% and 17.8%, respectively, in the placebo group. The reduction in pro-MMP-1 paralleled the maximum beneficial effects on swollen and tender joints, but not the ACR20 response, indicating that adalimumab may be associated with reduced joint destruction (13-15). Adalimumab also improved the physical function and quality of life of rheumatoid arthritis patients in this trial. These improvements were detected after 1-4 weeks of treatment (16). Sustained efficacy and no safety concerns were noted after 12 months of treatment. Only 19 withdrew due to adverse events, lack of efficacy or administrative reasons (17).

Adalimumab-treated RA patients showed similar rates of adverse events, serious adverse events, infections and serious infections compared to placebo-treated patients in a randomized, placebo-controlled safety study (18).

An open-label continuation study in 229 patients with DMARD-refractory RA who received 40 mg/week of adalimumab for 12 months confirmed the safety and sustained clinical efficacy of monotherapy with adalimumab (19).

A total of 544 patients with active RA who had failed previous DMARD therapy were administered adalimumab at doses of 20 or 40 mg either once weekly or once every other week for 26 weeks in a double-blind, randomized, placebo-controlled trial. Adalimumab was effective in improving the quality of life of these patients, as shown by the physical function, bodily pain, vitality and mental health scores measured using the SF-36 Health Survey. Adalimumab was also significantly more effective than placebo in terms of response rates (33.0-38.4% *vs.* 7.3%). Adalimumab was well tolerated, the most common adverse events possibly related to the drug being injection-site reactions, rash and headache (20-22).

A weekly dose of 20 mg of adalimumab administered for 2 years to RA patients maintained the improvement found for several endpoints after the first 12 weeks of treatment. After 24 months, the response rates were 76% (ACR20), 52% (ACR50) and 24% (ACR70), and compared to baseline, the HAQ Disability Index had

decreased from 1.70 to 1.12, the patient's assessment of pain from 71.1 to 31.5, and the physician's assessment of disease activity from 64.5 to 22.7 (23).

A double-blind, placebo-controlled clinical trial randomized 619 methotrexate-treated RA patients to receive either placebo weekly, 20 mg s.c. of adalimumab weekly or 40 mg s.c. of adalimumab every other week for 52 weeks. Both doses of adalimumab were comparably effective in inhibiting the progression of structural joint damage in these patients and were well tolerated. The drug significantly reduced disability, improved physical function and reduced fatigue in parallel with significant increases in the ACR respone rates compared with placebo (24, 25).

A retrospective analysis of 4 well-controlled phase II/III clinical trials of adalimumab characterized injection-site reactions and established an overall incidence rate of 20.3%. Most injection-site reactions were mild or moderate and consisted of eruption, inflammation, edema, hypersensitivity, pain and/or hemorrhage. The number of patients who discontinued the treatment due to these reactions was very low (0.3%) and in most cases the reactions resolved after a few injections (26).

A substudy in 64 RA patients participating in a 52-week, double-blind, randomized, placebo-controlled trial revealed that adalimumab did not modify normal immune function. After 24 weeks of treatment, the drug slightly increased the percentage of circulating lymphocytes, especially memory $CD4^+$ and $CD8^+$ T-cells, compared to placebo. Other elements of the immune response, including the number of $CD3^+$, $CD4^+$, $CD9^+$ or $CD25^+$ T-cells, $CD56^+$ NK cells, monocytes/macrophages, B- and T-cell proliferation, delayed-type hypersensitivity response or response to pneumococcal vaccination, were similar in both treatment groups (27).

A total of 47 patients with active RA were treated with adalimumab in monotherapy trials for 2 years. Comparison of radiographs of hands and feet at baseline and after 2 years revealed stable disease in 42% of patients. Changes in radiological scores after 2 years were correlated with C-reactive protein and disease activity score AUC. Adalimumab also reduced cartilage oligomeric matrix protein, soluble intercellular adhesion molecule-1, metalloproteinases and human cartilage glycoprotein-39 levels (28).

A study involving 12 patients with RA investigated the effect of adalimumab (0.5 mg/kg) on apoptosis and c-Jun/phosphorylated c-Jun induction before and after UVB irradiation. Adalimumab decreased c-Jun/phosphorylated c-Jun induction, suggesting a possible protective effect on photoaging, while having no effect on apoptosis and p53 expression (29).

Sustained efficacy and no safety concerns were reported from an open-label trial in 53 patients who received s.c. injections of 1 mg/kg of adalimumab at a frequency ranging from once weekly to once every 4 weeks, depending on the individual response to treatment, in combination with stable standard doses of methotrexate over a period of 30 months (30).

A randomized, double-blind, placebo-controlled clinical trial evaluated the pharmacokinetics, safety and efficacy of adalimumab in 120 patients with active RA. The patients were randomized to receive single ascending i.v. doses of 0.5-10 mg/kg of adalimumab or placebo and were then monitored for changes in symptom scores for at least 4 weeks or until disease deterioration. The symptom scores of the patients decreased dose-dependently shortly after administration of the antibody and the clinical response was maintained throughout the 4-week period in most patients; the highest dose produced an EULAR response in 100% of patients. Treatment with adalimumab was safe and well tolerated, and no dose-related increase in adverse events was found (31).

The STAR (Safety Trial of Adalimumab in Rheumatoid arthritis) study reported that the addition of adalimumab 40 mg once every other week to standard of care with DMARDs, corticosteroids and/or nonsteroidal antiinflammatory drugs (NSAIDs) for 24 weeks significantly increased the response rates of the patients (32).

The long-term efficacy and safety of adalimumab were evaluated in 42 RA patients administered a dose of 40 mg once every other week for 36 months. The response rates at the end of the study were 64% (ACR20), 45% (ACR50) and 24% (ACR70) (33).

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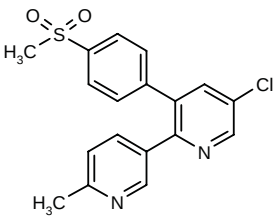
Etoricoxib



Etoricoxib (Arcoxia™) is a COX-2-selective inhibitor that was introduced last year by Merck, Sharp & Dohme (Merck & Co.) in the U.K., the first European country to approve the new coxib, for the once-daily symptomatic relief of osteoarthritis and rheumatoid arthritis and the treatment of acute gouty arthritis. Etoricoxib has also been approved in Peru, Mexico and Brazil. In the U.S., Merck & Co. plans to refile an expanded NDA for etoricoxib with the FDA in the second half of 2003. The original NDA was withdrawn on March 15, 2002, and since then the FDA has requested additional data on the acute pain indications for etoricoxib and additional cardiovascular safety data for the drug versus comparators other than naproxen. Merck also plans to submit additional efficacy data to support a new indication for ankylosing spondylitis, in addition to osteoarthritis, rheumatoid arthritis, chronic pain, acute pain, dysmenorrhea and acute gouty arthritis (1).

In NADPH-fortified human liver microsomes, etoricoxib was found to be metabolized by 6'-methylhydroxylation and the reaction was catalyzed primarily by CYP3A4 (40-90%), followed by other cytochrome P-450 forms (2).

The pharmacokinetics of a single 120-mg dose of etoricoxib were evaluated when taken alone and in combination with Maalox® 20 ml and calcium carbonate 10 ml in a crossover study in 12 healthy volunteers. The antacids had only slight effects on the drug's absorption (3).

Single oral doses of etoricoxib 120 mg, oxycodone/acetaminophen 10/650 mg or placebo were administered to 225 patients for relief of moderate to severe pain after removal of impacted third molars. Comparable efficacy was seen with the active treatments, which were significantly more effective than placebo. No serious adverse events were noted during the study (4).

Two randomized studies compared the analgesic effect of single doses of etoricoxib (60-240 mg) with placebo, 400 mg ibuprofen, 550 mg naproxen sodium or 600/60 mg acetaminophen/codeine for dental impaction pain. Optimal analgesic efficacy was achieved with a single dose of 120 mg etoricoxib, which was as effective as naproxen and better than placebo, all other analgesics save naproxen and a single dose of 60 mg of etoricoxib. The analgesic effects of 120 mg etoricoxib were detected at 24 min after dosing and lasted for more than 24 h. No safety issues emerged during the study (5). The results of this study and some that follow are summarized in Table III.

Data from several randomized, double-blind phase II/III trials of etoricoxib in patients with osteoarthritis, rheumatoid arthritis and chronic lower back pain have been reported. The trials involved over 3,000 patients who were treated with once-daily etoricoxib and 1,799 patients treated with diclofenac, ibuprofen or naproxen. The results showed a significant 43% reduction in treatment discontinuations due to nonselective NSAID-type gastrointestinal symptoms, as well as discontinuations due to gastrointestinal symptoms in general, on etoricoxib compared to the nonselective NSAIDs. Data from these trials also indicated a reduced need for gastroprotective agents and gastrointestinal comedication in patients treated with etoricoxib. In terms of renovascular safety, the incidences of lower extremity edema and hypertension were similar among the active treatments and did not appear to be dose-related for etoricoxib (60, 90 and 120 mg/day) (6-10).

Two randomized, placebo-controlled, 3-month trials evaluated the efficacy of etoricoxib 60 and 90 mg/day in 644 patients with chronic lower back pain. Evaluation of Roland-Morris Disability Questionnaires completed by patients showed that etoricoxib significantly improved functional status compared with placebo. Evaluation of treatment outcomes using the SF-12 Short Form Health Survey revealed that both etoricoxib doses significantly improved the physical component of the disease but did not change the mental component. Significant pain relief was seen on both doses of etoricoxib compared to placebo at 4 weeks. Improvement was reported as early as 1-2 weeks and maintained throughout the study. Etoricoxib was generally well tolerated (11-14).

The data from 12-week multicenter, randomized, double-blind phase III clinical trials showed that both etoricoxib 60 mg once daily and naproxen 500 mg b.i.d. improved the physical function, the ability to work and the quality of life of patients with osteoarthritis compared to placebo (15-18).

Patients with osteoarthritis of the knee or hip received treatment with etoricoxib 60 mg once daily (n=224) naproxen 500 mg b.i.d. (n=221) or placebo (n=56) in a randomized, double-blind, 12-week trial. According to Western Ontario McMaster's Osteoarthritis Index pain and physical function subscales and patients' global assessment of disease, etoricoxib and naproxen were equally effective and significantly superior to placebo in these patients. Therapeutic responses were rapid (by day 2) and were maintained throughout the study. The treatments were generally well tolerated (19).

