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ABSTRACTS

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Contents

I: Mechanisms and Treatment of Rheumatoid Arthritis

I-1: Evidence for the effects of infliximab

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Infliximab is a chimeric human/mouse anti-TNF-α monoclonal antibody composed of the constant regions of human IgG1-κ

coupled to the Fv region of a neutralizing mouse antihuman TNF-α antibody. Infliximab, in combination with methotrexate (MTX), is approved for use for reducing signs and symptoms and inhibiting the progression of structural damage in patients with moderate to severe rheumatoid arthritis (RA) with an inadequate response to MTX. It is also licensed for therapy of refractory moderately to severely active Crohn's disease. Moreover, it also appears to be highly efficacious in psoriatic arthritis and ankylosing spondylitis.

Infliximab was the first TNF-blocker investigated in a controlled clinical trial. In this early trial, it was shown to be highly efficacious as a monotherapy in patients who had failed multiple disease-modifying antirheumatic drugs (DMARDs). Subsequent trials analyzed its efficacy as an add-on therapy to MTX in patients who had insufficient response to a DMARD. The most comprehensive of these trials was the ATTRACT study, in which patients with insufficient response to MTX were randomized to receive either placebo or infliximab at four different regimens: 3 mg/kg every 4 or every 8 weeks, or 10 mg/kg every 4 or every 8 weeks. After 1 year of therapy, ACR 20 responses averaged 52% across the doses investigated (range 42%–59%), while on placebo added to preexisting, inadequate MTX therapy the response was only 17%. Radiographic progression, as assessed by a modified Sharp score, amounted to a mean progression of 7.0 in the control group, while it ranged from −0.7 to 1.6 in the groups receiving infliximab. This result is one of the most profound ever published, and reveals the significant disease-modifying effects of infliximab.

In addition to the data on RA, data from open trials on psoriatic arthritis and controlled trials on ankylosing spondylitis will also be presented. Data on toxicity will be mentioned only briefly, since they are part of another presentation.

In summary, infliximab is a highly active disease-modifying biologic with significant clinical and structural efficacy in RA, and has greatly expanded the therapeutic possibilities, particularly in patients in whom other agents were insufficiently effective.

I-2: Infliximab in the clinic and insights into its mode of action

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Infliximab (Remicade, Centocor), a chimeric monoclonal anti-TNF-α – specific antibody with neutralizing activity,[1] is licenced in North America and Europe for the treatment of rheumatoid arthritis (RA). In combination with methotrexate (MTX), its anti-inflammatory activity is sustained and augmented,[2] and an effective reduction of signs and symptoms, and of C-reactive protein, of up to 70% from the baseline is achieved.[3] The ACR 20 response is maintained in about 50% of patients for 2 years under randomized blind-trial conditions (the ATTRACT trial[4]).

In the target population of patients with active RA, despite treatment with multiple standard disease-modifying antirheumatic drugs (DMARDs), infliximab in addition to ongoing treatment with MTX showed remarkable inhibition of the progression of joint-space narrowing (cartilage damage) and bone erosions assessed by serial radiographs at the end of 54 weeks of treatment.[5] In contrast, in patients receiving placebo infusions and methotrexate, progressive joint damage was observed. In 39%–54% of patients, a negative change from baseline X-rays indicated complete arrest, or even reversal of damage, in infliximab-treated patients versus in 14% of patients receiving placebo and methotrexate.

These clinical trial data demonstrate the pivotal role of TNF-α in driving the inflammatory and tissue-degrading pathology of RA.[6] Studies on the mechanism of action of infliximab indicate that TNF-α is implicated in a number of pathogenic pathways, including cellular recruitment via induction of adhesion molecules and chemokines, downregulation of the cytokine cascade, and a reduction in angiogenesis and in the turnover of matrix metalloproteinases.[7]

Over 170 000 patients have been exposed to infliximab treatment to date, with an acceptable safety profile. Infusion reactions, infections such as tuberculosis, and lupus syndrome have been documented in a small proportion of patients. Steps to manage and avoid such adverse events have been incorporated in risk-management guidelines for use in clinical practice.

In 1992, infliximab was the first anti-TNF agent to enter clinical trials to treat RA. Other anti-TNF biologicals have followed, and are being presented at this symposium. The consistent efficacy of TNF blockade has established a new benchmark in the application of knowledge-based targeted therapies for RA.

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I-3: TNF inhibition with soluble recombinant human TNF receptors

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Etanercept is the only soluble receptor currently approved for use for rheumatoid arthritis (RA). It is a cloned and engineered fusion protein consisting of two identical chains of recombinant human TNF receptor (TNFR-p75) monomer fused to the Fc portion of

IgG1. It exerts its pharmacological effect by binding and rendering inactive both TNF-α and lymphotoxin. The dose indicated for RA is 25 mg twice weekly by subcutaneous injection. The $T_{\frac{1}{2}}$ is ±65 h. Pharmacodynamic analysis showed that in RA treatment there is a relationship between changes from baseline in the number of swollen joints, the number of painful joints, erythrocyte sedimentation rate (ESR) and concentrations of IL-6 and MMP-3. The safety and efficacy of etanercept has been assessed in multiple randomized double-blind controlled studies. The percentage of etanercept-treated patients achieving ACR20 responses was consistent across the trials, i.e., 60%–70%. Clinical responses generally appeared within 1–2 weeks after the initiation of therapy, and had almost always occurred by 3 months. After discontinuation, symptoms of arthritis generally returned within a month. Etanercept can be safely administered with methotrexate, but it is not yet clear whether the combination has additive or synergistic effects. Etanercept treatment resulted in a significant decrease in the progression of radiographic parameters of joint destruction. Etanercept was also safe and effective in the treatment of juvenile RA and psoriatic arthritis. In postmarketing reports, serious infections have been reported with the use of etanercept. Many of these serious events have occurred in patients with underlying diseases in addition to their RA, which could predispose them to infections.

I-4: IL-1 and IL-1Ra in rheumatoid arthritis

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Considerable evidence indicates that TNF-α and IL-1 are important mediators of inflammation and tissue destruction in rheumatoid arthritis. These proinflammatory cytokines are released by synovial tissue macrophages under the influence of direct T cell contact, T cell cytokines, and other inflammatory molecules. TNF-α and IL-1 promote tissue destruction through upregulation of adhesion molecule expression on endothelial cells, with enhanced migration of immune and inflammatory cells into the joint, and by direct stimulation of enzyme release from synoviocytes and chondrocytes.

A natural inhibitor of IL-1, called IL-1 receptor antagonist (IL-1Ra), is also produced by synovial macrophages, but not in sufficient amounts to inhibit the local effects of IL-1. IL-1Ra is a competitive inhibitor of receptor binding of IL-1. Because cells are sensitive to the occupancy of only a few IL-1 receptors per cell by IL-1, and large numbers of receptors are present on each cell, excess amouts of IL-1Ra are required to inhibit the biological effects of IL-1. An adequate ratio of endogenous IL-1Ra to IL-1 in specific tissues is important in preventing or modulating inflammatory disease.

The exogenous administration of recombinant IL-1Ra (anakinra) has been studied in the treatment of rheumatoid arthritis. This therapy is safe and efficacious in reducing both signs and symptoms, and in decreasing X-ray evidence of bone and cartilage destruction over 1 year. The addition of anakinra to methotrexate is also effective in patients poorly responsive to the latter madication. Studies in progress are determining the effects in RA of inhibiting both TNF-α and IL-1. Postmarketing surveillance of large numbers of treated patients will be necessary to determine the long-term safety of IL-1Ra, particularly the risk of serious infections and malignancies.

I-5: Anti-interleukin-6 therapy for rheumatoid arthritis

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Rheumatoid arthritis (RA) is an inflammatory autoimmune disease characterized by persistent synovitis, with synovial cell proliferation and destructive changes in the bone and cartilage of multiple joints. Interleukin-6 (IL-6) overproduction induces the emergence of rheumatoid factors, and an increase in γ-globulin, platelet counts, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A (SAA), and a decrease in albumin. IL-6 activates osteoclasts and induces bone absorption. IL-6 is also one of the key cytokines in the cytokine network of RA pathogenesis. IL-6 stimulates matrix metalloproteinase (MMP)-1 and -3 production from synovial cells synergistically with IL-1 or TNF-α, although IL-6 alone does not. IL-6 causes angiogenesis via induction of vascular endotherial growth factor (VEGF) synergistically with IL-1 or TNF-α. Thus, anti-IL-6 therapy may be effective for RA.

