Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Genentech/Biogen Idec/Roche's Rituxan stole the show with impressive results in rheumatoid arthritis (RA) – including some early radiographic data – that had rheumatologists eager to use it. In fact, many have already started using it off-label in lupus and a few refractory RA patients. ♦ Bristol-Myers Squibb's Orencia also was generating excitement, but doctors do not know how to choose between Orencia and Rituxan for TNF failures. ♦ Johnson & Johnson/Schering-Plough's golimumab (CNTO-148) appears, from Phase II data, to be on track to replace Remicade in RA. ♦ Roche's Actemra (tocilizumab) looks like another option for RA, but liver and lipid elevations are casting a shadow over the prospects for this agent. ♦ Amgen's denosumab was shown to be effective at increasing bone density in postmenopausal women, and Jazz Pharmaceuticals/Orphan Medical's Xyrem was shown to be efficacious for fibromyalgia, but Neurochem's Fibrillex had disappointing results in amyloidosis.

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For several years, new therapies have been changing the way rheumatologists treat rheumatic diseases and offering patients new hope, and the trend is continuing. Several promising new agents are on the near horizon, and rheumatologists appear eager to embrace them.

AA AMYLOIDOSIS

NEUROCHEM'S Fibrillex (NC-503) for AA amyloidosis

This first-in-class agent missed the primary endpoint in a two-year, randomized, double-blind, multicenter, international, 216-patient study, but researchers noted that there was still a 42% risk reduction for renal decline or death with the drug. Fibrillex is an oral glycosaminoglycan (GAG) mimetic – or amyloid disease-modifier – given BID, with a half-life of 10-20 hours. Three doses were tested: 400 mg, 800 mg, and 1200 mg BID.

24-Month Trial of Fibrillex

Measurement	Fibrillex (all doses)	Placebo	p-value
Demographics			
Underlying infections at baseline	21%	9%	0.01
Serum creatinine (sCr)	1.2	1.4	0.05
Discontinuations			
Completers	63 patients	61 patients	---
Voluntary withdrawal or lost to follow-up	4 patients	8 patients	---
Dropped for adverse events or serious adverse events	7 patients	13 patients	---
Results			
Primary endpoint: Stable or improved (≥50% increase in sCr)	73.0%	59.6%	0.063
Worse (≥50% reduction in sCr or ≥100% increase in sCr)	27.0%	40.4%	---
First "worse event"	29 events	45 events	0.025
≥100% increase in sCr	12%	25%	0.027
≥50% reduction in sCr	22%	39%	0.011

FIBROMYALGIA SYNDROME (FMS)
JAZZ PHARMACEUTICALS' Xyrem (sodium oxybate)

Jazz got this somewhat controversial agent (GHB, dubbed the date rape drug) with the purchase of Orphan Medical this past summer. Xyrem is approved for cataplexy associated with narcolepsy. The data presented in fibromyalgia met the primary endpoint, and there is a need for new agents in fibromyalgia. However, the data weren't overwhelming, and it isn't clear that the FDA will find it sufficiently compelling to approve an indication that could allow widespread use of Xyrem.

In addition, the drug has rapid absorption and a short half-life (0.5-1.25 hours), resulting in dosing that appears cumbersome: 4.5-9.0 mg administered BID at night as a liquid, with the first dose at bedtime, and the remainder four hours later in the night. That means, users would have to take it and then wake up to take another dose. An investigator defended the dosing regimen, pointing out that this way patients don't wake up with a hangover, "The advantage is the patient awakes with no drug effect…In my experience with patients taking this medication for as long as nine months and continuing to benefit, the benefit seems to come from a progressive change in these patients…as they begin to recover some physical and mental functions they were deprived of for lack of sleep." Xyrem also crosses the blood brain barrier and the placental barrier, so there would be concerns about pregnant women taking it.

In a 188-patient, 8-week, randomized, double-blind, placebo-controlled, parallel treatment study in patients with primary FMS, the primary endpoint – reportedly at the recommendation of the FDA – was for a composite endpoint of change from baseline in

1. ≥20% improvement in PVAS from electronic patient diaries at home three times a day.
2. ≥20% improvement in FIQ (fibromyalgia impact questionnaire).
3. much better or very much better on PGA (patient global assessment).

Researchers reported significant improvement on all primary outcome variables – in the composite and in PVAS, FIQ, and PGA as well as in sleep. A speaker said, "There was a high correlation between a decrease in pain and the increase in sleep…Oxybate was well tolerated, and we think there are ways the nausea might be avoided by changing the way the drug is administered in the beginning…The effect was clearly significant. On PVAS, it was clinically significant based on the 30% that is considered to be a reasonable clinical change. If we look at the number to treat (NTT), this agent is currently the most effective of agents, with an NTT of 4. Other available medications are in the NTT range of 5-7…The effect size is approximately the same with the two doses, so possibly a smaller dose may be effective…And this medication did not have any effect on depression or anxiety…The effect seemed limited to sleep, pain, and an overall sense of well-being."

8-Week Trial of Xyrem in Fibromyalgia *

Measurement	Placebo n=64	Xyrem 4.5 mg/day n=58	Xyrem 6.0 mg/day n=66
FMS duration >5 years	81.3%	58.6%	63.6%
Primary composite endpoint	10%	~36% (p<.05)	~25% (p<.05)
PVAS	---	p<.04	p<.03
PVAS 30% response	~14%	~27%	~28%
PGA	---	p<.03	Nss (p<.11)
Secondary endpoint: Jenkins sleep quality change	---	p<.005	p<.005
TTP	~1.5	~2.9 (p=.08)	~13.0 (p=.05)
Adverse events			
Any adverse event	3 patients	6 patients	12 patients
Dizziness	~3%	~6%	~12%
Nausea	~8%	~13%	~30%
Discontinuations			
Due to adverse events	3 patients	6 patients	12 patients
Lost to follow-up	0	1 patient	1 patient
Protocol error	2 patients	0	4 patients
Lack of efficacy	2 patients	0	1 patient

* All p-values are vs. placebo

OSTEOARTHRITIS: COXIBS

An analysis of coxib use from 1999-2003 by researchers at Brigham & Women's Hospital (with support from Pfizer) concluded that:

- There was an increased cardiac risk with Merck's Vioxx (rofecoxib), but not with Pfizer's Celebrex (celecoxib) or Bextra (valdecoxib).
- NSAIDs were not associated with an increased risk.
- Naproxen (Bayer's Aleve) is cardioprotective.
- The risk with Vioxx is apparent in the first 60 days of use.
- Baseline cardiovascular risk did not modify the future risk of events while using coxibs or NSAIDs.

