Trends-in-Medicine

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By Lynne Peterson

SUMMARY

The 48-week Rebif data from the EVIDENCE trial did not wow neurologists. Doctors believe the trial supports use of a high-dose interferon – that is, either Rebif or Betaseron. The outlook is for Rebif to capture up to 15% market share within a year, at the expense of both Avonex and Betaseron, with Copaxone also picking up a little share. Sources predicted that in 12 months the immunomodulatory market would break down: 34% Avonex, 33% Copaxone, 18% Betaseron and 15% Rebif, with Rebif patients coming equally from new patients and from switches. However, Rebif has several hurdles to overcome, including: painful injections, cost, neutralizing antibodies, compliance, and marketing. Thus, Rebif usage may increase as patients try out the newest drug, but then fall off. Biogen's Antegren appears safe and effective, and if the data holds up, it could capture significant market share. Cephalon's Provigil is catching on as a treatment for the fatigue so common with MS, and doctors predicted usage would continue to increase.

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This report is a look at only one topic at this meeting: **Multiple Sclerosis.**

Overview

There are an estimated 350,000 people with MS in the US, and about 250,000 of these have the relapsing-remitting form of the disease, and about half of these are on one of the four immunomodulatory drugs currently approved by the FDA to treat MS:

- **SCHERING AG's Betaseron** (interferon 1-β, marketed in the U.S. by Berlex), the first immunomodulatory to be approved by the FDA. Today Betaseron has about 25% market share.
- **BIOGEN's Avonex** (interferon β-1a), which has slightly more than half the U.S. market today.
- **TEVA PHARMACEUTICALS' Copaxone** (glatiramer acetate), which has been gaining market share as an alternative to the interferons.
- **ARES SERONO's Rebif** (interferon β-1a), the newest immunomodulatory, which was approved by the FDA in March 2002.

Serono was banned from exhibiting at the meeting or sponsoring any events because the AAN felt that the company had inappropriately used the AAN name in advertising company events during the AAN meeting last year. However, Serono was prominent at the meeting anyway, with Rebif a major topic of discussion. Two key issues at this meeting were (a) which of these drugs to use and (b) when to treat patients. Doctors were polled electronically at several sessions about their choice of therapy, and, on average, 48% indicated that they present all the options to patients and let the patients choose which drug they want to take. The remaining doctors tended to be strong supporters of one therapy or another, and few appeared to be convinced to change this position based on any data presented at this meeting.

Doctors who do make recommendations break down into two groups – those who prefer Copaxone and those who prefer the interferons. Then, among the interferon advocates, there is a debate over which interferon to use. One explained, "You need to consider the patient's lifestyle because you want to put patients on drugs with which they are likely to succeed."

Many doctors have become convinced that there is an advantage to high dose interferon therapy. However, in the minds of most neurologists, that translates to more frequent administration, and that means *either* Betaseron or Rebif. A speaker said, "We can't say one of these (three) drugs is better than another, but for groups of patients higher doses of interferons are better than lower doses…A double dose of Avonex given weekly showed no difference (benefit), so it may be the frequency of the injections (that provides the benefit). That doesn't

mean not to use Avonex. There are many patients on Avonex doing very well. Statistically, a group will do better on a higher dose interferon, but you pay a price in terms of more side effects, more injections, and probably a greater chance of developing neutralizing antibodies." Another source said, "If Betaseron has been used instead of Rebif in the EVIDENCDE trial, I believe the results would have been the same. I am very open to the idea that more frequent is better, but my bias is that the Rebif effect was likely due to more frequent dosing. Avonex is not necessarily superior to Rebif, but I'm not convinced Rebif is superior either – just the dosing frequency is better with Rebif."

