Trends-in-Medicine

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By Lynne Peterson

SUMMARY

♦ Abbott's Humira (D2E7) is poised for a strong launch, and it is likely to take share from Remicade but even more from Enbrel. The number of patients waiting for Enbrel supply to improve may be far smaller than Amgen estimates, and the company's credibility has been hurt with some doctors. ♦ The Phase II data was positive for Bristol-Myers Squibb's oral CTLA4Ig. ♦ Idec's Rituxan looks promising, with an effect that lasts six-months, but safety remains a concern, and the FDA is likely to require long term (3 year) trials. ♦ Preclinical data on Scios' p38-MAP kinases looks promising, but it is still very early. ♦ Use of Merck's Vioxx is expected to continue to decline due to publicity about cardiac toxicity, with Pfizer's Bextra picking up share.

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With Abbott's Humira (D2E7, adalimumab) on the horizon, the RA marketing wars are starting to heat up. According to an Amgen official, what rheumatologists want in a biologic is: efficacy 39%, sustained effect 21%, frequency of administration 17%, formulation 9%, long term safety data 8%, and no need for TB screening 5%.

While there is no head-to-head data on these three agents, speakers did compare and contrast them at a J&J sponsored-symposium. The symposium attracted a standing room only crowd, not only in the main ballroom but in several overflow rooms as well, and few doctors left early. What attracted doctors and kept them there was a well-balanced presentation of the three biologics for RA – Amgen's Enbrel (etanercept), Johnson & Johnson's Remicade (infliximab) and Humira. It was a soft-sell approach that went over very well with rheumatologists.

Among the interesting comments speakers made about the biologics were:

- **Class effects.** A New Hampshire doctor said, "Maybe we should separate these agents and not consider them a class." Another speaker commented, "Payors consider these drugs a class and won't allow use of another once a patient has failed one anti-TNF agent."
- **Route of administration.** A Maryland doctor said, "The choice of TNF won't be based on safety; it will be route of administration, reimbursement, etc…The short term efficacy of the TNFs in clinical trials appears to be equivalent despite their different routes of administration…I hypothesize that route of administration is only one of many predictors of patient adherence and will not be a determinant of outcome…Route of administration is only one of four variables – the others are duration of action, side effects, cost – that influence patient adherence to treatment."

Speakers pointed to key benefits of each of these drugs:

- ***Remicade*: automatic compliance and Medicare reimbursement.** With an infused drug, the doctor knows the patient got the full dose and when. A speaker pointed out that about 50% of patients are non-compliant with their medication regimen, and that the seriousness of a disease is not associated with better compliance, "Patients think they take their drugs more than they do, and they report higher compliance than is actual…(Thus,) the long-term effectiveness of a drug may be under-estimated because of poor patient adherence, and some non-responders may be non-adherent patients."
- ***Humira*: less frequent dosing and newness.**
- ***Enbrel*: long-term data.** However, a clinician said, "The Enbrel research will automatically transfer to D2E7."

Comparison of the Biologics

Measurement	Enbrel	Remicade	Humira
ACR20	72%	52%	66%
ACR50	48%	33%	54%
ACR70	29%	18%	27%
Advantages	• First biologic approved • Only biologic with a clinical trial for treatment of early RA • Only agent approved for treatment of psoriatic arthritis and juvenile RA • Only agent as sole therapy for RA • Longest-follow-up, long term data	• Medicare reimbursement • Compliance • Doctors make money on infusions • Ability to dose adjust • Response apparent in 2 weeks • Automatic compliance • Titration possible • Dose not limited by volume • Inhibits x-ray progression • Physician control • Rapid onset of action (2 weeks)	• Every-other-week dosing • Inhibits x-ray progression
ISR	37%	Most common adverse event.	19.5% Injection site reactions are the most common non-infectious adverse event
Serious infections	0.041 clinical trials v. placebo .007 post-marketing v. placebo • If patient does develop a serious infection, Enbrel has to be stopped. • 143 TB cases per 100,000 patients in US (expected level). • No increase in infection or malignancy	<1% .(030 per patient year) • 31 cases per 100,000 patients treated in U.S.	• 1.3% (vs. 1.9% placebo) • 6.2% at 40 mg vs. 0.6% placebo in MTX combination study • Incidence in MTX combination trial was 6.2% vs. 0.6% for placebo. • 5.3% (lower than placebo) severe or life-threatening adverse events • ~1% incidence of TB. The risk of reactivation of TB may be increased relative to controls. • Short-term safety profile similar to other TNF inhibitors.
Patients developing antibodies	11% •16 cases lupus-like illness post-marketing	49% • 39 cases of lupus-like syndrome post-marketing	N/A – but rate is the same IV and subcutaneous in health volunteers
Demyelination	No association	Post-market cases: 8 central demyelination 6 optic neuritis 4 GBS/CIDP	N/A
Safety	• Longest safety studies • Rare post-marketing events • Safety profile at least as good as other biologics	• More TB than other biologics	• Data not published yet • Least data of the 3 biologics
Route of administration	Twice weekly injections	Infusion -- Improves compliance.	Subcutaneous with 27 gauge needle Pre-filled syringes Special delivery device designed for RA patients
Issues	No dose flexibility	Need to increase dose over time	May take 12 weeks to show a response

One of the areas where the biologics do NOT appear to have efficacy is heart failure, and they may actually worsen or induce heart failure. The Enbrel heart failure trials – RECOVER and RENAISSANCE – were stopped for lack of improvement, and the Remicade ATTACH trial was stopped for increased mortality. An FDA official said, "There is a signal of a possible association of heart failure with the TNFs. Clinicians should be aware that TNFs may induce new-onset heart failure or exacerbate existing disease…Risk communication is going on now. We also are planning to have scientific communication in peer review literature to sensitize clinicians to this issue. It's important to point out there is a lot of under-reporting in passive reporting systems (like MedWatch), and we rely on people…to report these events...We can't make causal links, but it looks like it." The official then asked the audience if they had seen any heart failure they thought associated with a TNF but that they had not reported to the FDA, and at least two doctors raised their hand.