In an open-label multidose phase-I/II trial, 15 RA patients received an IV infusion with 2, 4, or 8 mg/kg humanized anti-interleukin-6 receptor antibody (MRA) every 2 weeks for 6 months. The treatment was well tolerated at all doses, without any serious adverse reactions. An increase in serum total cholesterol was detected as an MRA-related reaction in 10 of 15 (66%) patients. No new antinuclear antibody or anti-DNA antibody appeared. No anti-MRA antibody was detected. In 12 of 15 (80%) patients with detectable blood MRA during the treatment period, CRP, ESR, and SAA were completely normalized after the third dose. Increases in hemoglobin and serum albumin were also documented for all patients. MRA treatment normalized the serum levels of VEGF as well as matrix metalloproteinase (MMP)-1 and -3 in vivo in RA patients, predicting the protective effect of anti-IL-6 therapy on joint destruction of RA. The efficacy, assessed by the American College of Rheumatology (ACR) core set, was as follows: ACR20 60% and ACR50 6.7% at 6 weeks; ACR20 80% and ACR50 40% at 6 months. In the three patients whose blood MRA was rapidly eliminated, CRP decreased transiently. However, that state could not be maintained with treatment once per fortnight. These patients were men whose pretreatement levels of immune complex were high. The maintenance of trough MRA concentrations, rather than C_{max}, is critical to sustain the effects. MRA exhibited a nonlinear pharmacokinetic profile, and AUC and $T_{\frac{1}{2}}$ increased with repeated injections. The increased sIL-6R was found to complement MRA. Slight decreases in CH50, C3, and C4 and their inverse correlation with sIL-6R suggest that sIL-6R and MRA complex may be processed via the complement system. To study the efficacy of anti-IL-6 therapy further, a double-blind comparative late-phase-II trial in RA is ongoing in Japan and Europe.

II: "Water Front" in Arthritis

II-1: The role of IL-17 in joint destruction

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Interleukin-17 (IL-17) is a recently cloned cytokine secreted by activated memory CD4+ T cells, and modulates the early stages of

immune responses. IL-17 stimulates epithelial, endothelial, and fibroblastic stromal cells to secrete several cytokines, such as IL-6, IL-8, and G-CSF, as well as prostaglandin E2 (PGE2). IL-17 also stimulates the production and expression of proinflammatory cytokines IL-1-β and TNF-α by human macrophages. In 1999, we reported that IL-17 acts on osteoblastic cells, stimulating both cyclooxgenase (Cox)-2-dependent prostaglandin E_2(PGE_2) synthesis and receptor activator of NF-κB ligand (RANKL)/osteoclast differentiation factor (ODF) gene expression. RANKL/ODF in turn induced differentiation of osteoclast progenitors into mature osteoclasts. Thus, IL-17 may be involved in osteoclastic bone resorption in rheumatoid arthritis (RA) patients. Recently, several groups have reported that IL-17 plays important roles in both the immune response and joint destruction in patients with RA. Control of IL-17 expression in RA patients could provide directions for the development of new treatment strategies for joint destruction in RA patients.

II-2: Synoviolin: a novel membranous protein plays a central role in the formation of synovial joints and for pathogenesis of arthropathy

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Rheumatoid arthritis (RA) is one of the common disorders characterized by excess growth of articular synovial cells, so-called "pannus," and autoimmune reactions. To understand the pathomechanism of RA, we attempted to characterize rheumatoid synovial cells and found a novel membranous protein, Synoviolin (synovial cell+ protein). To verify its role, we overexpressed Synoviolin in mice. Overexpression of *synoviolin* causes arthropathy, which resembles RA. In addition, the heterozygote of *synoviolin(+/−)* is resistant to anticollagene antibody-induced arthritis. The homozygote of *synoviolin(+/−)* is lethal to embryos between E16 and 17 days. However, E12–15-day embryos showed striking phenotypes:

1. absence of joint formation;
2. residual webs;
3. no staining with alcian blue or alizarine red;
4. *synoviolin* expressing in the apical ectodermal ridge and condensed undifferentiated mesenchymal cells (data not shown).

These features of Synoviolin clearly indicate its importance in joint formation and pathogenesis for athropathy.

II-3: Joint destruction by rheumatoid synovial fibroblasts

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Rheumatoid arthritis (RA) is chronic inflammatory disease which leads to joint destruction. Joint destruction occurs not only in joint cartilage, but also in subchondral bone. In the last decade, numerous studies were undertaken to elucidate the molecular and cellular basis of joint destruction in this disease. However, the mechanism of joint destruction is still under intensive investigation. Several studies have demonstrated that RA synovial fibroblasts (RASF) play a pivotal role in the pathogenesis of joint destruction, although it is obvious that osteoclasts are involved in the degradation of bone. Recently, a novel molecule regulating bone degradation, osteoclast differentiation factor (ODF)/osteoprotegerin ligand (OPGL), was cloned. This is able not only to activate mature osteoclasts, but also to induce osteoclastogenesis. It is identical to the receptor activator of nuclear factor kB(NF-kB) ligand (RANKL) and the TNF-related activation-induced cytokine (TRANCE). We demonstrated the expression of ODF in RA synovium, and showed that RASF support the differentiation of peripheral mononuclear cells into thrombospondin-related anonymous protein (TRAP)-positive osteoclasts.

To explore the molecular mechanism of osteoclast differentiation in RA, we investigated the effects of inhibiting the expression of ODF/RANKL in RASF on osteoclast differentiation, using a retroviral vector encoding an antisense sequence against ODF/RANKL. RASF were transduced with the retroviral vector encoding antisense against ODF/RANKL. Successfully transduced RASF were selected by antibiotic selection. Nontransduced RASF were used as controls. Transduced and nontransduced RASF were co-cultured with peripheral blood monocytes (PBMC) from a healthy donor in the presence or absence of 1,25(OH)2vitamineD3 for 3 weeks. The 1,25(OH)2vitamineD3 was added only once, when the culture started, into the co-culture system. After 3 weeks co-culture, TRAP staining was performed to identify osteoclast-like cells. Whereas nontransduced RASF succeeded in supporting the differentiation of PBMC into osteoclast-like cells, retroviral vector encoding antisense against ODF-transduced RASF also supported osteoclast differentiation. It is of particular interest that this transduced RASF could support the differentiation of PBMC into TRAP-positive multinucleated osteoclast-like cells in the absence of 1,25(OH)2vitamineD3. These data suggest the RASF may play a role in the mechanism of bone destruction in RA through both an ODF-dependent as well as an ODF-independent pathway. Moreover, the ODF-independent pathway inducing the differentiation of PBMC into osteoclast-like cells may be independent of 1,25(OH)2vitamineD3.

II-4: Regulation of joint destruction by MAP kinases

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Despite an increased understanding of the aggressive characteristics of rheumatoid arthritis (RA) fibroblast-like synoviocytes (FLS), there is little information about which signal transduction pathways regulate joint destruction. Dissecting the role of MAP kinases has been hampererd by the lack of selective reagents that inhibit JNK, although effective p38 and ERK inhibitors have been described (SB203580 and PD98059, respectively).[1] The potential importance of JNK in RA was suggested by our studies demonstrating that cytokines such as IL-1 and TNF-α lead to efficient phosphorylation of JNK in RA FLS. These observations led us to hypothesize that activation of JNK, which induces c-Jun and the transcription factor AP-1, contributes to destruction of cartilage and bone in RA. MAP kinases play an important role in AP-1 activation, where AP-1 subunits can be phosphorylated at specific amino acid residues. c-Jun is phosphorylated at two N-terminal serines (amino acids 63 and 73) by at least three closely related c-Jun N-terminal kinases (JNK1, JNK2, and JNK3), which exist as multiple isoforms owing to alternative splicing. JNK2 binds c-Jun with at least a 25-fold higher affinity than JNK1, and is probably the more physiologically relevant activator of AP-1.

Three major MAP kinase families have been identified. In addition to the c-Jun N-terminal kinases (also called stress-activated protein kinases, or SAPK) described above, there are two other well-defined pathways: extracellular signal-regulated kinases 1 and 2 (ERK1/ERK2), also referred to as p42/p44 MAPKs, and the p38 MAP kinases. Each MAP kinase family is phosphorylated and activated by a cascade of specific kinases called MKK/MEKs. In general, this kinase cassette includes enzymes in series (from MAPKKK to MAPK) that serve as an "on–off" switch for the particular MAPK. There is still some controversy about the specificity of each enzyme and the degree of promiscuity for substrates, although some patterns of activation have been defined. For instance, MEK1 and MEK2 primarily activate ERKs, while MKK3 and MKK6 selectively activate the p38 kinases. MKK4, also called JNKK1 (as well as SEK), activates both p38 and JNK.[2] The more recently described MKK7 (JNKK2) appears to be more specific for the JNK pathway.[3,4] The relative contributions of each upstream kinase to mediators of joint destruction remain poorly defined.

