Trends-in-Medicine

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By Lynne Peterson

SUMMARY

In RA: Numerous new agents are in development, but rheumatologists are most excited about BiogenIdec/Genentech/ Roche's Rituxan in RA and SLE. Two Phase III trials of Bristol-Myers Squibb's abatacept were positive, but rheumatologists still don't know how to use it. ♦ In osteoporosis: The 18-month TOP trial of NPS Pharmaceuticals' Preos met its primary endpoint, moving a second PTH closer to FDA approval. Pfizer's next-generation SERM, lasoxifene, beat out Lilly's Evista in a Phase II osteoporosis trial. ♦ New Cox-2s, including Merck's Arcoxia and Novartis's Prexige, are likely to be delayed while the FDA works out new guidelines for Cox-2 clinical trials. Merck offered little to differentiate Arcoxia from Vioxx, and hints of CV issues plague both Arcoxia and Prexige. ♦ The data on Amgen's AMG-714 was not as positive as expected, and disappointing results were reported on Boehringer Ingelheim's BIIL-284, Genzyme/Cambridge Antibody's CAT-192, Human Genome Sciences' belimumab, and Novartis's ABN-912.

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The American College of Rheumatology (ACR) meeting kicked off with four failed trials, followed by a press conference with negative data on Genzyme's CAT-192, but it ended with four late-breaker trials that were all positive. In between, the meeting was packed with information on the wide range of new therapies being developed for arthritis and other autoimmune and tissue connective diseases. The cardiovascular safety of all Cox-2 inhibitors also was a major topic of discussion.

TNF INHIBITORS

The TNF inhibitors – Abbott's Humira (adalimumab), Amgen's Enbrel (etanercept), and Johnson & Johnson's Remicade (infliximab) – have been an important advance in the treatment of rheumatoid arthritis (RA), but they are not a cure, and some patients don't respond, respond less than optimally, or lose their response over time. Sources estimated that about 20%-30% of patients fail one of the TNF inhibitors. A South Carolina doctor said, "Usually, they fail within the first six to nine months."

Beyond the three approved TNF inhibitors and the one anti-IL1-a [Amgen's Kinaret (anakinra)], there are a huge number of new agents on the horizon to treat rheumatic diseases. By one estimate, there are 145 agents in preclinical development, and another 80 have reached the clinical trial stage in RA.

It might seem like a good idea to combine some of these new agents, but Dr. Edward Keystone of the University of Toronto warned that cost is likely to prohibit combination therapy. He said, "I think we learned a huge amount from Enbrel+Kineret…There are at least four animal studies that say if you block T-cells and TNF, there is a synergistic effect -- at least an additive if not a synergistic effect. That suggests maybe we should use some kind of combination therapy, but Enbrel+Kineret patients didn't get better, and there was a higher infection rate. That says that what happens in the systemic circulation isn't necessarily what happens in the joint. Your own immune system is very sensitive to change. My hypothesis was that (with Enbrel+Kineret) you altered the systemic immune system and not the joint as much."

Safety

A number of questions have been raised about the safety of TNF inhibitors, including:

➢ ***Is there increased risk of infection vs. other therapies with routine organisms, and do anti-TNFs affect the outcome of infections?*** An expert said,

"What I do – which is different from my colleagues – is routinely give patients a prescription for a broad spectrum antibiotic so they will have it available – to treat them like spleenectomized patients. I tell them if they have a temperature over 102 to take a broad spectrum antibiotic and go immediately to the emergency room, which is what we do with spleenectomized patients. This is not evidence-based, but I use it in my practice."

➢ ***Is there an increased risk of lymphoma in RA or psoriasis patients?*** Doctors are not certain, but most said they warn their patients that this risk is still unknown and is possible.

➢ ***Should you stop the anti-TNF before and after surgery?*** A speaker said, "At our center we hold TNF blockage before and after surgery for all patients."

➢ ***Can anti-TNFs be used in:***

- Hepatitis B and C patients? No.
- Multiple sclerosis patients? No, there is a clear worsening of MS symptoms with these agents.
- Heart failure? No. Amgen's Enbrel (etanercept) failed to show a benefit, and Johnson & Johnson's Remicade (infliximab) showed higher mortality. Abbott's Humira (adalimumab) is not thought to be safe either.

➢ ***Can patients be retreated after successfully eradicating the infection?*** Yes.

➢ ***Should all patients starting an anti-TNF receive pneumococcal vaccine, and does it work in this setting?*** A speaker said, "Obviously, yes, but there is some indication of reduced efficacy of the vaccine…All patients should get a flu vaccine, but we are seeing them turned away this year because they are not on an official high risk list."

FDA Safety Data on TNF Inhibitors
(from a Freedom of Information Request)

Measurement	Remicade	Enbrel
Tuberculosis	335 cases out of 233,000 patients	335 cases out of 113,000 patients
Atypical TMR	30	7
Histoplasmosis	39	3
Listeria	36	2
Aspergillis	29	10

The Value of TNF Inhibitor Therapy

A five-year survey of 3,900 RA patients found:

➢ Patients treated in the community with TNF inhibitors had less active and less severe RA than patients in randomized clinical trials.

➢ 71% of patients would not meet DAS/EULAR activity criteria (DAS>5.1).

➢ Anti-TNF therapy was associated with an absence of HAQ disability progression.

➢ An absolute change in HAQ disability (0.08 units) is less than in randomized clinical trials.

➢ Anti-TNF therapy appears to influence the course of RA favorably.

Mean Outcome of Biologic Therapy vs. No Biologic Therapy in RA

Measurement	With biologic (38.3%)	Without biologic (61.7%)	p-value
HAQ (0.3)	0.9	1.6	<.001
Pain (1-10)	3.2	4.2	<.001
Global severity (0-1)	2.8	3.6	<.001
SF36 physical component	34.5	30.5	<.001
SF 36 mental component	47.1	43.8	<.001

A U.K. study of the cost-effectiveness of TNF inhibitors in psoriatic arthritis – sponsored by Wyeth – found that Enbrel appears cost-effective in DMARD failures, with a 58% certainty that Enbrel is cost-effective at the cost of $54,846 per QALY threshold use by the National Institute for Clinical Excellence (NICE), a U.K. organization that provides guidance on treatments and care for people using the U.K.'s National Health Service.

Timeframe	Incremental cost of Enbrel per QALY
6 months	$121,738
12 months	$95,205
5 years	$68,371
10 years	$51,535

ABBOTT'S Humira (adalimumab)

➢ Most sources said their Humira patients are primarily new patients – or Enbrel/Remicade failures. They said very few patients are being switched from another TNF inhibitor to Humira. A rheumatologist with a very large practice explained, "If patients are around a lot of infection, I put them on Enbrel; otherwise, I use more Humira. Right now about 32% of my patients are on Enbrel, 50% on Remicade because they are Medicare patients, and 18% on Humira."

➢ Sources predicted that Humira use will continue to increase.

AMGEN'S Enbrel (etanercept)

➢ On average, sources estimated that 10% of their Enbrel patients are taking it once-weekly rather than every-other-week.

➢ Amgen was advertising the new 50 mg pre-filled syringe at its booth at ACR. Officials indicated it will be available by

the end of this year, but probably not before Christmas. Doctors agreed that it will be nice for patients and more convenient, but none predicted it would increase Enbrel's market share. A source said, "The syringe won't increase Enbrel use. It's just nice."

➢ The biggest threat to Enbrel market share, sources generally agreed, is BiogenIden/Genentech/Roche's Rituxan (rituximab). A doctor predicted, "Rituxan will get them all."

JOHNSON & JOHNSON'S Remicade (infliximab)

➢ The new lymphoma labeling for Remicade does not appear to have discouraged any doctors from using Remicade. Doctors said they simply explain to all patients that there may be an increased risk of developing lymphoma with any of the TNF inhibitors. One source said, "Patients called (about the Remicade lymphoma announcement), but we reassured them, and no one changed therapies…The rate per 100 patient years is 0.12 with Remicade, 0.09 with Enbrel, and 0.21 with Humira per the package inserts."