Safety of Coxibs

Drug	Number of patients	CV events	Incidence rate	Adjusted odds ratio
Celebrex	26,366	1,342	11.4	0.99
Vioxx	17,967	912	13.5	1.15
Bextra	3,060	112	11.4	0.96
Diclofenac	2,673	86	11.7	1.10
Ibuprofen	7,421	151	12.1	0.96
Naproxen	6,130	108	8.6	0.75
Other NSAIDs	11,221	292	11.2	0.95
Non-users	25,532	1,847	10.8	---

RHEUMATOID ARTHRITIS (RA)

Nearly three million Americans suffer from RA, which is a chronic disease causing pain, stiffness, and swelling of the joints. Worldwide the prevalence of RA is 0.5%-1.0%, and it is ~3 times more prevalent in women than men. About 2.1 million of these are diagnosed, and about 1.5 million of these have moderate-to-severe disease and will eventually go on a DMARD or a biologic.

Biologics have been the main growth driver of the RA market, but they are still extremely under-used; the majority of patients today are treated with conventional DMARDs (86%), with biologics only given to 14% of RA patients. Thus, low-dose methotrexate (MTX) therapy is generally the first-line therapy, with patients who do not respond completely to methotrexate increasingly being given a monoclonal antibody targeting tumor necrosis factor-a (TNF-a) – Amgen's Enbrel (etanercept), Abbott's Humira (adalimumab), and Johnson & Johnson's Remicade (infliximab). Bristol-Myers Squibb is expecting FDA approval for its first-in-class, once-monthly intravenous (IV) T-cell co-stimulation modulator, Orencia (abatacept), in the next few months, and Genentech/Roche's Rituxan (rituximab) may not be far behind that.

A poster presented by researchers from the National Data Bank for Rheumatic Diseases reported that the median time to initial treatment discontinuation was 4 years with Enbrel, 3.5 years with Remicade, and two years with Sanofi-Aventis's Arava (leflunamide). However, some patients resumed therapy after a break of six months or more, which would have increased the median time of therapy by ~6 months.

Dr. Ravinder Maini of Imperial College in London gave the opening address at ACR, and he made several interesting comments, including:

- Maybe even humanized antibodies are immunogenic.
- Phase II and Phase III trials have shown remarkably similar clinical data for Enbrel, Humira, and Remicade, with ~70% of patients responding, and 30% not responding. Those who do respond show gradations of response, with rapid improvement in signs, symptoms, physical function, and inhibition of structural damage.
- Early RA is the best time to treat RA. "One of the most interesting things that is beginning to emerge is that in disease of <2-3 year duration, anti-TNF+MTX leads to remission in 40%-50% of patients, in contrast to ~20% remission in patients with established disease."
- "In the context of a very expensive treatment like anti-TNF, it gives hope that there may be significant pharmacoeconomic benefit with these therapies."
- Almost a million patients have been exposed to TNF inhibitors, so there is a huge amount of safety data. "The emerging data on safety…(of TNF inhibitors) is reassuring in some ways…(But) the results of the clinical trials are insufficient to give a full safety picture. You need at least 10,000 patients exposed to assess if there is truly an increased incidence in lymphomas. The problem with lymphomas is that in clinical trials a 3-5-fold increase has been reported over the normal population." He said that a Swedish registry found a 2.9% rate with TNF inhibitors vs. 2.0% with background therapy. The British Society of Rheumatology has a biologics registry ongoing, with 8,500 of 10,000 planned patients enrolled, and so far this is not showing any increased lymphoma risk with TNF inhibitors.
- "I think it is safe to say anti-TNF therapy has now become a new standard of care, especially in patients with RA with moderate-to-severe symptoms…(But) more affordable TNF blockers are needed."

An Amgen-sponsored, retrospective study on the cost of TNF inhibitors found, not unexpectedly, that Enbrel is more cost-effective than Remicade or Humira. Researchers analyzed commercial claims from health plans in the West, Midwest, and Southeast, comparing average monthly RA-related costs (unadjusted).

Cost Effectiveness of TNF Inhibitors in RA

RA-related costs	Enbrel	Remicade	Humira
Drug costs	$ 1,121	$ 1,673	$ 1,304
Outpatient costs	$ 68	$ 198	$ 84
Hospital costs	$ 74	$ 78	$ 33
ER costs	$ 3	$ 4	$ 4
Total costs	**$ 1,266**	**$ 1,953**	**$ 1,425**

BRISTOL-MYERS SQUIBB'S Orencia (abatacept)

All rheumatologists questioned plan to use Orencia, at least initially, only in TNF failures. About half of the doctors questioned defined a TNF failure as someone who fails one TNF inhibitor, but the other half said they plan to try two TNF inhibitors before moving to Orencia or Rituxan.

Doctors have no idea yet how to choose between Orencia and Rituxan for TNF failures. Some said they will use Orencia first; others want to use Rituxan first. It is likely that, if both were available at the same time, they will base the choice on price or marketing. The profitability of doing more infusions with Orencia does not appear to be a factor in the choice.

Among the comments were:

- *Texas:* "There is no rational way now to choose. TNF inhibitors are now in our 'comfort zone,' so I think it will take physicians a year or longer before they are comfortable with something new. We know a lot about the adverse events with Rituxan, but getting rheumatologists to feel comfortable with that is a different issue. I'll probably use abatacept first because I've seen the data in the ***New England Journal of Medicine*** – especially if it is priced right. Rheumatologists will not be perused by the scientific data to choose one or the other. They both work well. The choice comes down to infusion reactions and cost, but we'll sort it out in the first year."

- *Georgia:* "The abatacept data are very strong. The more I read about abatacept, it appears good in TNF failures. The company is starting to market it. I'll probably use Rituxan in lupus but abatacept first in RA."
- *Southeast:* "I've used Rituxan in a few RA patients so far. It's no cure, but patients have had a good response, with re-treatment after ~9 months. There is still a major problem getting Rituxan paid for (off-label). Probably I'd use abatacept first, but I know less about that."

The issues for Orencia include:

- The memory of the Enbrel shortage is likely to make rheumatologists nervous about using Orencia until supply can be assured.
- Rituxan could be on the market at the same time as, or before, Orencia, and Rituxan may be more available than Orencia for several months.
- Doctors already have experience with Rituxan, which could give them a bias toward that agent.
- Orencia won't have the "wow" factor that Rituxan may have with patients, who may demand Rituxan. However, Orencia can have remarkable results as well – they may just take longer to be evident.