Neutralizing antibodies have been a concern with interferons for several years. A poster found that 67% of patients on immunomodulator therapy develop binding antibodies (BAbs), with a peak at month five of 81.5% followed by a drop to 28.6% at months 24. The researcher concluded that there is a correlation between BAbs and the clinical course of the disease. He said, "With Rebif, I expect the same pattern, but delayed. A Danish study found that 97% of Betaseron patients develop BAbs in two years, another study found 7%-8% of Avonex patients develop BAbs at two years, and about 13% of Rebif patients are expected to develop BAbs in one year. We are trying a course of cyclophosphamide early to depress BAbs, and that seems to work. Once BAbs are detected, you could give cyclophosphamide and eliminate the BAbs."

Rebif

Data was presented from EVIDENCE (Evidence for Interferon Dose Response: European-North American Comparative Efficacy Study Trial), a 677-patient, head-to-head comparison of Rebif and Avonex, which was the basis for the FDA's decision to allow Ares Serono to break Avonex's orphan drug status.

Experts agreed that, at six months, the data was quite convincing that Rebif is superior to Avonex in the first six months, but most sources were not impressed with the 12-month EVIDENCE data. In fact, there were no questions or comments from the audience when the 12-month data was presented; it was almost a ho-hum reaction.

- A Rebif researcher said, "The trial has to be seen as a whole...The difference between the groups gradually becomes less pronounced…The difference in the first 24 weeks was more than expected, and the difference in the second 24 weeks was about what was expected. Overall, we were able to show that in this period of ~1 year there was a substantial difference. I would take away the message that the difference is sustained throughout the trial rather than try to break it up into pieces."

- A doctor commented, "The message for me was that more frequent administration of high dose interferon has a more rapid onset of effect over a six-month period. The question is whether that will translate into a difference in long-term disease. There was a 3% reduction in relapses with Rebif in the first six months, but in the next six months there was no difference."

- Another expert said, "For people at huge risk -- with active disease, who have the potential for significant relapses over a fairly short period of time -- I am now more inclined to start Rebif in the beginning to allow me to get the disease under control fast. Then, I have to think whether I should switch the patient at six months to Avonex because of neutralizing. That is where I am heading."

- A Texas neurologist said, "I won't use much Rebif. I was disappointed with the EVIDENCE results at 48 weeks, though EVIDENCE investigators (and there were 20-25 sites) will buy into the positive six-month results and will be less critical of the whole study. I'm underwhelmed with a trial that performs like this in the second six months."

EVIDENCE Trial Results

Drug	24 weeks		48 weeks	
	Rebif 44 mcg SQ	**Avonex** 30 mcg IM	**Rebif** 44 mcg SQ	**Avonex** 30 mcg IM
Patients Relapse-free	**75%**	63%	62%	52%
Relapse Risk Reduction	**32%**	---	10%	---
Patients experiencing a relapse	**25%**	37%	52%	62%
Lesion free by MRI	**N/a**	N/a	***26%***	55%
Relapse rate per patient	**.29**	.39		
Patients forming neutralizing antibodies	**N/A**	N/A	25% (72 patients)	2% (7 patients)
Mean number of active lesions per scan	**0.9**	1.7	0.9	1.2
Time to progression	**43**	49	20	28

In terms of adverse events in EVIDENCE, Rebif had:

> Substantially (but not unexpectedly) more injection site reactions than Avonex

> More LFT abnormalities (27% vs. 8%)

> More leukopenia (36% vs. 1%)

> More neutralizing antibodies (25% vs. 2%)

The key criticisms of the EVIENCE trial included:

> It was too short, though the length was set by the FDA to answer the orphan drug question.

> The benefit tapered off during the second six months.

> The percent of patients with neutralizing antibody (NAb) formation was too high with Rebif at 48 weeks: 49% compared to 13% with Avonex (NAbs >20 NU/ml were 24% with Rebif and 2% with Avonex). A Rebif investigator said, "We saw NAb formation in the trial but not an effect on relapses. We can probably say NAbs have a substantial risk of exerting an adverse effect on efficacy, but if you go back to the Betaseron studies, it depends on how the antibodies are analyzed. And often if patient stays on therapy, the NAbs disappear." Most of the antibody formation occurred in the first nine months of therapy, but the final analysis of the NAbs has not been completed, and some patients have been and will be followed beyond 48 weeks, and that data will be presented in the future.