➢ From 30%-40% of Remicade patients experience dose creep – where patients need their dose increased (generally only up to a maximum of 8 mg/kg) or the interval between doses reduced, or both. A doctor explained how he handles these patients: First, I increase from 3 mg/kg to 5 mg/kg, and then 8 mg/kg. If I still need to do more, I then cut the time interval from six weeks to four weeks. I only have one patient on 10 mg/kg." Despite this issue, sources said they prefer to dose escalate Remicade patients to switching them to something else. Most said they would continue the dose escalation strategy even when abatacept is available, switching

Drugs in Development

Type of agent	Company/drug	Administration	Comments on activity in RA
Antisense, blocking mRNA	N/A	Parenteral	"Early results are encouraging." Waiting for Phase II and III results.
TACE	GlaxoSmithKline's GL-5402	Oral	Several are in early development, but GL-5402, though only in Phase I, is farthest along.
Soluble TNF (gene transfection via adenovirus)	Amgen's Enbrel	Intra-articular injection	This is disease modifying.
p38 MAP Kinase inhibitor that blocks AP-1 and signal transduction	Johnson & Johnson/ Scios's SCIO-469 (p38α)	Oral	19 companies have ~40 patents on p38s, but the problem has been significant hepatotoxicity in humans and neurological and cardiovascular toxicity in animals. "The selective p38α may resolve the toxicity problem."
IL-1 TRAP	Regeneron	Subcutaneous injection	Dosing may be the issue, but further dose-finding studies are being done. Clinical results so far are "not impressive," but the sedimentation rate and DAS score were significantly reduced.
Adhesion blockers	---	---	Preclinical studies look good, but there are no human studies yet.
Cytokine #1: IL-6: recombinant humanized anti-human IL monoclonal antibody	Chugai's MRA	IV	There is enough data to say this is "encouraging." Good results at 8 mg/kg (but low placebo rates): **Without MTX** / **With MTX** / **MTX only** ACR20 78.2% / 74% / 41% ACR50 40% / 53% / 29% ACR70 16% / 37% / 16%
Cytokine #2: IL-15	Genmab/Amgen's HuMax	Subcutaneous injection	From a small ~24-patient study, this appears a "reasonable approach."
Costimulatory molecules (recombinate fusion protein)	Bristol-Myers Squibb's abatacept (CTLA4Ig)	IV (15-minute infusion)	"Reasonable response" at the end of 12 months. There are indications this works. Phase IIb data showed: ACR20 58% ACR50 39% ACR70 19%
B-cell inhibitors (anti-CD20)	BiogenIdec/Genentech/ Roche's Rituxan (rituximab)	Infusion	Wide experience in non-Hodgkin's lymphoma. Administration with MTX appears best. So far, steroids have to be given -- at least with the first two infusions. Appears effective in RA, SLE, and psoriasis. Safety still a concern but no safety issues have arisen. Dosing schedules need to be better understood.
BLyS	Human Genome Sciences' belimumab		A 70-patient study in SLE (57 treated with drug, 13 placebo) found no change in clinical element of the disease, but a change in markers and no serious safety signal. The numbers are too small to determine safety.
Osteoclast	Amgen's AMG-162	Subcutaneous injection	"The data is tantalizing at best, certainly not definitive." It inhibits NTx and bone alkaline phosphatase at 9 months, and studies underway to see if this also inhibits bone erosions in RA.
Bisphosphenate	Novartis's Zometa (zoledronic acid, zoledronate)	5 mg IV given twice, 13 weeks apart.	At 6 months, 16% of patients demonstrated a decrease in the number of joint erosions from baseline with Zometa vs. none with placebo. Adverse events were comparable. The numbers were small, but this was a proof of concept, suggesting a trend.

to abatacept only when the maximum dose escalation is not sufficient.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Animal studies would indicate that SLE patients should not be given TNF inhibitors because they make animals worse, but anecdotal evidence in humans indicates there may be a group of SLE patients who benefit – and benefit dramatically – from TNF inhibitors. A speaker said these are patients with profusive polyarthritis, mainly musculoskeletal who can't come off steroids because of swollen joints, "In those patients, there has been dramatic improvement in the joints…A colleague said he had five (of these) patients who responded, so I tried it, and within weeks it was the best my patient had been in a long time…Certainly, with inflammatory polyarthritis it seems to have a dramatic effect."

DRUGS IN DEVELOPMENT AND NEW USES FOR EXISTING DRUGS

ACTELION'S Tracleer (bosentan)
Expanding the eligible population

The UNCOVER study by researchers at Johns Hopkins University found that pulmonary arterial hypertension (PAH) is common in patients with connective tissue disease (e.g., scleroderma) but largely undiagnosed. PAH is a major cause of morbidity and mortality in scleroderma (SSc) and mixed connective tissue disease (MCTD), and the prevalence was thought to be 5%-50% among SSc patients, 25% in MCTD, and 20% in SLE. However, this study, sponsored by Actelion, retrospectively reviewed the charts for 815 SSc and MCTD patients, looking for pulmonary hypertension (PH). They found that only 122 had been diagnosed with PH, but when the other 693 were examined by Doppler echocardiogram, one in seven (14%) had evidence of PH. Even more startling, 80% of those identified by echo already were exhibiting symptoms and had still gone undiagnosed.

The message needs to get out to rheumatologists that SSc and MCTD patients should be screened periodically for PH, an investigator said. He explained, "Patients with disease in the scleroderma family should be looking for pulmonary hypertension (PH) and doing an echo study periodically to detect it – because we now have new medications to treat PH…My practice is to screen yearly. You can select within the population some with higher risk – patients with older age onset, a limited form, certain autoantibodies that point in the direction of PH, falling lung function tests (such as low diffusion capacity), and any breathlessness symptoms…but my practice is to look yearly in scleroderma patients."

Once PH is identified by echo, patients must undergo a right heart catheterization to confirm the diagnosis. The investigator said, "We don't treat without confirming the diagnosis by right heart cath." Patients should not be put on Tracleer or another medication without the cath, he stressed.

Should asymptomatic PH patients be treated? The investigator said, "I think this is the new wave of research… Now that we have medications, early intervention in asymptomatic patients may prevent progression…But we need to find out if treating asymptomatic patients will make a difference." The EARLY trial (also sponsored by Actelion) of Tracleer in scleroderma patients with asymptomatic pulmonary hypertension (Class 2) may answer this question. The trial is about to start enrolling patients, and it will enroll about 150-200 patients and will last more than six months. The results are not expected for a couple of years.

AMGEN'S AMG-714 (IL-15)
Not as positive as expected

There was positive data on AMG-714 from an interim analysis of a Phase II dose-finding trial in RA, but the data was not as promising as hoped, and a presentation on AMG-714 was pulled from the ACR press conference schedule. In an open-label Phase I trial presented at ACR in 2003, AMG-714 was well-tolerated and appeared to have a clinical response.

The Phase II study presented this year looked at 118 TNF-naïve RA patients taking one of four doses of every-other-week subcutaneous infusions of AMG-714. However, two-thirds received concomitant MTX. There was a clinical effect shown at the highest doses, but a loss of effect occurred at Week 14, which a commentator said may or may not be real, pointing out that the number of patients in each arm was small.

Interim 14-Week Results of AMG-714 in RA

Measurement	Placebo n=23	AMG-714 40 mg n=21	AMG-714 80 mg n=23	AMG-714 160 mg n=22	AMG-714 280 mg n=21
ACR20 at Week 14	~35%	~40%	~45%	~60%	~58%
ACR50 at Week 14	1 patient	4 patients	7 patients	4 patients	5 patients
DAS score	---	Better than placebo	Better than placebo	Better than placebo	Better than placebo
Withdrawal due to worsening RA	26%	10%	9%	14%	5%
Any adverse event	57%	71%	52%	68%	57%
Infections	35%	14%	22%	18%	33%
GI side effects	26%	19%	13%	27%	10%
Injection site reactions	4%	19%	17%	18%	24%

Other findings from this trial:

- There were two serious adverse events – one DVT and one sepsis (at 80 mg).
- No antibodies have been seen out to 24 weeks.
- No deaths occurred.
- This preliminary data suggests that IL-15 may offer a therapeutic target.

A speaker also suggested that further trials of AMG-714 should focus on the phenotypes of the responders and non-responders. He said, "We may find there are subsets of patients who respond. We might imagine something where some patients respond to TNF vs. IL-6 vs. IL-15."

BIOGENIDEC/GENENTECH/ROCHE'S Rituxan (rituximab)
Early but exciting

There is no doubt that Genentech, at least, is committed to the development of Rituxan for RA, and probably SLE. Genentech officials and researchers have been at the ACR in force, and a dinner symposium on B-cell therapies – sponsored by Genentech – was very well attended.

Doctors are very interested in Rituxan – but sources all said they need to see more data before they would use it. A Texas doctor said, "The Phase II results are encouraging, but I'm not happy with the high steroids at the outset. Rheumatologists will be uncomfortable with high dose steroids." A community rheumatologist said, "The steroids are not an issue if they are only short-term." A South Carolina rheumatologist said, "Rituxan will hurt Remicade mostly. I won't switch patients already on a TNF inhibitor who are doing well…I'm more excited about Rituxan than abatacept because Rituxan appears to work in SLE. We have nothing in lupus…I probably won't give the steroids with Rituxan, just the Rituxan and a little solumedrol." A California doctor said, "The advantage of Rituxan is that it works well in a broad range of diseases. The disadvantage is the lack of data on long-term safety of B-cell depletion."

The Phase IIa data, which were presented some time ago, indicate Rituxan is effective in RA, and three open-label trials suggest it is probably effective in SLE.