GENENTECH/BIOGEN IDEC/ROCHE'S Rituxan (rituximab)

Genentech filed a supplemental BLA with the FDA in August 2005 for the treatment of refractory RA patients, and it was granted priority review on October 28, 2005, which makes it likely the FDA will decide on Rituxan in RA by the end of February 2006. A Genentech official said the company would launch Rituxan by the end of March 2006 if it is approved by the FDA action date. Experts at ACR were confident the FDA will approve Rituxan, and they expect it on the market by spring 2006. In fact, sources said Rituxan could be on the market at the same time – or even before – Bristol-Myers Squibb's Orencia.

Rituxan will be sold by both Genentech and Biogen Idec as it is in hematology. The companies will be targeting the ~3,118 prescribing rheumatologists, and the 350,000 patients who have been treated with a TNF inhibitor. If, as has been estimated, 60% of these remain on therapy, that would make the potential market size for Rituxan ~140,000 patients initially.

There has been a sea change in attitude among rheumatologists about the safety of Rituxan compared to just last year. Even the most conservative doctors now appear convinced of the safety of Rituxan. They've absorbed the company message that 730,000 patients had been safely treated with Rituxan as of October 2005. More importantly, though, about two-thirds of rheumatologists interviewed at ACR say they have already tried Rituxan off-label in either lupus patients or refractory rheumatoid arthritis (RA) patients. Without exception, their experience has been positive, so they will be a receptive audience for an FDA-approved Rituxan in RA.

The Phase III data on Rituxan in RA looked very good, and experts were very upbeat about the prospects for this genetically-engineered anti-CD-20 antibody. Researchers reported that Rituxan worked in patients who had failed on each of the TNF inhibitors (Enbrel, Remicade, or Humira), and the effect of a single course of Rituxan therapy lasted for six months or longer.

The six-month, randomized, multinational, placebo-controlled, 499-patient REFLEX trial studied 520 patients on stable doses of methotrexate who had not responded adequately to methotrexate and anti-TNF therapy. On average, patients had failed 2.5 DMARDs and an average of 1.5 TNF inhibitors; 60% of patients failed one TNF inhibitor, and 9% failed three TNF inhibitors.

On Days 1 and 15, patients were given either placebo or a single intravenous (IV) course of 1000 mg of Rituxan. All patients received a corticosteroid prior to each infusion and took a brief course of oral glucocorticoids between the two injections. Every four weeks for six months, patients were evaluated for evidence of toxicity and efficacy.

There were no new safety signals, and the most common adverse effects were infusion reactions, which investigators said were easily managed. Patients who dropped out of the placebo arm were given Rituxan, and Rituxan dropouts were given another standard-of-care therapy. Dr. Edward Keystone, a rheumatologist at the University of Toronto, said, "What (infusion reactions) we see with infliximab, we see with rituximab, but a little less. This is not like lymphoma where they have big time infusion reactions (with rituximab)." A Roche official said pre-medicating patients with IV steroids before Rituxan reduces the infusion reactions, and second infusions are better tolerated, with infusion reactions generally mild and Grade 1, which is "much different from the situation in non-Hodgkin's lymphoma (NHL). In NHL you have patients with a huge amount of circulating B-cells. We don't observe the same phenomenon (reactions) in RA patients."

The 24-week results of the DANCER trial of Rituxan also were presented. This trial found that (1) the 1000 mg x 2 dose of Rituxan is the most effective and (2) oral steroids do not appear to provide any significant contribution to efficacy. He said, "At ACR20 and ACR50 the two doses (500 mg x 2 and 1000 mg x 2) appear comparable, but at certain endpoints (e.g., ACR70 and EULAR good) the 1000 mg x 2 dose has a trend to more responders." There were no unexpected safety signals in the trial.

The safety and tolerability of repeated treatments with Rituxan was reviewed in a poster. The study looked at 192 patients from extensions of two Phase II clinical trials.

Phase III REFLEX Trial Results at Week 24 – Baseline and Safety

Measurement	Placebo n=201	Rituxan 1000 mg x 2 n=298
Demographics		
Swollen joint count (SJC)	22.9	23.4
Tender joint count (TJC)	33.0	33.9
DAS28	6.8	6.9
HAQ disability score	1.9	1.9
Completers	54%	82%
Average number of previous DMARDs	2.5	2.6
Baseline MTX mean dose	16.7	16.4
Discontinuations		
Total withdrawals	46%	18%
Due to lack of efficacy	39%	12%
Due to adverse events	<1%	3%
Due to infusion reactions	0	8 patients
Adverse events		
Infections per 100 patient-years	154.6	138.2
Serious adverse events	10%	7%
Serious infections	<1%	2%
Serious infections per 100 patient-years	3.7	5.2
Infusion reaction with 1st infusion	18%	23%
Infusion reaction with 2nd infusion	11%	8%
Serious infusion reactions	0	2 patients *
Nausea	2%	7%

* 1 anaphylaxis, 1 hypertension

Phase III REFLEX Trial Results at Week 24 – Efficacy

Measurement	Placebo n=201	Rituxan 1000 mg x 2 n=298	p-value
Primary and secondary endpoints			
Primary endpoint: ACR20	18%	51%	<.0001
ACR50	5%	27%	<.0001
ACR70	1%	12%	<.0001
DAS28	-0.34	-1.83	<.0001
EULAR remission	0	9%	---
EULAR moderate/good response	22%	65%	<.0001
Radiographic results			
Baseline radiographic score	~48	~48	---
Change in Sharp score	+1.2%	+0.6%	Nss
Joint space narrowing	+0.4	+0.2	0.0156
Erosion score	+0.8	+0.4	Nss
ACR20 response by rheumatoid factor (RF) status			
RF positive	19%	54%	<.0001
RF negative	12%	41%	0.0009

DANCER Trial Results at 6 Months

Measurement	Placebo n=122	Rituxan 500 mg x 2 n=123	Rituxan 1000 mg x 2 n=122
Prior TNF inhibitor therapy	27%	32%	27%
Average number of previous DMARDs	2.5	2.6	---
Baseline MTX mean dose	16.7	16.4	---
Results			
ACR20	28%	55%	54%
ACR20 in patients with no steroids	24.4%	56.1%	51.2%
ACR20 in patients with IV steroids	25.6%	46.3%	51.2%
ACR20 in patients with IV and oral steroids	33.3%	63.4%	60.0%
ACR50	13%	33%	34%
ACR70	5%	13%	20%
DAS28 (mean change)	-0.67	-1.79	-2.05
EULAR good	4%	14%	38%
EULAR remission	2%	8%	10%
EULAR low disease	4%	14%	29%
RF positive patients (by ITT)	54%	82%	---
Safety			
Any adverse event	70%	81%	85%
Infections per 100 patient-years	98.9	122.0	126.9
Serious adverse event	3%	7%	7%
Serious infections per 100 patient-years	3.2	0	4.7
Acute infusion reactions			
With first infusion	14%	32%	37%
First infusion with IV steroid	19%	19%	29%
With second infusion	8%	5%	6%