Other interesting anti-TNF findings included:

- A study by Caremark examined several employer-sponsored health plans and found that most patients are not taking and failing DMARDS before going on an anti-TNF. A Caremark official said, "We are considering a product that would limit coverage to patients who meet the treatment guidelines. We are evaluating whether there is payor interest now." A Pennsylvania clinician disputed the study's findings saying, "This is not what doctors do."
- A Kentucky doctor suggested step-down therapy may be the next step in RA therapy: Start with an anti-TNF and then lower the dose or discontinue it after the patient improves.
- A Scandinavian study found that 37% of RA patients age 20-70 (about 0.08% of the general population) are candidates for biologics, compared to the 15% previously thought to be candidates.
- A University of Pennsylvania Health Plan study found 0.04% of its members had =1 claim for RA.
- A U.K. study suggested that more patients would respond to Enbrel than Remicade if they had a choice of medication.

Measurement	Enbrel	Remicade
ACR20	.515	.335
ACR50	.311	.246
ACR70	.126	.119

PHYSICIAN PERSPECTIVE

Seventeen rheumatologists attending the meeting were questioned about how they intend to use the three biologics, and how they will choose among them, once Humira is approved by the FDA and the Enbrel supply shortage ends. Doctors said there is a lot of interest in Humira, and they predicted it will quickly capture significant market share – provided it is priced below Enbrel. However, use will be limited largely to patients with insurance, so managed care coverage will be an important issue to the success of Humira's launch. Doctors agreed that Medicare patients will continue to use Remicade.

The TNF outlook in 6 Months
(according to these rheumatologists)

Drug	Current TNF use	Expected Use 6 months after Humira approved
Enbrel	38%	28%
Remicade	62%	38%
Humira	0	38% (45% of new patients)

* assuming no Enbrel supply constraints.

Humira (D2E7) is expected to take more market share from Enbrel than from Remicade. A doctor said, "Although Enbrel has not been available (for new patients) for almost a year, doctors still feel it is an excellent drug and very effective. It isn't that they are saying they won't use it again. They still feel it is highly effective, and when there is access, they will use it, but the dilemma will be D2E7. That will really eat into the Enbrel market."

Many doctors will let patients choose which drug they want. A doctor said, "First, they will look at the patient's insurance. If there is a drug card, doctors will present Enbrel and Humira. If the patient doesn't have a drug card, we use Arava before methotrexate (MTX), and then add Remicade after that. Medicare patients will stay with Remicade because there is no Medicare reimbursement for Enbrel or Humira. Health plans are looking at algorithms for injectables, but currently there is a lot of patient choice where coverage doesn't dictate the agent used.

Sources said there are several groups of patients who will be candidates for Humira, including:

- **Patients switching from another agent to try something new.** Sources estimated that about 5%-10% of patients will do this. However, most doctors agreed that they will not switch patients doing well on Remicade or Enbrel.
- **TNF failures,** a growing group. One source estimated it is now about 20%-25% of patients due to non-response, toxicity and tolerability issues. A doctor said, "It's a little less for my group because we avoid CHF patients now."
- **Patients where the Remicade dose continues to creep up or more frequently.** Dose creep occurs with a substantial number of Remicade patients. A doctor said, "Going to one 10 mg dose every eight weeks doesn't help, but a 5 mg dose every four weeks is effective. We need to do that in 15%-20% of patients. Some doctors view that a more of a positive thing for physicians in that you can adjust the dose to fit the patient where with Enbrel you can't adjust the dose (you can decrease it but not increase it), so the general attitude at a recent meeting I attended was that it was more positive than negative. We usually start with 3 mg/kg and go up to 5 mg/kg, and now we consider dropping the interval from eight weeks to six weeks and then to four weeks."
- **Some new patients,** provided they have insurance coverage. The key D2E7 issues will be insurance and reimbursement, sources said. A rheumatologist comment, "Patient insurance will drive use."

Doctors were split on the importance of the convenience factor with Humira's every-other-week dosing.

- *Pro:* A New York doctor said, "Humira dosing is an advantage, and that is what patients will go for – longer duration." A New England doctor said, "Humira's administration will be a big factor."

- *Con:* A Michigan doctor said, "I'm afraid people will forget to take their medication on an every-other-week dosing schedule. Once a day is almost easier." A Tennessee doctor said, "Humira administration is not a big help. Only 1% of Enbrel patients doing well will switch for less frequent dosing."

Enbrel comments:

- *South Carolina:* "It works…but 10% of Enbrel patients may want to try the new drug."
- *Virginia:* "It's been around longer, and I know more about it. If I had a choice, I would use Enbrel, but there are patients who don't like shots or like fewer shots."
- *California:* "Enbrel's advantage is that it's been out longer."
- *Texas:* "I'll still use Enbrel because of the convenient dose, data and better safety."
- *Georgia:* "I'll try Enbrel first, then Humira because of dose creep with Remicade. Patients may prefer Humira, but the Enbrel experience counts."
- *New York:* "The TB issue will help Enbrel."
- *Ohio:* "Existing pediatric patients can't ethically be offered Humira. My preference will be Enbrel until there is a pediatric Humira study."
- *North Carolina:* "Fewer new patients will start on Enbrel."

Remicade comments:

- *South Carolina:* "At least 50% of patients don't have a drug card in our area."
- *New York:* "I'm very happy with Remicade. If Humira is comparable to Remicade, I'll use it first-line over Enbrel, and Enbrel will only be for patients who demand it."
- *New England:* "Patients on Remicade won't switch."