1. A Phase I study in seven patients with lupus who failed immunosuppressants. They received Rituxan 375 mg/m^2 in four weekly infusions. It was well-tolerated, and six substantially improved, with the improvements lasting 6-9 months.
2. A study in six patients with active SLE resistant to standard immunosuppressive therapy. On Days 1 and 14, they received 500 mg/m^2 Rituxan and 750 mg CTX IV, plus 30-60 mg of oral prednisone for 5 days before starting the Rituxan infusions. There was a dramatic reduction in BILAG within a month or two.
3. A study in 18 patients of three dosing regimens: low dose (100 mg/m^2), intermediate dose (375 mg/m^2), and high dose (375 mg/m^{2}x4). Rituxan was well-tolerated, and 64% of patients had profound B-cell depletion. The improvement persisted for 12 months.

Two year data on Rituxan in RA showed no change in IgG, no change in anti-tetanus antibodies, no increase in serious adverse events, including infections. The time to retreatment ranged from six to 18 months, with 55% of patients (200 patients) retreated. A researcher said, "The efficacy was not as good as the first time, but it was satisfactory."

Asked if he would use Rituxan in a patient who had an allergic reaction to another chimeric antibody, an expert said, "That has not been addressed, but truthfully, I'd probably worry about that."

There are infusion reactions with Rituxan, but they generally occur during infusion or up to 24 hours post-infusion. Experts do not believe these will be a barrier to usage.

The unanswered questions about Rituxan include:

- **What is the duration of clinical efficacy after a single course?**
- **How often should patients be treated (retreated) with Rituxan?** One source said that most experts are giving a second injection when a patient flares, not at a specific time point. He also said there also has been discussion of giving one dose of Rituxan before a TNF inhibitor, then giving it once a year to "keep the patient in control."
- **Is there an increased risk of serious infections or opportunistic infections?** There were serious adverse events in 4 of 80 patients in the Phase IIa trial, and there is more hypertension, hypotension, cough, back pain, and arthralgia with Rituxan vs. MTX. A speaker said, "There is a rate of 3.3% serious infection in the Phase IIa trial, so there are some serious infections. The numbers are small, and we need larger and longer databases to address this, but to think this is not an immunomodulator like other agents we use would be a misinterpretation." Another speaker indicated there has been one SLE patient who developed serum sickness seven days after a second infusion of Rituxan.
- **What are the long-term implications of B-cell depletion?** However, the wide experience with Rituxan in non-Hodgkin's has reassured many experts.
- **What is the role of biologics in combination with Rituxan?**
- **Will CMS reimbursement for infusions be cut?** In November 2004, CMS is scheduled to announce new physician payment rates for infusions. If the rates are cut to unprofitable levels, that could affect physician willingness to adopt this four-hour infusion therapy.

- **What is the impact on vaccinations,** including flu vaccines?
- **Will short-course high dose steroids be required** as were used in the Phase IIa trial?

Two key trials of Rituxan in RA are ongoing:

- **DANCER**, a Phase IIb trial with and without corticosteroids in combination with MTX in DMARD incomplete responders at 500 mg/m^2. Results from this trial are expected at the end of 2004. There is a Phase IIa/IIb extension of DANCER to evaluate the safety of retreatment with Rituxan.
- **REFLEX**, a Phase II trial of the efficacy and safety of Rituxan in combination with MTX in patients who are inadequate TNF responders. There also is a Phase II extension of this trial. The results of REFLEX are expected about a year from now.

BOEHRINGER INGELHEIM'S BIIL-284
No role for this agent in RA

BIIL-284 is a leukotriene-B4 (LTB4). It is an orally bioavailable pro-drug metabolized via esterases to two active metabolites. In mice, a 10 mg/kg dose was shown to inhibit disease progression in RA, and Phase I studies found a 150 mg dose given orally once-daily was safe and well tolerated. However, in a Phase II study in RA patients, it failed to show any clinical benefit. The Phase II trial was a randomized, double-blind, placebo-controlled, 90-day study of 342 patients in Europe and Canada. An investigator concluded, "This oral, potent, long-acting LTB4 receptor antagonist produced only modest and statistically insignificant improvement in RA patients…So, we can conclude, LTB4 is not a major contributor to the inflammatory process in RA. LTB4 is not a promising target for therapeutic intervention in RA."

The investigator dismissed possible explanations for the lack of effect, indicating this agent is probably dead in RA:

1. Inadequate dose or duration of therapy does not explain the limited efficacy. The maximal effects were seen with the second highest dose tested (25 mg) and by 28-56 days.
2. Limited efficacy is unlikely to be due to LTB4 receptor subtype selectivity since BIIL-284's active metabolites are equally potent on both BLT1 and BLT2 subtypes.

3-Month Results of BIIL-284 in RA

Measurement	BIIL-284 5 mg QD n=80	BIIL-284 25 mg QD n=83	BIIL-284 75 mg QD n=87	Placebo n=92
Primary endpoint: ACR20 at 84 days	20.0% *	28.9% *	28.7% *	18.5%
Total joint count change	14.3 *	13.9 *	12.7 *	13.5

* Nss vs. placebo

BRISTOL-MYERS SQUIBB'S abatacept (CTLA4Ig)
Positive data, plenty of potential, but an uncertain role

Two Phase III trials were presented at ACR (one orally and one as a poster), and both were positive. Abatacept is ahead of Rituxan in development – Bristol-Myers is expected to submit abatacept to the FDA by the end of 2004. But it is Rituxan, not abatacept, that appears to have doctors the most excited.

Sources were less sure where abatacept will fit.

- **Probably for TNF failures.** Experts estimated that 20%-30% of patients fail on anti-TNF therapy and would be candidates for abatacept. An investigator said, "This certainly is a good drug for TNF failures." Another rheumatologist said, "Abatacept takes a long time to work, so I don't think anyone would use it prior to a TNF."
- **Not first line immediately.** Any first-line use will likely depend on pricing. Sources indicated that if abatacept is priced comparably to Enbrel and Remicade, it will compete primarily with Remicade first-line because of the monthly infusions (even though they are only 30 minutes, they are still monthly). Rheumatologists may offer abatacept to all patients and let them choose, but sources indicated that the choice will be between injection (Enbrel) and infusion (Remicade or abatacept), not a clear three-way choice as with the MS drugs. A source said, "Abatacept is clearly not a first-line drug."
- **Not for patients doing well on a TNF inhibitor.**
- **Maybe in lieu of dose escalation of a TNF inhibitor.** Rheumatologists may be less inclined to do more than one dose escalation with Remicade, switching at that point to abatacept, some sources speculated.
- **Off-label in other indications.** A trial in SLE is due to start in the next month. Apparently, the trial design is being finalized now. The company also reportedly is planning a monotherapy trial without MTX.

The results of the one-year, randomized, double-blind, placebo-controlled, multicenter, Phase III AIM trial in 652 patients who had failed MTX were released by poster at ACR. In AIM 10 mg/kg of abatacept was administered in a single 30-minute intravenous infusion on Days 1, 15, and 29 and every 28 days thereafter.

Results were presented at ACR from the randomized, six-month, placebo-controlled, double-blind, Phase III ATTAIN trial in RA patients who had discontinued TNF inhibitor therapy due to an inadequate response. Patients in this trial were allowed to continue on a DMARD (e.g., MTX) but not a TNF. The trial met both primary endpoints, and safety appeared good.

Asked how he would use abatacept clinically when it is approved, the principal investigator, said, "I've never been a big fan of churning patients from one drug (TNF) to another...I'd move to a drug with a different mechanism of action rather than stay in the same family…There is no head-to-head or randomized clinical trial showing switching from one TNF to another is better than using this." He indicated none of the biomarkers checked – including CRP and IL-6 – could identify responders or non-responders.

The serious infection rates were similar in the two arms, though the types of infections differed substantially.

1-Year Results AIM Trial of Abatacept in RA

Measurement	Abatacept n=433	Placebo n=129	p-value
6-Month Results			
Primary endpoint: ACR20	67.9%	39.7%	<.001
Secondary endpoint #1: ACR50	39.9%	16.8%	<.001
Secondary endpoint #2: ACR70	19.8%	6.5%	<.001
Secondary endpoint #3: DAS28 <2.6	14.8%	2.8%	N/A
Secondary endpoint #4: ACR70 maintained for 6 consecutive months	14.2%	1.9%	N/A
1-Year Results			
Secondary endpoint #5: DAS28 <2.6	23.8%	1.9%	N/A
ACR20	73.1%	39.7%	<.001
ACR50	48.3%	18.2%	<.001
ACR70	28.8%	6.1%	<.001
Structural Damage at 1-Year (mean change from baseline)			
Paired radiographs	395 patients	214 patients	---
Erosion score	0.63	1.14	.029
Joint space narrowing score	0.58	1.18	.009
Total score	1.21	2.32	.012
Safety			
Any adverse event	87.3%	84.0%	---
Discontinuation for any adverse event	4.2%	1.8%	---
Serious adverse events	15.0%	11.9%	---
Discontinuations for serious adverse events	2.3%	1.4%	---
Serious infections	3.9%	2.3%	---
Deaths	0	0	---
Headache	17.6%	11.9%	---
Nasopharyngitis	15.2%	11.4%	---
Nausea	12.0%	11.0%	---
Diarrhea	10.9%	9.6%	---
URTI	10.9%	9.6%	---

The questions and issues that were raised about the AIM and ATTAIN trials and about abatacept in general include:

- **Why is the impact on the joint erosion score less than with the TNF inhibitors?** While the AIM data showed a statistically significant improvement in erosion scores with abatacept vs. placebo, the effect was less than is seen with TNF inhibitors. Abatacept researchers speculated that there may be a late catch-up effect with abatacept – that abatacept may take longer to show a comparable benefit, with the erosion benefit improving with time. AIM principal investigator Dr. Joel Kremer of Albany Medical Center said, "We see zero erosion with TNFs at one year but only about a 50% reduction with abatacept. The data is what it is. But the clinical response is in the same ballpark (as the TNF inhibitors). The people who pay attention to radiographic scores are not clinicians… And it could be the two-year (radiographic erosion) data will be better."