Table III: Clinical studies of etoricoxib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Back pain, osteoarthritis, rheumatoid arthritis	Randomized, double-blind, multicenter, pooled/ meta-analysis	Etoricoxib, 30-120 mg po od (n=2670) Diclofenac, 150 mg/d (n=232) Naproxen, 1000 mg/d (n=1126) Placebo	4028	Etoricoxib was effective in reducing treatment withdrawals due to gastrointestinal symptoms and the need for gastroprotective agents and comedications compared with nonselective COX inhibitors in patients with rheumatoid arthritis, osteoarthritis or lower back pain	6, 7
Back pain, osteoarthritis, rheumatoid arthritis	Randomized, double-blind, multicenter, pooled/ meta-analysis	Etoricoxib, 60-120 mg po od x up to 113 wk (n=3142) Diclofenac, 150 mg/d (n=232) Ibuprofen, 2400 mg/d (n=226) Naproxen, 1000 mg/d (n=1370)	4970	Etoricoxib reduced perforations, ulcers and bleeding compared with nonselective COX inhibitors in patients with osteoarthritis, rheumatoid arthritis or lower back pain	8
Back pain, osteoarthritis, rheumatoid arthritis	Retrospective	Etoricoxib, 60 mg/d (n=658) Etoricoxib, 90 mg/d (n=889) Etoricoxib, 120 mg/d (n=472) Naproxen, 1000 mg/d (n=1034) Ibuprofen, 2400 mg/d (n=226) Placebo (n=1491)	3348	The incidence rates of lower extremity edema and hypertension were low and similar between the active treatments and did not appear to be dose-related for etoricoxib	9
Back pain	Randomized, multicenter	Etoricoxib, 60 mg po od x 12 wk (n=109) Etoricoxib, 90 mg po od x 12 wk (n=106) Placebo (n=110)	325	Etoricoxib 60 and 90 mg daily was well tolerated and provided significant efficacy in pain relief and disability over 3 months in patients with chronic lower back pain, which was observed as early as 1 week after the initiation of therapy and maintained throughout the 12 weeks	12, 13
Back pain	Randomized, pooled/ meta-analysis	Etoricoxib, 60 mg x 12 wk (n=212) Etoricoxib, 90 mg x 12 wk (n=213) Placebo (n=219)	644	Etoricoxib 60 and 90 mg daily significantly improved the physical component of SF-12 Short Form Health Survey scores in patients with chronic lower back pain, without any change in the mental component	14
Osteoarthritis	Randomized, double-blind	Etoricoxib, 60 mg po od x 12 wk (n=436) Naproxen, 500 mg po bid x 12 wk (n=435) Placebo (n=108)	979	Etoricoxib and naproxen significantly improved SF-36 physical functioning and role-physical domain scores, indicative of patient daily physical activity, with an important impact on specific physical activities and work ability in patients with hip or knee osteoarthritis	16, 17
Osteoarthritis	Randomized, double-blind	Etoricoxib, 60 mg od x 12 wk (n=224) Naproxen, 500 mg bid x 12 wk (n=221) Placebo (n=56)	501	Etoricoxib and naproxen were generally well tolerated, equally effective and significantly more effective than placebo in osteoarthritis patients	19
Osteoarthritis	Randomized, double-blind, pooled/ meta-analysis	Etoricoxib, 60 mg po od x 12 wk Naproxen, 500 mg po bid x 12 wk Placebo	241	Etoricoxib was effective in patients with knee or hip osteoarthritis with or without additional hand osteoarthritis, suggesting that the drug provides overall symptomatic relief	20

Continuation

Table III (Cont.): Clinical studies of etoricoxib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Osteoarthritis	Randomized, double-blind, pooled/ meta-analysis	Etoricoxib, 60 mg po od x 12 wk (n=361) Naproxen, 500 mg po bid x 12 wk (n=336) Placebo (n=84)	781	Etoricoxib showed a rapid onset of action in patients with hip or knee osteoarthritis and the therapeutic benefits were sustained over the 24-h dosing interval	21
Osteoarthritis	Randomized, double-blind	Part 1: Etoricoxib, 5 mg qd x 6 wk (n=117) Etoricoxib, 10 mg qd x 6 wk (n=114) Etoricoxib, 30 mg qd x 6 wk (n=102) Etoricoxib, 60 mg qd x 6 wk (n=112) Etoricoxib, 90 mg qd x 6 wk (n=112) Placebo (n=60) Part 2: Etoricoxib, 30 mg qd x 8 wk (n=198) Etoricoxib, 60 mg qd x 8 wk (n=102) Etoricoxib, 90 mg qd x 8 wk (n=148) Diclofenac, 50 mg tid (n=102)	617	The efficacy seen with etoricoxib was better than that with placebo and similar to that with diclofenac in patients with knee osteoarthritis	22
Rheumatoid arthritis	Randomized	Etoricoxib, 90 mg po od x 12 wk (n=320) Naproxen 500 mg po bid x 12 wk (n=169) Placebo (n=315)	804	Etoricoxib was significantly more effective than placebo in rheumatoid arthritis in all the sub-domains of the Health Assessment Questionnaire, and was superior to naproxen in all sub-domains except Hygiene and Eating	23
Rheumatoid arthritis	Randomized, double-blind, multicenter	Etoricoxib, 90 mg po od x 12 wk (n=353) Naproxen, 500 mg po bid x 12 wk (n=181) Placebo (n=357)	891	Etoricoxib was well tolerated, more effective than placebo and similar to naproxen in treating patients with rheumatoid arthritis	24
Rheumatoid arthritis	Randomized, double-blind, multicenter, pooled/ meta-analysis	Etoricoxib, 90 mg od x 12 wk (n=323) Naproxen, 500 mg bid x 12 wk (n=170) Placebo (n=323)	816	Etoricoxib was well tolerated and more effective than placebo or naproxen in patients with rheumatoid arthritis	25, 26
Rheumatoid arthritis	Randomized, double-blind, multicenter	Etoricoxib, 10 mg od po x 8 wk (n=78) Etoricoxib, 60 mg od po x 8 wk (n=126) Etoricoxib, 90 mg od po x 8 wk (n=134) Etoricoxib, 120 mg od po x 8 wk (n=120) Placebo (n=123)	581	Etoricoxib doses of 90 and 120 mg demonstrated similar efficacy and were significantly superior to placebo. The efficacy and general tolerability of etoricoxib were maintained for up to 1 year	27
Rheumatoid arthritis	Randomized, double-blind, multicenter, pooled/ meta-analysis	Etoricoxib, 90 mg od x 12 wk (n=652) Naproxen, 500 mg bid x 12 wk (n=340)	992	Both etoricoxib and naproxen effectively improved quality of life in patients with rheumatoid arthritis	28
Rheumatoid arthritis	Randomized, double-blind, multicenter	Etoricoxib, 90 mg od x 12 wk (n=294) Naproxen, 500 mg bid x 12 wk (n=181) Placebo (n=242)	717	Etoricoxib and naproxen proved to be similarly effective, and significantly more so than placebo, in rheumatoid arthritis patients	29
Arthritis	Randomized, double-blind, multicenter	Etoricoxib, 120 mg po od x 8 d (n=75) Indomethacin, 50 mg po tid x 8 d (n=75)	150	Etoricoxib 120 mg once daily provided a rapid and highly effective treatment for acute gouty arthritis with efficacy similar to that of indomethacin. It was well tolerated and showed a more favorable safety profile than indomethacin	31, 32

A double-blind study randomized osteoarthritis patients to receive placebo, 500 mg naproxen b.i.d. or 60 mg etoricoxib once daily for 12 weeks. Both active treatments significantly improved disease manifestations in patients with osteoarthritis of the knee or hip and in those with additional osteoarthritis involvement of the hand (20, 21).

A clinical study involved 617 patients with osteoarthritis of the knee. In this multicenter, double-blind, randomized, placebo-controlled trial, patients with increased pain upon NSAID withdrawal were randomized to receive once-daily etoricoxib at doses of 5, 10, 30, 60 or 90 mg or placebo for 6 weeks, followed by continuation or reallocation to etoricoxib 30, 60 or 90 mg/day or diclofenac 50 mg t.i.d. for a total of 52 weeks. Significantly greater efficacy for etoricoxib compared to placebo was demonstrated in the first part, which was strongly dose-dependent. In the second part of the study, efficacy was generally maintained and the two higher doses were more effective than the 30-mg dose of etoricoxib. Etoricoxib and diclofenac showed similar efficacy. Etoricoxib was reported to be well tolerated in general over the entire study period, with no significant dose-related trend for adverse events (22).

A study conducted in patients with RA found that treatment with naproxen or etoricoxib gave similar efficacy results when measured using patient and investigator global assessment of disease activity or the Health Assessment Questionnaire (23, 24).

A double-blind, randomized, placebo-controlled clinical trial recently assessed the efficacy and safety of etoricoxib in 816 patients with RA chronically treated with NSAIDs who showed clinical worsening of the disease upon withdrawal of prestudy NSAIDs. The patients were randomized to receive placebo, 90 mg etoricoxib once daily or 500 mg naproxen b.i.d. for 12 weeks. Both etoricoxib and naproxen were well tolerated and significantly improved all primary efficacy endpoints (which included patient and physician global assessments of disease activity, and counts of tender and swollen joints) compared to placebo. Etoricoxib was superior to naproxen, as the former was associated with a significantly greater improvement in all primary efficacy endpoints and most secondary efficacy endpoints, including ACR20. In terms of quality of life, etoricoxib resulted in significantly greater improvement compared to placebo in all domains of the Medical Outcomes Short Form-36, and in greater improvement compared to naproxen in all domains, with a significant difference in 5 of 8 domains. The authors concluded that these data support the addition of etoricoxib to current therapeutic options for RA (25, 26).

Patients with worsening RA after withdrawal of NSAID therapy were treated with etoricoxib 10, 60, 90 or 120 mg p.o. once daily or placebo in an 8-week, multinational, randomized, double-blind study. Efficacy (patient and investigator global assessments of disease activity, patient global assessments of pain, assessments of disability) significantly superior to placebo was seen with the etoricoxib 90- and 120-mg doses, which demonstrated similar efficacy. The efficacy and general tolerability of etoricoxib were maintained for up to 1 year (27).