To evaluate the role of MAP kinases in collagenase gene expression and joint destruction in RA, we studied the activation of ERK, p38, and JNK in cultured FLS. All three kinase families are constitutively expressed by synoviocytes, and cytokines such as IL-1 lead to rapid phosphorylation of p38 and ERK in both RA and OA FLS. Of interest is that IL-1 and TNF-α-induced JNK activation was greater in RA FLS than in OA cells. This also correlated with higher collagenase gene expression in cultured RA cells. The differences between RA and OA were not due to variations in cytokine receptor density among the different diseases, and some stimuli, such as anisomycin or phorbol esters, were able to activate JNK in both RA and OA FLS. Therefore, proinflammatory cytokines known to be involved in synovial inflammation and extracellular matrix degradation lead to increased JNK activation in RA compared with OA FLS. This observation is also consistent with a recent study implicating JNK and AP-1 activation in Fas-mediated apoptosis in RA, but in not OA, synoviocytes.[5]

Additional studies in our laboratory suggest that JNK is the key MAPK involved in the induction of MMP genes in RA FLS. For instance, low concentrations of the selective p38 inhibitor SB203580, that completely inhibit p38 function, have little or no effect on IL-1-induced collagenase expression, AP-1 activation, or c-Jun expression. PD98059, which inhibits MEK1/2 and blocks ERK activation, slightly decreases collagenase mRNA accumulation. Because no selective JNK inhibitor was available, we used high concentrations of SB203580 as an alternative method to block JNK.[6] Although 25–50 μM SB203580 inhibits certain splice variants of JNK2, these concentrations block p38 as well as other kinases that might alter cellular function (including c-raf). Hence, it is a nonspecific tool for evaluating JNK function.

Because SB203580 has shortcomings as a JNK inhibitor, the precise role of JNK cannot be assessed without a more selective compound or genetic approaches to abrogate JNK function. We have a unique opportunity to evaluate the first specific JNK inhibitor in our system. The compound SP600125 inhibits JNK1 and 2 with an IC50 = 40 nM. SP600125 does not inhibit p38, ERK, or a variety of other kinases. Our preliminary studies demonstrate that SP600125 inhibits IL-1-induced c-Jun phosphorylation, c-Jun mRNA induction, and collagenase gene expression in FLS. However, the compound does not inhibit the basal levels of collagenase gene expression or c-Jun phosphorylation in cultured FLS. These data support our hypothesis that JNK plays a pivotal role in the regulation of cytokine-induced MMPs in FLS, and is a potential target for chondroprotective therapy.

The JNK pathway is considerably more efficient than either p38 or ERK as an enabler of AP-1-mediated gene transcription, and could contribute to increased MMP production in RA FLS. Since JNK also regulates cytokine gene expression (including TNF-α), we suggest that the MAP kinase profiles in RA cells could help explain the phenotype of rheumatoid FLS. Understanding the molecular events involved in JNK and AP-1 regulation could lead to more specific therapies that alter the natural history of RA.

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II-5: Pathogenesis of inflammatory arthritis

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II-6: Genomics of synovial cell activation and cartilage destruction

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"Genomics" reflects a wide variety of experimental approaches and interpretations derived from research in to genes and regulation of the synthesis of gene products.[1] Following the detection of genes in the activated synovium, there remains the challenge of exploring the function and hierarchy of the genes expressed (functional genomics).[2] Although it is well established that activated synovial fibroblasts are a major force mediating joint destruction in rheumatoid arthritis (RA), it is not known which proteinase(s) are the key enzymes responsible for cartilage and bone destruction.

Our laboratory uses gene transfer to explore the role of distinct enzymes. Novel ribozymes clearing the mRNA of cathepsin L and MMP-1 are compared to antisense constructs directed against the membrane-type matrix-metalloproteinases (MT-MMP-1) to determine the contribution of these proteinases to joint destruction.

In our search for the molecular basis of synovial cell activation, we examined the role of toll-like receptors (TLRs). Specifically, we

assessed the expression of genes for TLR2, TLR4, and TLR9 in synovial fibroblasts, and examined the downstream effects after stimulation of specific TLRs.[3,4]

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III: Regulation of Cartilage Differentiation and Destruction

III-1: Genetic regulation of cartilage differentiation and function

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A number of genes are critical for the formation of articular and growth plate cartilage during endochondral ossification and subsequent chondrocyte differentiation and maintenance of function. These genes include genes encoding transcription factors that control chondrocyte differentation, such as members of the SOX family and Cbfa1/Runx2, cytokines and their receptors (PTHrP, Indian hedgehog, vascular endothelial growth factor (VEGF), and Wnts), extracellular matrix components (collagens, proteoglycans, link protein, and matrilin), and matrix-degrading enzymes (MMPs and related enzymes).

This presentation highlights recent data on the regulation of joint and growth plate cartilage differentiation and function by cytokines and transcription factors, and considers the role of matrix in the development and maintenance of cartilage.

III-2: Modulation of chondrocytes differentiation by Wnt antagonist Frzb-1

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The Wnt antagonist Frzb-1 is expressed in the developing fetus. Frzb-1 expression is found initially in condensing mesenchyma, and subsequently in epiphyseal articular chondrocytes and prehypertrophic chondrocytes in the growth plates. Frzb-1 expression is eventually downregulated in the hypertrophic zone. This dynamic expression pattern suggests that Frzb-1 may play multiple roles in limb development. However, this role has yet to be solved. To address this issue, we carried out gain-of-function studies by misexpressing Frzb-1 in the developing limb. Retrovirally driven Frzb-1 misexpression caused joint dismorphogenesis, shortening of skeletal elements, and arrest of the chondrocyte maturation process, with consequent inhibition of mineralization, metalloprotease expression, and marrow/bone formation. Forced expression of Frzb-1 in cultured chondrocytes also inhibited matrix calcification and matrix metalloprotease activity. It is known that Frzb-1 antagonizes Wnt1 and Wnt8 actions. These Wnt signals are mediated by the b-catenin-LEF/TCF pathway, a canonical signaling pathway of Wnts. When Wnt1/8 binds the receptor, the free form of b-catenin in the cytoplasm is stabilized and tranlocates into the nuclei. This b-catenin interacts with LEF/TCF and transactivates the target genes. We next investigated the involvement of Frzb-1 in the modulation of the b-catenin-LEF/TCF signal in chondrocytes. Overexpression of Frzb-1 inhibited stabilization of b-catenin and antagonized Wnt8-induced stabilization of b-catenin in chondrocytes. Further, Frzb-1 inhibits the nuclear translocation of the b-catenin in chondrocytes. Constitutive activation of the b-catenin-LEF/TCF pathway stimulated maturation and matrix calcification in chondrocytes, while the inactivation of this signal inhibited them. We also found that b-catenin becomes detectable in the nuclei in hypertrophic chondrocytes, while it is dominantly localized in cytoplasmic proliferating and prehypertrophic cells, indicating that the b-catenin-LEF/TCF signal is activated in the hypertrophic chondrocytes, where Frzb-1 expression is downregulated. Taken together, this suggests that Frzb-1 might be a direct regulator of chondrocyte maturation by modulating the b-catenin-dependent Wnt signal in the process of endochondral ossification.

III-3: Histological analysis of abnormal endochondral bone formation in thanatophoric dysplasia

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Thanatophoric dysplasia (TD) is the most common form of lethal osteochondrodysplasia. In the absence of medical intervention, affected individuals die in the perinatal period with severe skeletal deformities that include shortening and bowing of the ribs and long bones. The molecular basis of TD type II is a point mutation, which results in a K650E substitution in the second tyrosine kinase domain of the fibroblast growth factor receptor type 3 (FGFR3). The K650E substitution results in constitutive activation of the receptor, which has been shown to mediate an inhibitory influence on chondrocyte proliferation and differentiation. The growth plates of tibiae harvested from medically aborted TD type II human fetuses of 18–20 weeks gestation revealed irregular and aggressive invasion of blood vessels, resulting in a lack of columnar organization of chondrocytes and a decrease in the zone of hypertrophic chondrocytes. Vascular endothelial growth factor (VEGF), which is known to regulate angiogenesis and endothelial invasion at the chondro-osseous junction, was intensely expressed in the mutant chondrocytes, while the expression of its cognate receptor Flk-1/KDR did not differ between the normal and mutant fetuses, suggesting that VEGF is upregulated in the $FGFR3^{K650E}$ cartilage. To further explore the relationship between FGFR3 and VEGF expression, chondrocytic cell line CFK 2 cells were transfected with cDNA encoding either wild-type FGFR3 or FGFR3 carrying the K650E mutation. VEGF expression, as expected, was upregulated in CFK 2 cells expressing the mutant receptor compared with those expressing wild-type FGFR3. In

summary, these studies demonstrate that constitutive activation of FGFR3 in chondrocytes stimulates VEGF expression and enhances vascular invasion in the growth plates of TD type II fetal bones. The defects in bone development associated with TD type II can therefore be attributed to aggressive vascular invasion of the epiphyseal growth cartilage, as well as to a decrease in chondrocyte proliferation.

III-4:

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III-5: Potential new anti-inflammatory therapeutic target in arthritis: peroxisome proliferator-activated receptor gamma (PPAR-γ)

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Recently, it was reported that peroxisome proliferator-activated receptors (PPARs) may be involved in the regulation of proinflammatory responses. Since it is well established that inflammation plays an important role in the triggering and/or the development of arthritis, we investigated their presence and activity in human articular joint tissues.