Humira comments:

- *Virginia:* "Patients are scared of new drugs with good reason…I've seen too many drugs take off the market. I'll explain the options, but with a bias."
- *South Carolina:* "I'll use more Humira than Enbrel because it is given less often, so is more convenient – and doctors want to try it…If it's cheaper, I'll recommend it over Enbrel…Health plans could try to force use of Humira first, but I don't think they will do that."
- *California:* "It may take longer than 6 months to capture huge share."
- *Texas:* "I want the drug out six to 12 months before I will use it. I'm cautious. There is no patient demand for Humira. Use will be a patient safety issue."
- *West Coast:* "If I were a patient, I would choose Enbrel or Humira, and everything equal, I would choose Humira."
- *North Carolina:* "It's hard to choose between Enbrel and Humira. Patients are stubborn. You can't talk them into a drug. Method of administration is the single most important factor in their choice of a drug."
- *New York:* "If Humira works, I'll opt for that as a matter of convenience. Diabetics don't have a problem with injections, but rheumatoids don't want to inject. It is more difficult to convince rheumatoids to inject, and it is harder for them to do the injections."

The number of new RA patients is declining. A doctor with a large group practice explained, "There is some information that the number of new rheumatoids is going down, and I think that is correct. The Abbott SONORA study which enrolled people who were newly diagnosed with RA had a heck of a time enrolling patients. I see about 625 patients a month and have about 2,000 active RA patients, but I don't think I see more than one new patient a month…Sometimes we see patients who've been treated for a year or so by a primary care doctor, but very few come in who just developed RA."

Not all RA patients are on an anti-TNF. A doctor explained, "About 60% of my RA patients are on a biologic if not more. The only reason the others aren't on one is that they can't afford it or refuse it. I'd like to have 80% on a biologic because they work so well."

A TNF is a TNF is a TNF. That's exactly what an FDA official said. A rheumatologist agreed, "More and more rheumatologists accept the fact that the three drugs (Enbrel, Remicade, Humira) prevent damage and may help cure damage, so they are more aggressive than they used to be (in prescribing them. Within the first four to six months of the onset of RA, they will be using these drugs."

Most of the prescriptions for biologics are written by a small number of specialists. In 2000, there were about 2,800 rheumatologists who saw =100 patients a week.

TB testing is a non-issue. A doctor said, "I think people got used to the skin test with Remicade, and some do it for Enbrel, too, but for most patients, we don't. We mostly don't do chest x-rays, either, just skin tests. The problem with chest x-rays is you can have abnormal one with rheumatoid patients, and then they want to know what caused it, and that leads to more investigations, bronchoscopy, etc., which delays the start of the drug for two or three months."

Rheumatologists are starting to market anti-TNFs therapy to dermatologists for psoriasis. A doctor said, **"**Only one of 13 dermatologists in my area likes to treat psoriasis, so the other 12 are more likely to refer the patients here for Remicade infusions. I plan to go out and market directly to the dermatologists, and I think other rheumatologists will do that, too."

Weekly Enbrel would make Enbrel more competitive with Humira. However, doctors expect Humira to be priced lower than Enbrel, and there was no data at the meeting on weekly Enbrel.

Humira STAR Safety Trial

Adverse Events	Humira n=318	Placebo n=318
All adverse events	86.5%	82.7%
Serious adverse events	5.3%	6.9%
Severe or life-threatening adverse events	11.9%	15.4%
Serious infections	1.3%	1.9%
Infections	52.2%	49.4%
Malignancies	4%	0
Other	7%	8%

Humira Three-Year Extension Study

(n=53, 79% completion)

Endpoint	Humira 40 mg Q2W
ACR20	64%
ACR50	45%
ACR70	24%

ABBOTT LABORATORIES' Humira (D2E7, adalimumab)

Humira, the first fully-human anti-TNF, was submitted to the FDA in April 2002, and Abbott is seeking a labeling for a dose of 40 mg every other week in RA, including inhibition of the progression of structural joint damage, maintenance of response after three years and impact on patients' quality of life. Abbott officials said the only dose that will be available, at least initially, is 40 mg – which can be administered every other week or, if doctors choose, every week.

Results of Humira ATTRACT and STAR Trials (Pivotal Phase III, 52-Week Trial)

Endpoint	*Humira 40 mg every other week (n=207)*	*Humira 20 mg weekly (n=212)*	*Placebo (n=200)*
Modified Sharp X-ray score			
Mean baseline score	72.1	66.4	66.4
Mean change at week 52	0.1	0.8	2.7
Median change at week 52	0.0	0.0	1.0
No new bone erosions	62%	N/A	46%
Erosion score			
Mean baseline score	41.4	36.7	37.2
Mean change at week 52	0.0	0.4	1.7
Joint space narrowing score			
Mean baseline score	30.7	29.7	29.2
Mean change at week 52	0.1	0.5	1.1
24-week ACR Scores			
ACR20	63.3%	60.8%	29.5%
ACR50	38.7%	40.1%	9.5%
ACR70	20.8%	17%	2.5%
52-week ACR Scores			
ACR20	58.9%	54.7%	24.0%
ACR50	41.5%	37.7%	9.5%
ACR70	23.2%	20.8%	4.5%
Adverse Events			
Injection site reaction	22.9%	N/A	23.5%
Upper respiratory infection	19.6%	N/A	13.5%
Sinusitis	15.3%	N/A	13.0%
Rhinitis	16.9%	N/A	16.5%
Withdrawals			
Total	23.2%	20.8%	30.0%
Due to adverse events	12.6%	7.5%	6.5%
Due to lack of efficacy	2.9%	2.8%	11.5%
Other	7.5%	10.4%	12.0%
Improvement in Quality of Life			
HAQ score (mean change)	.59	N/A	.25
SF-36 score (mean change)	8.5*	N/A	3.1*
FACIT fatigue score (mean change)	7.1**	N/A	3.3

Abbott officials appeared very optimistic about FDA approval of Humira, and FDA officials indicated the submission should go through fairly easily. Sources predicted that Humira could be approved by the end of 2002, but a February to March approval timeframe was considered more likely. An FDA official said, "It is a class thing. The (D2E7) label will be very easy. It will have the standard TB warning and safety information. We only need to discuss dosing…The biggest questions will be on the quality of the data since a lot of it comes from Eastern Europe." However, another FDA official raised questions about the lack of a correlation between an improvement in signs and symptoms with D2E7 and lack of radiographic progression. A Humira researcher also said, "The FDA is asking things the agency never asked before, including once something is approved, how will it be used."