Betaseron

Two-year data from the Italian, investigator-initiated INCOMIN trial (funded only by institutional sources, not any drug company) also dealt a blow to Avonex, which in this case lost in a head-to-head comparison to Betaseron. Researchers reported at the AAN meeting last year on the first 12 months of the INCOMIN trial, and they found that patients on Betaseron fared better than patients on Avonex in almost every measurement, and the differences were statistically significant.

The two-year data INCOMIN data also favored Betaseron. The trial was criticized for being too small and not fully blinded, but, in combination with the EVIDENCE data, it appears to be convincing doctors that frequent administration of an interferon is best and that frequency matters.

Two-Year INCOMIN data

Measurement	Avonex n=92	Betaseron N=96
# relapse free	36%	51%
Worsening	30%	14%
New T2 lesion free	26%	55%
MRI activity-free (149 patients)	25%	51%
PD/Tw BOD changes	11.7%	-2.8%

Berlex was geared up at this meeting, ready to meet the competitive challenge from Rebif. Sales reps were convincingly ticking off a list of what they believe are advantages of Betaseron, including:

- A strong support system for doctors and patients.
- A nurse program that was started in November 2001. There are 25 nurses across the country, though not in every state, who can help with patient issues.
- Less painful injections than Rebif. An injection site reactions can be minimized with antihistamine use.
- Active ingredient dosing nearly as high as Rebif. The weekly dose of high dose Rebif is 152 mcg, compared to 875 mcg of Betaseron, but this doesn't reflect the active agent (in MIU), which each company measures differently. Betaseron sales reps insisted that it is complicated to compare the amount of active agent, but that they are almost as high with Betaseron as with Rebif.
- A new high-dose Betaseron trial is getting underway.
- A new, room temperature formulation will go on sale in mid-May 2002. This will be the first immunomodulatory agent that doesn't require refrigeration. A sales rep suggested that the cold temperature of Betaseron may be one cause of the site reactions, so this formulation may have fewer reactions.
- Betaseron is available in pre-filled syringes.

A source suggested there are three groups of doctors who use most of the Betaseron today:

1. General neurologists "who have not kept up with the newer drugs, and this is the oldest, most familiar agent."
2. Some MS experts who are moving Betaseron patients to Rebif.
3. Strong Copaxone advocates who are anti-Biogen but whose patients want an interferon.

Copaxone

Few sources were big Copaxone advocates, and it is the first choice of very few sources. However, nearly every doctor has a significant percentage of patients on this agent (on average 26%). Furthermore, sources **predicted Copaxone use would grow an average of 2% over the next year.** A doctor said, "I find too many interferon patients don't stay on them, so I prefer this." A New Jersey doctor said, "Copaxone will gain because of the neuroprotective story. The company also is selling it on less side effects and six year data – though that doesn't wash with me."

Copaxone takes several months to have an effect, and most doctors are not convinced it is as efficacious as interferons, but some patients choose it to avoid the flu-like symptoms associated with interferons or because there is some data that it has a long-term, sustained effect. A speaker offered some

cautions about that claim: "The Teva sales reps say, and the company advertises, that the sustained clinical benefits of Copaxone in relpsing-remitting MS (RRMS) have been observed for six years. A benefit with the drug if it is continued has been shown, and it was a surprisingly positive long-term effect. But I would caution your interpretation of this. This was a continuation study, and patients who declined the opportunity to continue in the trial had a higher annual rate of relapses and a greater proportion worsened on study. So, essentially they selected for responders or patients destined to do well. Eighty-three percent of patients did go on, but 27% of these were later lost to follow-up. And there was an inappropriate control (for this extension study); the 1,099 natural history controls were not ideal – they had not been purged of progressive disease patients.

Teva sales reps also were doing a good job of handling questions about the advantages of their product over Rebif. Among key points they were making included:

- Pre-filled syringes.
- Copaxone must be refrigerated but not all the time. The drug can be left out for up to seven days, they said.
- Lack of flu-like side effects.