6-Month Results from ATTAIN Trial of Abatacept in RA

Measurement	Abatacept 10 mg/kg n=258	Placebo n=133	p-value
Discontinuations			
Overall	13.6%	25.6%	---
Due to adverse events	3.5%	33.8%	---
Due to side effects	5.4%	20.3%	---
Efficacy (mean change from baseline)			
Primary endpoint #1: ACR20	50.4%	19.5%	<.005
ACR50	20.3%	3.8%	<.005
ACR70	10.2%	1.5%	<.005
Primary endpoint #2: HAQ	-.48	-.11	<.001
DAS28	-1.97	-.95	<.05
DAS28 <2.6	17.1%	N/A	---
ACR20 Response in Subgroups			
Patients with prior TNF failure	53.5% (n=256)	23.1% (n=133)	<.001
Prior Enbrel failure	45.9%	18.6%	---
Prior Remicade failure	57.1%	20.6%	---
Prior failure of both Enbrel and Remicade	38.2%	18.2%	---
Safety			
Serious adverse events	10.5%	11.3%	---
Serious infections	2.3% pneumonia and sepsis	2.3% no sepsis or pneumonia	Nss
Neoplasms – benign and malignant	1.6%	0.8%	---
Headache	12.4%	5.3%	---
Nasopharyngitis	7.8%	6.0%	---
Nausea	6.6%	6.8%	---
Acute infusional adverse events	5.0%	3.0%	---

- **Long-term data is needed.** Dr. Kremer said, "We need long-term data on abatacept. AIM is nice, but it doesn't wrap a ribbon around the safety with abatacept."

- **In AIM, abatacept efficacy did not plateau by six months as the TNF agents do.** An investigator said, "There may be a cumulative effect between six and 12 months – or it could be a vagary of this trial."

- **Side effects.**
  - Do side effects increase over time? A Bristol-Myers Squibb official said that side effects in AIM at six months were not collected, so it is impossible to determine if they worsened between six and 12 months in this trial.
  - Is there an increase in serious infections with abatacept? One expert said, "There is no signal of a serious infection rate above placebo." An investigator agreed, "There is no side effect issue with this." There has been one case of possible TB, but that was not proven. So far, abatacept has been tested in 2,000 patients.

- **How and when should abatacept be used?** Dr. Kremer said, "About 25% of TNF inhibitor patients shift agents annually. And there is a backlog of TNF failures and non-responders and patients who were put off by the TNF data or lymphoma reports. In two years, if the safety data continues to be good, abatacept will be a very attractive first choice…Rheumatologists are already programmed to do infusions, and there could be some inherent advantages to a half-hour infusion vs. a longer infusion. Abatacept won't necessarily hit Remicade hardest – that is unpredictable – but if a patient has had infections, the TNFs may be less attractive than abatacept…Abatacept could expand the market (for RA therapies), but we are not getting the referrals we should." Another expert predicted, "Abatacept probably will be started after the TNF inhibitors, but over time adoption will move up as the average doctor gets experience with it. Comfort will develop over time. By the end of this meeting, rheumatologists should be convinced it works."

According to sources, the key advantages of abatacept are that it:

- Works and the results are consistent.
- Is in the "same general category" as TNF inhibitors.
- Has a different mechanism of action.
- The infusion is shorter than for Remicade.

The main disadvantages they cited are that it:

- Is infused.
- Doesn't have long-term data yet.
- Physicians do not have hands-on clinical experience with it yet, which one source predicted will affect the adoption curve.

ENCYSIVE'S Thelin (sitaxsentan) Works in scleroderma patients with pulmonary hypertension

Researchers did a post-hoc (not pre-specified) analysis of the Phase III STRIDE-1 trial of Thelin (an oral, once-daily, selective ET-a antagonist) in pulmonary arterial hypertension, looking only at the 42 patients (33 evaluable) in the trial with a tissue connective disease (primarily scleroderma). For this analysis, both dosage arms were pooled. Researchers found a similar benefit in these patients as to the patients as a whole in STRIDE-1. A second Phase III trial in pulmonary arterial hypertension is underway, and the last patient recently was seen for the first time. It should be completed in February, and the results are expected at the American Thoracic Society meeting in May 2005.

Tissue-Connective Patients in STRIDE-1

Measurement	100 mg Thelin n=16	300 mg Thelin n=17	Placebo
6 minute walk	Improved 20 meters (p<.027)		Worsened by 38 meters
Improvement in NYHA Class	More than placebo (p=Nss)		---
Results of right heart catheterization	Modest reduction in pressure		---
Pulmonary vascular resistance	Improved (p<.05)		---
ALT >3xULN	0		---

A poster presented preliminary results frmo a single-center study, sponsored by Encysive, of Thelin in 11 patients who discontinued Tracleer for liver (LFT) abnormalities or deterioration in functional capacity and six minute walk. Researchers reported that:

- No Tracleer patients with LFT abnormalities had that problem with Thelin.
- One patient with clinical deterioration of Tracleer had transient LFT abnormalities, which resolved spontaneously without stopping Thelin.
- One NYHA Class IV patient died.

Comparison of Tracleer and Thelin

Measurement	Tracleer	Thelin
ETA Ki	0.41.nM	0.45 nM
ETA:ETB ratio	20:1	6500:1
Metabolized by	CYP3A4/2C9	CYP3A4/2C9
Eliminated by	Hepatic	Hepatic/renal
Effect on bile salt export pump/bilirubin	Inhibits/accumulates	No effect/ no efficacy
Effect on p.glycoprotein	Induces	No effect

GENZYME/CAMBRIDGE ANTIBODY'S CAT-192
Not potent enough

Data from a 45-patient trial of this human monoclonal antibody was disappointing. Targeting TGF-β may work, but this agent is not potent enough, and it is unlikely that CAT-192 will be taken forward. However, Cambridge Antibody reportedly has other antibodies in its library and is looking for a more potent one to test.

In this trial, CAT-192 administered by IV infusion at 0.5 mg/kg, 5 mg/kg, and 10 mg/kg were compared to placebo. It was well-tolerated, with no obvious treatment-associated morbidity or mortality. The trial was not powered to look at efficacy, and a researcher said, "We didn't see any clear treatment effect on biomarkers or skin sclerosis score…but this was a six-month study and probably too short to establish efficacy…TGF-β remains an attractive target…but it may be more appropriate to develop more potent anti-TGF-β agents that block more than one isoform."

HUMAN GENOME SCIENCES' belimumab
Not effective in SLE

A 70-patient study in SLE (57 treated with drug, 13 placebo) with belimumab (BLyS, a human monoclonal LymphoStat-B), found no change in clinical element of the disease, but a change in markers and no serious safety signal. The numbers are too small to determine safety. An expert said, "In the right illnesses, it may have a role – for example, lupus. It may be better in lupus and Sjogren's than RA."

IMMUNOMEDICS' epratuzumab
Looks promising in lupus but very early

A study of this humanized anti-CD22 monoclonal antibody in 14 SLE patients found the mean infusion time was 31.5 minutes (range 23-86 minutes). There were no infusion reactions. Adverse events included:

- One patient with sleepiness at the first infusion, attributed to the pre-medication IV antihistamine. This was changed to an oral antihistamine and there were no problems with the next three infusions.
- One patient with herpes zoster, which developed after the second infusion but responded to antivirals.

Epratuzumab in SLE

Measurement	Week 4	Week 12	Week 24
B-cell depletion	N/A	58%	54%
Mean BILAG	~ 4.5%	~ 6%	~ 6.5%
BILAG 50% reduction	9 of 23 patients	8 of 14 patients	1 of 7 patients
Patient global assessment of disease activity	Good	Better	Continued to improve

- One case of otitis media after the fourth infusion, which responded well to antibiotics.
- One patient with elevated liver enzymes.

Other findings included:

- No antibodies were detected.
- There was a consistent decrease in B-cells after treatment, lasting from 24 hours post-infusion through Week 12. B-cell depletion was 58% at Week 12 and 54% at Week 24

Researchers concluded epratuzumab is safe and well-tolerated, moderately decreased B-cell levels, and produced symptomatic improvement in all patients starting with the first infusion. Most patients retained the clinical benefit for ≥ six months.

