

Matrix metalloproteinase inhibitors in rheumatic diseases

D R Close

Abstract

The rheumatic diseases continue to represent a significant healthcare burden in the 21st century. However, despite the best standard of care and recent therapeutic advances it is still not possible to consistently prevent the progressive joint destruction that leads to chronic disability. In rheumatoid arthritis and osteoarthritis this progressive cartilage and bone destruction is considered to be driven by an excess of the matrix metalloproteinase (MMP) enzymes. Consequently, a great number of potent small molecule MMP inhibitors have been examined. Several MMP inhibitors have entered clinical trials as a result of impressive data in animal models, although only one MMP inhibitor, Ro32-3555 (Trocade), a collagenase selective inhibitor, has been fully tested in the clinic, but it did not prevent progression of joint damage in patients with rheumatoid arthritis.

The key stages and challenges associated with the development of an MMP inhibitor in the rheumatic diseases are presented below with particular reference to Trocade. It is concluded that the future success of MMP inhibitors necessitates a greater understanding of the joint destructive process and it is hoped that their development may be accompanied with clearer, more practical, outcome measures to test these drugs for, what remains, an unmet medical need.

(Ann Rheum Dis 2001;60:iii62–iii67)

Impact of joint destruction in the rheumatic diseases

One of the strongest predictors of long term outcome in rheumatoid arthritis (RA) and osteoarthritis (OA) is progressive structural joint damage. Because these diseases generally strike in the middle years, the chronicity leads to a gradual decline in the patients' ability to perform everyday functions, a gradual increase in disability, and, in many patients, major surgical intervention in an attempt to halt or partially reverse the process.^{1,2} The disability associated with progressive joint damage is costly, and in 1991 the annual cost of knee replacements in the USA alone was estimated to be in excess of a billion dollars.³ The association between work related disability and the degree of joint damage, as determined by radiographic outcome, has shown that patients with RA who have worse radiographic scores (stages III and IV) also have greater work related disability than those who have a lesser degree of joint damage (stages I and II).⁴

Consequently, protecting the patient from a loss of articular cartilage and erosion of bone at any point during the disease might be of benefit by reducing the level of future disability as well as reducing the overall economic burden to the healthcare providers. Thus much attention has now been focused on measuring the contribution of joint destruction in the rheumatic diseases and on joint destruction as a major target for therapeutic intervention.⁵

Traditional treatments for RA and OA predominantly deal with joint pain and inflammation, and although a number of these have subsequently been shown to slow joint damage in RA, there is essentially still no intervention that achieves the same result in OA. However, of the disease modifying antirheumatic drugs (DMARDs) commonly used in RA, van Riel *et al* reported that only methotrexate, sulfasalazine, and aurothioglucose significantly slowed the rate of joint destruction,⁶ and methotrexate, generally the DMARD of choice, could not completely prevent continued cartilage and bone loss.⁷ More recently, the addition of leflunomide to the rheumatologists' arsenal has provided an additional option in slowing joint destruction,^{8,9} despite its hepatic limitations. In addition, the emergence of the anti-tumour necrosis factor (anti-TNF) agents, etanercept and infliximab, and the interleukin 1 (IL1) receptor antagonist, anakinra, have all shown in pivotal trials that they can slow or even, in some cases, halt the joint destructive process. However, the safety of these treatments and effectiveness in comparison with traditional DMARDs in the long term are the main concerns about these innovative treatments for RA. In addition, low dose oral glucocorticoids are still one of the mainstays in treating rheumatic disease and their ability to retard joint damage has been confirmed,¹⁰ but even the combination of DMARDs and steroids is neither adequate nor specific in preventing rheumatic joint damage.

As the joint destructive mechanisms of RA and OA have become better understood, attention has focused on the development of new treatments that specifically target and inhibit this process. These have so far taken the form of small molecule, oral inhibitors of the matrix metalloproteinases (MMPs), the enzymes considered to be primarily responsible for cartilage and bone damage.

Clinical development of MMP inhibitors

MMPs IN THE RHEUMATIC DISEASES

The MMPs are a collective of over 20 zinc-containing endopeptidases that include the gelatinases, stromelysins, and collagenases, released as inactive zymogens and becoming

Department of Clinical Science, Roche Products Ltd, Broadwater Road, Welwyn Garden City, Hertfordshire AL7 3AY, UK
D R Close

david.close@roche.com

Accepted 28 June 2001

Table 1 Examples of MMP involvement in tissue remodelling in normal and pathological conditions. Adapted with permission from ref 12.