The results from two identical multicenter, double-blind clinical trials in patients with RA that had worsened after discontinuation of NSAID therapy showed that both etoricoxib (90 mg once daily) and naproxen (500 mg b.i.d.) induced analgesic and antiinflammatory effects that were directly correlated with an improvement in the quality of life (28).

Of 891 rheumatoid arthritis patients randomized, 687 completed treatment with either placebo, etoricoxib 90 mg once daily or naproxen 500 mg b.i.d. in a 12-week, multinational trial. Etoricoxib and naproxen proved to be similarly effective, and significantly more so than placebo (ACR20 response rates of 41%, 59% and 58% in the placebo, etoricoxib and naproxen groups, respectively). Etoricoxib was generally well tolerated (29).

Patients with ankylosing spondylitis (n=387) enrolled in a randomized trial were assigned etoricoxib 90 or 120 mg once daily, naproxen 500 mg b.i.d. or placebo for 6 weeks. The pooled etoricoxib groups showed superior improvements in patient assessments of spine pain, global disease activity and functional status compared with placebo and naproxen. Both etoricoxib doses were well tolerated and demonstrated similar efficacy (30).

Etoricoxib was compared to indomethacin for the treatment of acute gouty arthritis in a randomized, double-blind trial. Patients (n=150) were given either etoricoxib 120 mg p.o. once daly or indomethacin 50 mg p.o. t.i.d. for 8 days. Assessments of pain in the study joint by patients, as well as clinicians' and patients' global assessments of response and joint tenderness, revealed equivalent efficacy for indomethacin and etoricoxib. Both drugs acted rapidly and were generally safe and well tolerated, etoricoxib showing a better safety profile than indomethacin, with fewer drug-related adverse events (31, 32).

A method for the treatment or prevention of chronic prostatitis or chronic pelvic pain syndrome containing a COX-2 inhibitor has been claimed. Exemplified COX-2 inhibitors are celecoxib, parecoxib, rofecoxib, valdecoxib, meloxicam, flosulide, nimesulide, etoricoxib, NS-398, DUP-697, SC-58125, SC-58635 and RS-57067 (33).

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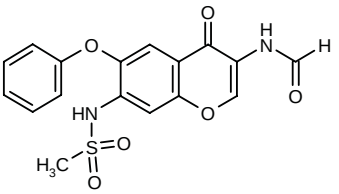
Iguratimod



Iguratimod is in late-stage development in Japan by Toyama in conjunction with Eisai, with regulatory filing scheduled for this year. It is also in phase II evaluation in South Africa, but development has been discontinued in the U.S. and Europe due to the large number of drugs already in development there for rheumatoid arthritis.

The antiarthritic activity of iguratimod (T-614) in terms of NF-κB regulation was evaluated in a human monocytic leukemia cell line (THP-1 cells). The agent inhibited LPS-stimulated production of TNF-α, IL-6 and IL-8 in a concentration-dependent manner and attenuated mRNA expression of these cytokines. Additionally, iguratimod prevented TNF-α and LPS-stimulated activation of NF-κB without blocking IκBα degradation, suggesting that it may inhibit the transcription of various cytokines through the suppression of NF-κB activation (1).

The mechanism of action of iguratimod was investigated using RA synovial fibroblast-like cells cultured in the presence of TNF-α. Exposure to iguratimod suppressed TNF-α-induced IL-6, IL-8 and monocyte chemoattractant protein-1 (MCP-1) production and accumulation of IL-6 and IL-8 mRNA. Furthermore, NF-κB translocation from the cytoplasm to the nucleus was impeded (2).

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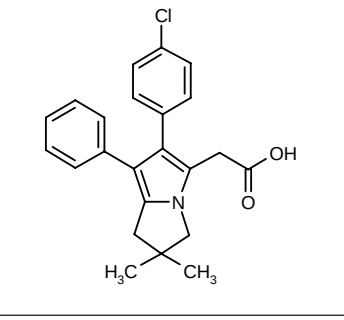
Licofelone



Licofelone (ML-3000) is a late-stage investigational agent for the treatment of osteoarthritis which is being developed by Merckle and its EuroAlliance partners Alfa Wassermann and Lacer. Although licensee Forest terminated its agreement with Merckle for the development of the compound when it failed to meet endpoints required by the FDA for approval in the U.S. in two pivotal tritals, Merckle and its EuroAlliance partners remain committed to bringing licofelone to the market and are in discussions with potential partners. The ongoing clinical program to support the registration of licofelone in Europe remains unaffected by the situation in the U.S. (1-3).

Licofelone inhibits both COX-1 and COX-2, as well as 5-lipoxygenase (5-LO) and may have potential in thrombosis and vascular disorders in addition to inflammation. *In vitro* studies in stimulated human polymorphonuclear leukocytes (PMNs)/platelets demonstrated its ability to inhibit the production of arachidonic acid metabolites at concentrations of 10 μM or less. It was also found to inhibit PMN/platelet adhesion at concentrations below 25 μM and to concentration-dependently inhibit PMN aggregation and degranulation. It also inhibited the production of superoxide anions, elastase release and homotypic aggregation in fMLP-, complement fraction C5a- and PAF-stimulated PMNs with IC_{50} values below 25 μM. These results confirm the inhibitory effect of licofelone on 5-LO/COX and demonstrated its ability to inhibit the generation of arachidonic acid metabolites through PMN/platelet crosstalk and the regulation of PMN responses relevant to the inflammatory process (4-6).

In peripheral blood monocytic cells challenged with LPS, licofelone inhibited IL-1β and TNF-α release, as well as PGE_2 and LTB_4 secretion. PGE_2 was also reduced by indomethacin, which additionally increased IL-1β and TNF-alpha production. Celecoxib reduced PGE_2 production, and the 5-LO inhibitor ZD-2138 reduced LTB_4, IL-1β and TNF-α production (7).

In human primary osteoarthritis osteoblasts, the finding of a shunt to the lipoxygenase pathway suggested

that licofelone may decrease bone remodeling during osteoarthritis (8, 9).

Confirmation that COX-1 is a specific target of licofelone was obtained using platelet-rich plasma or washed platelet suspensions from citrated human whole blood. Licofelone at concentrations as low as 1 μM completely prevented platelet aggregation induced by threshold aggregating concentrations of arachidonic acid. In contrast, no effect was found for licofelone on aggregation stimulated by collagen/adrenaline in aspirin-treated platelets, or on platelet activation induced by thrombin or its mimetic peptide TRAP (10).

Licofelone has proved effective in animal models of inflammation, pain, fever, asthma and thromboembolism while being devoid of gastrointestinal toxicity. In the rat carrageenan-induced paw edema model, it gave an ED_{50} of 17 mg/kg p.o. In contrast to indomethacin, licofelone as single or multiple oral doses of up to 300 mg/kg produced no gastric mucosal damage (11-13).

Further experiments demonstrated that while both licofelone and indomethacin significantly reduced PGE_2 levels in the stomach and inflamed rat paw, licofelone, unlike indomethacin, did not increase gastric mucosal LTB_4 levels, significantly reduced paw LTB_4 levels and did not induce leukocyte adherence to rat mesenteric venules. These findings thus confirm that the gastric-sparing properties of licofelone are related to its ability to inhibit 5-LO (14).

Licofelone (20 or 80 mg/kg/day) was injected into rats with adjuvant arthritis in a 28-day study. No side effects were seen with the treatment, which reduced joint erosion, synovial cell proliferation and the appearance of fibroproliferative pannus (15).

Licofelone was evaluated for its effects on the gastric mucosa of rats both alone and following 2 weeks of aspirin treatment, and compared to celecoxib. After treatment with aspirin at a dose of 50 mg/kg/day, the animals were administered placebo, licofelone (10, 30 or 100 mg/kg) or celecoxib (30 mg/kg). Aspirin treatment significantly increased the gastric damage score, markedly reduced PGE_2 and thromboxane levels and increased COX-2 expression in the gastric mucosa. Although celecoxib had no effect on the gastric mucosa by itself, it significantly enhanced the damage in aspirin-treated rats. In contrast, licofelone spared the gastric mucosa when given alone and did not worsen mucosal damage in the aspirin-treated animals (16).

The therapeutic effects of licofelone were evaluated in a canine model of osteoarthritis induced by sectioning the anterior cruciate ligament of the right joint. The animals were treated with placebo or licofelone at doses of 2.5 and 5 mg/kg/day p.o. starting on the day after surgery and continued for 8 weeks. Serum levels considered therapeutic were measured in licofelone-treated dogs. The compound significantly decreased the size and grade of cartilage lesions both macroscopically and histologically compared to placebo-treated dogs. Although no significant differences were seen among treatment groups as regards synovial inflammation, licofelone produced a significant decrease in PGE_2 levels in synovial fluid and in LTB_4 production in synovial membranes, as well as a marked decrease in collagenase 1 levels in cartilage and IL-1β levels in synovial membrane (17-20).

Licofelone could reduce the progression of experimental osteoarthritis in a canine model by decreasing the levels of chondrocyte apoptosis. Such an effect was found following treatment with therapeutic doses of licofelone (2.5 and 5.0 mg/kg/day) (21).

In a pharmacokinetics study, young and elderly healthy volunteers received 200 mg licofelone b.i.d. for 5 days and a final dose of 200 mg on the morning of the sixth day. The pharmacokinetic characteristics and the rate of gastrointestinal absorption of licofelone were similar in both types of subjects; elderly subjects showed an AUC value 20% higher than that measured in young subjects, although the authors of the study believed that this difference was not likely to be clinically significant. Good tolerance was found in both study groups (22).

In another pharmacokinetic study, 12 healthy volunteers were given licofelone 200 mg b.i.d. plus placebo for 9 days and warfarin 20 mg on day 3. After a washout period, another 9-day treatment period was initiated. No pharmacokinetic interaction between licofelone and warfarin was seen, as indicated by the similarity of warfarin concentrations during coadministration of placebo or licofelone (23).

The mucosal tolerability of licofelone was evaluated in 121 healthy volunteers who received licofelone 200 or 400 mg b.i.d., naproxen 500 mg b.i.d. or placebo for 4 weeks. Lanza mucosa scores of the stomach and duodenum were similar with either dose of licofelone and placebo and superior to those with naproxen, indicating that the effect of licofelone on the gastric and duodenal mucosa was slight (24). These results are summarized in Table IV.