INCYTE'S INCB-3344, a CCR2
Early *hint* of efficacy in RA

Incyte researchers presented data showing that INCB-3344 is anti-inflammatory but not immunosuppressive in a mouse model of delayed type hypersensitivity (DTH). The mice were treated for seven days with 60 mg/kg orally BID, and showed a "significant response." Then, three doses were tested – 30 mg/kg BID, 50 mg/kg BID, and 100 mg/kg BID – and there was a clear dose response curve.

In primates with active TB, a once-daily, oral administration of INCB-3344 had a "profound" impact on the DTH response. A researcher said, "We were encouraged that we were able to cause an anti-inflammatory response in higher animals."

Overall, the conclusions from these studies were that INCB-3344 has significant anti-inflammatory activity – through clinical and histological signs – and no immunosuppression. A researcher said, "Internally, we've done some work (in RA), and we don't see an exacerbation of disease. We actually see some reduction in disease – in a mouse model."

JOHNSON & JOHNSON/SCIOS'S SCIO-469 (a selective p38α)
No news but experts still hopeful

A number of preclinical studies have shown this agent may work, and ~19 companies have ~40 patents on p38s. The problem has been significant toxicity – hepatotoxicity in humans and neurological and cardiovascular toxicity in animals. A speaker commented, "The selective p38α may resolve the toxicity problem…p38α may be more selective, and it has less hepatotoxicity than other p38s."

NOVARTIS'S ABN-912
Disappointing preliminary results

A first-in-man study of ABN-912 failed to show any evidence of clinical efficacy at any dose (from 0.3 mg/kg to 10 mg/kg).

120-Day Results of ABN-912

Measurement	Placebo n=12	ABN-912 0.3 mg/kg	ABN-912 1.0 mg/kg	ABN-912 3.0 mg/kg	ABN-912 10.0 mg/kg
Serious adverse events	1 patient	1 patient	1 patient	**0**	**0**
Adverse events	33 patients	16 patients	17 patients	1 patient	28 patients
Patients without any adverse event	1 patient	1 patient	1 patient	0	3 patients
Change in DAS28	Down 0.8	Up 0.5 *	Down 0.7 *	Down 0.1 *	Down 0.1 *
Change in CRP	-6	3 *	-4 *	+11 *	+22 *
Change in CD68+ macrophages	-98	-96	-38	-55	+201

* Nss

ABN-912 is a monoclonal human anti-MCP-1 (monocytic chemotactic protein-1) antibody (IgG4). The study was a randomized, placebo-controlled, sequential dose escalation trial in 45 active RA patients on MTX. Patients were infused two weeks apart and then followed for 120 days.

NPS PHARMACEUTICALS' Preos (rhPTH 1-84) Reduces new and recurrent fractures in RA

The 18-month, randomized double-blind TOP trial met its ACR20 primary endpoint, and it showed daily subcutaneous injections of 100 µg Preos reduced vertebral fractures in patients who had never had a vertebral fracture as well as patients with prior vertebral fractures. The trial enrolled 2,532 RA patients without the most severe osteoporosis, just low BMD, not prior fractures; the average age in TOP was 64.4, and 19% had a previous vertebral fracture. Baseline serum calcium in TOP was 9.7 mg/dL (which also is higher than other studies), and 9% of patients had a baseline serum calcium >10.2 (the ULN).

18-Month TOP Results with Preos

Measurement	Preos	Placebo	p-value
Primary endpoint: Vertebral fractures (by ITT analysis with LOCF)	1.32%	3.37%	.001
New vertebral fractures in patients with a previous vertebral fracture (per protocol analysis, n=1,870)	4.24%	8.94%	.04
New vertebral fractures in patients ***without*** a previous vertebral fracture (per protocol analysis)	0.67%	2.08%	.028
Secondary endpoints (change from baseline)			
Lumbar spine BMD by DXA	+7.2%	Slight decrease	---
Total hip BMD	+2.2%	N/A	---
Femoral neck BMD	+2.5%	N/A	---
Safety			
Death	0.2%	0.1%	---
Serious adverse event	8.3%	7.0%	---
Any adverse event leading to discontinuation	11.5%	16.3%	---
Discontinuations due to hypercalcinuria	2.4%	1.0%	---
Headache	1.4%	0.4%	---
Nausea	4.4%	0.2%	---
Vomiting	1.1%	0.1%	---
Dizziness	0.8%	0.2%	---
Serum calcium >10.7	21%	3%	---

The trial did raise some safety issues, though researchers insisted they are not "of any consequence." They included:

- Approximately 10% of patients at early scheduled visits had serum calcium >10.7 mg/dL (which is above ULN), and overall 21% of Preos patients and 3% of placebo patients had a serum calcium >10.7 mg/dL.
- There was no clinically significant changes in serum creatinine.
- <1% of patients discontinued for hypercalcemia.
- Uric acid went up about 7% with Preos.

PFIZER'S lasoxifene Beats out Lilly's Evista (raloxifene)

Lasoxifene is a next-generation SERM in development for the prevention and treatment of osteoporosis in postmenopausal women. A two-year comparison of lasoxifene and Lilly's Evista (raloxifene) in 410 postmenopausal women found lasoxifene was statistically more effective than either placebo or Evista in lipid metabolism, effect on BMD, markers of cardiac risk, and markers of bone turnover. At ACR, a Pfizer official presented the BMD results from this Phase II, double-blind, head-to-head study.

In the Phase II trial, lasoxifene was shown to be safe and well tolerated. The incidence of adverse events was similar for all treatment groups, and most were mild to moderate. There were more hot flushes, leg cramps, and leukorrhea (vaginal moistness) in the lasoxifene patients. Lasoxifene also appeared safe on the reproductive tract:

- No histopathologic changes on endometrial biopsy.
- No endometrial hyperplasia or endometrial cancer cases. A change in endometrial thickness of about 1 mm was seen, but no change was seen on biopsy, so an expert suggested this is due to a "hydration effect."
- No increase in vaginal bleeding with either lasoxifene or raloxifene.
- No increase in uterine prolapse. Researchers reportedly have done extensive work on this and found nothing.

2-Year Lasoxifene Results

Measurement	Placebo n=83	Lasoxifene 0.25 mg/day n=82	Lasoxifene 1.0 mg/day n=82	Evista 60 mg/day n=163
Lumbar Spine BMD				
Primary endpoint: Least squares mean change from baseline	-1.7%	+1.8% *#	+2.2% *#	-0.1% *
Responders (≥ 0%)	28%	72% *#	79% *#	48% *
Strong responders (>3%)	4%	36%	39%	24%
Response > -3%	65%	90% *#	93% *#	77% *
Hip BMD				
Least squares mean change from baseline	-0.2%	+1.9% *	+1.3%	+1.5% *
Responders (≥ 0%)	36%	74% *	70% *	65% *
Strong responders (>3%)	13%	36%	31%	28%
Response > -3%	79%	94% *	93% *	92% *
Markers of Bone Turnover (change from baseline)				
NTx	-7.0%	-35.5% *#	N/A	-15.6% *
Osteocalcin	-13.1%	-39.7% *#	N/A	-28.0% *

* p≤ 0.05 vs. placebo # p≤ 0.05 vs. raloxifene

Based on the results of this trial, the 0.25 mg dose was used in Phase III, where studies in prevention have been completed and an 8,500-patient fracture trial is ongoing, but the data from that trial are not expected for about two years. In the future, less frequent dosing may be possible; Pfizer has been exploring both twice-a-week and once-a-week dosing.

PFIZER'S Mirapex (pramipexole)
May treat for fibromyalgia but side effects are a question

Mirapex, a dopamine 3 receptor agonist, already is approved to treat Parkinsonism (at 1.5 mg/day), and it is used off-label for restless leg syndrome. Now it appears it may work at a higher dose in fibromyalgia as well. Data from a 14-week, 286-patient, double-blind, randomized, placebo-controlled, single-center trial. In this study, patients were given a PPI prophylactic for nausea protection, and the dose of Mirapex was titrated up in 0.5 mg increments to 4.5 mg/day.

For this study, the site advertised for patients, and 286 people responded, with 60 meeting the criteria for randomization. There were 5-6 withdrawals in each arm, further reducing the trial size.

The two interesting findings with this drug were the positive effect on weight (actual loss vs. weight gain with placebo) and an increase in morning sleepiness with Mirapex. A speaker said, "We may be improving inhibition of arousal, thereby allowing normal sleep."