PPARs are ligand-activated transcription factors, and belong to a family of the steroid/thyroid/retinoic acid nuclear receptor superfamily. To date, three PPARs, α, β, and γ, have been identified and cloned. The binding of PPAR ligands leads to PPAR activation and heterodimerization with retinoic X receptor (RXR). The PPAR/RXR heterodimers bind to specific peroxisome proliferator response elements, or PPRE, located upstream of responsive genes. PPARs can be activated by a number of compounds that may be classified as synthetic ligands, including the fibrate class of hypolipidemic drugs, antidiabetic drugs, some nonsteroidal anti-inflammatory drugs (NSAIDs), and natural ligands including fatty acids, eicosanoids, and their derivatives. One natural ligand of PPAR-γ belongs to the prostaglandin family, the 15 deoxydelta-12,14-prostaglandin J_2 (15d-PGJ_2).

Interleukin-1-β (IL-1-β) is an important mediator of several catabolic processes involved in the joint destruction characteristics of osteoarthritis and rheumatoid arthritis. Upon activation by IL-1-β, chondrocytes and synoviocytes produce degradative factors, including matrix metalloproteases (MMP) and nitric oxide (NO). We investigated the expression and function of PPAR-γ in human chondrocytes and synoviocytes. We examined the effects of PPAR-γ activation on IL-1-β-induced expression and synthesis of MMP-13 and NO in chondrocytes, and of MMP-1 in synoviocytes.

The treatment of cells with PPAR-γ ligands BRL 49653 and the naturally occurring 15d-PGJ_2 dose-dependently decreased IL-1-β-induced MMP and NO production. The inhibitory effect of PPAR-γ activation was not restricted to IL-1-β, as TNF-α- and IL-17-induced MMP and NO production were also inhibited by 15d-PGJ_2. Northern blot analysis revealed that both MMP and the inducible NO synthase (iNOS) mRNA levels were inhibited in the presence of 15d-PGJ_2. Furthermore, 15d-PGJ_2 diminished MMP- and iNOS-promoter activity (luciferase reporter system) in transiently transfected human cells. Co-transfection of MMP or iNOS promoters with a PPAR-γ expression vector greatly accentuated the inhibitory effects of 15d-PGJ_2.

The transcription factors AP-1 and NF-κB are believed to mediate the IL-1-β upregulation of MMP and iNOS promoter activities, respectively. Data showed that 15d-PGJ_2 diminished the activity of AP-1, as examined following gel shift assay. Moreover, activation of AP-1 and NF-κB-luciferase reporter plasmids by co-transfection with a MEKK1 expression vector was compromised by the addition of a PPAR-γ expression vector, and completely blocked by treatment of the transfected cells with 15d-PGJ_2.

In summary, our data suggest that 15d-PGJ_2 inhibits MMP and iNOS expression at the transcriptional level in human chondrocytes and synoviocytes through activation of PPAR-γ, with the resultant antagonism of AP-1 and NF-κB transactivation of target promoters. Furthermore, the PPAR-γ signaling pathway presents a novel target for therapeutic intervention in arthritic diseases.

III-6: Knee osteoarthritis progression evaluated by magnetic resonance imaging and a novel quantification imaging system

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Existing methods used to evaluate osteoarthritis (OA) progression, such as cartilage degradation, are imperfect. The aim of our study was to evaluate the reliability of a novel imaging software tool that assesses cartilage thickness and volume using magnetic resonance images (MRI) of the knee. For the *validation* of our imaging system, the objectives were to assess measurement reliability, i.e., to determine if there are differences between readings of the same image made by the same reader approximately 2 weeks apart (reader test–retest), and if there are differences between readings of the same image made by different readers (agreement between readers), and to determine if there are significant differences between the cartilage volume readings obtained from two MRIs of the knee acquired a few hours apart (positioning and image acquisition test–retest).

Forty-eight MRIs of the knees of normal subjects, patients with different stages of knee OA, and a subset of duplicate images were systematically and blindly quantified by three independent readers using our imaging system. The following cartilage areas were analyzed to compute volume: total cartilage, lateral and medial compartments, and lateral and medial femoral condyles.

The reliability of the measurements was assessed using intraclass correlation (ICC). For the total cartilage, ICC ranged between 0.986 and 0.995 ($P < 0.0001$), for the compartments it ranged between 0.981 and 0.997 ($P < 0.0001$), and for condyles between 0.978 and 0.997 ($P < 0.0001$). These high ICC values indicate the high reliability of the measurements among the readers. Test–retest data showed excellent consistency, with a correlation coefficient of 0.99 ($P < 0.0001$), and no significant difference between the test and retest visits ($P = 0.779$).

To assess the *sensitivity to change* of our method, 36 patients with symptomatic knee OA were recruited for the study and had MRI acquisition of the knee at baseline, 6 months, and 1 year of follow-up. These images were systematically analyzed and quantified using the software. The attrition of cartilage volume is computed

by contrasting the MRI at 6 months and at 1 year to the baseline value. The disease progression was also contrasted at each time-point to classic knee OA evaluation variables, co-medication consumption, physical examinations of the knee, and standardized semiflexed knee radiographs done at baseline and at 1 year. Grade IV radiographs were an exclusion criteria.

The patients' mean age was 63.1 years (range 39–78 years), 74% were women with an average body mass index (BMI) of 31. Preliminary data on knee OA progression (percentage cartilage volume losses from baseline) computed at 6 months and 1 year of follow-up were already striking and statistically significant (mean and SEM) (Table 1).

Table 1. *P* value = <0.001 for all measurements, and the *t*-test at 6 months and 1 year

	Total cartilage	Medial compartment	Medial femoral condyle
6 months	−1.81% (0.43)	−2.11% (0.65)	−3.34% (0.96)
1 year	−2.38% (0.51)	−3.91% (1.41)	−5.03% (1.33)

Comparisons of clinical and radiological data were also made. The results show that this imaging system is extremely reliable regardless of the reader used, and has high test–retest validity. The image acquisition is also highly reproducible, and shows a high sensitivity to change. This study represents an important step in the overall validation of an imaging system designed to follow the progression of human knee OA and assess disease-modifying OA drugs.

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IV: Recent Advances in Osteoclast Biology

IV-1: Recent advances in osteoclast biology

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In 1997, Tsuda et al. cloned an osteoclastogenesis inhibitory factor (OCIF) which markedly inhibited osteoclast formation in mouse co-cultures. OCIF was identical to osteoprotegerin (OPG). OPG was a secreted member of the tumor necrosis factor receptor family, and inhibited osteoclast differentiation by preventing cell-to-cell interaction between osteoclast progenitors and bone marrow-derived stromal cells. The discovery of OPG facilitated the molecular cloning of osteoclast differentiation factor (ODF), which stimulated osteoclast differentiation in the absence of stromal cells. ODF was a ligand of OPG, and was found to be identical to a receptor activator of NF-κB ligand (RANKL). Thus, RANKL appears to be an important regulator of both osteoclastogenesis and immune response.

In 1999, we demonstrated that IL-17 similarly stimulated RANKL gene expression in osteoblasts and induced osteoclast differentiation in co-cultures of osteoblastic cells and bone marrow cells. The osteoclast formation induced by IL-17 was completely blocked by OPG. We also demonstrated that IL-17 induced PGE_2 synthesis by osteoblasts but not by osteoclast progenitors. NS398, a selective inhibitor of Cox-2, inhibited not only IL-17-dependent RANKL gene expression in osteoblasts, but also osteoclast formation in co-cultures in response to IL-17. Therefore, it is suggested that IL-17 induces RANKL synthesis via PGE_2 synthesis by osteoblastic cells, which in turn stimulates osteoclast formation.

Recently, we and several other groups demonstrated that T cells directly induce osteoclastogenesis through the expression of RANKL on T cells. We also demonstrated that the ratio of the concentration of soluble RANKL to that of OPG is significantly higher in synovial fluids of RA patients than in those of patients with OA or gout. Thus, RANKL and OPG may play important roles in osteoclastic bone resorption in RA patients.

IV-2: Increase in the development of multinucleated bone-resorbing giant cells in bone marrow of severe reumatoid arthritis

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In patients with severe rheumatoid arthritis (RA), marked destruction is frequently observed in joints affected with severe osteoporosis of the subchondral areas. This type of joint destruction is characterized by compressive collapse of the articular surface due to severe juxtaarticular osteoporosis. In such cases, the presence of multinucleated giant cells and myeloid cells is considerably increased around trabecular bone in the subchondral area.