Avonex

Biogen was surprisingly low-key at this meeting. Sales reps in the booth, when asked by doctors why they should prescribe Avonex instead of Rebif in light of the EVIDENCE data, simply responded, "Just read the published Phase III trial results." They made no attempt to cite any advantages of Avonex – not even the less frequent injections or antibodies issues – or to guide doctors as to what to look for in the Phase III trials. One said, "It is difficult to make the assertion that 24 week data is enough. This is not a 24-week disease."

At the same time, sources were confident that Biogen would not easily give up market share to Rebif. One source said Biogen is planning a head-to-head, retrospective study comparing patients with less aggressive disease of Avonex and patients with more aggressive disease on high dose Rebif or Novantrone. He commented, "It won't answer anything, but it will be good for marketing."

Immunex's Novantrone (mitoxantrone)

Novantrone is reserved for patients who have aggressive disease or who progress despite best therapy – when the interferons fail. It isn't a first-line drug because of the potential for cardiac problems as the drug accumulates in the patient. Novantrone is used when the interferons fail. A speaker said, "The ideal patient for this, since it is chemotherapy, is a patient worsening in a step-wise way despite our best efforts to treat, who has no cardiac risk factors and no history of malignancy, and who will accept the risk of amenorrhea."

A retrospective safety study of 802 patients in France, concluded: "Novantrone is well tolerated up to a mean cumulative dose of 70 mg/m2. After 2,489 patient years of exposure, two patients have developed therapy-related AML (.25% incidence). This incidence, though low, is greater than the risk in the general population." An American expert warned, "The take-home message is that with excellent care you can reduce the likelihood of irreversible heart disease, but I wouldn't like the message to go to this audience that this is a safe drug. There are patients who died of congestive heart failure in the U.S. We are very cautious of acute heart failure."

Speakers and other sources generally believe there is a role for Novantrone, but the side effects limit its use. Several doctors reported that patients like the action of this drug so much that they sometimes change doctors, and don't tell the new doctor that they have been on Novantrone, so that they can continue to receive it past the maximum approved dose.

THE IMMUNOMODULATOR OUTLOOK

Fifteen clinicians – from small private practices as well as large MS centers – were interviewed at the meeting about their current and planned future use of each of these agents. Sources agreed Rebif is unlikely to expand the number of patients on an immunomodulator, but they predicted Rebif and Copaxone would gain market share over the next year, at the expense of both Avonex and Betaseron.

Immunomodulatory Drug Usage

Drug	Current Usage	Expected usage in 12 months	Change
Avonex	43%	34%	Down 9%
Copaxone	31%	33%	Up 2%
Betaseron	24%	18%	Down 6%
Rebif	2%	15%	Up 13%

Attitudes toward Rebif were relatively positive. A Texas doctor said, "The evidence is not really good that the higher Rebif dose will be better than Avonex, and the frequency of administration with Rebif is an issue." A Florida doctor said, "The higher Rebif dose may be better than Betaseron, but I need to see more data." A New Jersey doctor said, "I have mixed emotions about Rebif. Rebif is no different than Betaseron, but a high dose interferon is good." A North Carolina doctor said, "Rebif use would be even higher after a year if the decision were up to doctors, but some patients prefer the weekly administration of Avonex or the lack of flu-like side effects with Copaxone." A Missouri doctor said, "The initial efficacy data indicates Rebif is better than Avonex, so if I'm using an interferon, I'll tell patients I think Rebif is best." A speaker said, "I prefer Rebif over Betaseron. I will no longer prescribe Betaseron for new patients. I'll tell patients that there is a minor but distinct advantage of Rebif over Betaseron – including pre-mixed syringes and 15% fewer injections. There is no advantage of Betaseron over Rebif… but apparently the pH of the Rebif solution makes it more painful, so I will be watching that."