14-Week Trial of Mirapex for Fibromyalgia

Measurement	Calcium carbonate placebo n=21	Mirapex n=39	p-value
Withdrawals	5 patients	6 patients	
Completers	16%	33%	---
Patients on a stable dose of narcotics	67%	44%	.09
Primary endpoint: Change in MDHAQ 10 cm VAS pain score from baseline	- 9%	- 36%	<.01
Change in FIQ	-5%	-25%	<.05
17 point Hamilton depression score	Up ~ 9	Up ~ 29	N/A
Safety			
Nausea	71%	79%	.83
Weight loss	10%	40%	.01
Weight gain	57%	21%	.01
Infection	24 %	37%	.23
Increased anxiety	0	18%	.04
Diarrhea	0	17%	.06
AM somnolence	0	16%	.06
Dizziness	1%	13%	.84
Vomiting	0	13%	.10

REGENERON'S IL-1-TRAP
Disappointing Phase II results

The results of a 12-week, randomized, placebo-controlled Phase II trial of weekly subcutaneous injection of IL-1-TRAP in 199 RA patients were disappointing. Patients in this trial had to have failed at least one DMARD and could not be on a concomitant TNF. An investigator described the results as

12-Week Phase II Results of IL-1-TRAP

Measurement	Placebo n=55	IL-1-TRAP 25 mg n=46	IL-1-TRAP 50 mg n=48	IL-1-TRAP 100 mg n=50
	Primary endpoint: ACR Response			
ACR20	30.9%	34.8%	20.8%	46%
ACR50	9.1%	17.4%	10.4%	20%
ACR70	3.6%	--	--	10%
EULAR good/moderate responders	26 %	36%	33%	46%
Any adverse event	86%	91%	90%	92%
Injection site burning	34%	30%	39%	34%
URI	11%	22%	6%	4%
Serious adverse events	2 patients *	0	2 patients *	0
Death	0	0	0	0

*Not felt to be drug-related, and all resolved.

"not as robust" as might have been expected, and another expert commented that the results were "not impressive."

The key findings, on an intent-to-treat (ITT) basis with last observation carried forward (LOCF) were:

- The sedimentation rate and CRP decline in a dose-dependent manner.
- A clinically and statistically significant improvement from baseline in DAS28 was achieved with the highest dose (100 mg/week).
- <5% of patients developed antibodies, and there was no detectable effect of the antibodies on safety or efficacy.
- 100 mg/week may represent the minimally effective dose clinically.
- The therapy was well tolerated.

An investigator offered two possible reasons for the trials' failure:

- **Too few patients.** "If we had had 100 patients per arm, then the 100 mg effect would have been statistically significant."
- **Background therapy.** "It is possible that allowing patients to receive different background DMARDs contributed to the high placebo response rate and confounded the ability to discern a treatment effect."

SERONO'S Rebif (IFN-β1a)
No efficacy in RA

A six-month, randomized clinical trial in 208 patients with active RA on stable MTX treatment found no benefit to Rebif given three times a week at either 2.2µg/injection or 44 µg/injection. There also was a high dropout rate. There was no significant reduction in the progression of joint damage by Sharp score or by biomarkers. An investigator concluded, "(Rebif) does not appear to influence disease activity or joint destruction in RA patients." He did not think higher doses or more frequent administration would boost efficacy but suggested that other ways to deliver Rebif to the site of the inflammation (e.g., intra-articular injection may be required to achieve clinical efficacy).

6-Month Results of Rebif in RA

Measurement	Placebo	Rebif 2.2 µg/injection	Rebif 44 µg/injection
Dropouts	27%	25%	44%
Change from baseline in Sharp score	1	1	0
ACR20	~28%	~38%	~22%

TAP PHARMACEUTICALS' Febuxostat
Better than allopurinol for treating gout

Positive results were reported from the 760-patient, 52-week, randomized, double-blind, multicenter, pivotal, Phase III trial of once daily, oral febuxostat at two doses (80 mg and 100 mg). Febuxostat is a non-purine, selective inhibitor of xanthine oxidase (NP-SIXO) for lowering elevated uric acid levels associated with gout. In this trial febuxostat was compared to allopurinol, the current standard of therapy. Patients did not have to be allopurinol failures to get in this trial, and researchers didn't know how many had been pre-treated with allopurinol.

The trial met its primary endpoint, with both doses of febuxostat reducing sUA more effectively than allopurinol. There were four deaths in the trial, but all were reported as unrelated to the study drug. Researchers said, "Subjects with average post-baseline sUA<6.0 showed greater reductions in gout flare incidence and in tophus area over time than subjects with average sUA>6.0 mg/dL. A rheumatologist commented, "The data look good. Febuxostat will make a big impact on allopurinol."

52-Week Results of Phase III Trial of Febuxostat

Measurement	Febuxostat 80 mg/day	Febuxostat 100 mg/day	Allopurinol 300 mg/day
Primary endpoint : % of patients with sUA<6.0 on the last 3 study visits	53% (p<.001)	62% (p<.001)	21%
sUA<6.0	81%	82%	39%
% reduction in tophus area from baseline	83.4%	65.5%	49.7%
Discontinuations			
Overall	34%	39%	26%
Due to gout flare	4%	11%	4%
Safety			
Any adverse event	25%	24%	23%
Liver function abnormalities	4%	5%	4%
Diarrhea	3%	3%	3%
Headaches	1%	2%	3%
Serious adverse events	4 patients *	8 patients * (unrelated to drug)	8 patients * (unrelated to drug)

*Cardiovascular events were the most common serious adverse events.

THE CARDIOVASCULAR SAFETY OF COX-2 INHIBITORS

It appears there is a long and tough road ahead before new, second-generation cyclooxygenase-2 (Cox-2) inhibitors gain FDA approval, and it looks especially bad for Novartis's Prexige because it (1) already has shown a CV signal, and (2)

it is the most selective of all the Cox-2s. The FDA hasn't decided what to do about the Cox-2s currently in development, and they are saying little in public, though an official said they are providing more guidance privately to sponsors. However, it appears highly likely that there will be long delays in approval of other Cox-2s – especially if there is any signal of an excess of CV events with a particular agent. There will be a public advisory committee meeting leading to new guidelines, but they are likely to take a fair amount of time to finish. In the meantime, the FDA will be "carefully scrutinizing" new agents.

NSAIDs and Cox-2 Selectivity

Cox-1 Selectivity *(least down to most)*	Cox-2 Selectivity *(most down to least)*
	Novartis's Prexige (lumiracoxib)
	Merck's Vioxx (rofecoxib)
	Merck's Arcoxia (etoricoxib)
	Pfizer's Bextra (valdecoxib)
	Etodolac
	Boehringer Ingelheim's Mobic (meloxicam)
	Pfizer's Celebrex (celecoxib)
Diclofenac	
Ranbaxy's Nalfon (fenoprofen)	
Ibuprofen	
Naproxen	
Aspirin	
Merck's Indocin (indomethacin)	
Pfizer's Ansaid (flurbiprofen)	
Ketorolac	

MERCK'S Vioxx (rofecoxib)
Doctors are sorry to see it go

The first scientific presentation of the APPROVe trial results on which Merck made the decision to withdraw Vioxx (rofecoxib) from the market was made at ACR. A Merck official reviewed the history of cardiac safety of Vioxx, concluding that prior to APPROVe, the risk of cardiovascular (CV) events in randomized trials was:

- Higher compared with naproxen
- Similar to non-naproxen NSAIDs
- Similar to placebo – but there was limited data beyond two years

Dr. Robert Bresalier, a gastroenterologist with MD Anderson Cancer Center and a member of the APPROVe steering committee presented the findings of APPROVe, a multicenter (107 centers in 30 countries), randomized, placebo-controlled, double-blind trial to determine the effect of three years of 25 mg Vioxx on the recurrence of colon polyps. The CV assessment was pre-specified. As of August 16, 2004, there were 118 investigator-reported CV events in APPROVe – 70 thrombotic events and 49 APTC events. The curves separated between Vioxx and placebo at 18 months, with – interestingly – the placebo curve flattening out at that point but the Vioxx curve continuing to rise. No difference was found by subgroup analysis – not by hypertension, hyperlipidemia, age, diabetes, aspirin use, etc. Small increases in blood pressure were seen, but Dr. Bresalier said a preliminary analysis found no link, "The mechanism for the difference between the groups remains uncertain, but analyses are ongoing and the patients will be followed for one year after the protocol." A Merck official added, "We did analyses on patients with hypertensive adverse events to see if they were the same ones with CV events...and they were not…The effect size we saw is much larger than you would have expected from the magnitude of the changes in blood pressure." An FDA official also called the placebo flattening "interesting."

Preliminary CV Data from APPROVe Trial

CV events	Event rate per 100 patient years		Relative Risk
	Vioxx	Placebo	
Confirmed CV events	45	25	---
Thrombotic	.75	1.48	1.96 (p=.007)
APTC	.48	1.08	2.25 (p=.008)

Merck officials offered these comments on the APPROVe data and Vioxx:

- "Clearly, the FDA needs more public input…and the indications for the class remain unclear."
- The efficacy data on Vioxx in colorectal cancer will be ready in spring 2005 and will be presented at a major medical meeting, though which one is not yet clear.
- On whether patients are still at risk after stopping Vioxx: "There is no data on that…APPROVe has a one year off-treatment period, and we are continuing to follow that…That will be a limited data set, but hopefully it will answer that question."
- "The relative risk was similar in both high and low (CV) risk patients."
- On whether Vioxx is ever likely to come back on the market for a subset of patients or a more narrow indication: "At this point, there is no intention to do that."