There were a significant number of drop-outs in the Humira pivotal trial, but an Abbott official said the company did several analyses of the data, including last observation carried forward (LOCF) and completors, and the results were consistent. He commented, "If a patient left the study, even if that patient was doing well, it was considered a failure for the analysis." Thus, the dropouts are unlikely to be a problem with the FDA. (NOTE: even though the drop-outs were high, the analysis was done differently than the Alcon anecortave data analysis).

Neither FDA officials nor doctors were impressed with the STAR safety trial. One official told a speaker, "I hope you advised the company not to provide this data to the FDA...What is academically interesting or important is not necessarily the same for regulatory approval." A doctor added, "I think there is value to this trial, but I'm not sure what it is."

AMGEN'S ENBREL (etanercept)

Amgen continues to add to the stack of positive data supporting the value of Enbrel in rheumatoid arthritis. An official estimated that the total anti-TNF opportunity is 1.3 million patients, but most use currently is in severe patients, with only a little use in moderate disease. He said, "We think Enbrel will have a role in the large, uncaptured opportunity of the 49% of patients on a traditional DMARD. Only 7% of patients are on a biologic, split pretty equally between Enbrel and Remicade. About 74% of patients are on methotrexate, 13% on Enbrel, 12% on Remicade, 6% on Arava and 3% on Kineret."

New data presented at the meeting indicates Enbrel rapidly and effectively improves the signs and symptoms of psoriatic arthritis – both the arthritis and the psoriasis. In a 205-patient trial, patients received either placebo or Enbrel (25 mg twice weekly) for six months, followed by a six month rollover extension of all patients to Enbrel. The primary endpoints were (a) improvement signs and symptoms by ACR20 and (b) prevention of structural damage (by radiography, measured as change in Sharp score). Concomitant use of MTX and corticosteroids was permitted. A researcher concluded: "The rate of progression was significantly inhibited with Enbrel vs. placebo, and in the open label period the true rate of progression in the placebo patients may have been inhibited by their exposure to Enbrel, so the rate of difference may be even greater (in favor of Enbrel)…Enbrel inhibits structural damage as early as six months…This is the first study to show anything stopped progression of psoriatic arthritis." Another researcher summarized, "Enbrel significantly inhibits joint destruction, bone erosion, and joint space narrowing."

Enbrel ACR20 Results in Psoriatic Arthritis

Measurement	Placebo n=104	Enbrel n=101
% of patients on glucocorticoids	11%	15%
ACR 20		
3 months	15%	59%
6 months	13%	50%
12 months	---	70%
Mean changes		
Sharp score at 6 months	~.5	0 (p=.0006)
Sharp score at 12 months	1.0	-0.03 (p=.0001)
Erosion score at 12 months	+.66	-.09???
Joint space narrowing at 12 months	+.34	+.05

Numerous additional analyses of this data were completed, and Enbrel showed a statistically significant benefit over placebo in all of them, including: inclusion or exclusion of DIPs; with and without MTX; excluding outliers (top and bottom 10%); disease status; and disease duration by sex, age weight.

However, the combination of two Amgen drugs -- Enbrel and Kineret -- has not proven beneficial. An Amgen official said, "The addition of Kineret did not provide added benefit, and there were some added side effects, so we are not recommending this."

The shortage of Enbrel continues to affect use, and it has affected Amgen's credibility with some doctors. Several doctors interviewed at the meeting commented that they are unlikely to believe the shortage is over when and if Amgen announces it is. Rather, they said they plan to wait and see if supply really will keep up with demand. One doctor commented, "We've heard over and over from the company that the Enbrel shortage was going to be over – but it still isn't. and what will happen if everyone started using it when supply improved? Would we have another shortage?" Another said, "Can we really believe the company when it

says the shortage is over? I don't want to put patients on Enbrel and have a supply problem again."
An Amgen official said the new Rhode Island facility will be inspected by the FDA in November 2002 and should be approved and operating in 1Q03, and he indicated there are patients who have been waiting for Enbrel, "About 6,000 have been waiting less than three months, about 8,000 have been waiting three to six months, and about 12,000 have been waiting six to nine months; 32,000 people are on the waiting list. We have started putting patients on Enbrel, while carefully watching the supply." A rheumatologist put the number much lower, saying, "Maybe 10,000 patients nationally are waiting for Enbrel, that's a reasonable number. I have one patient waiting for Enbrel. Usually we don't like to wait, we want to get them on something. But once it is available again, with doctors making money on Remicade, the split will be about 50/50 between Remicade and Enbrel."

Amgen officials downplayed the possibility of a physician backlash due to the shortage. One official said, "How much 'heat' (anger) is in the system? Our marketing results show us doctors were upset, but they still believe in this product. The brand equity is just incredible. While the upset is there, it appears short-lived. It was directed at Immunex, and Amgen has stepped up, and they've welcomed Amgen stepping up to the plate…We do not want to let existing patients go into short supply again…We are confident that when we have supply restored, the best product – Enbrel-- will re-establish itself as the gold standard."

Despite the shortages, the FDA approved the RADIUS-2 trial, the second phase of a five-year, 10,000-patient study comparing the safety, efficacy and treatment patterns of patients. The drug used to initiate RADIUS-2 was produced in the Rhodes Island plant.