However, there does not appear to be much if any pent-up demand for Rebif. Doctors said they have had few calls or questions from patients about Rebif yet. A Colorado doctor said he has two patients who are considering switching to Rebif, but that his last two new patients chose Betaseron, saying they didn't want to try Rebif because it was "too new." A Texas doctor said, "I haven't had any calls for Rebif, and that surprised me because I expected a barrage of calls."

Rebif patients, sources said, are likely to come 50% from new patients and 50% from switches from other agents. On average, sources estimated that 16% of their patients switch drugs each year. A source said, "The annual switch rate is about 20%, but it's only about 10% at MS centers, which now do more add-on therapy instead of switching patients."

A study published in 1999 of the NARCOMS 25,000-patient registry reported that switching and drop outs are significant with these drugs.

Patients Who Change or Discontinue Immunomodulatory Therapy
(average annualized rate)

Drug	% patients who stopped therapy at some point	% patients who switched drugs at some point
Betaseron *(between 1995- 1999)*	71% (18%)	43% (11%)
Avonex *(between 1996- 1999)*	40% (13%)	28% (7%)

However, sources pointed out several factors that must be kept in mind when interpreting these figures: (1) The NARCOMS figures were not annualized, (2) The data was collected for a longer period for Betaseron, (3) Avonex was introduced during the registry period, (4) All MS patients are not represented, (5) This was patient-reported data, and (6) not data was provided on Copaxone, which was approved by the FDA in 1996.

Sources also pointed out that there are several factors – particularly pain, compliance, cost and neutralizing antibodies – which will affect the market share that Rebif is able to achieve. **The key arguments against Rebif were**:

> Rebif has a higher pH, which reportedly makes it more painful to inject than Betaseron.

> The drop-out rate may be high. In the PRISMS extension study with Rebif, a speaker said there was a high drop out rate at the high dose (44 mcg).

> Berlex and Biogen both have a reputation for good marketing, so Ares Serono will face a marketing challenge. A source warned, "If Serono is not careful with the general neurologists who are a little jaded with all the marketing now, its effort may backfire."

> Rebif is priced at about a 20% a premium to its competitors, with both the 22 mcg and 44 mcg doses costing the same. A source said, "Some insurance companies are sending doctors letters discouraging use of Rebif over Betaseron because of the cost."

> Doctors may have not have the expected level of success with the drug if the lower dose is used. A source warned, "The 22 mcg dose may be a starter dose, but people will use that. There is no requirement to go to the higher 44 mcg dose. MS specialists won't go for the 22 mcg dose, but a substantial number of general neurologists will do that, and general neurologists see about 65% of the MS patients."

> Antibodies are an issue, perhaps a big issue.

> Compliance with every-other-day injections is likely to become a problem. A source said, "I prefer Avonex because of patient compliance. My anecdotal experience is that less frequent needles lead to better compliance."

> Serono reportedly has already generated some ill will among doctors and patients by withdrawing a trial "reward." A source said, "Serono was testing a new delivery device in a six-week, 2,500-patient trial (1,800 in the U.S.) and patients were told that, for participating, they would get three months of free drug at the end of the trial. That offer was rescinded after the trial was complete, and that didn't go over very well with patients."

Some experts are considering using Rebif for just six months. One said he may stop Rebif after six months and switching patients to Avonex. Another plans to give patients both Copaxone and Rebif for the first six months and then discontinue the Rebif.

COMBINATION THERAPY

Neurologists are coming to the conclusion that MS patients, like cancer patients, are likely to need combination therapy. Among the combinations being considered and/or studied are:

Betaseron plus Novantrone. A small study of adding Novantrone to Betaseron in patients with worsening disease was discussed. The results indicated this is safe and well-tolerated, with no serious adverse events, though there was some short-lived neutropenia at 14 days post-infusion. In this trial, relapse rates decreased 64%, a decrease in both frequency and volume of gadolinium-enhancing lesions, but no change in the functional EDSS score. A speaker said, "The data is limited by the small number of patients, but it suggests this combination is safe in patients with a suboptimal response to Betaseron."