The gastrointestinal tolerability of licofelone was maintained when combined with low-dose aspirin. Two clinical studies found that the incidence of endoscopically diagnosed ulcers in osteoarthritic patients receiving licofelone (400 mg b.i.d.) was 5.6% for patients concomitantly treated with low-dose aspirin and 2.4% for patients who took no aspirin. Both values were in the range reported for placebo-treated patients in comparable published studies; for comparison, gastrointestinal ulcers were reported by 25.6% and 23% of osteoarthritic patients receiving 500 mg naproxen b.i.d. with and without low-dose aspirin, respectively. Licofelone may therefore be useful in the treatment of osteoarthritis patients who also need to take aspirin due to a high risk of cardiovascular disease (25).

A study in 148 patients with osteoarthritis compared 200 mg licofelone b.i.d. and 500 mg naproxen b.i.d. for 12 weeks. The results of this study revealed that naproxen was as effective as licofelone, but the former induced a higher percentage of gastrointestinal adverse events than the latter (26). These results are summarized in Table IV.

Table IV: Clinical studies of licofelone (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized	Licofelone, 200 mg po bid x 4 wk Licofelone, 400 mg po bid x 4 wk Naproxen, 500 mg po bid x 4 wk Placebo	121	Licofelone had little or no effect on gastroduodenal mucosa, with a gastrointestinal profile similar to placebo and clearly superior to that of naproxen	24
Osteoarthritis	Randomized, multicenter	Licofelone, 200 mg po bid x 12 wk Naproxen, 500 mg po bid x 12 wk	148	Licofelone showed excellent gastrointestinal and general tolerability and had similar efficacy as naproxen in the treatment of osteoarthritis	26

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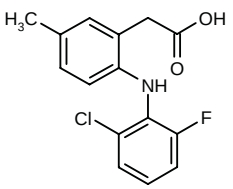
Original monograph - Drugs Fut 1995, 20(10): 1007.

Lumiracoxib



Lumiracoxib (COX-189, Prexige™), a selective COX-2 inhibitor developed by Novartis, is under regulatory review in the U.S. and the E.U. for the treatment of osteoarthritis, rheumatoid arthritis, acute pain and primary dysmenorrhea. The marketing applications are based on data from clinical studies involving over 13,000 adult patients around the world (1).

The international TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial) trial is investigating the safety, tolerability and efficacy of lumiracoxib for the treatment of symptoms of arthritis and pain over 12 months in comparison to the NSAIDs naproxen and ibuprofen. The gastrointestinal safety of lumiracoxib compared to the other drugs will be the primary endpoint, with cardiovascular safety as a secondary endpoint. More than 18,000 patients are to be enrolled worldwide in the trial, including men and women over the age of 50 who are symptomatic sufferers of osteoarthritis (2).

The selectivity of lumiracoxib as a COX-2 inhibitor was assessed *in vitro* by measuring TxB_2 levels (an indicator of COX-1 activity) and PGE_2 levels (an indicator of COX-2 activity) in human whole blood. Compared to rofecoxib and celecoxib, lumiracoxib was an equally strong inhibitor of PGE_2 production but a less active inhibitor of TxB_2 production. The COX-2 selectivity of lumiracoxib was 100- and 1,400-fold higher than that of the NSAIDs diclofenac and naproxen, respectively (3).

A randomized, double-blind, placebo-controlled study conducted in 48 healthy subjects revealed that the single-dose pharmacokinetic parameters measured for lumiracoxib increased proportionally with dose over the range 25-800 mg (4). The results of this study and some that follow are summarized in Table V.

Lumiracoxib is primarily cleared by the liver, providing the rationale for a trial evaluating the effect of liver impairment on the pharmacokinetics of this agent. Patients with moderate hepatic impairment and healthy matched controls were administered lumiracoxib (400 mg) as a single dose. No significant differences were observed in the C_{max}, AUC or t_{max} values between the two groups. The results indicate that dose adjustments of lumiracoxib may not be necessary in patients with mild or moderate hepatic impairment (5).

The potent and selective COX-2 inhibitor has been compared to placebo and naproxen for its gastroduodenal effects in a double-blind, randomized, parallel trial in 60 healthy subjects. Twenty subjects each received lumiracoxib 200 mg b.i.d., naproxen 500 mg b.i.d. or placebo for 7 days. Lumiracoxib was well tolerated as regards vital signs, ECG, laboratory parameters and endoscopy. In contrast to naproxen which produced gastroduodenal erosions in 13 of 20 subjects, none of the subjects given lumiracoxib or placebo had erosions on day 8. The lack of effect *ex vivo* on serum TxB_2 levels compared to naproxen was consistent with the selectivity of lumiracoxib for COX-2 (6).

In another study, lumiracoxib (up to 600 mg/day) was well tolerated following multiple oral administration in healthy volunteers. C_{max} and AUC rose dose-proportionally on day 1 and steady-state dose proportionality was confirmed for both parameters in the dose range 50-200 mg b.i.d. The $t_{1/2}$ was 3-6 h, with little or no accumulation observed following multiple dosing. The agent was without effect on ADP/collagen-induced platelet aggregation at all doses studied (7).

A crossover study in 24 healthy volunteers compared the pharmacokinetics, safety and inhibitory activity of placebo, naproxen (500 mg b.i.d.) and lumiracoxib (800 mg once daily). Lumiracoxib was reported to have a similar inhibitory activity and a better gastrointestinal safety profile than naproxen, as the former caused no gastroduodenal injuries and had no effects on gastric mucosal prostaglandin synthesis or bowel permeability (8-10).

The pharmacokinetics of lumiracoxib (up to 400 mg/day) were investigated in patients with knee or hip primary osteoarthritis in a randomized, placebo-controlled trial. The pharmacokinetics of the agent were dose-proportional and time-independent in these patients. The pharmacodynamics of lumiracoxib appeared to be influenced by the pharmacokinetics in an effect compartment in which the kinetics were slower than in plasma (11).

Table V: Clinical studies of lumiracoxib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind, multicenter	Lumiracoxib, 25 mg po (n=6) Lumiracoxib, 50 mg po (n=6) Lumiracoxib, 100 mg po (n=6) Lumiracoxib, 200 mg po (n=6) Lumiracoxib, 400 mg po (n=6) Lumiracoxib, 800 mg po (n=6) Placebo (n=12)	48	Lumiracoxib was safe and well tolerated at single doses of up to 800 mg in healthy volunteers	4
Healthy volunteers	Randomized, double-blind, multicenter	Lumiracoxib, 200 mg po bid x 7 d (n=20) Naproxen, 500 mg po bid x 7 d (n=20) Placebo (n=20)	60	Compared with naproxen, lumiracoxib had a favorable placebo-like gastrointestinal tolerability profile in terms of gastric and duodenal erosions in healthy volunteers	6, 9
Healthy volunteers	Randomized, double-blind	Lumiracoxib, 50 mg po bid x 9 d Lumiracoxib, 100 mg po bid x 9 d Lumiracoxib, 200 mg po bid x 9 d Lumiracoxib, 300 mg po bid x 9 d Lumiracoxib, 400 mg od x 9 d	40	Lumiracoxib was safe and well tolerated with multiple oral administration at doses of up to 600 mg daily over 9 days in healthy volunteers	7
Healthy volunteers	Randomized, double-blind, crossover	Lumiracoxib, 800 mg od Naproxen, 500 mg bid Placebo	24	Lumiracoxib showed similar potency to naproxen as a COX-2 inhibitor and had a better gastrointestinal safety profile	8, 10
Osteoarthritis	Randomized, double-blind, multicenter	Lumiracoxib, 200 mg od x 13 wk (n=487) Lumiracoxib, 400 mg od x 13 wk (n=491) Celecoxib, 200 mg od x 13 wk (n=481) Placebo (n=243)	1702	Compared with celecoxib, lumiracoxib was equally well tolerated and induced a greater analgesic effect in patients with osteoarthritis	14
Osteoarthritis	Randomized, double-blind, multicenter	Lumiracoxib, 200 mg po od x 13 wk (n=264) Lumiracoxib, 400 mg po od x 13 wk (n=260) Celecoxib, 200 mg po od x 13 wk (n=260) Ibuprofen, 800 mg po tid x 13 wk (n=258)	1042	Lumiracoxib showed a safety and gastrointestinal tolerability profile superior to that of ibuprofen and similar to that of celecoxib, with a lower incidence of gastroduodenal ulcers compared to ibuprofen	15, 16
Osteoarthritis	Randomized, double-blind, multicenter	Lumiracoxib, 50 mg po bid x 4 wk (n=98) Lumiracoxib, 100 mg po bid x 4 wk (n=96) Lumiracoxib, 200 mg po bid x 4 wk (n=99) Lumiracoxib, 400 mg po od x 4 wk (n=99) Diclofenac, 75 mg po bid x 4 wk (n=94) Placebo (n=97)	583	Lumiracoxib was well tolerated and highly effective at the 400 mg dose, with activity comparable to that of diclofenac, in the treatment of osteoarthritis; the response rate was higher with the od regimen compared with the bid regimen	17

The results from a recent clinical trial demonstrated the good tolerance and effective, rapid and prolonged relief of dental pain with lumiracoxib at a dose of 400 mg. This double-blind, randomized, parallel-group study included 202 subjects with moderate to severe pain following extraction of 2 or more impacted third molars. Subjects were randomized to treatment with a single dose of lumiracoxib of 100 or 400 mg, ibuprofen 400 mg or placebo. The study reached its primary endpoint in terms of pain relief. The median times to onset of analgesia were 38 min for lumiracoxib 400 mg, 42 min for ibuprofen 400 mg, 53 min for lumiracoxib 100 mg and > 12 h for placebo, with significant differences for all active treatments compared to placebo. The median times to rescue medication on lumiracoxib and ibuprofen were also significantly longer than placebo, being 7 h on lumiracoxib 100 mg, 8 h on ibuprofen and > 12 h on lumiracoxib 400 mg compared to about 2 h on placebo (12).

Measurement of variables such as pain intensity difference, pain relief, time to onset of analgesia and patient global evaluation revealed that single doses of 400 or 800 mg of lumiracoxib were equally safe and more effective than placebo or a single dose of 50 mg of rofecoxib in reducing postoperative pain after removal of 2 or more molars (13).