Repeated Courses of Rituxan in RA

Measurement	1st course n=192	2nd course n=141	3rd course n=25
Any adverse event	80%	60%	60%
Grade 3/4 serious adverse event	19%	8%	0
Adverse events leading to withdrawal	<1%	1%	0
Infectious adverse events	36%	21%	24%
Infectious serious adverse events	<1%	3%	0
Neoplasms	<1%	1%	0
Hypotension (decrease >30 mmHg)	9%	3%	5%
Hypertension (increase >20 mmHg)	5%	4%	---
Pruritis/rash/urticaria	10%	4%	---
Throat issues	7%	4%	3%
Infusion-related adverse events			
Any	43%	21%	16%
Grade 1	49.9%	45.9%	80.0%
Grade 2	37.2%	50.0%	20.0%
Grade 3	8.5%	5.0%	0

Asked if, in the real world, patients really are likely to stop all TNF inhibitors eight weeks before starting Rituxan, a Biogen official said, "That question centers on what might be safety concerns of a patient coming off a TNF inhibitor and then going onto peripheral B-cell depleting therapy. We are collecting longer term and future data to answer this. The data to date suggest patients who did not respond adequately to (Rituxan) therapy and went on to other agents, including TNF inhibitors, appear to have adequate safety."

Asked why there is a greater decline in IgM than IgA, etc., the Biogen official said, "Seven to 10% of patients experience immunoglobulin drops in the oncology setting. In REFLEX, the drops seem a little more pronounced of IgM. This appears, in part, to be related to drops in rheumatoid factor (about a 55% drop in RF), and certainly that comprises a larger percentage of the IgM. This is something we are following long-term, but on-average, patients remain within normal limits, and we haven't identified any clear safety issues."

Some doctors predicted that an average of 60%-70% of patients who fail one or more TNF inhibitors would be given Rituxan, but others insisted that most patients would get Orencia first and Rituxan only if they also fail Orencia.

- *Dr. Stanley Cohen of Radiant Research in Dallas, a former ACR president:* "While TNF blockers are an extremely beneficial therapy, from 20%-40% of patients stop responding or don't respond to a TNF inhibitor. For those patients, adding rituximab to the treatment management plan may spell the difference in success…This therapy will be used in daily practice in patients with incomplete or minimal response to anti-TNF therapy."
- *Dr. Eric Matteson, a rheumatologist at the Mayo Clinic:* He said he would try two TNF inhibitors before moving to Rituxan. "We know that approximately 35%-40% of patients who fail one TNF inhibitor will do well on another one. After a second TNF failure, I would consider Rituxan."
- *Dr. Keystone:* He estimated that 70% of his TNF failures would get Rituxan, and the other 30% Orencia. He said he would not use Rituxan off-label first-line, "We don't know the long-term safety. When we know that, and when we know if we can use a biologic after it, then maybe I'll use it first-line. But Rituxan has a slow onset of action, and we don't have the radiographic data yet, and we have 7-10 years data on TNF inhibitors."

What's the definition of a TNF failure? Dr. Keystone said, "Patients are generally considered TNF failures if they have active disease while on a TNF inhibitor, even if it is not the maximum dose of that inhibitor." Another expert commented, "We (already) have a lot of patients who've passed through all the TNF inhibitors…RA patients are very well adapted to their pain…When something works, it re-sets the pain level…and it becomes very difficult for patients to accept going back to a very painful state again…As wonderful as TNF inhibitors have been, they have left us with a major problem – a lot of patients whose expectations have been raised."

Among the remaining questions about Rituxan in RA include:

- **What is the long-term safety vs. other biologics?**
- **What happens to antibody levels and what is the impact of human antichimeric antibodies (HACA) on efficacy?**
- **Can you use safely a biologic (a TNF inhibitor) after Rituxan while B-cell levels remain depleted?**
- **How many TNF inhibitors should be tried before Rituxan?**
- **Should patients get their vaccinations – for pneumonia, flu, etc. – prior to Rituxan?** Dr. Keystone said, "There is nothing that says you should vaccinate first, but I would."
- **What is the duration of effect after a single course of Rituxan? A second course?**
- **What impact do Fc-receptor polymorphisms have on response to treatment with Rituxan?**
- **Would early treatment or prolonged treatment result in higher response rates?**
- **What are the effects on long-term radiographic damage and long-term disability?** Genentech and Biogen officials defended the radiographic data in REFLEX (especially vs. the Orencia radiographic data), explaining that
  1. These were patients who were non-responsive to a TNF inhibitor.
  2. The Rituxan and Orencia patient populations were different. Rituxan patients had failed a TNF inhibitor, but Orencia patients only had to fail a DMARD.
  3. A lot of placebo patients in REFLEX got rescue medication, and Rituxan still was much better than placebo.
  4. A 50% reduction in radiographic measures "is actually very good data."
- **In long-term responders, is tolerance re-established?**
- **What is the best dose?** Initially, most experts said they plan to give two 500 mg infusions (1000 mg per course) of Rituxan, but if patients don't respond satisfactorily, they may increase this to two 1000 mg (2000 mg per course). However, Genentech and Roche officials were recommending starting with two 1000 mg infusions. The 1000 mg x 2 dose is what Genentech expects will be approved by the FDA.
- **What is the role of steroids/DMARDs used with Rituxan?** Experts said they plan to give an IV glucocorticoid with Rituxan, but oral steroids do not appear necessary. Roy Fleishman, M.D., of St. Paul University Hospital in Dallas said, "Infusion-related events are fewer with IV vs. oral glucocorticoids. 100 mg of methylprednisilone just before the infusion is enough...There is no doubt the IV steroid helps, but the question is the dose."

➢ **When should patients be re-treated?** Experts agreed that Rituxan will probably be given only when patients flare, not scheduled every six months, for maintenance. Dr. Keystone said, "A TNF flare is rapid. With Rituxan there is a slower flare. It is likely there will be some markers – B-cells or CRP perhaps. There will be time to get Rituxan on board, which is very different from TNF inhibitor flares…I've heard that the more you give Rituxan, the longer the duration between administrations." However, Genentech and Roche officials were recommending re-treatment at regular, pre-specified intervals, not waiting for patients to flare to re-treat.