We have identified the generative process *in vitro* for these tartrate-resistant acid phosphatase (TRAP)-positive multinucleated cells which would be involved in the pathogenesis of accelerated bone resorption in juxtaarticular bone in RA patients. Initially, we found that interstitial fibroblastic cells in the synovia and bone marrow of RA patients exhibit an almost identical function to nurse cells demonstrating pseudoemperiporesis in mouse thymus. Labeled nurse-like cells, these cells from the synovial tissue, and bone marrow of patients with RA support highly activated blood cells through pseudoemperiporesis. Peripheral-blood monocytes from healthy individuals are supported by co-cultured nurse-like cells from synovial tissues of patients with RA, and activate and differentiate into mononuclear cells positive for CD14 and TRAP within 5 weeks of culturing. These mononuclear cells then fuse and differentiate into multinucleated giant cells following stimulation with IL-3, IL-5, IL-7, and/or granulocyte-macrophage-colony-stimulating factor. This fusion into multinucleated giant cells from CD14(+) mononucleated cells is also induced by iliac bone marrow supernatant from some patients with severe RA. Multinucleated giant cells have the ability to form pits on dentin sections, suggesting bone resorptive activity.

The number of TRAP(+) multinucleated cells were found to increase in iliac bone marrow of patients with severe RA compared with patients with mild RA, and postmenopausal or senile women. These results indicate that multinucleated giant bone-resorbing cells generated from monocytes may play a role in accelerated bone resorption, resulting in bone erosion or severe osteoporosis of juxtaarticular bone in RA patients.

Accelerated bone resorption resulting in bone erosion or severe osteoporosis of juxtaarticular bone is the characteristic finding in patients with rheumatoid arthritis (RA). Bone erosion or severe osteoporosis is major cause of joint destruction and clinical problems, especially in patients with severe RA. Histologically, bone-resorbing tartrate-resistant acid phosphatase (TRAP)-positive multinuclear cells are present, with surrounding abundant fibroblast-like cells, in the synovial tissues and bone surface of destructive joints of patients with RA.

IV-3: A therapeutic vaccine approach to inhibit pathological bone destruction

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The receptor activator of NF-κB ligand (RANKL) is a novel member of the family of tumor necrosis factor cytokines, and is critically involved in osteoclast differentiation and activation. It is therefore important for normal bone development. There is also accumulating evidence that osteoclasts play important roles in pathological bone destruction such as rheumatoid arthritis, and the natural inhibitor of RANKL, osteoprotegerin (OPG), has potent therapeutic effects on such conditions. We developed a simple and effective method for active immunization against self-RANKL. As a RANKL vaccine, a modified recombinant murine RANKL protein, with N-terminus truncated murine RANKL modified to incorporate the promiscuous T helper epitope, was generated. Immunization with the compound induced a rapid T-cell-dependent polyclonal and sustainable anti-RANKL autoantibody response in mice. No apparent macroscopic abnormality was observed in any organs of the immunized animals. To investigate the therapeutic effects of the RANKL vaccine on pathological bone destruction, we utilized a mouse model of rheumatoid arthritis and an ovariectomy model. SKG mice develop RA-like symptoms and periarticular bone destruction at 2 months of age. RANKL vaccine immunization significantly reduced the onset of arthritis in these mice, almost completely abolished the bone destruction, and dramatically reduced the osteoclast number in the periarticular region. We then examined the effect of the vaccine on the ovariectomy model. The RANKL-vaccinated mice were resistant to bone loss in response to ovariectomy, and both the osteoclast number and the bone resorption surface were significantly reduced. These results demonstrate that a therapeutic vaccine approach targeting RANKL can be used to inhibit bone destruction in various pathological conditions such as osteoporosis and rheumatoid arthritis.

IV-4: A complex containing Pyk2, Src, and Cbl regulates αvβ3 integrin-mediated signalling, osteoclast motility, and bone resorption

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The signalling events downstream of integrins that regulate osteoclast attachment and motility are only partially understood. We found that a trimolecular complex comprising Src, the focal adhesion protein Pyk2, and the protooncogene Cbl functions to regulate osteoclast adhesion and motility. Activation of the integrin αvβ3 (VnR) induces the Ca_i-dependent and Src-independent autophosphorylation of Pyk2 at Tyr 402. This phosphorylation leads to the formation of a consensus binding motif for the SH2 domain of Src, which is then recruited to the complex and associates with Pyk2, itself bound directly or indirectly, to the cytoplasmic tail of the β subunit of the VnR. This binding recruits Src to the adhesion site and displaces the intramolecular inhibitory interaction of Tyr 527 with Src SH2, leading to Src kinase activation and the Src SH3-dependent recruitment and phosphorylation of c-Cbl. Full activation of Src kinase is then achieved with autophosphorylation at Tyr 416. This event creates a consensus binding motif for the PTB domain of Cbl, which is shown to bind to phosphorylated Tyr 416, inhibiting Src kinase activity. The Cbl PTB domain-dependent decrease in Src kinase activity is paralleled by a similar decrease in integrin-mediated adhesion. This series of events, and particularly the Src-dependent phosphorylation of Cbl, leads to the Cbl RING finger-dependent recruitment of the ubiquitin system to the molecular complex at the adhesion site, and the ubiquitination and subsequent degradation of Cbl and Src. Thus, this cycle ensures the rapid assembly and disassembly of adhesion structures, and the rapid attachment/detachment necessary for osteoclast migration. Consistent with the hypothesis that this complex regulates osteoclast motility, deletion of c Src, Pyk2, or c-Cbl in mice leads to a decrease in osteoclast migration and bone resorption. Furthermore, adenovirus-induced overexpression of mutants of these three proteins in osteoclasts inhibits bone resorption in vitro. Thus, binding of the VnR integrin to the bone surface induces the formation of a Pyk2/Src/Cbl complex in which Cbl is a key regulator of Src kinase activity and of cell adhesion and migration.

IV-5: The mechanisms of TNF-α and RANK ligand-induced osteoclastogenesis

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Inflammatory osteolysis is the most prevalent form of clinically significant bone loss. While tumor necrosis factor-α (TNF) is pivotal to the pathogenesis of this condition, the means by which the cytokine recruits osteoclasts (OCs), and thus promotes bone destruction, are unknown. To determine if TNF acts directly on OC precursors, we isolated a pure population of murine myeloid cells, which form a confluent layer of OCs when cultured with the receptor activator of NF-κB ligand (RANKL). TNF, at any concentration, fails to induce differentiation of macrophages into OCs in the absence of RANKL. In contrast, TNF dramatically stimulates osteoclastogenesis in macrophages primed by <1% of the levels of RANKL required to induce OC formation alone. Mirroring their combined effects on osteoclast formation, TNF and RANKL markedly potentiate both NF-κB and SAPK/JNK activity, two signaling pathways which are essential for osteoclastogenesis. These data suggest that while TNF alone does not prompt osteoclastogenesis, it does so when stromal/osteoblast-produced RANKL is present at constitutive levels. To test this hypothesis, we established co-cultures of marrow stromal cells from TNF-receptor $(TNFr)^{-/-}$ mice with OC precursors isolated from $TNFr^{+/-}$ mice. TNF strongly stimulates OC formation in these cultures in the absence of exogenous RANKL. This observation confirms that TNF in vitro directly targets OC precursors in the presence of nonstimulated levels of RANKL. To test this hypothesis in vivo, we transplanted stromal- and T-cell-depleted marrow from GTRosa26(Rosa) transgenic mice, which constitutively express β-galactosidase in all cell lineages, into irradiated $TNFr^{-/-}$ mice and $TNFr^{+/-}$ littermates. The chimeric animals were administered TNF or vehicle, and OC commitment was determined both in vivo and ex vivo.

All OCs generated were of Rosa origin. TNF, when administered in vivo, markedly increases OC numbers in both $TNFr^{+/-}$/Rosa and $TNFr^{-/-}$/Rosa mice. Thus, while TNF alone does not stimulate osteoclastogenesis, it does so both in vitro and in vivo in the presence of a stromal environment which expresses nascent levels of RANKL by directly targeting OC precursors.

To determine why RANKL, but not TNF, is osteoclastogenic, we crystallized RANKL and resolved its structure. RANKL self-associates as a homotrimer with four unique surface loops, that distinguishes it from other TNF-family cytokines. Mutagenesis of selected residues in these loops aborts RANKL's osteoclastogenic capabilities, thus identifying specific structural components of RANKL, but not TNF, which endow it with the unique capacity to promote OC differentiation.

V: Evidence of Drug Therapy for Rheumatoid Arthritis

V-1: Future directions in the management of rheumatoid arthritis and an overview of the role of new drugs

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The approach to the treatment of rheumatoid arthritis (RA) is undergoing a dramatic change. This is based on accumulated information which shows that patients with aggressive synovitis, usually rheumatoid factor and/or HLA-DR "disease-epitope" positivity, have a poor prognosis, with 50% of these patients becoming disabled in the first 5–10 years of disease, 90% by 20 years, and their life expectancy being shortened by 5–10 years. Joint damage leading to this disability occurs in an early and accelerated fashion, with 90% of patients having joint damage in the first 2 years of disease, and 50% in the first 6–12 months after diagnosis.