Normal	Pathological
Development	Rheumatoid arthritis
Wound healing	Osteoarthritis
Joint remodelling	Metastases
Tissue homeostasis	Periodontal disease
Ovulation	Angiogenesis
Trophoblast implantation	Emphysema
Postpartum uterus involution	Multiple sclerosis
	Left ventricular remodelling
	Aortic aneurysm

active only when the propeptide is cleaved. They have a key role in normal connective tissue remodelling and, therefore, their release, activation, and inhibition by their natural inhibitors—namely, α_2 -macroglobulin and the tissue inhibitors of metalloproteinases (TIMPs), are usually tightly regulated. The MMPs are constitutively expressed and between them can degrade all components of the extracellular matrix.¹¹ They have been implicated in a number of pathological conditions (table 1),¹² can be produced in response to the proinflammatory cytokines TNF and IL1,¹³ and are found in excess in the arthritic joint.¹⁴

It is considered that an imbalance between excessive levels of many of the MMPs, coupled with inadequate TIMP levels, facilitates the joint destructive process, and this has been demonstrated in both RA and OA cartilage extracts.¹⁵

One of the key requirements in developing an MMP inhibitor is determining the *in vivo* relevance of specific MMPs in a specific disease (table 2).¹⁶ Increased MMP-3 (stromelysin) has been reported to correlate with radiographic scores in RA.^{17, 18} In the MMP-3 knockout mouse, the cartilage and bone damage induced by collagen arthritis is comparable with that of the wild-type mouse,¹⁹ suggesting that specific inhibitors of this enzyme would be of no benefit; other stromelysin inhibitors have also failed to provide joint protection in animal models (Roche internal communication). In contrast, under normal physiological conditions, the collagenases (MMP-1, MMP-8, and MMP-13) are the only MMPs that can cleave collagen and may hold the key to pathological cartilage destruction. Indeed, MMP-1 has been shown to be present at the site of RA erosions.²⁰ Articular cartilage is constructed of fibrils of collagen triple helix (mainly collagen II) that form a fibrillar network supporting additional macromolecular structures such as the proteoglycans. The

integrity of this structure provides resistance to loading compressibility and tensile strength and can be maintained with a constant turnover of proteoglycan, whereas this is not the case with collagen fibres, which once damaged may lead to the permanent and progressive joint damage seen in RA and OA.²¹

Consequently, selectively inhibiting the collagenases, in particular with a new synthetic MMP inhibitor, would seem to be an attractive therapeutic objective.²²

SELECTING AN MMP INHIBITOR FOR A RHEUMATIC DISEASE

Many inhibitors of the MMPs have been synthesised over the past 15 years and have been extensively reviewed elsewhere.^{23–25} In addition to the rheumatic diseases, the main therapeutic focus of these inhibitors has been directed at preventing metastatic growth and related angiogenesis where MMPs are considered crucial.

Development of MMP inhibitors has been based on known interactions between the enzyme and their substrates/inhibitors in order to design molecules that specifically chelate the zinc ion and block the active site. These new inhibitors can be divided into carboxylates and amino-carboxylates, phosphinates, sulphhydryl derivatives, and hydroxamates, of which the hydroxamates are considered to possess the most potent zinc binding group. One problem has been the necessary subtlety of the MMP inhibition profile of these compounds. Because many of the MMPs related to disease are also expressed constitutively the key questions are:

- To what degree should they be inhibited to maintain an appropriate safety margin and would such a molecule be more efficacious if it possessed a broad spectrum of MMP inhibition?
- Alternatively, would this be best served by specifically targeting enzymes such as the collagenases that seem to facilitate the key irreversible step to joint destruction?

Both approaches have been used, although despite the variety of inhibitors so far produced, very few of these drugs have progressed into the clinic or to a stage at which these questions might be answered.