Avonex plus Copaxone. Additional data was presented from the extension phase of the 32-patient CombiRx trial presented at the AAN last year on the safety of the combination of Avonex and Copaxone. The original trial was six months, and researchers reported this year on nine and 12 month safety. They concluded there was no increase in Gd-enhancing lesions compared to baseline (either as a group or for individual patients), no serious adverse events related to the combination, and no new adverse events. A speaker said, "I think we showed safety by the absence of new gd activity and a lack of adverse events. This is tantalizing information, but the numbers were small." Plans for a Phase II trial of 750-1,000 patients (with three arms – Avonex, Copaxone and combination) are expected to be submitted to the NIH in June 2002.

SHOULD MS BE TREATED EARLIER?

There is a debate raging in the neurology community over the need for early treatment of mild disease. The CHAMPS (Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study) found that Avonex is beneficial in delaying the onset of clinically definite MS in high-risk patients who have experienced the recent onset of a first demyelinating event but who do not yet have clinically definite MS. The 311-patient European ETOMS (Early Treatment of MS) trial comparing Rebif and placebo found that Rebif is beneficial in the early treatment of MS, but the results were less impressive than in CHAMPS.

At one session, a doctor from the Mayo Clinic made the con argument, and a doctor from SUNY took the pro position, quipping, "What can I say except if I get MS, don't send me to Mayo. These aren't the best, end-all therapies; they are just the first."

At another debate on this topic, a doctor on the pro side said, "I think early treatment is better than delayed treatment, but I would be cautious about saying we have data to demonstrate that. I believe in early treatment, but I think the evidence is mostly theoretical." Another doctor in favor of early treatment said, "I think we have data, not hard evidence but hints, to encourage early treatment." On the con side, a doctor said, "I really do believe that about 20% of MS patients do well with their disease without treatment."

Arguments made against simply treating every MS patient:

- The effect is definite but small.
- Uncertain partial relapse reduction will translate into delayed clinical disability.
- Other anti-inflammatory strategies have not helped in the long-term.
- The effect on clinical disability is marginal, at best.
- Neutralizing antibodies concern, and using these drugs may make them unavailable later in the disease when they may be more necessary.
- There is an inability to differentiate between responders and non-responders.
- There has been an observed trend in trials and in clinical practice for patients to change or stop the drugs.
- There is a lack of benefit on clinical disability progression and atrophy in secondary progressive MS (SPMS) despite an effect on relapses and inflammation on MRI.
- They are expensive drugs.
- There is no long-term data. A speaker said, "If we treat patients early, are we really thinking of treating them for 30 years with these therapies?"

Among the arguments **in favor of early treatment** are:

+ Axonal damage occurs early in disease.

+ Relapses do not appear to be a reliable market of the rate of atrophy.
+ Most patients will develop permanent disability.
+ Benign disease cannot be predicted reliably at disease onset.
+ Therapeutic benefits of disease-modifying drugs are clinically significant.
+ Delaying therapy may be detrimental.

Among the arguments **against early treatment** are:

– Current treatments are only partially effective.
– We only know short-term data, but patients are asked to take these drugs indefinitely.
– The drugs are extremely expensive.
– Patients generally don't like taking the drugs.
– It is hard to know in an individual patient if the drug is working.
– High dose interferons cause neutralizing antibodies in a large number of patients and that reduces their benefit.

In this environment, what do doctors tell their RRMS patients? One said, "In early MS, the drugs have all been shown to work." Indeed, doctors said their biggest concern is getting patients on therapy and choosing a therapy with which patients will comply. As a result, many doctors just tell them what drugs are available and let the patients choose. An expert said, "I tell patients (that with immunomodulatory therapy):

- There is a treatment advantage with each drug.
- The short-term advantage is a reduction in the relapse rate and possibly relapse severity.
- Three relapses will become two relapses.
- I hope the MRI benefit will result in a long-term clinical advantage, but that is unproven.
- Interferons appear to work more quickly than Copaxone.
- There is some evidence the higher dose interferons work better than lower dose interferons, but the side effects increase.
- Copaxone is better tolerated but less potent and slower to work, and it may have a long-term benefit."