A multicenter, randomized, double-blind study compared the efficacy and safety of lumiracoxib 200 or 400 mg once daily with celecoxib 200 mg once daily and placebo administered for 13 weeks to patients with

osteoarthritis of the knee. Compared to placebo, lumiracoxib was associated with significant improvement in all primary and secondary endpoints. Moreover, lumiracoxib significantly decreased overall pain intensity and was found to be superior to celecoxib over the first 8 weeks of treatment when administered at a daily dose of 400 mg; comparable efficacy was seen at week 13. All study groups showed a similar incidence of adverse events, serious adverse events and discontinuations due to adverse events (14).

A multicenter, double-blind clinical trial that included 1,042 osteoarthritis patients revealed that the incidence of gastroduodenal ulcers and erosions was significantly lower after treatment for 13 weeks with lumiracoxib (200 or 400 mg once daily) than with either celecoxib (200 mg once daily) or ibuprofen (800 mg t.i.d.) (15).

The safety and tolerability profile of two different doses of lumiracoxib (200 and 400 mg once daily) were better than those of ibuprofen (800 mg t.i.d.) and essentially similar to those of celecoxib (200 mg once daily). The difference between lumiracoxib and ibuprofen was statistically significant for gastrointestinal ulcers and resulted in relevant differences in the percentage of patients who discontinued the treatment (16).

A study evaluated the percentage of osteoarthritis patients who responded to lumiracoxib with a 20% reduction from baseline in overall pain intensity and found that the efficacy of a daily dose of 400 mg lumiracoxib was similar to that of a full dose of diclofenac (75 mg b.i.d.) (17).

A randomized clinical trial that included 180 adult patients determined that a daily dose of 400 mg of lumiracoxib was well tolerated and as effective as naproxen 500 mg twice daily in reducing the intensity of moderate to severe postoperative pain (18).

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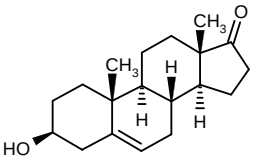
Original monograph - Drugs Fut 2002, 27(8): 740.

Prasterone



Genelabs Technologies' MAA for prasterone (GL-701, Anastar™, Prestara™ in the U.S., formerly Aslera™), a proprietary oral formulation of dehydroepiandrosterone (DHEA), has been validated by the EMEA, indicating that the review process has begun. The application was made under the E.U. centralized procedure and requests approval for prasterone for the improvement of systemic lupus erythematosus (SLE) disease activity and/or reduction in glucocorticoid doses in women with active SLE. Genelabs developed the compound under license from Stanford University and has exclusively licensed the product to Watson for North America (1-9).

The application is based primarily on data from 2 double-blind, randomized, placebo-controlled phase III trials (GL94-01 and GL95-02) that together compared prasterone to placebo in 572 women with mild to moderate SLE. Separately, the company has announced the initiation of a confirmatory phase III trial, study GL02-01. The trial will be a multicenter, randomized, placebo-controlled, double-blind study involving around 150 women with SLE receiving glucocorticoids. The primary endpoint will be bone mineral density (BMD) at the lumbar spine, and the treatment will be either 200 mg/day prasterone or placebo over 6 months. The FDA issued an approvable letter to Genelabs in August 2002 for the drug, contingent upon the successful completion of an additional clinical trial providing evidence to confirm the positive effect on BMD. Genelabs' GL95-02 study enrolled 381 women with lupus who received prasterone for up to 1 year. In this population, a group of patients were evaluated for BMD. Thirty-seven of these patients were on trial medication for a full year and were treated with glucocorticoids for at least 6 months prior to the initiation of the trial. Mean BMD of both the lumbar spine and hip significantly increased in the patients treated with prasterone, compared to decreases in the placebo group. The differences between the groups were statistically significant (9).

Prasterone and placebo were compared for their effect on serum lipids in female SLE patients treated with antimalarials or corticosteroids. At 3 months, prasterone reduced HDL cholesterol and total triglycerides by approximately 13%, possibly due to enhanced clearance. Triglyceride reductions were most evident in patients taking both antimalarials and prasterone (10).

A randomized, double-blind, placebo-controlled trial examined treatment of women with mild to moderate SLE with oral prasterone 200 mg/day. Treatment was given for 1 year and 381 patients were randomized. Prasterone produced a response in over 60% of patients and was well tolerated (11). The results of this study and the two that follow are summarized in Table VI.

The reduction of prednisone doses in female patients with SLE (n=191) under treatment with prasterone was evaluated in a randomized, double-blind, placebo-controlled trial. In addition to prednisone 10-30 mg/day, patients received placebo or prasterone 100 or 200 mg/day for 7-9 months. Prednisone doses were reduced in patients with stable or improved disease. The percentage of patients with a sustained reduction in prednisone dose to 7.5 mg/day or less for at least 2 months was significantly greater with prasterone 200 mg than with placebo (55% *vs.* 41%, respectively) (12).

In an evaluation of treatment effect on BMD, prasterone 200 mg/day or placebo was administered to 37 female SLE patients who had received steroids for at least 6 months. The prasterone-treated patients had significant improvements over placebo in BMD at 1 year, and the greatest benefit was seen in postmenopausal patients (13).

1. *Genelabs submits MAA for lupus drug in Europe*. DailyDrugNews.com (Daily Essentials) Jan 3, 2003.

Table VI: Clinical studies of prasterone (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Systemic lupus erythematosus	Randomized, double-blind	Prasterone, 200 mg/d po x 12 mo Placebo, po od x 12 mo	381	Prasterone was safe and had good activity in systemic lupus erythematosus	11
Systemic lupus erythematosus	Randomized, double-blind	Prednisone, 10-30 mg/d + Prasterone, 100 mg po x 7-9 mo (n=63)$ Prednisone, 10-30 mg/d + Prasterone, 200 mg po x 7-9 mo (n=64) Prednisone, 10-30 mg/d + Placebo (n=64)	191	Reduction of prednisone doses in patients with stable or improved disease was possible in significantly more patients receiving prasterone 200 mg than among those given placebo	12
Osteoporosis	Randomized, double-blind	Prasterone, 200 mg/d po x 1 y → Prednisone, </=10 mg po od (n=18)$ Placebo x 1 y → Prednisone, </=10 mg po od (n=19)	37	Prasterone increased bone mineral density and showed good results in women at risk for osteoporosis	13

2. *Approvable letter for Genelabs Technologies' Prestara, formerly Aslera*. DailyDrugNews.com (Daily Essentials) Aug 30, 2002.

3. *Genelabs permitted to seek E.U. approval for Aslera under centralized procedure*. DailyDrugNews.com (Daily Essentials) June 21, 2002.

4. *Genelabs expects Aslera NDA response by August 2002*. DailyDrugNews.com (Daily Essentials) May 30, 2002.

5. *Watson's Aslera scheduled for March FDA Arthritis Advisory Committee review*. DailyDrugNews.com (Daily Essentials) Jan 16, 2001.

6. *Genelabs' NDA for Aslera deemed unapprovable by FDA*. DailyDrugNews.com (Daily Essentials) June 27, 2001.

7. *Review of Aslera NDA rescheduled for April*. DailyDrugNews.com (Daily Essentials) Feb 21, 2001.

8. *FDA Arthritis Advisory Committee meets to review Aslera NDA*. DailyDrugNews.com (Daily Essentials) April 20, 2001.

9. *Prasterone to be reviewed by EMEA*. DailyDrugNews.com (Daily Essentials) Jan 13, 2003.

10. Schwartz, K., Gurwith, M. *Differential effects of prasterone (Aslera™) on lipid profiles in female SLE patients on treatment with antimalarials or corticosteroids*. Lupus 2001, 10(Suppl. 1): S102.

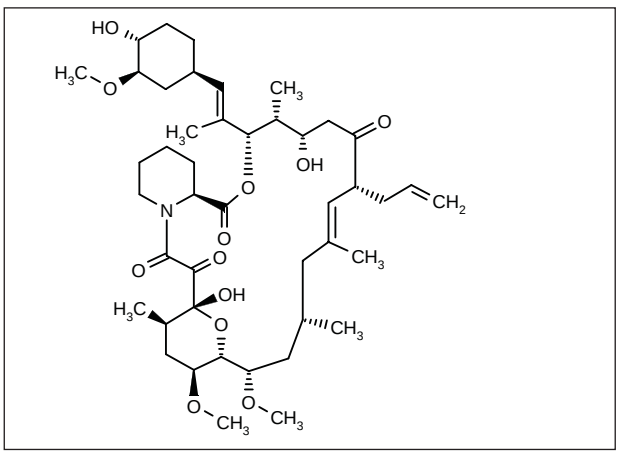
11. Mease, P., Merrill, J., Lahita, R., Petri, M., Ginzler, E., Katz, R., Gluck, O., Schwartz, K., Gurwith, M. *Prasterone (Aslera™) improves systemic lupus erythematosus*. Lupus 2001, 10(Suppl. 1): S10.

12. Petri, M.A., Lahita, R.G., van Vollenhoven, R.F. et al. *Effects of prasterone on corticosteroid requirements of women with systemic lupus erythematosus: A double-blind, randomized, placebo-controlled trial*. Arthritis Rheum 2002, 46(7): 1820.

13. Mease, P., Ginzler, E., Gluck, O., Schiff, M., Schmeer, P., Gurwith, M., Schwartz, K. *Improvement in bone mineral density in steroid-treated SLE patients during treatment with prasterone (Aslera™)*. Lupus 2001, 10(Suppl. 1): S102.

Original monograph - Drugs Fut 1995, 20(6): 575.

Tacrolimus



Tacrolimus (FK-506) is currently marketed by Fujisawa as the immunosuppressant Prograf®, and as Protopic® for the treatment of atopic dermatitis. Fujisawa is also developing the drug for chronic rheumatoid arthritis and inflammatory bowel disease. In Japan, it is being developed for vernal conjunctivitis and perennial allergic conjunctivitis in an eye drop formulation, and Sucampo has acquired exclusive rights to develop and market the eye drop formulation in the U.S. and Europe for the treatment of dry eye, vernal conjunctivitis and perennial allergic conjunctivitis (1).

Rats with adjuvant-induced arthritis were treated with tacrolimus 1-5.6 mg/kg or methotrexate 0.1-1 mg/kg p.o. on study days 15-24. Tacrolimus suppressed hind paw inflammation and hyperalgesia and reduced TNF-α levels in the hind paws. Methotrexate had lesser effects on paw inflammation and hyperalgesia, and greater toxicity. Tacrolimus-treated rats, but not methotrexate-treated rats, recovered the loss of grip strength associated with adjuvant-induced arthritis (2, 3).