PRECLINICAL MODELS OF ARTHRITIS AND MMP INHIBITORS

For many of the MMP inhibitors developed for a number of indications, the animal model data have been extremely impressive. Not least of

Table 2 MMP association with rheumatic disease. Adapted with permission from ref 16

MMP group	Common nomenclature	Substrate	Rheumatic disease
Collagenases			
MMP-1	Fibroblast collagenase	Collagens I, II, III, VII, X	RA fibroblasts and erosion sites
MMP-8	Neutrophil collagenase	Collagens I, II, III	RA fibroblasts/OA cartilage
MMP-13	Collagenase 3	Collagens I, II, III	RA synovium/cartilage
Stromelysins			
MMP-3	Stromelysin 1	Proteoglycan, proMMP-1, 8, 9	RA, OA sera, and synovial fluid
MMP-10	Stromelysin 2	Aggrecan, gelatin	
MMP-11	Stromelysin 3	Weak stromelysin activity	
MMP-7	Matrilysin	Aggrecan, gelatin, fibronectin	OA cartilage
Gelatinases			
MMP-2	Gelatinase A	Gelatin, minor collagens, elastin	Synovium, femoral head lesions.
MMP-9	Gelatinase B	Gelatin, minor collagens	Raised in RA sera and synovial fluid

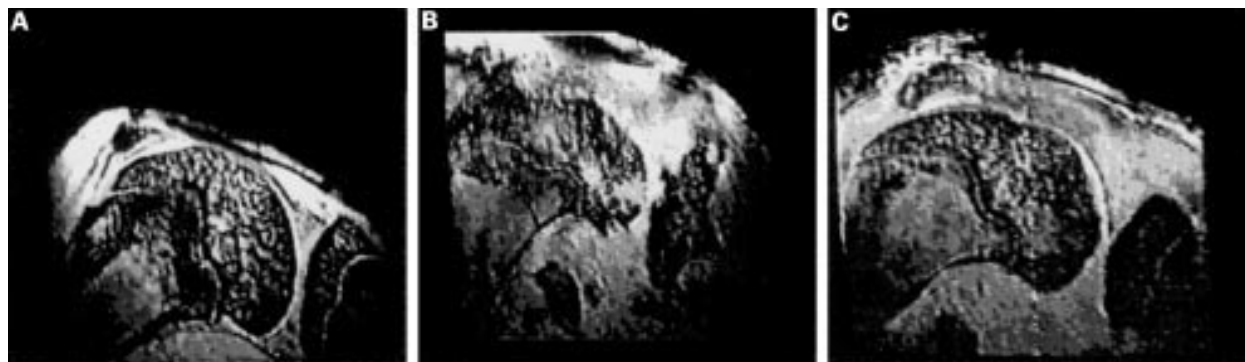


Figure 1 Prevention of joint damage by the MMP inhibitor, Trocade: magnetic resonance imaging of the rabbit knee *P acnes* model. (A) Normal control; (B) arthritic control, illustrating cartilage/bone damage and synovitis; (C) arthritic knee + Trocade, illustrating protection of cartilage/bone despite synovitis.

these MMP inhibitors is Trocade (Ro32-3555)—a hydroxamic acid that selectively inhibits the collagenases (MMP-1 $K_i=3.0$ nM, MMP-8 $K_i=4.4$ nM, MMP-13 $K_i=3.4$ nM) and has relatively low activity against other MMPs (MMP-3 $K_i=527$ nM, MMP-2 $K_i=154$ nM, MMP-9 $K_i=95$ nM, MMP-7 $K_i=42$ nM). Trocade has been shown to prevent IL1 mediated degradation of bovine cartilage in vitro, while in vivo it provides significant cartilage protection in the rat sponge/cartilage mycobacterium adjuvant model. Perhaps the most impressive preclinical data are the effect of Trocade in a *P acnes* induced model of RA in both the rat and rabbit.²⁶ In this model, sensitization is performed by intra-articular injection of *P acnes*, followed by rechallenge four weeks later, and over the following two weeks an acute destructive synovitis develops.

Figure 1 shows the magnetic resonance imaging (MRI) scan of a rabbit knee of a normal control; the *P acnes* control, illustrating synovitis, cartilage, and bone erosions; and the ability of 50 mg/kg/day of Trocade to prevent both articular cartilage and bone destruction despite the continuing synovitis. These data provide strong evidence of the potential for MMP inhibitors to treat continuing rheumatic tissue destruction but also highlight the fact that they would not be expected to affect the inflammatory process (seen in figs 1B and C as the opaque background), which would have to be controlled by additional treatments.