An investigator-initiated U.K. study looked at re-treatment with Rituxan in 24 lupus patients. After the first cycle of Rituxan, the duration of response lasted an average of 7 months, and after the second cycle (7 patients), the duration of response was an average of 13 months. One patient who developed HACA after cycle 2 got a humanized anti-CD-20 instead of Rituxan for the third cycle and then remained well for one year. Researchers concluded: "Re-treatment is safe. The duration of benefit after each cycle was frequently longer than the period of B-cell depletion. The mean duration of response vs. initial response suggests an added benefit of re-treatment. Rituxan is probably a viable treatment option in refractory lupus patients."

Genentech officials declined to provide any guidance on how often patients could or should be re-treated with Rituxan, except to say that a count of 8 swollen and tender joints is the criteria for re-treatment in the current open label extension study. An official pointed out, "CD-19 counts do not appear to have any association with any efficacy outputs…So, we do not base re-treatment on CD-19 count, just on physical clinical findings."

In the REFLEX and DANCER trial extension studies, patients are being re-treated based on a tender joint count (TJC) of 8, but in the Phase III trial re-treatment will be "in a more rigorous fashion to get patients into remission as opposed to a more flare design, which the current open label designs are using." A Biogen official said, "A patient with a TJC of ≥8 doesn't necessarily mean flare. They could have some improvement but still some active joints fulfilling the criteria."

➢ **Are there biomarkers that will help guide when to re-treat?** A poster by Roche Diagnostics researchers suggested that reductions in serum amyloid protein A (SAA) levels could have a role in predicting a response to Rituxan.

Ongoing and future studies

Two trials of Rituxan in DMARD-incomplete responders (DMARD-IRs) in RA are being started:

➢ **MTX-IR**, a 495-patient trial of Rituxan+MTX looking for a reduction in signs and symptoms, starting in November 2005.

➢ **XRAY**, an 852-patient trial looking for a reduction in signs and symptoms, inhibition of structural joint damage, to start in 1Q06.

Genentech officials said there have been some "cautious discussions" about exploring a combination trial of Rituxan and a TNF inhibitor in the future, but they declined to give any more details on this.

JOHNSON & JOHNSON/SCHERING-PLOUGH'S golimumab

Data presented at ACR suggest that J&J may have a replacement for Remicade – golimumab (CNTO-148), a sub-cutaneous injection that only needs to be given once a month. J&J also reportedly is planning an IV form of CNTO-148.

In a double-blind, placebo-controlled, 172-patient Phase II trial, CNTO-148 was shown to effectively reduce the signs and symptoms of RA in patients also getting a stable dose of methotrexate (10 mg/week). The trial met the primary end-point, which was a statistically significant ACR response in all the CNTO-148 doses combined plus a statistically significant ACR20 response in at least one specific dose. Investigators reported no unexpected adverse events.

The median trough levels of CNTO-148 were all reported to be above the minimal clinically effective level. CNTO-148 was shown in animal studies to be 2.5-4 times as potent as Remicade. Researchers offered three reasons for this:

1. CNTO-148 binds more tightly to TNF receptors.
2. It binds to a different TNF epitope.
3. It is a fully human antibody, which they speculated would make it much less immunogenic as well.

However, there were a few questions about this trial, including:

➢ Not every dose had a statistically significant effect on ACR20. An investigator explained that this was due to the ACR20 criteria which counted any patient whose methotrexate or prednisone dose was increased as a non-success. He said, "That happened even though patients were doing well…That standard was not applied to the ACR50 and ACR70."

➢ The placebo ACR20 rate was high. An investigator said this did not confound the trial, "It was high, but it has been higher than that in other trials…and despite the fact that there was a marked placebo response, there was still a statistically significant difference between placebo and (overall) drug response."

➢ None of the doses tested was statistically significant in all three measurements – ACR20, ACR50, and ACR70.

➢ There was no clear dose response curve.

Only once-monthly dosing will go forward in the Phase III trial, which is expected to start in December 2005, and both 50 mg once-monthly and 100 mg once-monthly will be tested. An investigator said, "The once-monthly dosing was chosen because of (1) convenience and (2) the efficacy is clinically indistinguishable from every two week dosing."

CNTO-148, which is expected to be available in both the once-monthly subcutaneous injection and an IV version, is likely to replace Remicade entirely, at least in RA. Dr. Matteson said, "Remicade may still have a role, for example in forms of inflammatory bowel disease where Enbrel is not effective but Remicade is, such as Crohn's disease."

How will physicians choose among all the anti-TNF therapies when CNTO-148 is available? The principal investigator of this dose-finding trial, Dr. Jonathan Kay of Harvard Medical School said, "Not all patients will respond to every biologic therapy. There are patients who don't respond to Enbrel who respond to Remicade and vice versa, and there are patients who don't respond to either." Dr. Kay described one of his patients who received CNTO-148: "He was a man who was unable to work. With this, he has no disease activity. He shovels snow now, goes dancing with his wife, and went back to work. Before this therapy, he was so frustrated by his lack of response to methotrexate that he was feeling depressed about the future of his life."

Other experts were also optimistic about CNTO-148. Dr. Matteson said, "For me, I think this would be the first-line drug (in RA) because it is fully human, convenient, and so far has shown good efficacy and safety." Dr. Keystone said, "It's good. It works well. There are no antibodies, so it is less immunogenic, but we won't know for sure until we do the Phase III trial."

Schering-Plough has licensed the marketing rights to golimumab in all countries except the U.S., Japan, China, Taiwan, and Indonesia. A Phase III trial is expected to start in early 2006. Besides RA, golimumab is being investigated in ankylosing spondylitis and psoriatic arthritis, and it may be tested in asthma in the future.

ROCHE'S Actemra (tocilizumab, IL-6, MRA)

Roche officials indicated the company plans a global filing of Actemra in active RA in 2007. So far, ~1,500 patients have been treated with Actemra. In the early trials, Actemra looks effective, but the FDA likely will be carefully watching the side effects – increases in lipid levels, increases in liver function tests (LFTs), and neutropenia. The LFT elevations are the most concerning.

The results from SAMURAI, a one-year Phase III Japanese monotherapy trial in RA patients with an inadequate response (TJC ≥6 or SJC ≥6) to at least one DMARD or immuno-suppressant, showed good efficacy but continuing concerns about liver and lipid elevations.