The possibility of pharmacokinetic interactions between tacrolimus and methotrexate following concomitant administration of the two agents was evaluated in patients with RA on stable methotrexate therapy. All 90% confidence intervals for the calculated pharmacokinetic parameters were within 80-125%, indicating no drug interaction between these agents (4).

A multicenter phase II study enrolled 168 RA patients resistant or intolerant to methotrexate who were randomized to placebo or tacrolimus 1, 3, or 5 mg once daily in a double-blind fashion. The study lasted 24 weeks, and methotrexate was discontinued before randomization. ACR20 response rates were dose-dependent (15.5%, 29%, 34.4% and 50%, respectively, in the placebo and tacrolimus 1, 3 and 5 mg groups). Withdrawals due to lack of efficacy were common in the placebo group and withdrawals for toxicity were common in the high-dose tacrolimus groups. The results indicated that the optimal tacrolimus dose was between 1 and 3 mg/day (5). The results of this study and some that follow are summarized in Table VII.

Patients with RA (n=896) enrolled in an open-label trial received tacrolimus 3 mg/day for 1 year (111 patients had received tacrolimus 2 or 3 mg/day for at least 3 months in a previous trial). An interim analysis indicated that the treatment was effective, with an ACR20 response rate of 37.6%. Tacrolimus was well tolerated for up to 18 months and the incidence of adverse events did not increase with extended treatment (6).

Rheumatoid arthritis patients intolerant or resistant to at least one DMARD (n=464) were given tacrolimus 2 or 3 mg/day or placebo in a randomized, double-blind trial. After 6 months, ACR20 response rates of 21.4% and 32% were measured for the 2- and 3-mg doses, respectively. Tacrolimus monotherapy was safe and well tolerated in these patients (7).

An open-label trial including 80 RA patients who were partial responders to methotrexate investigated treatment with methotrexate (maximum tolerated dose) plus tacrolimus (3 mg/day). After 6 months of therapy, an ACR20 response rate of 52.5% was measured, and the treatment was considered safe and well tolerated (8).

Table VII: Clinical studies of tacrolimus (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Rheumatoid arthritis	Randomized, double-blind, placebo-controlled, multicenter	Tacrolimus, 1 mg od x 24 wk (n = 69) Tacrolimus, 3 mg od x 24 wk (n = 64) Tacrolimus, 5 mg od x 24 wk (n = 64) Placebo (n = 71)	168	Tacrolimus demonstrated dose-related efficacy in patients with refractory rheumatoid arthritis resistant or intolerant to methotrexate, although withdrawals due to toxicity were common in the higher dose groups	5
Rheumatoid arthritis	Open	Tacrolimus, 3 mg/d x 12 mo Tacrolimus, 2 mg/2 x >/=3 mo → 3 mg/kg/d x 12 mo Tacrolimus, 3 mg/2 x >/=3 mo → 3 mg/kg/d x 12 mo	896	Tacrolimus was effective and well tolerated for up to 18 months in rheumatoid arthritis patients	6
Rheumatoid arthritis	Randomized, double blind, placebo-controlled	Tacrolimus, 2 mg/d x 6 mo (n = 154) Tacrolimus, 3 mg/d x 6 mo (n = 153) Placebo (n = 157)	464	Tacrolimus monotherapy was safe, well tolerated and demonstrated efficacy in rheumatoid arthritis patients intolerant or resistant to 1 or more disease-modifying antirheumatic drugs	7
Rheumatoid arthritis	Open	Methotrexate, 15 mg/wk (median) + Tacrolimus, 3 mg/d x 6 mo	80	Tacrolimus plus methotrexate was safe, well tolerated and effective in patients with rheumatoid arthritis who were partial responders to methotrexate	8

Macrolides have been found to be useful for inducing chondrogenic differentiation, providing a method for the treatment or prevention of cartilage damages, particularly rheumatoid arthritis and osteoporosis. A preferred compound is tacrolimus, which was found to induce chondrocyte differentiation of ATDC5 cells in a concentration-dependent manner (9).

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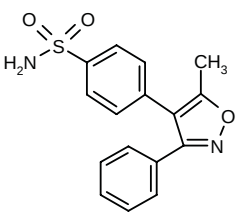
Valdecoxib



Pharmacia and Pfizer have codeveloped the anti-inflammatory and analgesic agent valdecoxib (SC-65872, Bextra®), an oral, second-generation COX-2 inhibitor for the treatment of osteoarthritis, rheumatoid arthritis and pain.

Valdecoxib was launched for the first time in the U.S. early last year for the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis in adults, and for the treatment of primary dysmenorrhea. It is also available in Canada. In Europe, the CPMP has recommended approval of valdecoxib and it will be marketed there by Pharmacia as Valdyn®, by Pfizer as Kudeq®and by Pharmacia-Pfizer as Bextra®. In global clinical trials involving over 5,000 patients, it demonstrated comparable efficacy and an improved gastrointestinal (GI) safety and tolerability profile compared to conventional NSAIDs, *i.e.*, naproxen, ibuprofen and diclofenac. In controlled arthritis studies, the use of the drug at the recommended dose (10 mg once daily) has not been associated with an increased risk of cardiovascular or renal complications as compared to NSAIDs. The recommended dose for menstrual pain is 20 mg b.i.d. (1-7).

In late 2002, the FDA, Pharmacia and Pfizer advised healthcare professionals about new warnings and information on the product labeling of the drug following postmarketing reports of serious adverse events. Since Pharmacia began marketing the drug in March 2002, cases of serious skin and hypersensitivity reactions have been reported. These include Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme. Although these adverse events are rare, these cases, some of which were serious/life-threatening requiring hospitalization, occurred in patients with and without a history of allergic-type reactions to sulfonamides (8).

The pharmacokinetics of valdecoxib (10-80 mg p.o.) in healthy adults were found to be dose-proportional with respect to total plasma exposure following a single dose, according to the results from an open-label, crossover study. Following multiple doses of valdecoxib (2-50 mg b.i.d), increases in plasma exposure at steady state were linear. The agent was well tolerated in both studies (9).

A total of 8 healthy volunteers received a 50-mg oral dose of [^{14}C]-valdecoxib. Valdecoxib was found to be extensively metabolized, with 9 metabolites identified; in plasma, most of the radioactivity was associated with valdecoxib and its hydroxylated metabolite M1. Approximately 76.1% and 18% of the radioactive dose was recovered in feces and urine, respectively. The *O*-glucuronide conjugate of M1 and the *N*-glucuronide conjugate of valdecoxib accounted for 23.3% and 19.5% of the total administered dose, respectively and were the major urinary metabolites. Recovery of unchanged valdecoxib in urine and feces was 3% and < 1%, respectively (10).

A total of 62 healthy subjects were included in a double-blind, randomized, placebo-controlled clinical trial that compared the antiplatelet effects of a supratherapeutic dose of valdecoxib and those of conventional NSAIDs. The subjects were randomized to receive valdecoxib (40 mg b.i.d.), naproxen (500 mg b.i.d.), diclofenac (75 mg b.i.d.) or placebo for 7.5 days. The measurement of platelet aggregation, bleeding time and serum TxB_2 levels at baseline and every day throughout the study revealed that valdecoxib did not modify these parameters, whereas both naproxen and diclofenac decreased platelet aggregation compared to placebo. It was concluded that valdecoxib might be a safer therapeutic option than NSAIDs for the treatment of perisurgical pain (11, 12). A similar study enrolled 65 healthy adults 65 years of age or over who were randomized to treatment with valdecoxib 40 mg b.i.d., ibuprofen 800 mg t.i.d. or placebo over 7.5 days. Valdecoxib had no significant effect on platelet aggregation induced by several agonists, serum TxB_2 levels or bleeding times, whereas ibuprofen significantly altered hemostasis (13, 14). The results of these studies and some that follow are summarized in Table VIII.

The risk of gastroduodenal ulcers with 6.5 days of treatment with valdecoxib 40 mg b.i.d., naproxen 500 mg b.i.d. or placebo was evaluated in a randomized, double-blind, placebo-controlled trial in 186 healthy elderly volunteers. None of the subjects had an upper GI ulcer at baseline. Repeat endoscopy on day 7 revealed that valdecoxib- and placebo-treated subjects had signficantly lower rates of upper GI ulcers than patients taking naproxen (15).

Patients with osteoarthritis of the knee were randomized to valdecoxib (5, 10 or 20 mg once daily), naproxen (500 mg b.i.d.) or placebo. Valdecoxib (10 and 20 mg) demonstrated similar efficacy to naproxen and all drug treatment regimens were superior to placebo. The incidence of upper GI ulceration was significantly lower in patients randomized to the 5- and 10-mg valdecoxib regimens as compared to the naproxen group; all valdecoxib regimens were comparable to placebo (16, 17).

Results of a multicenter, randomized, double-blind, parallel-group study involving patients with osteoarthritis (having 10 or less gastric or duodenal erosions and no ulcers at pretreatment) showed that valdecoxib (10 or 20 mg daily for 12 week) had a significantly lower risk of gastroduodenal ulcers than ibuprofen (800 mg t.i.d.) or diclofenac (75 mg b.i.d.). Significantly fewer patients treated with valdecoxib (4% for both doses) developed ulcers as compared to ibuprofen (14%) and diclofenac (13%); valdecoxib was not significantly different from placebo (4%). The incidence of patients with an erosion or an ulcer was also significantly less in the valdecoxib (23% and 24% for the respective doses) and placebo (21%) groups as compared to ibuprofen (55%) and diclofenac (37%) (18).