The efficacy of Trocade has also been shown in the ST/ORT mouse model of OA.²⁷ In this model oral dosing with Trocade prevented the characteristic cartilage and bone changes, as shown by histological analysis and radiographic imaging.

Ro113-0830 is another MMP inhibitor that when given orally has shown preclinical efficacy, this time by the prevention of cartilage damage in the rabbit meniscectomy OA model.²⁸ The inhibition profile of this compound differs from Trocade as it does not inhibit MMP-1 but is effective against MMP-8, MMP-13 and several additional MMPs, including MMP-2 and MMP-9.

If one considers that these preclinical models reflect the human pathological mechanism, then it provides strong evidence that the collagenases at least play a significant part in joint

destruction, which would benefit from such an MMP inhibitor.

Clinical development of MMP inhibitors in rheumatic disease

PHARMAKOKINETICS

The early development of MMP inhibitors was greatly restricted by a lack of oral bioavailability. An example of this was the broad spectrum inhibitor, batimastat (BB94), developed for oncology, which owing to its poor solubility had to be given by intraperitoneal injection.²⁵ Consequently, this compound was replaced by marimastat (BB2516), also a broad spectrum inhibitor with improved oral bioavailability, but still at a low 10%. In contrast, the more recent Bay-12-9566, another relatively broad spectrum inhibitor with activity against gelatinase and stromelysin, developed in both oncology and OA, has an oral bioavailability in excess of 80%. Moreover, this compound has been shown to be present in synovial fluid on daily dosing of 10 and 25 mg.²⁹ The progress in designing MMP inhibitors with good pharmacokinetics is reflected in the study by Hemmings *et al*, detailing the multiple ascending dose study with Trocade in patients with RA.³⁰ This was a four week study with doses of between 25 and 150 mg given once daily. Trocade maximal absorption was achieved within three hours of dosing and demonstrated a terminal half life of 24–28 hours, with no accumulation. The free trough levels of once daily Trocade at all doses indicated that the IC_{50} for collagenase would be met throughout a 24 hour period, suggesting that efficacy would be achieved at these exposures.

RADIOGRAPHIC OUTCOME ASSESSMENT

There are a number of challenges in the clinical evaluation of these compounds. Essentially, the task is to measure structural damage, and whether or not the chosen MMP inhibitor can significantly prevent it. Radiographic imaging is currently the only validated method for assessing structural damage. For RA, these radiographs tend to be of the hands and feet and scored using the Sharp or Larsen scales. For OA, radiographic outcome may be measured using the 1995 OARS atlas for joint space narrowing as a measure of cartilage loss and osteophytes of the knees, and joint space

narrowing, osteophytes, and erosions for affected joints of the hands. Rates of progression vary greatly between patients, which means that large patient numbers are needed, possibly in excess of 200 for each arm of the trial. In addition, to evaluate the effectiveness of an MMP inhibitor over time, the expected rate of progression has to be estimated in order to assess the sample size as well as the target profile for the inhibitor to prevent progression.

A realistic study length is also needed, over which significant radiographic progression is expected to occur. Currently, the minimum required duration of pivotal trials for a label claim of prevention of structural damage is one year for RA and two for OA. Logistically, these studies require a large number of trial centres and, crucially for the assessment of radiographic outcome, the equipment and techniques for obtaining them must be standardised. Efficacy of the MMP inhibitor depends on comparing the follow up and baseline radiographs in a blinded manner. This is best achieved by using a single central facility with a team of validated readers to ensure consistency of radiographic scoring and minimal variability, especially as the expected progression of joint damage over one or two years may be minimal. At this point it would be pertinent to mention MRI as a promising replacement for radiographs. The prospect is that MRI may be more sensitive over time to continuing joint damage and may reduce the duration of trials and the patient numbers required. However, MRI facilities are not always readily available and the technique is not, as yet, validated.

BIOCHEMICAL MARKERS OF STRUCTURAL DAMAGE

Much work has also been carried out in attempting to define specific and sensitive surrogate biochemical markers of disease progression.¹⁸⁻³¹ Ultimately, these may help predict which patients have continuing joint disease, and reduce the need to obtain radiographs or be a more cost effective method of determining whether treatment is effective. Many biochemical entities, including the MMPs themselves, have been suggested to fulfil this role. However, clearly, much work still needs to be done before this objective is achieved.