Phase II Results of CNTO-148 at 16 Weeks

Measurement	Placebo n=35	CNTO-148 50 mg Q4W n=35	CNTO-148 50 mg Q2W n=34	CNTO-148 100 mg Q4W n=34	CNTO-148 100 mg Q2W n=34	All CNTO-148 n=137
Discontinuations						
Total	17.1%	11.4%	17.6%	14.7%	5.9%	12.4%
Due to adverse events	8.6%	5.7%	8.8%	5.9%	2.9%	N/A
Due to unsatisfactory treatment effect	8.6%	5.7%	2.9%	8.8%	N/A	N/A
Efficacy						
Primary endpoint: ACR20	37.1%	62.9% (p=.031)	50.0% (p=.281)	55.9% (p=.119)	79.4% (p<.001)	62.0% (p=.008)
ACR50	5.7%	40.0% (p<.001)	23.5% (p=.036)	29.4% (p=.009)	32.4% (p=.005)	31.4% (p=.002)
ACR70	0	8.6% (p=.077)	14.7% (p=.018)	17.6% (p=.009)	8.8% (p=.072)	12.4% (p=.028)
DAS28: good/moderate	54.3%	77.1%	64.7%	67.6%	83%	73.7%
DAS28: remission	0	5.7%	11.8%	8.8%	11.8%	9.5%
Adverse events						
≥1 adverse event	79.4%	91.9%	N/A	75%	83.3%	N/A
Serious adverse events	5.9%	10.8%	6.3%	6.3%	8.3%	8% *
≥1 injection site reaction	11.8%	13.5%	6.3%	15.6%	36.1%	N/A
≥1 infection	38.2%	32.4%	18.8%	28.1%	25%	N/A
Death	0	0	0	0	0	0
TB	0	0	0	0	0	0
Lymphoma	0	0	0	0	0	0

*** 2 cases of pneumonia, 1 unrelated lung cancer, 1 cardiac tamponade, and 1 cardiac failure.**

Patients were excluded from the trial if they used a TNF inhibitor in the prior three months. During the trial, they were not allowed to use steroids, but they were allowed to have a change in dose and type of DMARD. In this trial each patient got 13 infusions (8 mg/kg every 4 weeks) over one year. Researchers reported that ACR50, ACR70, and DAS28 all showed continuous improvement with tocilizumab over 52 weeks. However, in the first four weeks of therapy total cholesterol, HDL, LDL, and triglycerides all increased above control and remained at the same slightly elevated level for the remainder of the trial.

The liver elevations were described as mild, transient, and reversible, with no evidence of clinical hepatitis in any of the patients with elevated liver enzymes. The periodicity of the elevations coincided with the frequency of the Actemra administration, especially at the beginning of the treatment.

Liver Enzyme Elevations with Actemra

Therapy	Number of patients	Patients with ALT≥2.5	Patients withdrawn due to ALT elevations
Actemra monotherapy	159	2%	0
Actemra+MTX	151	11%	3%
MTX monotherapy	49	0	0

A Roche official said that 2% of Actemra monotherapy patients (3 patients) and 11% of patients (17 patients) on combination Actemra+MTX therapy had ALT≥2.5xULN, "The liver appears to adapt over time, which is linked to the mechanism of action of the drug…What is important is that the elevations observed all resolved…The FDA required us to enroll patients (in the Phase II trial) with higher baseline ALT." Another official said, "If the ALT elevations are dose dependent, then having the 4 mg dose will give us more flexibility." One patient reportedly had ALT≥5xULN, and that patient stopped the drug. Officials insisted that, based on the information they have so far, there is no reason to change the treatment regimen for Phase III.

Mild, non-fasting elevations of total cholesterol, HDL, and triglycerides also were reported, but a Roche official said lipid elevations also have been reported in patients with RA who were successfully treated with DMARDs. She insisted there is no clear temporal association between lipid elevations and ALT increases, but the lipid increases are inversely related to CRP levels, "Any time CRP decreases, we do observe increases in total cholesterol."

Roche officials insisted they are not concerned about the increases in lipid levels, explaining: "They occur very

Planned or Ongoing Actemra Trials

Study arms	Number of patients	Patient population	Endpoint
Actemra 4 mg/kg+MTX Actemra 8 mg/kg+MTX MTX	630	MTX partial responders	ACR20 at Week 24
Actemra 4 mg/kg+MTX Actemra 8 mg/kg+MTX MTX	1,170	MTX partial responders	ACR20 at Week 24 Sharp score at Weeks 52 and 104 Physical function at Week 104
Actemra 8 mg/kg DMARDs	1,200	Partial DMARD responders	ACR20 at Week 24
Actemra 4 mg/kg+MTX Actemra 8 mg/kg+MTX MTX	570	Anti-TNF failures	ACR20 at Week 24
Actemra 8 mg/kg MTX	550	MTX-naïve patients	ACR20 at Week 24

1-Year Results of Japanese Phase III SAMURAI Trial of Actemra

Measurement	Control n=148	Actemra n=158
Withdrawals	27	24
Withdrawals due to adverse events	N/A	17
Demographics		
RA duration	2.4 years	2.2 years
Number of previous DMARDs	2.8	2.7
TJC	14.4	15.3
SJC	11.9	12.5
CRP	4.9	4.7
DAS28	6.8	7.0
Erosion score	71.0 mm/hr	70.9 mm/hr
Total Sharp score (TSS)	31.0	28.3
Results		
ACR20	35.5%	89.2%
ACR50	13.8%	70.1%
ACR70	5.5%	47.1%
DAS28 remission	3.4%	56.1%
TSS	6.12	2.34 (p<.01)
Erosion score	3.21	0.85 (p<.001)
Joint narrowing score	2.91	1.49
Adverse events		
Any	82.1%	89.2%
Nasopharyngitis	32.4%	35.7% (Nss)
Rash	4.1%	10.8%
Diarrhea	9.0%	8.3%
Nausea	1.4%	5.7%
Headache	2.1%	7.0%
Eczema	4.1%	5.7%
Infections	4.1%	7.6%
Upper respiratory infections	0.7%	1.3%
Pneumonia	1.4%	1.9%
LFT ≥2xULN	1.0%	1.3%

quickly…They are really a function of a decrease in inflammatory factors, such as CRP…After an immediate increase of total cholesterol, the levels stay where they are…it is ***not*** a continuous increase."

Since this is a humanized antibody, infusion reactions are not expected. The most common treatment-emergent serious adverse events with Actemra were reported to be:

- Aggravation of RA.
- Sepsis (2 cases with high dose combination therapy).
- Anaphylactic/allergic reactions – in the low dose mono-therapy group, which is not the dose going forward.