Cardiovascular Safety of Vioxx in Osteoarthritis

Trial	CV event rate per 100 patient years			Relative risk
	Vioxx	Non-naproxen NSAIDs	Naproxen	
OA Studies	2.05	1.89	---	1.09
VIGOR	1.67	---	0.7	2.3

The impact of the Vioxx withdrawal

Is the CV problem with Vioxx a class effect?

A Cox-2 expert said, "One has to be very careful on what one means by class – and consider what a Cox-2 selective agent is …It is probably true that sustained Cox-2 inhibition may dispose to thrombosis…but the differences among the Cox-2 inhibitors must also be considered – the effects on blood pressure and PK/PD differences…Cumulative data indicate that patients treated with rofecoxib have increased risk for hypertension, CHF, and CV thrombotic events compared to other NSAIDs…Comparably robust data also indicate that celecoxib does not share these properties…(But) there is insufficient population-based data to determine whether the other Cox-2 selective agents confer an increased CV risk."

Are there any mechanistic explanations that differentiate the Cox-2 inhibitors?

Merck officials could not cite any compelling or mechanistic differences between Vioxx and Arcoxia (etoricoxib) that would suggest Arcoxia is safer, but Novartis researchers offered several reasons that Prexige (lumiracoxib) may be safer than Vioxx – despite an early signal among CABG patients.

Do Cox-2 selective agents have a different CV risk profile than traditional NSAIDs?

An FDA official said, "At this point, there is no definitive evidence. The agents differ in degree of selectivity, and dose response may be an important factor. Traditional NSAIDs may differ in CV toxicity profiles – everyone should remember this." Another expert said there are signals with other NSAIDs, citing these two examples: "If ibuprofen is given before aspirin, it may limit the cardioprotective effects of aspirin…(And) there is a higher risk of admission for CHF in Vioxx and non-selective NSAIDs but not with Celebrex."

MERCK'S Arcoxia (etoricoxib) Delayed in U.S. because of questions about cardiovascular safety

The withdrawal of Vioxx made this an even more important potential product for Merck, and shortly after the ACR meeting, the FDA gave Merck an approvable letter for Arcoxia, asking for additional data.

This was not surprising since Merck officials and researchers at ACR were unable to offer any explicit ways in which Arcoxia is different from Vioxx that might suggest why Arcoxia shouldn't have the same cardiovascular (CV) risk as Vioxx. An FDA official said, "We know it raises blood pressure and increases salt retention, but there isn't extensive long-term data. We will have to take a close look at it."

The question of an elevated CV risk with Vioxx first arose with the results of the VIGOR trial, and Arcoxia appears to show the same early signal. However, Merck officials denied that VIGOR contained a "missed" signal – and they insisted there isn't any CV risk signal with Arcoxia. A Merck official said, "You need to take into account the time course…People are confusing what you see with naproxen, and what is seen in APPROVe…With Vioxx, lumiracoxib, etc., you see differences vs. naproxen early – in the first year… It is unclear if (the CV risk) is a class effect or an effect that might extend to other NSAIDs as well…What we saw in APPROVe is very different from what we saw in VIGOR. Over 10-months (in VIGOR), we saw an early separation of curves, with rates lower with naproxen than Vioxx…Over that same treatment period, there is no difference between Vioxx and placebo or non-naproxen NSAIDs (especially diclofenac)…So, it is difficult to view VIGOR as a signal. Given what we've seen with Arcoxia and lumiracoxib – where all seem similar over a year, and the only outlier is naproxen, you have to wonder what is different about naproxen."

On the negative side:

- The half-life of Arcoxia is longer than for Vioxx (22 hours vs. 17 hours).
- Arcoxia's Cox-2 selectivity is similar to Vioxx. One expert described it as slightly less selective than Vioxx (see page 15), but a Merck official disagreed, saying, "The selectivity of Cox-2s depends on the assay used…By the assay we use Arcoxia is 100, Bextra 30-35, and Vioxx 7-8…And the clinical significance of selectivity, in my opinion, is not determined…I believe Arcoxia is more selective."
- The relative risk of CV events with Arcoxia was 1.7 vs. naproxen – which is fairly comparable to the 2.0 relative risk of Vioxx vs. naproxen in the VIGOR trial. Dr. Sean Curtis, Director of Clinical Research for Merck, said, "In terms of a signal, we acknowledge and see a difference in events rates vs. naproxen. The so-called signal observed (with Vioxx) in APPROVe was vs. placebo and was not observed until after 18 months of exposure…so the Arcoxia data to me are consistent with a cardio protective effect of naproxen, not a negative effect of Arcoxia."

Dr. Curtis made these other points about Arcoxia:

- "It is like other drugs in the class…Like other Cox-2s, it works in a way it was designed to work."
- "Arcoxia is molecularly distinct from other compounds, and, based on the development program, it has unique properties."
- "It has a favorable PK profile – early and high concentrations which seem to translate into early efficacy."
- "The half-life is consistent with once-a-day dosing."
- "There is a large amount of efficacy data that support this drug."
- "All these drugs (Cox-2s), despite the chemical entity/structure, functionally inhibit Cox-2…but they are all different structurally and…you shouldn't, a priori, apply the safety findings of a drug in a class to other drugs in a class."

- "We presented a pooled analysis of all CV safety data (on Arcoxia)…and in that analysis, we show similar rates of confirmed thrombotic events (all CV events)…They are similar for Arcoxia, placebo, and non-naproxen NSAIDs…There is a decrease in (CV) event rates on naproxen vs. Arcoxia, and we've seen that with other Cox-2 inhibitors – Vioxx and lumiracoxib – so we have data from three compounds that show a similar pattern vs. naproxen…Naproxen could be acting like aspirin in reducing (CV) events…The rates of confirmed (CV) events vs. diclofenac are very similar as well as to placebo…The outlier is the comparison to naproxen, and there is a plausible explanation for that."

The poster presentation on the large (7,111-patient), one-year, randomized, double-blind EDGE trial did little to settle this issue. The trial met its primary endpoint of fewer GI events than the NSAID diclofenac, and there was no difference in CV risk between Arcoxia and diclofenac.

1-Year Results of the EDGE Trial of Arcoxia

Measurement	Arcoxia n=3,593	Diclofenac n=3,518	p-value
Discontinuations Due to			
Any cause	40.5%	45.8%	---
Lack of efficacy	9.7%	10.6%	---
Adverse events	18.2%	22.9%	---
Primary endpoint: GI adverse events	~ 8%	~ 15.5%	<.001
GI adverse events (as a rate per 100 patient years)	9.41	19.23	<.001 (relative risk 0.5)
Clinical serious adverse events	8.3%	8.7%	---
Edema-related adverse events	0.9%	0.7%	.435
Hypertension-related adverse events	2.3%	0.7%	<.001
Hepatic adverse events	0.3%	5.2%	<.001
Cardiac and Cerebral Event Rate within 14 Days of Treatment Discontinuation			
All cardiac events	0.97	0.73	---
AMI	0.68	0.42	---
Sudden cardiac death	0.07	0.04	---
Cardiac events in unstable angina patients	0.22	0.27	---
Cerebrovascular events	0.25	0.27	---
Peripheral vascular events	0.11	0.15	---
Cardiac and Cerebral Event Rate within 28 Days of Treatment Discontinuation			
All cardiac events	0.96	0.77	---
AMI	0.65	0.51	---
Sudden cardiac death	0.07	0.04	---
Cardiac events in unstable angina patients	0.24	0.26	---
Cerebrovascular events	0.27	0.29	---
Peripheral vascular events	0.14	0.29	---

Merck has others trials underway that may shed more light on the CV safety of Arcoxia, but they still may not be definitive since the trials are not placebo-controlled. Dr. Curtis said, "When we combine EDGE with other studies ongoing, we will have >35,000 additional patients beyond the development program, and many will be treated >18 months and some >3 years…So there is a mechanism to continue to assess safety…and we will have CV safety data from three studies in 35,000 patients, with the goal that Arcoxia is similar to diclofenac in terms of CV safety. We feel the existing development plans will clearly provide a large amount of safety data." These trials include:

- **MEDAL.** This is a large trial (23,500) patients, but 40%-50% have dropped out, though a researcher said this was not due to the withdrawal of Vioxx. MEDAL is not expected to reach its event-driven primary endpoint – CV safety – until early 2006.
- **EDGE-2.** This has a similar design to EDGE, but it is in 4,000 RA patients. The results are due about the same time as the MEDAL results.

Another poster reported on an open-label, six-week, single-center, 22-patient, U.K. study (sponsored by Merck) which found that Arcoxia decreases the need for biologic therapy in ankylosing spondylitis, but has no effect on MRI results.