CONCURRENT RA TREATMENT DURING MMP INHIBITOR TRIALS

Because MMP inhibitors do not influence the inflammatory or pain components of these diseases (TACE, the closely related metalloproteinase TNF convertase inhibitor, is not included here), trials have to be conducted in patients who still require their normal background drug treatment, which in the case of RA, in particular, may also affect the radiographic outcome of the trial. Consequently, these trials require that patients continue to receive stable DMARD treatment, with prescribing guidelines and even stratification and covariate analysis for clinically required oral steroids during the study. Realistically, a drug that the patient feels has no short term benefit may not only affect compliance during the trial but also may heavily influence whether the patient is willing to continue

in a long term trial, which is needed for an MMP inhibitor development.

Further to this, MMP inhibitors, as with some traditional RA treatments such as methotrexate, are likely to be teratogenic. Thus counselling is required and reliable contraceptive use in female patients and male patients with partners of child bearing potential.

REGULATORY ISSUES

Although preventing structural joint damage is now a recognised goal of rheumatic disease treatment, there is still a great deal of debate over how this translates into clinical benefit for the patient. The long term objective is evident, in that the structural integrity of the joints, and therefore the function of the affected joints, will be maintained in the patient treated effectively. This is especially the case in later stage disease, and particularly in RA where the disability becomes more related to the degree of joint damage rather than synovitis, as in early disease. Essentially, this means that radiographic scores and the effect that an MMP inhibitor may have in retarding their progression is considered to be a surrogate for long term benefit. Consequently, if an MMP inhibitor is approved based on radiographic data, then trials would be expected to continue to prove that the prevention of joint damage shown by the radiograph prevents disability. This may require a study duration of five or more years. If the study is a comparator trial it may be difficult to retain patient numbers should the drug be approved and become available during the lifetime of these trials. This in turn may compromise the chances of achieving the primary endpoint owing to too few patient numbers.

TRIAL FINDINGS WITH MMP INHIBITORS: EFFICACY

Despite the amount of activity in this therapeutic approach, few MMP inhibitors have entered clinical trials and none of these have been successful. Trocade is the only MMP inhibitor to have completed clinical trials designed to assess its efficacy. However, despite the preclinical data and favourable pharmacokinetics the radiographic scores of the patients with RA were not improved. These observations led to the termination of Ro113-0830 studies in OA.

TRIAL FINDINGS WITH MMP INHIBITORS: SAFETY

Bay-12-9566 was being developed for use in oncology and OA, but all studies were stopped as a result of safety data from the oncology trials.³²

Clinical trials with an earlier broad spectrum inhibitor MMP inhibitor, Ro31-9790, were stopped once preclinical evidence of tendinitis was found. Interestingly marimastat, also a broad spectrum MMP inhibitor, has been associated with dose dependent musculoskeletal toxicity in oncology patients as shown by stiffness and pain of the joints, particularly the shoulders and hands.³³⁻³⁴ It has been suggested that specific MMPs are responsible for these events, though no musculoskeletal problems were reported during clinical development with either Trocade or Bay-12-9566, MMP

inhibitors of differing profiles, and the mechanism responsible remains unclear.

To date the only available drug considered to have inhibitory activity against the MMPs is tetracycline, licensed as periostat for periodontal disease. However, clinical trials in RA failed to show a significant difference between minocycline and placebo on the progression of joint damage, though some positive trends were identified.³⁵

Future of MMP inhibitors in the rheumatic diseases

A more complete understanding of the joint destructive process and the identity of the relevant MMPs and non-MMPs that are directly responsible holds the key to the future development of MMP inhibitors in the rheumatic diseases. This may yet require a more subtle approach, in that additional enzymes such as the cathepsins, and any feedback mechanisms involving the MMPs, their inhibitors and, possibly, non-MMPs, may need to be considered as a whole before we can find an MMP inhibitor that proves clinically effective in each of the target diseases.

Moreover, we should also continue to question the validity of the animal models used to test these compounds, as highlighted by the failure of Trocade to replicate the preclinical efficacy in patients with RA, and use histological techniques to establish that the chosen inhibitor can reach and inhibit its target at the pathological interface.

The complex issues of clinical development of MMP inhibitors in rheumatic diseases and assessing outcome bring their own challenges. These would be helped significantly if measurement of joint damage could be made by more sensitive methods, such as MRI, which may reduce study duration, sample size, and interpatient variability. However, the absolute relevance of prevention of structural joint damage as a surrogate marker of functional benefit to the patient remains, though considerable efforts are being made to interpret fully the value of such outcome measures, which will hopefully resolve some of the concerns of rheumatologists and the regulatory authorities.