The financial impact on society is significant. The disease is estimated to occur in 1%–2% of the general population, and may be the most common cause of disability that is potentially reversible if correct management of the illness is begun early. Using conservative data from the Health Interview Survey, a national probability sample of the noninstitutionalized population in the United States from 1989 to 1991, Yelin noted that an average of 1.74 million people met the criteria for RA. These individuals made 19.65 million physician visits at a cost of $1.5 billion in 1994 terms; hospital admissions numbered 540000, accounting for $3.2 billion; wage losses amounted to $3.8 billion. Thus, the costs of complications of RA, i.e., hospitalizations, operations, and lost wages, far exceed the costs of patient visits to physicians, and emphasize that "an ounce of prevention is worth a pound of cure."

In considering these outcomes and looking at new therapeutic strategies for the treatment of disabling RA, it is important to keep certain points in mind: aggressive RA is not benign or indolent; joint damage occurs early and sustained remission is rare; RA inflammation is complex, and traditional drugs used individually have not controlled the inflammation satisfactorily for a sufficient period to prevent joint damage and disability; the efficacy to toxicity ratio of second- and third-level disease-modifying antirheumatic drugs (DMARDs) appears to be superior to the traditional first-line nonsteroidal anti-inflammatory drugs (NSAIDs); and most importantly, patient outcomes appear best with early treatment and control of inflammation.

While traditional therapy has often been based on empirical drug use, often of drugs developed for other reasons, a new era of therapy is developing based on a scientific understanding of the rheumatoid inflammatory process. As will be discussed, this understanding, which is based on the physiology and pathophysiology of T- and B-lymphocytes, macrophages, and pro- and anti-inflammatory cytokines, including tumor necrosis factor (TNF) and interleukin-1 (IL-1), has led to the production of potent and effective drugs to counteract this inflammatory process. This is reflected in clinical improvements in patients, not only adding "years to life," but just as importantly, adding "life to years," an effect not seen with traditional drugs.

To optimize therapy for these patient, and to reduce morbidity as well as disability and mortality, the biological response modifiers, new synthetics, and novel agents will need to be used early, before joint damage and drug resistance can occur, and in all likelihood they will need to be used in combination to counteract the complex inflammatory processes in several critical areas.

For the first time in the therapy of RA, we are seeing a combination of evolving treatment strategies (early use, combinations) coupled with dedicated, new effective drugs, a combination that has the ability to improve the quality and quantity of life, improve personal and family relationships, and normalize work and occupational activities, which will reduce the enormous burden on families and society.

V-2: Evidence for a reduction of side-effects by selective COX-2 inhibitors

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are extensively used worldwide, but they are commonly associated with gastrointestinal (GI) complications. It is believed that serious GI complications such as ulcers and bleeding events due to NSAIDs are related to the inhibition of cyclooxygenase-1 (COX-1) enzyme, while clinical effectiveness in the reduction of pain and inflammation is related to the inhibition of COX-2. Three newer COX-1-sparing (or COX-2 selective) NSAIDs that do not inhibit COX-1 are presumably less likely to cause such problems. Meloxicam is a novel NSAID that has been widely used in more than 90 countries with over 30 million prescriptions. The other new agents, celecoxib and rofecoxib, both of which have been shown to have a greater COX-1-sparing effect, have recently been introduced.

Purpose

For meloxicam, we reviewed the incidence of serious upper GI (UGI) complications, including perforations, obstructions, and hemodynamically significant bleeding events, in a pooled-data analysis of meloxicam clinical trials that were at least 3 weeks in duration and included at least 20 patients per arm. We also examined the same outcomes in the completed trials CLASS and VIGOR.

Results

The results of this review are shown in Table 1–3.

Table 1. POBs meloxicam analysis

Drug	No. patients	Exposure (days)	No. events	Crude %	Rate per 100 patient years
Placebo	736	56	0	0	0
Meloxicam 3.75	154	61	0	0	0
Meloxicam 7.5	10158	33	3	0.03	0.32
Meloxicam 15	2960	179	9	0.30	0.62
Diclofenac 100 mg	5464	35	9	0.16	1.72
Naproxen 750 mg	243	117	1	0.41	1.29
Piroxicam 20 mg	5371	41	16	0.30	2.66

Table 2. POBs CLASS study – all patients[a]

	No. patients	No. events	Crude %	Rate per 100 patient years
Celecoxib 400 mg	3987	17	0.43	0.73
Diclofenac 75 mg BID	1996	10	0.50	0.93
Ibuprofen 800 mg TID	1985	11	0.55	0.98

[a] Based on the results of the entire study period of 12 months

Table 3. POBs VIGOR study[a]

	No. patients	No. events	Crude %	Rate per 100 patient years
Rofecoxib 50 mg	4047	16	0.39	0.59
Naproxen 1000 mg	4029	37	0.92	1.37

[a] Based on the entire study period of 12 months

Conclusion

The risk of clinically significant UGI events with these newer agents is low, but these results need to be balanced against other safety concerns.

V-3: Evidence for the effects of leflunomide

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Leflunomide is a new class of disease-modifying antirheumatic drug (DMARD), converted on first-pass metabolism through the liver into its active metabolite A77 1726, which has anti-inflammatory and immunomodulatory properties. The primary mode of action is thought to be selective inhibition of *de novo* pyrimidine synthesis by blocking the rate-limiting enzyme dihydroorotate dehydrogenase. Activated CD4+ T cells proliferate rapidly during the progression of rheumatoid arthritis (RA), a process that uses *de novo* pyrimidine synthesis. Leflunomide acts to inhibit T cell proliferation by preventing pyrimidine generation and subsequent DANN synthesis. In addition, it was recently shown that leflunomide exerts its anti-inflammatory activities by preventing the generation of proinflammatory Th1 effectors and promoting Th2 cell differentiation.

Leflunomide was first shown to be active in a placebo-controlled Phase II study of patients with active disease. Several recent Phase III studies have demonstrated the efficacy and safety of leflunomide for up to 2 years in patients with active RA. In these studies, leflunomide was directly compared with methotrexate and sulfasalazine. Leflunomide was shown to be superior to placebo and at least as effective as sulfasalazine or methotrexate in improving individual signs and symptoms of RA. In a recent study, not yet published, it was also demonstrated that after an observation period of 5 years, leflunomide still was effective in a significant portion of patients with an acceptable profile of side effects.

Without doubt, leflunomide is a valuable new immunomodulatory compound for the treatment of RA, which can be used as a first-line DMARD in treating RA patients. In addition, leflunomide seems to be an ideal compound for combination therapies with other DMARDs such as methotrexate, or with new biologically active agents, especially TNF-á and IL-1 blocking principles.

V-4: Etanercept: clinical update

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Etanercept (Enbrel) is currently the only soluble TNF receptor approved for clinical use. It is a dimeric construct in which two soluble p75 TNF receptors are linked to the Fc portion of the human IgG1. The dimeric construct confers high affinity, and the linkage to the Fc portion of IgG1 confers a prolonged half-life.

Initial clinical trials of etanercept were conducted in adults and children with advanced, refractory rheumatoid arthritis (RA). In these studies, etanercept was more effective than placebo in relieving the signs and symptoms of RA, and in reducing inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein in both adults and children with RA.[1–3] Etanercept, added on to a background of methotrexate (MTX), was also more efficacious than MTX alone.[4] More recently, patients with early RA and other inflammatory conditions have been studied. In adult patients with early RA (≤3 years duration), etanercept treatment was associated with a profound reduction in the rate of radiographic progression.[5] In addition, it was slightly more effective than MTX in slowing the rate of joint erosions, and in reducing clinical signs and symptoms of disease. Etanercept also proved to be very effective in the treatment of psoriasis and psoriatic arthritis, either alone or in combination with MTX.[6] A small controlled trial of etanercept in ankylosing spondylitis has demonstrated superior efficacy compared with placebo for reducing signs and symptoms of the disease. Currently, two trials are in progress to test the efficacy of etanercept for the treatment of Wegener's granulomatosis.

In controlled clinical trials, etanercept has generally been well tolerated, with no major organ toxicities. Injection site reactions occurred in approximately 33% of etanercept-treated patients, but these are self-limiting. No significant differences in the incidence of serious adverse events were observed between the treatment groups in these trials. However, since the drug was approved, a variety of serious adverse events have been reported to the FDA surveillance database. These include rate reports of opportunistic infections such as tuberculosis and fungal infections, and of bone marrow dyscrasias and demyelinating-like illnesses. These will be reviewed and discussed.

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V-5: Remote effects of infliximab for RA patients

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Biological agents directing against tumor necrosis factor (TNF) have been used to treat inflammatory diseases such as rheumatoid arthritis (RA) and Crohn's disease, and have had a great impact

not only in the management of the disease, but also in our understanding of the pathogenesis.