There was no information on weekly Enbrel (50 mg) at the ACR, and the company promised information on this program at its New York analyst meeting in November 2002 – but that was later postponed. A clinician commented, "Maybe 30% of my patients are on weekly Enbrel already at 25 mg/week, and these patients are less likely to change to D2E7."

Amgen offcials made it clear that they are not going to sit back and let Humira come in and take Enbrel market share without a fight. An Amgen official said the company has done a lot of analysis and experimented with different scenarios (including pricing), but wouldn't discuss details of that "war-gaming." Officials cited several points they are likely to make in marketing:

- **Low dropouts.** "A Swedish registry that tracks patients on biologics found that, at 18 months, 55% of Remicade patients were still on the drug and ~80% of Enbrel patients still on that drug."
- **Efficacy.** "Efficacy is the driving parameter to doctors…I think that will and that is where Enbrel is yet to be beaten."
- **Long term data.**
- **Consistent response.** "What we've seen is a fairly consistently response that is maintained. We aren't seeing more and more patients respond after two or three years, but we are seeing a maintained response."
- **Manufacturing.** "Amgen has unparalleled background, depth, knowledge, and experience in quality manufacturing of complicated biologics."

OTHER AGENTS ON THE MARKET OR IN DEVELOPMENT

AVENTIS

- **Arava (leflunomide).** In March 2002, Public Citizen charged there is a link between liver problems and liver toxicity with Arava and called for the drug's removal from the market. However, a speaker defended Arava and attempted to calm fears about this issue. He said that in the last six months there was no statistically significant difference between Arava and placebo in terms of reported liver problems, and in a review of 10,767 patients, including 5,433 Arava patients over 3.5 years, there was no increase in hepatic side effects, co-morbidity, hospitalizations or liver biopsies. "This drug is safe…By summer 2002, there had been 322 deaths reported in patients on Arava (over 3.5 years), and none were from hepatic disease…and the hospitalization rate with was 2.68 for MTX and 2.03 for Arava…We studied 10,000 patients and found no liver biopsy abnormalities attributed to Arava and no hepatic deaths attributed to Arava…The death data is probably the best…we are unable to capture events for people who drop out of the study. So if a patient is taking Arava or MTX and…drops out of the study and then has side effects, we can't tell that…but that is the problem with every ascertained method. We do write to physicians and get hospital records and know as much as we can."

- **Cathepsin S inhibitor.** This is in preclinical development, but is due to start a Phase I trial in 2003.

BRISTOL-MYERS SQUIBBS'S CTLA4Ig (BMS-188667)

This fusion protein binds to CD80 and CD86. In RA, it is infused over 30 minutes once, again at 15 days and then monthly. The dose being developed is 10 mg. A researcher commented, "If the data holds, I'd use this before Remicade because there is no toxicity." Another expert said, "CTLA enrollment went faster than expected. It is easier to give, and that's part of the excitement."

A Phase III trial is due to start in December 2002. Asked how this agent is likely to fit in treatment programs for RA, a speaker responded: "It is conceivable but speculative that it

could be used with other agents. It could be combined with Arava or methotrexate…Most of us don't think of this as an IV competitor. The primary outcome is getting the patient better, and there are many ways to skin that cat. How you give it doesn't matter as much as getting the patient better…There appears to be an incremental improvement over time. We do see a response at one month, but at what point it is clinically meaningful or statistically significant, I don't know yet…The 12-month data were somewhat better than the six-moth data. The conclusion is that this drug is safe, effective and well tolerated. The ACR results are comparable to the results achieved with other biologic cytokine inhibitors…The 2 mg/kg benefit is not worth the added side effects, but if the 10 mg/kg dose works, then we need to evaluate the combination (with MTX), and those studies are in progress or

Phase IIb Results of CTLA4Ig

ACR Score	Placebo	2 mg CTLA4Ig	10 mg CTLA4Ig
Six Month Data			
ACR20	35.3%	41.9%	60%
ACR50	11.8%	22.9%	36.5%
ACR70	1.7%	10.5%	16.5%
12-Month Data			
ACR20	36%	42%	63%
ACR50	20%	23%	42%
ACR70	N/A	N/A	21%
Discontinuations	~28%	~15%	~11%
Total adverse events	94.1%	99.0%	90.4%
Diarrhea	6.7%	9.5%	13.0%
Rash	5.9%	5.7%	9.6%
Serious AE	3 pts	8 pts	3 pts

Measurement	CTLA 2 mg+Enbrel n=85	Placebo+Enbrel n=36
Discontinuations		
Total	20.05	38.9%
Due to AE	7.1% (6 patients)	2.8% (1 patient)
For lack of efficacy	12% *	33%
ACR Score		
ACR20	48.2% *	27.8%
ACR50	25.9%	19.4%
ACR70	10.6% *	0%
Another analysis		
ACR20	44.7	26.8
ACR50	25.9	19.4
ACR70	10.6 *	0
With inclusion of CRP		
ACR20	41.2	25.0
ACR50	23.5	13.9
ACR70	9l.4	0
# of tender painful joints	28.7 down to 17	29.5 down to 22.1
Adverse events at 6 months	88.2%	86.1%

* p<0.05

IDEC'S Rituxan (rituximab)

Early data on this an anti-CD20, anti-B-cell agent looks promising, with two infusions producing an improvement that lasts about six months, but the numbers in the Phase II trial were small (122 patients of 161 patients, with about 30 in each of four arms). The effect appears to be additive with both MTX and cylcophosphamide. An expert said, "B-cells disappear for seven to nine months and sometimes as long as 18 months. It is very unusual for them to come back before six months. We have been retreating patients, some more than four years, and we don't seem to have any increasing problems with toxicity. The concern is what happens if you keep patients depleted repeatedly over time, but for patients often their benefit continues after the Bcells come back." Another expert said, "It is too early to safe if Rituxan is safe (in RA)." A third expert said, "Rituxan appears to work, but it is only one trial. You have to give it with MTX…It is a good molecule, but it has to be a safer agent (to succeed).