As we progress through the decade of bone and joint, we should perhaps take a new look at the possibilities for an MMP inhibitor to treat rheumatic diseases because we are still faced with a significant gap in the rheumatologists' therapeutic armamentarium.

I thank my Roche colleagues, Tim Shaw and Randall Stevens, for their contributions to this manuscript.

- 1 Paulus HE, van der Heijde DMFM, Bulpitt KJ, Gold RH. Monitoring radiographic changes in early rheumatoid arthritis. *J Rheumatol* 1996;23:801-5.
- 2 Scott DL, Adebajo AO, El-Badaway S, Kirwan JR, van de Putte LBA, van Riel PLCM. Disease controlling anti-rheumatic therapy: preventing or significantly decreasing the rate of progression of structural damage. *J Rheumatol Suppl* 1994;41:36-40.
- 3 Quam JP, Mitchet CJ, Wilson MG, Ilstrup DM, Melton LJ, Walrichs SL. Total knee arthroplasty: a population-based study. *Mayo Clin Proc* 1991;66:589-95.
- 4 Meenan RF, Yelin EH, Nevitt M, Epstein WV. The impact of chronic disease: a sociomedical profile of rheumatoid arthritis. *Arthritis Rheum* 1981;24:544-9.

- 5 GREES Report. Recommendations for the registration of drugs used in the treatment of rheumatoid arthritis. *Br J Rheumatol* 1998;37:211-15.
- 6 Van Riel PLCM, van der Heijde DMFM, Nuver-Zwart IH, van de Putte LBA. Radiological progression in rheumatoid arthritis: results of 3 comparative trials. *J Rheumatol* 1995;22:1797-9.
- 7 Weinblatt ME, Trentham DE, Fraser PA, Holdsworth DE, Falchuk KR, Weissman BN, et al. Long-term prospective trial of low dose methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;31:167-75.
- 8 Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multi-centre trial. European Leflunomide Study Group. *Lancet* 1999;353:259-66.
- 9 Schiff M, Kaine J, Sharp J, Strand V. X-ray analysis of 12 months treatment of active rheumatoid arthritis with leflunomide compared to placebo or methotrexate [abstract]. *Arthritis Rheum* 1998;41(suppl):S155, abstr 736.
- 10 Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. *N Engl J Med* 1995;133:142-6.
- 11 Woessner JF Jr. Matrix metalloproteinases and their inhibitors in connective tissue remodeling. *FASEB J* 1991;5:2145-54.
- 12 Stevens R. Presentation; ACR 2000: State of the art review of matrix metalloproteinase inhibitors (oral presentation).
- 13 Krane SM, Amento EP, Goldring MB, Goldring SR, Stephenson ML. In: Glavert AM, ed. *Research monographs in cell and tissue physiology*. Vol 15. Amsterdam: Elsevier, 1988:179-95.
- 14 Brinckerhoff CE. Joint destruction in arthritis: metalloproteinase in the spotlight. *Arthritis Rheum* 1991;34:1073-5.
- 15 Martel-Pelletier J, Fujimoto N, Obata K, Cloutier J-M, Pelletier J-P. The imbalance between the synthesis level of metalloproteinases and TIMPs in osteoarthritic and rheumatoid arthritis cartilage can be enhanced by interleukin-1 [abstract]. *Arthritis Rheum* 1993;36(suppl 9):S191.
- 16 Shaw T. Inhibition of matrix metalloproteinases in rheumatoid arthritis. In: Wolheim F, Firestein G, Panayi G, eds. *Rheumatoid arthritis: the new frontiers in pathogenesis and treatment*. Oxford: Oxford University Press, 2000: 551-6.
- 17 Posthumus MD, Limburg PC, Westra J, van Leeuwen MA, van Rijswijk MH. Serum matrix metalloproteinase 3 in early rheumatoid arthritis is correlated with disease activity and radiological progression. *J Rheumatol* 2000;27:2761-8.
- 18 Roux-Lombard P, Eberhardt K, Saxne T, Dayer JM, Wollheim FA. Cytokines, metalloproteinases, their inhibitors and cartilage oligomeric matrix protein: relationship to radiological progression and inflammation in early rheumatoid arthritis. A prospective 5-year study. *Rheumatology (Oxford)* 2001;40:544-51.