Comparison of Rituxan and Actemra

Comparator	Rituxan	Actemra
Target	CD-20 on B-cells	Human anti-IL-6
Method of action	B-cell reduction	Inhibition of IL signaling
Dose	IV on 2 days per course (~6 months)	IV every 4 weeks
Treatment strategy	Combination with MTX	Monotherapy and combination with MTX and other DMARDs
Target population	TNF failures	General RA patients
Efficacy measures	ACR20-50-70, EULAR	ACR20-50-70, EULAR
Safety	Infusion reactions, slight increase in infections	Cholesterol, LFT, CBC changes, slight increase in infection

Other RA Agents Worth Watching

CAN-FITE BIOPHARMA'S CF-101. This Israeli company recently completed a Phase IIa trial, but only interim data from that trial were available at ACR. CF-101 is an oral, BID small molecule A_3 adenosine receptor agonist with good safety and no serious adverse events so far. The company planned to submit to the FDA for an IND by the end of November 2005 and hopes to start a Phase IIb trial in the U.S. in March 2006.

CHELSEA THERAPEUTICS' CH-1504. Phase I data in healthy volunteers were presented for this MTX analog, which is being developed for both RA and psoriasis. A Phase II trial is expected to start in 1Q06. An official said the theoretical advantages of CH-1504 over MTX include:

- No evidence of CH-1504 being metabolized.
- Possibly less toxic (especially fewer GI side effects).
- No ALT elevations, so perhaps less hepatotoxicity.
- Perhaps the dose could be increased higher than is feasible with MTX.
- The cost is expected to be only "marginally higher" than MTX.

CORTICAL'S COR-100140, a once daily oral MIF (macro-phage migration inhibitor factor) antagonist to treat RA. This Australian company also believes COR-100140 may be useful in atheroma, lupus, multiple sclerosis, and colitis. Wyeth may be interested in this.

LILLY/APPLIED MOLECULAR EVOLUTION'S AME-527. Interim data from an ongoing, single-center Phase II trial (AME-527-0301) were presented. Researchers reported that the optimal dose is 10 mg weekly by subcutaneous injection, and all patients at this dose achieved ACR20 or better at one or more visits. Human anti-human antibodies (HAHA) were detected in six of 11 subjects, but the clinical significance is not known.

A researcher said no other Phase II trials are currently underway. The advantages of this agent over Rituxan may be better bind and perhaps more efficacy. The researcher said that in chimps, there were "better drug levels" with AME-527.

NOVARTIS'S Gleevec (imatinib). A Japanese cell line study suggested Gleevec may be worth exploring in RA.

RIGEL'S R-406. A poster presented the results of a PK study of this syk kinase inhibitor in human male volunteers. Five doses were tested – 80-250-400-500-600 mg – and they showed a dose-dependent inhibition of CD63. The highest dose, 600 mg, was associated with dizziness.

ROCHE'S:

- R-1503, a protein kinase inhibitor in Phase II.
- R-1295, a dual integrin antagonist in Phase I.
- R-1594, an anti-CD-20 in Phase II.

OSTEOPOROSIS: AMGEN'S denosumab (AMG-162)

Two-year results from a Phase II study were reported at ACR showing that denosumab increased bone mineral density (BMD) in postmenopausal women. Denosumab is a fully human monoclonal antibody to RANK ligand with an average half-life of 34 days. It does ***not*** bind to TNF-α, TNF-β, TRAIL, or CD-40L.

In this randomized, double-blind, placebo-controlled, dose-ranging, multicenter, 412-patient trial, seven subcutaneous doses of denosumab were compared to both placebo and 70 mg weekly of Merck's Fosamax (alendronate):

- 6 mg, 14 mg, and 30 mg once every three months (Q3M).
- 14 mg, 60 mg, 100 mg, and 210 mg once every six months (Q6M).

The women enrolled had a baseline lumbar spine BMD T-score between -1.8 and -4.0, or a hip or femoral neck T-score between -1.8 and -3.5. The study found serum concentration

is dose dependent, and median trough concentrations at Months 18 and 24 showed no accumulation with repeat dosing. Among the findings were:

- **Neutralizing antibodies:** None reported over 24 months.
- **Lumbar spine BMD results:** The graphs indicated that lumbar BMD with placebo and 14 mg denosumab was worse than with Fosamax, but all other doses of denosumab were significantly better than Fosamax.
- **Hip/femoral neck BMD results:** BMD declined with placebo but increased with Fosamax, and all denosumab doses showed a statistically significant greater increase than Fosamax.
- **Distal 1/3 radius BMD:** Placebo showed the greatest decrease, with Fosamax better but still showing a decrease in BMD. All denosumab doses showed a statistically significant increase in BMD vs. Fosamax.
- **Bone markers:**
  - **Urine NTX/creatinine.** Fosamax quickly decreases these and keeps them depressed by about 50%. All denosumab doses (except 14 mg) showed a quick decrease and maintained that decrease better than Fosamax. The 14 mg dose showed repeated sharp spikes and drops.
  - **Bone-specific alkaline phosphatase.** All denosumab doses showed a similar pattern of decline, except 14 mg, which again showed repeated sharp spikes and drops.

Researchers concluded that denosumab significantly increased BMD at all measured skeletal sites vs. placebo and that BMD with the 60 mg dose was similar to – and at some sites – greater than Fosamax. The agent was well-tolerated, and there was a significant reduction in markers of bone turnover compared to placebo, and this was rapid, sustained, and reversible.

Amgen reportedly has decided to take the 60 mg dose forward into Phase III. In addition, a 7,800 patient fracture study is underway and fully enrolled.

24-Month Phase II Denosumab Trial Results

Measurement	Placebo n=46	Denosumab (all doses) n=319	Fosamax n=47
Completers	83%	81%	85%
Adverse events	93.5%	92.0%	93.5%
Serious adverse events	8.6%	13.4%	13.0%
Upper respiratory infections	17.4%	24.2%	23.9%
Infections	54.3%	64.3%	65.2%
Serious infections	0	1.9%	0
Serious neoplasms or malignancies	4.3%	3.2%	2.2%

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Rituxan may find first-line use after a steroid in lupus, vasculitis, Sjogren's syndrome, and ITP. Dr. Keystone said, "Rituxan is likely to have a major impact in lupus." A 10-patient, independent Japanese study also found Rituxan effective in refractory SLE involving the central nervous system. Remissions were rapid and lasted >20 months. A Phase I/II trial is ongoing.

Rheumatologists already are using Rituxan off-label in lupus with good results. A Maryland doctor said, "I've tried it, and it was helpful." However, a Canadian doctor said, "I'd like to use Rituxan, but we have a hard time getting it in Canada. Oncologists get an allotment for their disease, so for us to steal it away from them is very difficult."