Interim Phase II 6-month Results of Rituxan in Rheumatoid Arthritis

Measurement	Rituxan (1 g x 2) + MTX (n=~30)	MTX (n=~30)
ACR20	80%	33%
ACR50*	50%	10%
ACR70	23%	0
Adverse Events		
Hypotension	17%	17%
Hypertension	23%	20%
Exacerbation of RA	7%	47%
Rash	3%	3%
Flushing	3%	7%

An FDA official was asking questions about Ig levels and hypotension. He said, "The B cell reduction is a concern…The infusion reactions in non-Hodgkin's Lymphoma are 'quite impressive,' so we need to watch for them in this (RA)…For approval, it doesn't have to be better than all available products, but we wonder if head-to-head studies should be done. We can't require them, but we can suggest them and encourage doctors to push sponsors to do them."

What if Rituxan is associated with more infections than the anti-TNFs? The FDA official said, "If it is markedly worse, we may need to think about it and maybe take it to an advisory panel. If it were aplastic anemia and there were other agents, that would be problematic."

The FDA official also indicated that the agency is likely to require long-term data on Rituxan in RA. He said, "Protective antibodies might decay over time, so we might want longer safety data, and data on how soon antibodies return. The company probably will need longer-term data, though that is not official. And the company may need to explore other doses." A researcher said, "The Rituxan data looks fabulous, and at half the cost, it will take the market…but I'm not surprised the FDA seems to want longer term data."

University of Rochester researchers studied Rituxan in lupus (SLE) independent of Idec Pharmaceuticals. One of the researchers said:

- "I'm not sure if I would repeat it after the first dose."
- "The B-cell depletion was variable and not directly dose related."
- "The high dose (35 mg/m^{2}x4) makes the most sense."
- "There was no infusion reaction as in NHL."
- "There was a high level of HACA in 25% of patients in the low and medium dose – a finding unprecedented in the lymphoma experience. The consequences are unknown, but experience with other monoclonal antibodies suggests they may be associated with an increased risk of infusion-related reactions or increased clearance of Rituxan."
- "The adverse events raise concerns and warrant close monitoring." These included: 1 case each of right thigh abscess, DVT, TIA, Bell's palsy, and enlarged parathyroid gland, and 2 cases of shingles."

The study concluded: "Rituxan may be a promising SLE treatment. However, variable B-cell depletion, high level HACAs and serologic inefficacy suggest it may need to be used in combination with high doses of steroids and/or other immunosuppressant medications."

ROCHE

- **RO-113-0830**. This MMPI is not in human trials yet, but sources suggested keeping an eye on it. It is being looked at for knee osteoarthritis and other indications. Safety may be the issue, and infections, cardiac problems and skin reactions should be watched.
- MRA. This humanized anti-interluekin-6 (IL-6) receptor is being developed for RA. An international Phase III trial is planned to start in 2003. A double-blind, placebo-controlled Phase II trial of 162 patients indicated the monoclonal antibody is safe and effective.

Phase II MRA Results

Measurement	MRA 8 mg	MRA 4 mg	Placebo
ACR20	78%	57%	11%
ACR50	48%	N/A	1.9%
ACR70	16.4%	20%	0

SCIOS'S p38-a MAP Kinase

Scios has two small, molecule, oral p38-α MAP kinases in development, SCIO-469 (a first generation, in Phase IIa) and SCIO-323 (second generation, still pre-clinical). p38-a MAP kinase regulates three relevant pathways in rheumatoid arthritis: TNF-a, IL-1ß, and Cox-2.

Preclinical Data on Scios' p38-MAP Kinases

Issue	SCIO-469	SCIO-323
Status	First generation, Phase IIa half-completed	Second generation, completing pre-clinicals now
Half life in rats	1.2 hours	3.1 hours
Doses tested in rats	10 mg/kg, 40 mg/kg	10 mg/kg, 30 mg/kg, 90 mg/kg
Human dose	In the range of 100 mg tablet	N/A
Dose response	Yes, best results at 40 mg/kg	Yes, best results at 90 mg/kg
Preclinical results	40 mg basically prevented progression of diseases, with the action beginning within the first day. Radiographically, there was a dramatic effect at 40 mg but not at 10 mg.	All doses had radiographic reduction. Dramatic visual reduction in foot edema.

In a rat study of SCIO-469, rats were immunized with type II collagen on Day 0 and developed disease on Day 10. All animals had arthritis going in, so this was a treatment program, and the rats were given the drug daily by mouth from Day 10-28. A researcher with Scios said they found, "No reduction in IgG antibodies to type 2 collagen by ELISA assay, no suppression of delayed type hypersensitivity to type 2 collagen...In summary, there was inhibition of validated targets, immunosuppression was not evident, and there were beneficial actions in experimental arthritis that were quite dramatic: regressed panus, regressed established clinical disease ($p<.001$), reduced radiographic structural damage ($P<.002$)."

A speaker also emphasized the overall advantages of agent like this: "The advantage of an oral small molecule…is that it will be a lot cheaper to create…and it is unlikely there will be much immune response to them."

The human dose will be significantly lower than that administered to mice, but company officials declined to specify the dose being used in the Phase IIa trial. An official said, "Rats are 10-times less sensitive (to p38), and we designed our human dose considering the high rat metabolism. But every dose we've tried had a biologic effect in Phase I." Another company official said that the drug may not need to be on board all the time for a durable response, which may mean it will be able to be dosed intermittently – and that may lower the infection risk.

A Phase IIa trial of SCIO-469 currently is underway and is about 50% enrolled. It should be completed by the end of 1Q03. Results may be presented at the American College of Rheumatology meeting in 2003, but top-line results probably will be available sooner, perhaps on the company's first quarter earnings call. The design of this trial is:

- 120 patients, with 61 patients enrolled as of the end of October 2002.
- Patients are divided into 3 cohorts of 40-patients each. When one cohort finishes and is reviewed and approved by the DSMB, the next cohort may begin.
- 6 doses are being tested in combination with MTX. The company will do monotherapy later, if it proves viable with MTX first.
- Patients are treated for 30 days and then followed another 30 days, making this a 60-day trial.