This same expert tells his SPMS patients:

- Interferons may have a role.
- Copaxone has not yet been studied in this form of the disease.
- Interferons reduce the relapse rate but their effect on slowing progression is uncertain and modest at best.
- I don't start interferons or use Copaxone in this setting.
- If patients are on an interferon and want to stay on it, that is their choice.

NEW THERAPIES IN DEVELOPMENT

Several areas are being explored, including monoclonal antibodies, stem cell transplants, neuroprotection (excito-toxicity) and axonal regeneration.

BIOGEN/ELAN's Antegren (natalizumab, humanized anti-α4β1 MAb). The data from a 213-patient randomized, double-blind, placebo-controlled trial of two doses (3 mg/kg and 6 mg/kg) vs. placebo in RRMS was positive, showing the antibody works – as long as the therapy is continued, indicating it would be long-term chronic therapy. There was a 50% reduction in relapses with the higher dose. Patients received the drug for six months and then were followed for another six months post-therapy. A speaker said, "I would guess very little gets into the CNS, so I think it is acting early and at the cerebral endothelium."

Within a month of stopping this once-a-month IV therapy, patients worsen to the point placebo patients are at (worse than baseline). An investigator said, "The two treatment arms reached a (benefit) nadir between months 2 and 6, and returned to baseline by month 9, though there was a delayed return with the 6 mg/kg dose…This is potentially promising while it is administered, but there is no prolonged effect."

Randomized Trial of Antegren

Measurement	Placebo	Antegren 3 mg/kg	Antegren 6 mg/kg
Number of relapses	***24%***	24%	N/A
Patients with relapses	***24%***	21%	23%
# of relapses (6-12 months)	***24***	24	26
# of patients with relapses	***21***	21	23

**statistically significant*

Safety is not a concern, investigators and other experts agreed. However, three cases of (mild) serum sickness were reported, one in each of the three arms of the trial, but doctors did not appear concerned with this. Reportedly, all three patients came from the same center and the same doctor, and were identified clinically, not by laboratory testing, so sources doubted the validity of any association between serum sickness and Antegren, but they admitted this is an area that

needs to be watched, and one warned that another case of serum sickness in a drug arm could be a killer for the drug.

In addition, over the first six months, 11% of patients developed antibodies, though the significance of this was not discussed. A source said, "I was very impressed with the safety. I think it would be a huge mistake – and there would be a lot of recoil – if Biogen stopped the trial early. I've treated more than 30 patients so far with Antegren, and I'm excited about it. If it gets approved, I think I'd be using it for 65% of my patients within a year. It would completely replace Rebif and Betaseron and cut my Avonex use in half. I'd present all my patients with the Antegren option, and if patients had even one attack in a year, I'd switch them to Antegren."

HOFFMAN-LA ROCHE's CellCept (mycophenolate mofetil), a rheumatoid arthritis medication, is starting to get increased attention by neurologists treating MS. A source said, "You will hear more about this in MS. It is already gaining use in myasthenia gravis."

BRISTOL-MYERS SQUIBB's CTLA4-Ig. Reportedly, the company is investigating whether this liver treatment agent works in MS. A Phase I study is underway, and a researcher said it has "a very good side effect profile."

ILEX/LEUKOSITE's Campath (alemtuxumab), an IV fusion protein. A source said, "I think this will be a tough sell for several reasons: (1) The FDA wants this to be a three-year trial. (2) The trial will compare Campath vs. an interferon; Betaseron would be a poor choice, so maybe they'll use Avonex or Rebif. (3) Side effects may be an issue. (4) It will be difficult to enroll patients in this trial." One possible advantage is that it is all human, so there should not be any antibody issue.

TEVA PHARMACEUTICALS' oral Copaxone (copolymer-1). The key trial of oral Copaxone failed last fall, and a source said the company has not yet decided whether to try a higher dose (>50 mg) "because there was a small hint of activity at 50 mg." ♦