- 19 Mudgett JS, Hutchinson NI, Chartrain NA, Forsyth AJ, McDonnell J, Singer II, et al. Susceptibility of stromelysin 1-deficient mice to collagen-induced arthritis and cartilage destruction. *Arthritis Rheum* 1998;41:110-21.
- 20 Woolley DE, Crossley MJ, Evanson JM. Collagenase at sites of cartilage erosion in the rheumatoid joint. *Arthritis Rheum* 1977;20:5625-8.
- 21 Campion GV, Hardington TE. Articular cartilage. In: Maddison P, Isenberg D, Woo P, Glass D, eds. *Oxford textbook of rheumatology*. Oxford: Oxford University Press, 1993:233-41.
- 22 Vincenti MP, Clark IM, Brinckerhoff CE. Using inhibitors of metalloproteinases to treat arthritis. Easier said than done? *Arthritis Rheum* 1994;37:1115-26.
- 23 Bottomley KM, Johnson WH, Walter DS. Matrix metalloproteinase inhibitors in arthritis. *J Enzyme Inhib* 1998;13:79-101.
- 24 Becket PR, Whittaker M. Matrix metalloproteinase inhibitors. *Expert Opinion in Therapeutic Patents* 1998;8:259-82.
- 25 Morphy JR, Millican TA, Porter JR. Matrix metalloproteinase inhibitors: current status. *Curr Med Chem* 1995;2:743-762.
- 26 Lewis EJ, Bishop J, Bottomley KMK, Bradshaw D, Brewster M, Broadhurst MJ, et al. Ro 32-3555, an orally active collagenase inhibitor, prevents cartilage breakdown in vitro and in vivo. *Br J Pharmacol* 1997;121:540-6.
- 27 Brewster M, Lewis EJ, Wilson KL, Greenham AK, Bottomley KMK. Ro 32-3555, an orally active collagenase selective inhibitor prevents structural damage in the STR/ORT mouse model of osteoarthritis. *Arthritis Rheum* 1998;41:1639-44.
- 28 Lollini L, Haller J, Eugui EM, Womble SW, Martin R, Campbell J, et al. Disease modification by RS-130830, a collagenase-3 selective inhibitor, in experimental osteoarthritis (OA) [abstract]. *Arthritis Rheum* 1997;40(suppl):S87, abstr 341.
- 29 Sunndaresan PR, Shah A, Heller AH. Penetration of Bay-12-9566 in synovial fluid and effect of age and gender on the pharmacokinetics of Bay-12-9566. Annual meeting of the American Society of Clinical Pharmacology 1998:1-129.
- 30 Hemmings FJ, Farhan M, Rowland J, Banken L, Jain R. Tolerability and pharmacokinetics of the collagenase-selective inhibitor Trocade™ in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2001;40:537-43.

- 31 Wollheim FA. Serum markers of articular cartilage damage and repair. *Rheum Dis Clin North Am* 1999;25:417-32.
- 32 Hughes S. Bayer drug casts shadow over MMP inhibitors in cancer. *Scrip* 1999;2477:20.
- 33 Rasmussen HS, McCann PP. Matrix metalloproteinase inhibition as a novel anticancer strategy: a review with special focus on batimastat and marimastat. *Pharmacol Ther* 1997;75:69-75.
- 34 Nemunaitis J, Poole C, Primrose J, Rosemurgy A, Malfetano J, Brown P, *et al*. Combined analysis of studies of the effects of the matrix metalloproteinase inhibitor marimastat on serum tumor markers in advanced cancer: selection of a biologically active and tolerable dose for longer-term studies. *Clin Cancer Res* 1998;4:1101-9.
- 35 Bluhm GB, Sharp JT, Tilley BC, Alarcon GS, Cooper SM, Pillemer SR, *et al*. Radiographic results from the minocycline in rheumatoid arthritis (MIRA) trial. *J Rheumatol* 1997;24:1295-302.



Direct Access to Medline

Medline

Link to Medline from the homepage and get straight into the National Library of Medicine's premier bibliographic database. Medline allows you to search across 9 million records of bibliographic citations and author abstracts from approximately 3,900 current biomedical journals.

www.annrheumdis.com