Development of Vertex's p38 kinase was halted due to brain hemorrhaging, but a researcher said this does not appear to be a problem with this the Scios agents, "Tracer studies were done, and there is no significant crossing into the brain. The comparison of the various p38s are a toxicity issue, and depend on how selective the agent is for p38-α and the structure of the molecule...the other structure had problems with liver toxicity, and we've not seen that either. And we are more selective for p38…There is no signal in animals of CNS toxicity. From an efficacy basis, this (SCIO-469) is very exciting, and from a toxicity standpoint, we have seen no problems so far." A Scios official added, "This is a more selective agent than many, and it is not just selectivity but structure that is different. (Lack of) crossing of the blood brain barrier may be due to structure, not selectivity." Another Scios official said, "We have a different molecule that was identified in-house, has lower toxicity, and is further along in development."

Among other companies with a p38 in development are:

- Merck -- preclinical
- Pfizer/Pharmacia – preclinical
- GlaxoSmithKline – Phase 1. (An earlier p38 reportedly failed, but this is a new agent.)
- Boehringer Ingelheim – Phase II in Europe, but there was a report that this is having problems.

WYETH/GENOME THERAPEUTICS's LRP5 receptor blocker

This first started getting attention at the ASBMR meeting in September 2002, and it was the topic of a talk at the ACR meeting as well. A researcher said, "Studies using mice, frogs, fruit flies, and cultured pluripotent stem cells all indicate that Lrp5 functions in the Wnt signaling pathway. Thus, the Wnt pathway appears essential to normal bone mass accrual…I think that turning this gene on selectively may be a way to increase everyone's bone mass 5%-10% and avoid the complications of osteoporosis." The concern with any Lrp5 agent – and what will need to be watched – is whether it also increases breast cancer or colon cancer. Wyeth is searching now for a small molecule that could inhibit Lrp5, and researchers are very optimistic about this.

OSTEOPOROSIS

STATINS

➢ **Bone.** Researchers reported that all but one of the statins -- Novartis' Pravachol (pravastatin) -- have been shown to stimulate bone formation, though AstraZeneca's Crestor (rosuvastatin) may have less effect than the others. A speaker said, "Cerivastatin (Bayer's Baycol) is two or three times as potent as simvastatin at doing this…A simvastatin experiment in rats shows 5 mg/kg/day increased bone formation 30% and 10 mg/kg/day upped it 52%…Most of the statins are equi-potent around 1 micromolar, but cerivastatin is far more potent than the others, and one has no effect at all – pravastatin, which has different chemical properties and is not taken up by hepatic cells -- or by bone cells that we can tell…A statin is not a statin is not a statin. We cannot generalize across the board. All of the statins have similarities but important differences in hydrophobicity, potency, cell uptake, first-pass metabolism, PK, toxic potential, and cell selectivity."

While statins are best delivered orally for cholesterol lowering, dermal delivery may be better for bone effects. A speaker said, "I suspect the oral agents are unlikely to be beneficial because they are not delivered to the periphery in sufficient amounts, but I think there may be a role for statins with dermal delivery. Topical administration leads to higher blood levels, blood levels are maintained higher, and there is much less variation (than with oral delivery) because of the absence under these circumstances of first pass metabolism, so avoiding first pass and the liver may lead to better effects on bone. We delivered lovastatin (Merck's Mevacor) dermally and found increased rat bone volume after only 5 days of therapy…a 166% increase in bone from 1 mg/kg/day and the same with 5 mg/kg/day...(So) short term exposure leads to a prolonged effect."

➢ **Myopathy.** An NIH official provided an overview of the myopathy issue with statins. He said more than 1,000 cases of

myopathy with a statin have been reported through MedWatch to the FDA, "Epidemiologic studies suggest the risk per 100,000 patient years is from 6 to 164 depending on the agent…Rhabodmyolysis symptoms can begin one day or six years after a statin was started."

Frequency of Signs/Symptoms with Statins

Sign/Symptom	Patient Frequency
Myalgia	10%-15%
Muscle weakness	<5%
Muscle tenderness	<8%
Rhabdomyolysis	<1%

The NIH official said there are three syndromes reported in subjects taking lipid-lowering agents:

- Slowly progressive non-inflammatory syndromes (thousands of cases)
- Rhabdomyolysis syndromes (hundreds to thousands of cases, with more than 70 deaths reported to the FDA so far)
- Inflammatory myopathy syndromes (dozens of cases)

The possible mechanisms of action are:

1. Abnormal drug metabolism which alters the PK/PD of the drug
   a. Drug-drug or drug-food or drug-infectious agent interactions
   b. Possible genetic risk factors
   c. Altered elimination due to cardiovascular, hepatic or renal disease
2. Abnormal susceptibility of target organs
   a. Pre-existing myopathies
   b. Abnormal muscle membrane turnover

Among the suggested strategies for minimizing the possibility of myopathy with statin use are:

- Use the statin alone for non-HDL goals
- Consider dietary approaches
- Use niacin rather than fibrates
- Keep the dose of the statin and the fibrate as low as possible
- Dose the fibrate in the morning and the statin in the evening
- Avoid or cautiously use the combination of statin and fibrate in renal impairment to minimize drug-drug interactions, and teach patients to recognize symptoms

An FDA official said, "We now have thousands of reports of myopathy at the FDA…One relatively good epidemiologic study in the U.K. found the overall incidence to be 2.3 cases per 100,000 person years…We have to consider that any agent effective at lipid lowering will have a risk of myopathy."