Measurement	Baseline	6 weeks	Implications
Primary endpoint #1: 50% decrease in BASDAI	---	41%	Nss
Primary endpoint #2: Absolute decrease of 20 mm (2 cm)	5.8 cm	3.0 cm	Met
Secondary endpoint #1: % of patients with ASAS20	---	64%	---
Secondary endpoint #2: number of patients with MR lesions at sacroiliac and lumbar spine	---	N/A	No effect
Withdrawals	2 patients (1 for lack of effect, 1 for side effects)		
Side effects	2 edemas		

NOVARTIS'S Prexige (lumiracoxib) Facing regulatory hurdles

Prexige (lumiracoxib) is a highly selective, second-generation Cox-2 inhibitor that Novartis is developing for arthritis and pain management. In September 2003, the FDA said that before a decision on the approvability of Prexige could be made, Novartis had to submit:

1. The results of the TARGET trial comparing Prexige to naproxen and ibuprofen in 18,325 patients. This trial showed no statistically significant increase in CV risk, and a more favorable blood pressure effect profile vs. the two NSAIDs.
2. Additional data in hip osteoarthritis. This trial is ongoing.
3. Additional data in acute pain.

The assumption appears to be that the outlook for this Cox-2 inhibitor has worsened since the withdrawal of Vioxx, but Novartis researchers made a case for Prexige having less CV risk than Vioxx.

On the negative side:

- Prexige showed a CV signal in TARGET. A Merck researcher (sic) said, "In the TARGET data, the relative risk for cardiovascular event with lumiracoxib was 1.7 vs. naproxen. The relative risk for etoricoxib (Merck's Arcoxia) was 0.83, suggesting other NSAIDs, not just Cox-2 inhibitors may have some CV event rate."
- It is the most selective of all the Cox-2s.
- Experts believe the FDA will take a cautious approach to all new Cox-2 inhibitors.

On the positive side:

- Prexige has a short half-life (4 hours), compared to 17 hours for Vioxx and 22 hours for Arcoxia.
- It is the only acidic Cox-2 (ph 4.8), which makes it more like an NSAID in this respect.
- In contrast to the other coxibs, Prexige is not a tricyclic, is not neutral, and has a sulfa group.

The FDA Perspective

Experts are worried the FDA will be tougher on approvals of all drugs, particularly those in classes where safety questions have previously been raised, post the Vioxx withdrawal. One doctor suggested the FDA would take a "once burned, twice shy" approach and may require larger patient numbers. He did not think there is any increased risk (of withdrawal) for existing TNFs, but he pointed out that the lymphoma risk placebo over all the TNF trials is zero. As a result, he is "concerned in the back of my mind about it (lymphoma), but it is not in the front of my mind – now."

Dr. Janet Woodcock, Acting Deputy Commissioner for Operations at the FDA, reviewed coxibs and CV safety in a special session at ACR. Dr. Woodcock's general comments included:

- "Coxibs are among the most toxic drugs for a non-life threatening indication. They have hepatotoxicity, CV toxicity, renal toxicity, etc."
- "Differences in the toxicity profile among traditional NSAIDs have not been definitely shown."
- "We are far from understanding the complex mechanisms that may lead to this (CV risk)…I doubt it's one single mechanism alone."
- She cited several difficulties in evaluating the CV risk of coxibs:
  - Generally, long-term placebo-controlled trials can't be done in arthritis.
  - Placebo-controlled data are the most interpretable because the CV effects of the comparators are not established.
  - Suspicions of CV toxicity means trials in high risk groups need careful scrutiny – "because of the ethics."
  - Higher risk groups take aspirin – and this often confounds the results.
  - Many studies lack statistical power to detect the event rates seen in APPROVe.
  - On the outlook for other coxibs: "Premarket requirements normally don't include an exhaustive evaluation of every possible adverse event…The FDA will have to look at the size of the safety database, etc., for the future for these agents… However, we have trade-offs here in getting products on market and determining the adverse event profile."

Dr. Woodcock's comments about Pfizer's Celebrex (celecoxib) included:

- "VIGOR (Vioxx) showed an increased CV event rate. CLASS (a Celebrex trial) did not show an increased rate – but the event rate was quite low in the placebo arm."
- A retrospective cohort study in 2002 found an increased CV risk with Vioxx over ibuprofen, naproxen, and Celebrex. A new case control study in 2004 in patients over age 65 found a CV odds ratio of 1.17 for Vioxx and 0.95 for Celebrex.
- A randomized clinical trial comparing Vioxx and Celebrex in hypertensive OA found more edema and a more pronounced blood pressure change with Vioxx over six weeks.
- "There are ongoing studies with celecoxib, and the FDA is very interested in these…There are two ongoing colon polyp trials that are…fully enrolled… Both DSMBs get data updates and have issued statements that they are aware of the Vioxx withdrawal and have determined there is no indication for stopping these trials. These DSMBs meet again in late fall, and we will get an update at that time."

Dr. Woodcock's comments about Pfizer's Bextra (valdecoxib) included:

"An increased rate of CV events has been reported in high risk (CABG) patients vs. placebo, so, in an acute setting here is another case of a increased CV event rate observed. Valdecoxib can increase blood pressure and lead to edema as well."

Dr. Woodcock's comments about Novartis's Prexige (lumiracoxib) included:

- "In the TARGET trial of OA patients over age 50, there was no CV difference overall, but when we looked at a

subgroup analysis, the rate of non-fatal MI was significantly higher for lumiracoxib vs. naproxen, even though the difference was not statistically significant…The (CV) rate for lumiracoxib was lower than for ibuprofen, but the statistical power to differentiate those two was fairly low."

The next steps the FDA will take include:

- Watching the outcome of the Celebrex trials ongoing.
- Explore the Bextra data.
- Carefully scrutinize new agents.
- Hold a public advisory committee meeting sometime early in 2005 to discuss CV safety as a step toward preparing new guidelines.

What does the Vioxx withdrawal mean for approval of other coxibs?

Dr. Woodcock said, "ICH guidances usually call for 1,500 patients total, including 300-600 for over six months and 100 for 12 months. This is not sufficient for the kind of side effects (with Vioxx)…Frequently, the size of the premarket safety database is determined by the efficacy trial needs, not by what you want to know about safety…Class-specific concerns can affect the need for testing."

Dr. Woodcock also outlined some of the problems with relying on post-market detection of side effects:

- The FDA cannot condition approval on performance of post-marketing studies for safety.
- Sponsors can do post-marketing studies to obtain an additional safety or efficacy claim.
- MEDWATCH is useful for detecting rare side effects that are otherwise uncommon in the population.
- The FDA cannot require additional safety studies subsequent to approval. The FDA can only move to take a drug off the market.

MEDICARE REIMBURSEMENT

The outlook for infused agents – Remicade, abatacept, Rituxan, etc. – may depend on the final Physician Fee Schedule for 2005 that CMS will release on November 1, 2004. Right now, rheumatologists make (a little) money on the ~ $180 infusion fee. If that is cut substantially, they may be less interested in doing infusions or using drugs that must be infused. A CMS official said, "There is not a lot I can say, but I can say that I think you will be pleased with some parts of it…The RUC looked at your (rheumatology's) comments, and there were discussions…I think you will be happy that you weighed in on this issue."

Another Medicare program that will impact rheumatology drugs is the Replacement Drug Demonstration. It covers three injectables – Humira, Kineret, and Enbrel. Participants in this program:

- Must have Medicare part A or B.
- Medicare must be the primary payer.
- They must have a signed statement from a physician verifying need.
- They cannot have comprehensive outpatient prescription drug coverage from any other insurance.
- They must live in the U.S. or Washington, D.C.

MISCELLANEOUS

Statins

A speaker said, "There are both clinical and biologic reasons to consider them, but it is unlikely they will have a profound effect. There may be a modest effect. But even if they don't affect patients clinically, they might...prevent damage over time…But I wouldn't be jumping for joy (over statins)."

BIOGENIDEC/ELAN'S Antegren (natalizumab, humanized anti-α4β1 MAb)

Sources knew little about development of Antegren in RA, and they didn't have any perceptions of safety or efficacy.

SYNTA PHARMACEUTICALS

This company is working on an oral, small molecule IL-12/IL-23 for psoriasis, Crohn's, and possibly RA.

JOHNSON & JOHNSON'S OrthoVisc (hyaluronan) vs. GENZYME'S Synvisc (hylan) in Osteoarthritis (OA)

The author of a poster on OrthoVisc said he has switched entirely from Synvisc to OrthoVisc because injection site reactions are less with OrthoVisc in OA. However, he was not sure that doctors who tried Synvisc and got disillusioned with it will come back very quickly if ever to any hyaluronan. He said, "At the end of the day, I think more studies need to be done."

22-Week Results of OrthoVisc

Measurement	30 mg 4 weekly	30 mg 3 weekly	Arthrocentesis
WOMAC score ≥20%	74.5%	64.7%	64.5%
WOMAC score ≥40%	65.4%	52.2%	48.8%
WOMAC score ≥50%	57.0%	45.0%	43.5%
Pain at Week 12	-34.9%	-25.0%	-27.9%
Pain at Week 22	-29.5%	-25.5%	-24.6%
Investigator Global Score	-22.0%	-19.7%	-15.4%
Patient Global Score	-33.3%	-25.5%	-25.4%

♦