In Japan, a chimeric anti-TNF monoclonal antibody, infliximab, has been tested for its efficacy and safety in early phase II and late phase II/III clinical trials. We give a brief overview of the Japanese clinical trials for infliximab, and compare the study design to those carried out in other countries. The striking distinction was that the administration schedule of infliximab was only three times at 0, 2, and 6 weeks in early phase II, and then four infusions every 8 weeks in the late phase II/III trials. After these infusions, infliximab was stopped and conventional disease-modifying antirheumatic drugs were started.

In both trials, the percentage of patients fulfilling American College of Rheumatology (ACR) 20% and ACR 50% criteria at 10 weeks, which is the primary end point, was comparable to trials carried out in the United States and Europe, confirming the high level of efficacy and tolerability. We expected to observe an exacerbation of the disease when infliximab infusions were stopped. Although the disease activity was somewhat increased for a few months after the infusions, about 50% of the patients exhibited a fair clinical response at 54 weeks in early phase II trials, which introduces the possibility of a "remote effect" of triple infusions of infliximab. To search for factors predicting this good response to infliximab, we utilized gene chips to screen the marker molecules with a significant change in mRNA level before and after the treatment.

Given the recent warnings about the increased risk of tuberculosis with infliximab, the indications and dosing schedule of this powerful biological drug should be carefully considered. In this respect, the Japanese experience and the detailed characterization of the results may help to establish a sophisticated therapeutic program for infliximab.

VI: Surgical Treatment of Rheumatoid Arthritis, Follow-up Results and New Challenge

VI-1: Clinical outcome of surgical treatment in rheumatoid arthritis, with special reference to indications in the rheumatic hand and foot

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The outcome of surgical interventions in rheumatoid diseases largely depends on priorities, timing, and staging, as well as the correct indication. As far as indication is concerned, it is widely agreed that radiological Larsen, Dale, and Eek (LDE) staging should be used as a guideline (Fig. 1). In the vast majority of rheumatoid lesions, a proper indication for joint surgery can be derived from this scheme. The prophylactic effects of surgical procedures, i.e., the prevention of further deterioration or the development of secondary changes, can generally be realized in stages LDE I–III, which is the area of pure synovectomy, whereas beyond stage III additional reconstructive interventions are indicated.

However, in a number of inflammatory conditions it is more useful to rely on a more functionally oriented staging system. The Simmen classification (Table 1) is useful for rheumatic wrists because early arthrodesis should be carried out in type III cases, whereas synovectomy and Darrach's procedure, arthroplasty, or partial arthrodesis are more beneficial for types I and II.

There are many types of wrist endoprostheses (e.g., Meuli, Volz, GUEPAR) which can lead to maintenance of the functional

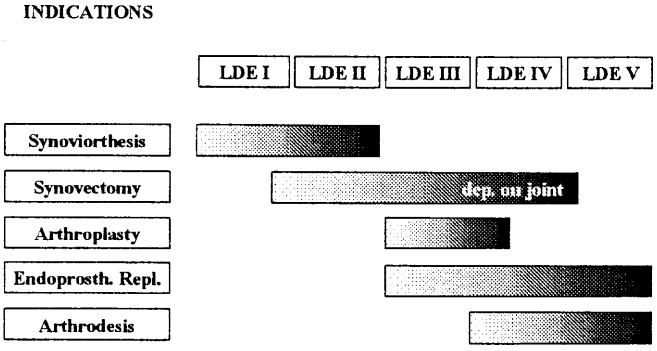

Fig. 1. Radiological staging according to Larsen, Dale, and Eek (*LDE*)

Table 1. Radiological and functional classification in the wrist, according to Simmen et al.

Type I	Development of spontaneous ankylosis
Type II	Development of secondary osteoarthritis
Type III	Disintegration (mutilans type, carpal collapse)

Simmen I and II, self-stabilizing; *Simmen III*, destabilization

capacity of the hand, but good bone stock is absolutely essential for a reasonable result. Silicone rubber arthroplasty is considered to be obsolete nowadays. Depending on the individual's needs and demands, wrist fusion, according to Mannerfelt (96% satisfaction; studies from the North-West German Centre for Rheumatology) or according to Nalebuff, represents a safe procedure which contributes to considerable pain relief and grip strength.

In the rheumatic thumb, arthrodesis of the MP-I, the IP-I, or both joints is usually a better solution than silicone arthroplasty of the MP-I with respect to grip strength and pain relief. Combined arthrodesis of the destroyed MP and IP joints results in a strong pinch grip and a 3-point grip.

A flexible implant arthroplasty of the CMC-I has shown excellent results (96% very good or good, FU 6.3 years; studies from the North-West German Centre for Rheumatology), but the inclusion of an implant at this level is not necessarily needed. Suspension arthroplasty according to Epping offers adequate results (87% very good or good, FU 6.9 years) and specific complications associated with the silastic material are avoided.

In boutonnière and swan-neck deformities up to grades 2 and 3, respectively, various soft tissue and release procedures have been developed. Amongst these, the methods recommended by Heywood, Littler, and Matev for buttonière deformity are widely used, whereas dermodesis and tenodesis are recommended in stages 1 and 2, and Littler's release and Nalebuff's procedure are indicated in stage 3 of a swan-neck deformity. In more advanced stages, arthrodesis of the PIP (eventually plus a DIP arthrodesis) and, depending on the involvement of the MP joint, a combination with MP arthroplasty is indicated.

The long-term results of silastic arthroplasty of the MP joints are impressive, and still represent the gold standard in finger arthroplasty (86% very good or good, FU 12.2 years; studies from the North-West German Centre for Rheumatology). Nevertheless, in less severe cases, nonconstrained finger implants for the MP and PIP level should be considered.

Artificial replacement of the talocrural joint reportedly leads to good results (TPR, New Jersey, Mayo, STAR). The low-contact stress designs seem to be advantageous. For the STAR design, a 10-year survival rate of 75% in rheumatoid arthritis cases was calculated. However, the bone stock must be adequate, and talar necrosis is a clear contraindication. It is also important to correct

the back of the foot and fuse the subtalar joint at the same time, if necessary. Arthrodesis of the talocrural, the subtalar, the TN, and the CC joints, as well as combinations of these, is indicated for severely destructive conditions. On the other hand, fusions at these levels may lessen the function of the lower limb very considerably, and arthrodesis still remains an attractive alternative with respect to pain-free stability. Depending on bone quality, external fixators, i.e., nails, screws, staples, or a combination of these, are used. Even so, the results of total ankle arthroplasty are less predictable.

It should be noted that the talonavicular joint is affected in 98% of cases during the course of rheumatoid arthritis (studies from the North-West German Centre for Rheumatology). At the same time, this is the key joint for further deterioration or collapse of the back of the rheumatic foot. Therefore, it is strongly recommended that the TN-joint is fused at an early stage of the disease.

According to Tillman, correction of the front of the foot can be performed by a safe and highly improved method, consisting of a Hueter–Mayo procedure on the great toe in combination with Hoffmann's metatarsal head resection of the second to fifth ray. The results are very satisfactory with respect to pain relief, walking ability, foot shape, and functional parameters (76% very good or good, FU 13.5 years; studies from the North-West German Centre for Rheumatology). However, the toe function decreases during the course of follow-up. Therefore, it may be advisable to consider fusion of the MT-I joint as an alternative. Arthrodesis at this level might result in better load-bearing capacity of the first ray.

In inflammatory joint disease, the polytopic pattern of joint destruction and the involvement of the surrounding soft tissues requires a surgical strategy with respect to priorities, timing, staging, and local aspects, as well as with regard to the general value of different surgical procedures. Therefore, not only from a psychological standpoint, it is prudent to start with a "winner" operation, i.e., TKA, THA, forefoot reconstruction, dorsal wrist synovectomy and reconstruction, MP and IP fusion in the thumb, CMC-I arthroplasty, or flexor tenosynovectomy of the hand, if it is at all possible.

VI-2: Surgical treatment of cervical lesions on RA patients: image-guided surgery

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Objectives

Cervical disorders caused by rheumatoid arthritis (RA) include atlantoaxial instability and subluxation in the mid- and lower cervical spine. These conditions sometimes cause myelopathy and/or severe pain, which impair the quality of life of RA patients, and surgery may be indicated. Posterior procedures using wiring or hook systems have been employed, but these sometimes resulted in loss of reduction and/or nonunion. C1–2 transarticular screws have recently been adopted by many surgeons to achieve C1–2 stabilization, and pedicular screws have also become an option to achieve occipitocervical and intercervical stabilization. Both techniques provide greater biomechanical stability than conventional posterior fusion methods. However, these procedures are technically demanding and have potential risks of neurovascular injuries. To improve the accuracy of screw placement in the cervical spine of patients with RA, this department has adopted an image-guidance system, and the usefulness and limitations of this technique are described.

Patients and methods

Eighteen patients with cervical instability, including atlantoaxial instability due to rheumatoid arthritis, received instrumentation surgery under an image-guidance system. All the patients had myelopathy, and two had severe neck pain. Neural and vascular injury was evaluated, and postoperative computerized tomography (CT) was used to determine the accuracy of screw placement.