Relative Risk of Myopathy with Statins

Drug	Relative Risk per 100,000 person years	Cases of fatal rhabdomyolysis	Rate of rhabdomyolysis
All statins	7	74	.15
Pravastatin	27	3	.04
Simvastatin	6	14	.12
Lovastatin	N/A	20	.2
Fluvastatin	N/A	0	0
Atorvastatin	N/A	6	.04
Cerivastatin	N/A	31	3.16
Fibrates	42	---	N/A
Fenofibrate	164	---	N/A
Bezafibrate	39	---	N/A

Asked if the FDA wants doctors to report all myopathy-related symptoms, the official said, "The FDA wants serious, non-recognized adverse events reported. They consider myopathy and rhabdomyolysis a recognized event with these agents. They are labeled as having these problems, so the FDA is really interested in what else might be out there."

A Merck official said, "We are focusing on the basic science of myopathy because it so hard to get a clinical read on the issues…The best data today is from the Heart Protection Study (HPS) of 20,536 patients (10,269 on simvastatin 40 mg and 10,267 on placebo), which found the annualized risk of myopathy with simvastatin was about 0.01%. This translates in this group to 70 major events averted for each case of myopathy…It turns out that cerivastatin in rats causes tremendous myopathy; we can melt the muscles of rats (with cerivastatin)…There may be (a cellular) compensatory response (to cholesterol synthesis reduction), and that may be the cause of the myopathy. We tested that theory with DNA arrays…and our preliminary data suggest we will be able to define a set of genes associated with statin-induced myopathy in rats…Merck has demonstrated that 160 mg fenofibrate has no significant effect on the PK of simvastatin (manuscript in preparation)…So, our conclusions are that…not all statins are equal in their interactions, and not all fibrates are equal as perpetrators (of an interaction)."

PROTEASOME INHIBITORS

Proteasome inhibitors appear to stimulate bone formation even more than the statins. A speaker said, "I'm not sure if any of these drugs will turn out to be useful for osteoporosis, but they are a powerful proof of concept. They identify a molecular target that can be utilized for drug discovery."

COX-2 INHIBITORS

Six doctors at the meeting were questioned about their Cox-2 use. They generally agreed:

- There is little interest in a new Cox-2 – unless it has some clear-cut advantage in terms of cost, onset of action, less frequent dosing, etc.
- The currently approved Cox-2s are relatively comparable in terms of efficacy. An Oklahoma dcotor said, "there is no real difference in the three (Vioxx, Bextra, Celebrex)."
- Vioxx use has been hurt by reports of an association with cardiac problems, edema and hypertension, even though most doctors are not convinced there is an inrease MI risk with Vioxx.
  - A New York doctor said, "The media made (the cardiovascular risk) a patient concern, and patients are driving us away from Vioxx."
  - Another doctor said, "We are using very little Vioxx because of the hypertension, edema and MI concerns. I've really seen edema and hypertension with Vioxx."
  - A Georgia doctor said, "I'm very concerned with the cancer and cardiovascular issues with Vioxx. I think the hypertension is a class effect, but I'm not sure about the MI risk."

There was an interesting exchange between a speaker and an FDA official:

FDA: "What is the best comparator (for Cox-2 trial), and what are your thoughts on whether the renal effects on hypertension and edema, which are dose dependent and appear higher with Vioxx (Merck, rofecoxib) than other NSAIDS, with no dose dependent effect with Celebrex (Pfizer, celecoxib)?

Speaker: "It is largely driven by regulatory requirements. It is good to have comparators, but if they differ pointedly, then you are not testing one single hypothesis but two as shown by the CLASS trial (of Celebrex). So, we should work together with regulatory authorities to see whichever hypothesis is being tested, so that it is just one and not two. If you want to compare a highly selective Cox-2 with a non-selective Cox-2, we should pick a really non-selective NSAID."

FDA: **"**The studies are probably telling us that all the NSAIDs are probably not the same."

Average Cox-2 Prescriptions by Specialty

Drug	Rheumatologists	PCPs	Orthopedists	Other	Total
Celebrex					
Average daily dose	335.72	260.02	252.40	269.81	267.86
Average number of pills	1.76	1.42	1.3	1.5	1.45
Vioxx					
Average daily dose	27.51	28.05	28.31	29.30	28.2
Average number of pills	1.1	1.09	1.07	1.13	1.09

Source: Merck poster

NOVARTIS'S Prexige (lumiracoxib, Cox-189)

The 200 mg dose of Prexige appears equivalent to (and 400 mg Prexige better than) 200 mg Celebrex in treating pain associated with osteoarthritis of the knee. However, there was no clear dose-response curve.

13-Week Prexige Trial

Measurement	400 mg qd (n=491)	200 mg qd (n=487)	Celebrex 200 mg (n=481)	Control
Serious Adverse Events	2.5%	2.9%	2.9%	3.3%
Gastrointestinal effects	3.7%	4.5%	4.0%	2.5%

PFIZER'S Bextra (valdecoxib)

The most interesting information on this agent came from a rheumatologist who said, "The way the company launched it was wrong. They took us to dinner and had a telephone conference with an anesthesiologist, and all she talked about was pain, but it's not approved for that -- just OA and RA – so the company broke the FDA regulation on how to market the drug. And then, the next talk was by an orthopedist, and all he talked about was pain, too. In talking to the sales reps, I've found that some reps quit because sales were so bad…Bextra was a me-too. It may be as effective as Naprosyn (Roche, naproxen), but I'm not sure of the efficacy."

MERCK'S Vioxx (rofecoxib)

Three-month data from the ADVANTAGE trial looked at hypertension with Vioxx compared to naproxen patients. Researchers concluded that there was no difference between Vioxx 25 mg and naproxen 200 mg. There also was no difference in thrombotic events.

The ongoing TARGET trial compares Prexige 400 mg qd to ibuprofen 800 mg t.i.d. and naproxen 500 mg b.i.d. in >18,000 patients.