Valdecoxib was the subject of several presentations at the EULAR 2001 meeting. A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial was conducted in 642 patients with osteoarthritis of the knee comparing doses of valdecoxib of 0.5, 1.25, 2.5, 5 or 10 mg b.i.d. or 10 mg once daily to naproxen 500 mg b.i.d. and placebo for 6 weeks. Valdecoxib dose-dependently improved signs and symptoms of osteoarthritis, with significantly greater efficacy compared to placebo on all primary efficacy measurements – Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis and Western Ontario and McMaster's Universities (WOMAC) Osteoarthritis Index – except at the lowest dose of 0.5 mg b.i.d. The doses of 5 mg b.i.d., 10 mg

Table VIII: Clinical studies of valdecoxib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized	Valdecoxib, 40 mg bid x 7.5 d (n=15) Naproxen, 500 mg bid x 7.5 d (n=15) Diclofenac, 75 mg bid x 7.5 d (n=16) Placebo (n=16)	62	No effect on platelet aggregation and bleeding time was observed with valdecoxib in healthy volunteers, suggesting an improved safety profile over conventional NSAIDs, especially in patients at risk of bleeding complications	11, 12
Healthy volunteers	Randomized, double-blind	Valdecoxib, 40 mg po bid x 7.5 d Ibuprofen, 800 mg po tid x 7.5 d Placebo	65	Results showed a lack of effect of valdecoxib on platelet function, serum thromboxane B_2 levels or bleeding times in healthy elderly volunteers	13, 14
Healthy volunteers	Randomized, double-blind	Valdecoxib, 40 mg po bid x 6.5 d (n=60) Naproxen, 500 mg po bid x 6.5 d (n=60) Placebo (n=61)	181	Valdecoxib showed a considerably lower risk of developing upper gastrointestinal ulceration compared to naproxen	15
Osteoarthritis	Randomized, double-blind, multicenter	Valdecoxib, 5 mg od x 12 wk (n=201) Valdecoxib, 10 mg od x 12 wk (n=206) Valdecoxib, 20 mg od x 12 wk (n=202) Naproxen, 500 mg bid x 12 wk (n=205) Placebo (n=205)	1019	Valdecoxib 10 and 20 mg was as effective as naproxen 500 mg bid in the treatment of localized osteoarthritis and better tolerated, with a safety profile comparable to that of placebo, particularly regarding the risk for gastrointestinal ulcers	16, 17, 20
Osteoarthritis	Double-blind, multicenter	Valdecoxib, 10 mg po od x 12 wk (n=189) Valdecoxib, 20 mg po od x 12 wk (n=198) Ibuprofen, 800 mg po tid x 12 wk (n=184) Diclofenac, 75 mg po bid x 12 wk (n=187) Placebo (n=178)	936	Valdecoxib showed a significantly lower risk of upper gastrointestinal ulcers than ibuprofen and diclofenac in patients with osteoarthritis	18, 25
Osteoarthritis	Randomized, double-blind, multicenter	Valdecoxib, 0.5 mg po bid x 6 wk Valdecoxib, 1.25 mg po bid x 6 wk Valdecoxib, 2.5 mg po bid x 6 wk Valdecoxib, 5 mg po bid x 6 wk Valdecoxib, 10 mg po bid x 6 wk Valdecoxib, 10 mg po od x 6 wk Naproxen, 500 mg po bid x 6 wk Placebo	642	Valdecoxib was well tolerated and doses of 5 mg bid and 10 mg od or bid showed similar efficacy to naproxen in patients with symptomatic knee osteoarthritis	19
Osteoarthritis	Randomized, double-blind, multicenter	Naproxen, 500 mg bid x 12 wk (n=118) Valdecoxib, 5 mg od x 12 wk (n=120) Valdecoxib, 10 mg od x 12 wk (n=111) Placebo (n=118)	467	Valdecoxib 10 mg was well tolerated and as effective as naproxen and more effective than valdecoxib 5 mg and placebo for the treatment of symptomatic hip osteoarthritis	21, 22, 50
Osteoarthritis	Randomized, double-blind, multicenter	Valdecoxib, 10 mg od x 12 wk (n=111) Naproxen, 500 mg bid x 12 wk (n=118) Placebo (n=117)	346	Several symptom scale scores revealed that valdecoxib was as effective as naproxen in the treatment of hip osteoarthritis	23
Osteoarthritis	Randomized, double-blind, multicenter	Valdecoxib, 10 mg od x 12 wk (n=204) Valdecoxib, 20 mg od x 12 wk (n=219) Ibuprofen, 800 mg tid x 12 wk (n=207) Diclofenac, 75 mg bid x 12 wk (n=212) Placebo (n=210)	1052	Compared to ibuprofen and diclofenac, valdecoxib was as effective in improving the symptoms of patients with osteoarthritis and was associated with a lower incidence of gastrointestinal ulcers	24
Osteoarthritis	Randomized, double-blind, multicenter	Valdecoxib, 10 mg po od x 12 wk (n=200) Valdecoxib, 20 mg po od x 12 wk (n=217) Ibuprofen, 800 mg po tid x 12 wk (n=203) Diclofenac, 75 mg po bid x 12 wk (n=207)	827	Valdecoxib (at both 10 and 20 mg po od) was more effective than ibuprofen and diclofenac in terms of dyspepsia-related health, and showed less pain intensity in the SODA questionnaire in patients with symptomatic osteoarthritis	26

Continuation

Table VIII (Cont.): Clinical studies of valdecoxib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Osteoarthritis, rheumatoid arthritis	Randomized, double-blind, multicenter	Valdecoxib, 20 mg bid x 14 wk (n=345) Valdecoxib, 40 mg bid x 14 wk (n=355) Naproxen, 500 mg bid x 14 wk (n=364)	1064	Compared to naproxen, valdecoxib at doses of 20 or 40 mg bid was associated with a lower incidence of gastroduodenal ulcers in patients with osteoarthritis or rheumatoid arthritis	27, 30
Osteoarthritis, rheumatoid arthritis	Randomized, double-blind, multicenter	Valdecoxib, 1-5 mg po od x 6-12 wk (n=292) Valdecoxib, 10 mg po od x 6-12 wk (n=416) Valdecoxib, 20 mg po od x 6-12 wk (n=315) Valdecoxib, 40 mg po od x 6-12 wk (n=120) Placebo (n=399) Conventional NSAIDs, po od x 6-12 wk (n=459)	2001	Valdecoxib resulted in a lower incidence of gastroduodenal ulcers in comparison with conventional NSAIDs in elderly patients	28
Osteoarthritis, rheumatoid arthritis	Pooled/ meta-analysis	Valdecoxib, 5-80 mg od x 12-26 wk (n=4362) Naproxen, 500 mg bid x 12-26 wk (n=1181) Diclofenac, 75 mg bid x 12-26 wk (n=711) Ibuprofen, 800 mg tid x 12-26 wk (n=207) Placebo (n=973)	7434	The incidence of clinically significant ulcer complications was similar with valdecoxib or placebo and lower than with traditional NSAIDs in patients with osteoarthritis or rheumatoid arthritis	31
Osteoarthritis, rheumatoid arthritis	Randomized, double-blind, pooled/ meta-analysis	Valdecoxib, 10 mg od x 12 wk (n=751) Valdecoxib, 20 mg od x 12 wk (n=632) Naproxen, 500 mg bid x 12 wk (n=766) Placebo	2149	Valdecoxib was as effective and well tolerated as naproxen in patients with osteoarthritis or rheumatoid arthritis	32
Rheumatoid arthritis	Randomized, double-blind, multicenter	Valdecoxib, 10 mg od x 12 wk (n=209) Valdecoxib, 20 mg od x 12 wk (n=212) Valdecoxib, 40 mg od x 12 wk (n=221) Naproxen, 500 mg bid x 12 wk (n=226) Placebo (n=222)	1090	Valdecoxib at daily doses of 10, 20 or 40 mg was better than placebo and as effective as naproxen in patients with rheumatoid arthritis. Valdecoxib was well tolerated and at lower levels was associated with a lower incidence of abdominal pain, dyspepsia and constipation compared to naproxen	33, 34, 37
Rheumatoid arthritis	Randomized, double-blind, multicenter	Valdecoxib, 20 mg po od x 26 wk (n=246) Valdecoxib, 40 mg po od x 26 wk (n=237) Diclofenac-SR, 75 mg po bid x 26 wk (n=239)	722	Valdecoxib (20-40 mg od) was as effective as diclofenac for the treatment of rheumatoid arthritis, but with a superior gastrointestinal tolerability. The valdecoxib 40-mg dose did not provide additional benefit over the 20-mg dose	35
Rheumatoid arthritis	Pooled/ meta-analysis	Valdecoxib, 10 mg od x 12 wk (n=435) Valdecoxib, 20 mg od x 12 wk (n=431) Naproxen, 500 mg bid x 12 wk (n=444)	1310	Valdecoxib at a daily dose of 10 or 20 mg was more effective than placebo in patients with rheumatoid arthritis	36
Arthropathy	Randomized, double-blind, multicenter	Valdecoxib, 20 mg po bid x 48 h + Morphine, 2 mg iv (until establishment of pain control) (n=73) Valdecoxib, 40 mg po bid x 48 h + Morphine, 2 mg iv (until establishment of pain control) (n=73) Placebo + Morphine, 2 mg iv (until establishment of pain control) (n=71)	217	Valdecoxib was well tolerated and reduced the amount of morphine needed in the management of pain in patients undergoing hip arthroplasty	46

once daily and 10 mg b.i.d. were the most effective and showed comparable efficacy to naproxen. No significant differences were observed among groups as regards adverse events (19).

A double-blind clinical trial that compared the efficacy of valdecoxib and naproxen in the treatment of patients with osteoarthritis of the hip established that valdecoxib at daily doses ranging from 5 to 20 mg was as effective as 500 mg b.i.d. of naproxen in improving the patients' symptoms. Valdecoxib also showed a better safety profile than naproxen, as the former was associated with a lower number of patients withdrawing from the study due to gastroduodenal ulcers (20).

Patients with osteoarthritis of the hip were randomized to receive valdecoxib (5 or 10 mg once daily), naproxen (500 mg b.i.d.) or placebo for 12 weeks. At the

end of the treatment, both the Patient's Global Assessment of Arthritis score and the Physician's Global Assessment of Arthritis score decreased significantly more after administration of valdecoxib or naproxen than with placebo. Valdecoxib 10 mg/day was better than valdecoxib 5 mg/day and equivalent to naproxan 500 mg. Both doses were well tolerated (21, 22).

Results of a multicenter, randomized, double-blind study in patients with moderate or severe osteoarthritis of the hip showed that treatment for 12 weeks with valdecoxib at 10 or 20 mg once daily was as effective as naproxen 500 mg b.i.d. in improving symptoms (23).

A double-blind, randomized, placebo-controlled clinical trial that included a total of 1,052 patients reported that valdecoxib (10 or 20 mg once daily) was as effective as ibuprofen (800 mg t.i.d.) or diclofenac (75 mg b.i.d.) in improving the symptoms of osteoarthritis but was associated with a lower incidence of GI ulcers and symptoms (24).