Rituxan would be the first significant new drug to be introduced to treat lupus in more than 30 years. However, even without any new therapies, Canadian researchers reported the health and survival of lupus patients has steadily improved over the last 35 years. They attributed the improvement to more aggressive treatment and less use of steroids.

The researchers studied data on 1,184 lupus patients (representing 10,744 patient-years) who had been followed with clinical and laboratory evaluations every two to six months from 1970 to 2005. They found that survival rates in patients with lupus have been improving, and the overall level of disease activity seems to be improving as well. Dr. Murray Urowitz of Toronto Western Hospital, an investigator in the study, said, "This data indicate that more aggressive use of immunosuppressants and other therapies, even with reduced steroid use, may be having an impact…We know people are not dying of lupus as early and signs seem to suggest that we are coming up with better algorithms for treatment."

While the use of steroids typically given to patients to treat the disease remained constant, their cumulative doses given decreased, and the use of immunosuppressives increased. Dr. Urowitz said, "One thing has changed – the percent of pure Caucasians has decreased (in our population), while the number of black and Chinese have increased…So, we would expect, if anything, that lupus would get worse with this population shift because the literature indicated blacks and Chinese have a more severe form of lupus than Caucasians, but that was not, in fact, what happened."

The good news is that lupus patients are dying much less frequently than they used to die, but the mortality rate is still more than three times that for the normal population. Dr. Urowitz said, "Lupus patients are dying less frequently, they have less disease, and perhaps the reason is that they are presenting with less active disease, and are being treated with less cortisone and more other drugs." The improvement in lupus patients' health and survival was not due to them coming in to be diagnosed or treated earlier, Dr. Urowitz insisted.

Longitudinal Observational Study of Canadian Lupus Patients

Measurement	1970-1978 n=228	1979-1987 n=363	1988-1996 n=260	1997-2005 n=333	p-value
Female	89.0%	83.2%	92.3%	88.0%	.37
Age at presentation	35.3	35.2	35.8	32.5	0.018
Disease duration at presentation	3.7 years	3.2 years	3.3 years	4.7 years	0.01
SLEDAI-2K at presentation	11.9	11.0	8.7	9.6	0.0001
Steroid use	83.3%	69.7%	74.6%	79.6%	0.97
Cumulative steroid dose	19.7 gm	18.6 gm	16.2 gm	15.8 gm	0.0028
IS	27.6%	25.4%	41.3%	55.3%	<0.0001
SMR	14.4	6.93	4.52	3.27	---
Dead	14.0%	8.3%	3.8%	1.8%	<0.0001
AMS	9.7±7.5	7.7±6.0	5.5±3.9	6.0 ± 4.2	<0.0001
SLICC	1.0±1.6	0.6±1.0	1.1±1.6	1.0 ± 1.4	0.18
CAD	7.9%	5.8%	3.5%	3.6%	0.014
AVN	6.1%	2.8%	7.7%	3.9%	0.84
Mortality frequency vs. the normal population	14.4 times worse	6.9 times worse	4.5 times worse	3.2 times worse	---

In addition to Rituxan, there are other promising lupus drugs on the horizon, including:

➢ **HUMAN GENOME SCIENCES' LymphoStat-B (belimumab).** In October 2005, the company announced that a large (4,490-patient), randomized, double-blind, placebo-controlled, multicenter trial in SLE failed to meet either of the primary efficacy endpoints – a reduction in signs and symptoms at 24 weeks or an increase in time-to-flare over 24 weeks – but a statistically significant effect was seen in seropositive patients (who were 75% of the patients in the study). The company has not given up on LymphoStat-B (a BLyS inhibitor), and a Phase III trial is still planned. Experts also defended continued development of this agent. A lupus expert said, "If a patient fails Cytoxan (Bristol-Myers Squibb, cyclophosphamide), then I give Rituxan, and if a patient fails Rituxan – and a few do – I'd give LymphoStat-B." Another expert said, "It would be a mistake to say BLyS does not work. The company has suggested the data indicate that, in a subset of patients who can be identified by serologic criteria, they can show benefit. I personally have some concerns that the population of people studied may have undermined (the trial) …The randomization was between placebo and treatment, and I think it will be interesting to see if this was relatively mild lupus patients in who you could ethically accept randomization to placebo. In that case, control may have done pretty well, making it hard to see a benefit in the treatment groups. So there are a variety of reasons not to jump to the obvious (negative) conclusion here…But there are also biologic reasons for thinking BLyS would not work. APRIL reacts to some of the same receptors that BLyS reacts to, and some others. So, a monoclonal antibody against BLyS shouldn't interfere with APRIL signaling, and you might have a more effective inhibitor if you used a fusion protein."

➢ **LA JOLLA PHARMACEUTICALS' Riquent (abetimus sodium, LJP-394).** This B-cell toleragen received an approvable letter from the FDA earlier this year, but the FDA requested a Phase III trial showing clinical benefit, and the company is trying to raise the funds to do that.

➢ **NOVARTIS'S Gleevec (imatinib).**

➢ **ROCHE'S tocilizumab (IL-6).** An NIH study is fully enrolled and waiting for data maturation. Dr. Urowitz said, "It is enticing to think this will work, but so far it is all theoretical."

➢ **TEVA PHARMACEUTICALS' edratide.** A poster on a mechanism of action study suggested this subcutaneous agent may have utility in SLE.

➢ **ZYMOGENETICS/ARES SERONO'S TACI-Ig.** This fusion protein, which binds to both BLyS and APRIL, is in Phase II development. Dr. Urowitz said, "The concept is great…It is better than BLyS…TACI-Ig may have a more dramatic effect, but don't think you can knock this disease out with one bullet. There is no magic bullet for lupus."

➢ **Interferon agonists.** An expert warned, "These might be risky."

➢ **Statins.** A study found that starting statins early in the disease is important.

Meanwhile, use of Plaquenil (Sanofi-Aventis, hydroxychloroquine) in lupus, is continuing to increase. A lupus expert said, "More attention is being paid to this older, oral, hypolipidemic agent for the prevention of vascular events. This is what's hot in lupus." Dr. Urowitz added, "The increase in Plaquenil use has been dramatic and will continue. It is sort of the standard of care now."

MISCELLANEOUS

ACTELION'S Tracleer (bosentan). A Spanish study suggested this endothelin antagonist may have utility in Raynaud's Phenomenon, ischemic digital ulcers, and cutaneous fibrosis in patients with systemic sclerosis.

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