Results

The mean fiducial error at intraoperative registration ranged from 0.3 mm to 0.8 mm (average 0.5 mm). There were no neurovascular complications, and screw placement was extremely accurate. Myelopathy improved to some extent in all cases. No instrumentation failure, loss of reduction, or nonunion had occurred at a final follow-up.

Conclusions

Image-guidance systems are useful tools in preoperative planning and in the application of transarticular and pedicular screw placement in the cervical spine of patients with rheumatoid arthritis.

VI-3: Wrist and ankle joint reconstruction in RA patients

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It is clear that the wrist and ankle joints show many anatomical similarities, and they are the keystones for the functions of more distal joints. However, there is one big difference between these two joints: the wrist is a nonweight-bearing joint, and ankle is a weight-bearing joint. This should be kept in mind when considering the reconstruction of wrist and ankle joints.

Good stability at these joints is prerequisite for favorable hand and foot functions. Some mobility is also necessary for the wrist to perform dexterous hand functions, and for the ankle to enable the patient to stand and walk smoothly. In reconstructive procedures for these joints, stability has priority over mobility.

The wrist and ankle joints are frequently involved in RA, and the level of the activities of daily life (ADL) decreases considerably with progression of the disease. For deteriorated wrist and ankle joints, arthroplasty or arthrodesis, combined with synovectomy, have been performed to raise the level of ADL. To date, arthroplasty has not always provided favorable long-term results, and arthrodesis was considered to be the most reliable procedure for wrist and ankle joints in cases of Larsen–Dale–Eek (LDE) grade III or higher.

During the period between 1981 and 2000, we performed TSA in 5 joints in the upper limbs, TEA in 77, TWA in 4, and MCP Swanson in 205. In the lower limbs, we performed THA in 303 joints, TKA in 887, TAA in 35, and MTP Swanson in 200. The clinical results of TWA and TAA were unsatisfactory, although there were satisfactory results of arthroplasties in other joints.

Four wrist arthroplasties with a Swanson implant failed owing to infection, stem fracture with particulate synovitis, or imbalance of the joint with implant loosening. Thereafter, we began to perform limited wrist arthrodesis (radiolunate or radiolunotriquetral arthrodesis in 140 joints) for moderately deteriorated wrists in LDE grades II, III, or IV, and with a preserved midcarpal joint.

With this procedure, ulnar shift of the carpus was prevented and good stability was obtained, with some mobility of the wrist. In severely deteriorated wrists in LDE grades IV or V with subluxation of the carpus, total wrist arthrodesis with the use of an intramedullary rod (modified Nalebuff's method) was indicated in 78 joints. When carpal bone resorption was severe in the mutilating type of disease, an iliac bone block was grafted to restore carpal height.

TAA (KYOCERA ceramic type) were performed in 35 ankle joints with localized destruction at the talocrural joint, but with minimal deformity. Arthrodesis was performed in 33 joints with extended destruction at the subtalar joint with severe deformity. In the TAA group, loosening and sinking of the implant was noted in 43% of the operated joints, and destruction at the subtalar joint appeared and progressed with some pain and deformity. In the arthrodesis group, most patients were satisfied with painless joints in spite of a pseudoarthrosis rate of 25%. In recent years, an intramedullary rod with a fin has been developed for arthrodesis, and the union rate has increased considerably owing to secure fixation. The overall results of arthrodesis were better than those of TAA.

VI-4: A prospective multicenter functional outcome study of arthroplasty in glenohumeral inflammatory arthritis

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Purpose

To assess and compare the functional outcomes of hemiarthroplasty and total shoulder arthroplasty for end-stage glenohumeral inflammatory arthritis.

Methods

Many surgeons used a single implant system (Global-tm, Depuy). A pre- and postoperative visual analogue scale (VAS), a simple shoulder test (SST), an activity list, a physical examination, and radiographic evaluation were employed for assessments.

Results

The study covered 144 cases. Just over 24 months' data were available for 59 cases, including 35 HA and 24 TSA. The female to male ratio was 3 to 1, and the mean age was 60 years. All parameters of the VAS improved. HA and TSA showed no difference. SST scores showed a significant improvement in function ($P < 0.05$) overall. The activities of daily living improved in 35%–46% of patients. Range of motion improved overall. Significantly better active elevation was seen in TSA, and when glenohumeral alignment was achieved postoperatively there were significant VAS differences compared with cases where alignment was not achieved. This included overall pain ($P = 0.05$), and overall quality of life ($P = 0.05$). For all cases in which alignment had been restored, active total elevation significantly outperformed. HA postoperatively, i.e., 131° vs. 85° ($P = 0.004$). Active external rotation and passive elevation were better for TSA vs. HA, i.e., 48° vs. 29° ($P = 0.023$) and 144° vs. 104° ($P = 0.006$), respectively. Glenoid erosions were noted in 12% of HA. In these cases, diminished motion and comfort were observed to coincide with the onset of the erosion. Full-thickness rotator-cuff tears were present in 54% of HA and in 25% of TSA. In the presence of a full-thickness rotator-cuff tear, preoperative rest and sleep comfort VAS were significantly higher (i.e., more pain) ($P = 0.005$ and $P = 0.029$, respectively). Postoperatively, the presence of a tear did not influence VAS, STT, ROM, or alignment.

Conclusions

HA and TSA improves the functional outcome for patients with glenohumeral inflammatory arthritis. When glenohumeral alignment is restored, (a) pain relief and functional parameters are improved even more, and (b) motion is significantly better for TSA. Glenoid erosions will occur in the absence of glenoid resurfacing. This can potentially result in pain, instability, and functional loss.

VI-5: Total hip arthroplasty in RA patients

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Cemented total hip arthroplasty (THA) has been the traditional treatment for pain and disability of the hip in rheumatoid arthritis (RA) patients. However, several studies of cemented THA outcomes have shown higher rates of complications and loosening of components in RA patients than in patients with osteoarthritis (OA). RA patients are distinctly different from patients with OA because of osteopenic boned, medial and axial protrusio acetabulid, and frequent use of oral steroids, antimetabolic agents, and nonsteroidal anti-inflammatory drugs. A long-term follow-up of cemented THA procedures at this institute showed that the major issues for both OA and RA were cemented acetabular component-loosening, ultra-high-molecular-weight polyethylene (UHMWPE) wear, and cement fracture. Therefore, in 1990 we started to use a cementless CoCr acetabular shell and a femoral stem with an extensive porous surface structure, a modular UHMWPE acetabular liner, and a Biolox alumina ceramic head. The survival rate over 10 years is still 100% in RA patients. Our results for cementless THA in RA patients are promising. Ingrowth potential did not appear to be compromised by the potentially poor bone quality in these patients, as all acetabular femoral implants showed signs of bone fixation. To address complications such as postoperative dislocation and UHMWPE wear, we have recently introduced two types of bearing couple: a highly cross-linked UHMWPE liner with a metal or ceramic femoral head, and a metal–metal bearing couple with a large head diameter ranging from 38 mm to 58 mm. We report our clinical experience of cementless THA in RA patients, and our latest perspective on the selection of implants.

VI-6: Total knee replacement for rheumatoid arthritis

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Rheumatoid arthritis affects a large number of patients, 90% of whom have involvement of one or both knees. Total knee replacement is a successful solution for this condition, with the

majority of patients having pain relief and functional improvement. The long-term success with cemented total knee replacement in patients with rheumatoid arthritis has been attributed to low demand and limited functional ability.

VI-7: Patient expectations: quantifying the results

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The essence of meeting patients' expectations is in first knowing the patient, second knowing their expectations, and third providing adequate information in an effective manner to educate the patient about the realistic outcomes one can obtain from total knee and total hip replacement surgery.

Knowing the patient is accomplished by adequate history-taking. Inquiry forms are presented to the patient, which are completed mainly by the patient and partially by the orthopaedic staff.

A portion of this initial survey and evaluation involves stratifying the patients actual (i.e., representative not maximal) daily or weekly activity level. A self-administered questionnaire is also included. Staff are encouraged to use this not only to assess the patient's initial status, but also to gauge their progress in activity improvements after the operation. This is a new, unique instrument, which has been developed in this department specifically for this purpose.

Providing the patient with proper information about what they might expect is outlined in two documents. One is an outline of discussion points, and the other is a brief summary of what is said relating to those points.

The final element of achieving the goal of meeting patients' expectations is the use of audiotapes to make a personalized recording for the patient and their family and friends. We have studied this particular technique, and details of its use and results have been accepted for journal publication. The equipment routinely utilized consists of two inexpensive standard cassette recorders with an ordinary microphone. One tape is a record of discussions and questions during the entire time spent with the patient, and the second is a copy of the attending surgeon's discussions directly with the patient. The second tape is the one which is given to the patient. The first is kept in the office not for medicolegal purposes, but more practically as a back-up for the ordinary dictation record.