The risk of upper GI ulcers was determined in 936 osteoarthritis patients taking valdecoxib 10 or 20 mg once daily, ibuprofen 800 mg t.i.d., diclofenac sodium 75 mg b.i.d. or placebo in a randomized, double-blind, placebo-controlled study. Endoscopy evaluations at 12 weeks showed that the incidence of gastroduodenal, gastric and duodenal ulcers was significantly lower in patients receiving valdecoxib or placebo (25).

The Severity of Dyspepsia Assessment (SODA) Questionnaire was used in a double-blind, placebo-controlled, parallel study to compare the effects of valdecoxib (10 or 20 mg once daily), ibuprofen (800 mg t.i.d.) and diclofenac (75 mg b.i.d.) on dyspepsia-related health of patients suffering from osteoarthritis. Patients receiving either dose of valdecoxib showed better dyspepsia-related scores and lower pain scores than those treated with the other study drugs (26).

Results of a multicenter, double-blind, parallel-group study involving 1,217 patients with osteoarthritis or rheumatoid arthritis showed that long-term treatment with suprathreshold doses of valdecoxib (40 mg b.i.d. for 14 weeks, *i.e.*, 2-4-fold greater than the optimal dose for arthritis) had a significantly lower risk of gastroduodenal ulcers than naproxen (500 mg b.i.d. for 14 weeks). The overall rates of ulcers for all patients were 66% in the naproxen group and 27% and 15%, respectively, in groups receiving 20 and 40 mg valdecoxib. There was no significant difference in ulcer rates between the groups receiving different doses of valdecoxib. A significantly higher incidence of ulcers was seen in the osteoarthritis subpopulation receiving 40 mg as compared to 20 mg valdecoxib (16% *vs.* 6%). However, these rates were still significantly lower than the rate obtained for osteoarthritis patients treated with naproxen (36%) (27).

Analysis of pooled data from 7 randomized, double-blind, placebo-controlled trials comparing valdecoxib (10-20 mg) with NSAIDs in patients with osteoarthritis and rheumatoid arthritis revealed significantly lower incidences of gastroduodenal ulcers in patients under 65 (3.5% *vs.* 8.6%) and over 65 (4.6% *vs.* 18%) years of age. Furthermore, a low incidence of cardiovascular events and renal adverse events was associated with therapeutic doses of valdecoxib (28). A meta-analysis of 10 clinical trials was undertaken to compare the GI safety and tolerability of valdecoxib, NSAIDs and placebo in osteoarthritis and rheumatoid arthritis patients. The incidence of GI events was similar between placebo and valdecoxib and was significantly lower with valdecoxib than with nonselective NSAIDs. The safety findings were true for patients above and below 55 years of age (29).

The incidence of gastroduodenal ulcers in 1,064 patients with osteoarthritis or rheumatoid arthritis was found to be lower after treatment for 14 weeks with valdecoxib (20 or 40 mg b.i.d.) than with naproxen (500 mg b.i.d.) (30).

A total of 8 clinical trials randomized 7,434 patients with osteoarthritis or rheumatoid arthritis to receive valdecoxib (5-80 mg daily), NSAIDs (naproxen, diclofenac or ibuprofen) or placebo for 12-26 weeks. The incidence of clinically significant upper GI complications was lower with placebo or valdecoxib than with the NSAIDs (31).

Pooled data from 4 randomized, double-blind, placebo-controlled studies demonstrated that treatment for 12 weeks with valdecoxib at 10 or 20 mg once daily was as effective as naproxen 500 mg b.i.d. in improving the symptoms of both elderly (65 years and over) and nonelderly (< 65 years) patients with osteoarthritis or rheumatoid arthritis (32).

The response rate among patients with rheumatoid arthritis after administration of daily doses of 10-40 mg of valdecoxib for 12 weeks was similar to the rate found with a daily dose of 500 mg b.i.d. of naproxen and significantly higher than with placebo. Lower valdecoxib dose levels were associated with a lower incidence of abdominal pain, dyspepsia and constipation compared to naproxen (33, 34).

A randomized, double-blind, parallel-group study conducted in patients with rheumatoid arthritis compared the efficacy of 20 or 40 mg of valdecoxib once daily to 75 mg diclofenac b.i.d. for 28 weeks. All therapeutic regimens gave similar efficacy scores. However, diclofenac was associated with a significantly higher incidence of GI ulcers (35).

Pooled data from 2 pivotal 12-week, randomized, double-blind, placebo-controlled studies showed that treatment with valdecoxib 10 or 20 mg once daily was as effective as naproxen 500 mg b.i.d. in improving the symptoms in rheumatoid arthritis patients who were being treated with highly effective DMARDs such as etanercept and methotrexate (36).

A multicenter, randomized, double-blind clinical trial compared the safety and efficacy of valdecoxib (10, 20 or 40 mg once daily), naproxen (500 mg b.i.d.) or placebo in a population of 1,090 patients with rheumatoid arthritis. After 12 weeks of treatment, both naproxen and valdecoxib were well tolerated and consistently better than placebo in improving the pain scores and number of swollen joints of the patients (37).

The incidence of serious thrombotic events with valdecoxib treatment (10-80 mg/day) was compared to that with naproxen (500 mg b.i.d.) and placebo using data from 4 randomized trials enrolling a total of 3,218 patients with rheumatoid arthritis. No difference in the incidence of thrombotic events or myocardial infarction was found among treatment groups (38).

In a double-blind, placebo-controlled trial, 284 healthy adults received single-dose valdecoxib (10, 20, 40 or 80 mg) or placebo prior to surgery to remove 2 ipsilateral impacted third molars. Valdecoxib treatment was well tolerated and effectively relieved postoperative pain, with the 40-mg dose being more effective than the 10- or 20-mg doses. No additional analgesic effects were observed with the 80-mg dose (39).

The analgesic efficacy of valdecoxib 20 or 40 mg was compared with that of the combination of oxycodone 10 mg/acetaminophen 1000 mg or placebo in 2 randomized studies. A total of 406 patients undergoing oral surgery were included in the trials. With valdecoxib, the onset of analgesia was as rapid and the level of relief as high as with oxycodone/acetaminophen. The duration of the analgesic effect and tolerability were superior with valdecoxib, however (40).

Patients who had undergone surgical extraction of 2 or more third molars requiring bone removal were randomized to receive valdecoxib (40 mg) or rofecoxib (50 mg) for postsurgery pain relief. Significantly more rapid onset of analgesia, onset of pain relief and lower pain intensity were experienced by those patients administered valdecoxib. Additionally, fewer patients in the valdecoxib cohort required rescue medicine and were more satisfied overall with their study medication. Both drugs were equally well tolerated; the most common adverse events observed were headache, alveolar osteitis and nausea (41).

A randomized, double-blind study compared the efficacy of a single dose of 40 mg of valdecoxib, 50 mg of rofecoxib and placebo in patients with moderate or severe postoperative dental pain. Compared to placebo, both valdecoxib and rofecoxib induced significant and similar total pain relief at 6 h after administration. Valdecoxib was well tolerated and showed a faster onset of action than rofecoxib, with a greater improvement in pain intensity difference at 30 min after administration. The mean time to onset of analgesia was estimated to be 26 min with valdecoxib and 36 min with rofecoxib (42).

A crossover, randomized, double-blind clinical trial reported that a single dose of 20 or 40 mg of valdecoxib was significantly better than placebo and as effective as a single dose of 500 mg of naproxen in improving menstrual pain associated with primary dysmenorrhea. Valdecoxib was well tolerated (43, 44).

In a multicenter, double-blind, randomized study, 209 patients undergoing knee replacement surgery were randomized to receive valdecoxib (20 or 40 mg) or placebo as soon as they could tolerate oral medication following surgery, and subsequent doses at 12, 24 and 36 h after the first dose or until discontinuation of morphine. Morphine administration by a patient-controlled analgesic pump began following administration of study medication. Efficacy was assessed by measuring the total amount of morphine consumed over the first 24 and 48 h following the first dose of valdecoxib. Compared to placebo, overall during the 48 h postsurgery, morphine consumption by patients receiving valdecoxib 20 and 40 mg was reduced by 16.3% and 24.2%, respectively. Furthermore, a higher percentage of patients treated with valdecoxib plus morphine (79-84%) described their study medication as “good” or “excellent” compared with 70% of the placebo plus morphine patients. In addition, patients receiving valdecoxib 40 mg plus morphine reported greater reductions in pain intensity than those receiving placebo, even though those patients consumed more morphine. No significant differences were seen in the incidence of adverse events, although the incidence of fever was significantly higher among patients receiving morphine plus placebo compared to those given morphine plus valdecoxib (45).

In a multicenter, double-blind study that included 217 patients with primary hip arthroplasty, administration of valdecoxib at doses of 20 or 40 mg b.i.d. for 48 h reduced by an average of 40% the amount of morphine needed for postoperative pain relief (46, 47).

A single oral dose of valdecoxib (20, 40 or 80 mg) or placebo was administered to 223 patients prior to undergoing bunionectomy. Postoperative pain was effectively relieved by valdecoxib, especially with the higher doses. The treatment was well tolerated (48).

Valdecoxib administered as single oral doses ranging from 10-80 mg was reported to be safe and effective in providing anesthesia to patients suffering from mild or moderate postoperative pain after oral surgery or bunionectomy (49).

A multicenter, double-blind clinical trial compared the safety and tolerability of naproxen (500 mg b.i.d.), valdecoxib (5 mg or 10 mg once daily) or placebo administered for 12 weeks to 467 patients with osteoporosis. Both doses of valdecoxib were better than placebo and as effective as naproxen in improving the symptoms of osteoporosis. The GI tolerance of valdecoxib was better than that of naproxen, as the percentage of patients who withdrew from the study due to GI adverse events was lower (4.2% and 4.5% with 5 and 10 mg of valdecoxib, respectively, compared to 11.0% with naproxen) (50).

A method for the treatment or prevention of chronic prostatitis or chronic pelvic pain syndrome containing a COX-2 inhibitor has been claimed. Exemplified COX-2 inhibitors are celecoxib, parecoxib, rofecoxib, valdecoxib, meloxicam, flosulide, nimesulide, etoricoxib, NS-398, DUP-697, SC-58125, SC-58635 and RS-57067 (51).

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