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Quick Pulse

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ALEMTUZUMAB IN MULTIPLE SCLEROSIS

On October 23, 2008, the ***New England Journal of Medicine*** published the results of the Phase II CAMMS-223 trial of Genzyme/Bayer's alemtuzumab vs. Merck Serono's Rebif (44 µg TIW) in relapsing-remitting multiple sclerosis (RRMS). There were no surprises in the data, just slightly more detail than previously presented. Alemtuzumab (which is FDA-approved as Campath to treat chronic lymphocytic leukemia) was given by IV infusion over three to five days once a year.

There were no statistically significant differences between the two doses of alemtuzumab (12 mg and 24 mg), so pooled results were reported as well as dosing results. The investigators reported, "There were no significant differences in safety or treatment effect on disability between patients receiving two cycles of alemtuzumab and those receiving three cycles. However, there was evidence of the waning of treatment efficacy on the rate of relapse…Efficacy was maintained over 36 months even though 77% of alemtuzumab-treated patients did not receive the planned third cycle of therapy at Month 24 because of safety concerns."

The investigators added, "Although our study suggests that alemtuzumab is more effective than interferon-beta-1a (Rebif) when given at the earliest stages of relapsing-remitting multiple sclerosis, our findings raise the difficult issue of exposing young adults who have little disability to a drug having potentially serious adverse effects…Risk minimization measures…should be considered mandatory for the safe future use of alemtuzumab…If improvements in disability after alemtuzumab are sustained, there would be important implications for the management of multiple sclerosis."

In an accompanying editorial in the ***New England Journal of Medicine***, Dr. Stephen Hauser of the University of California, San Francisco, noted that the CAMMS-223 results "clearly demonstrate the dramatic beneficial results of alemtuzumab on the rates of relapse and sustained disability and on MRI metrics of inflammation and atrophy progression." However, he said the side effects "dampen any enthusiasm for its routine use in patients with multiple sclerosis until more is known about its long-term safety and sustained efficacy."

Dr. Hauser had several criticisms of the trial:

- **Single-blind study.** However, investigators emphasized that the trial was rater-blinded.
- **High rate of discontinuations in the Rebif arm** ("a surprisingly high 41% at Month 36"). Investigators explained that this was due mostly to lack of efficacy.
- **Early termination.** The trial was stopped early after three patients developed idiopathic thrombocytopenic purpura (ITP), two of whom died.

The benefits of alemtuzumab come at what Dr. Hauser called "a substantial price."

- **Thyroid autoimmunity in nearly one-quarter of treated patients.** Dr. Hauser said, "The very high prevalence of this complication in patients with multiple sclerosis suggests a special, unique predisposition in this population." A Genzyme official added, "Only 12% of alemtuzumab patients experienced sustained hyperthyroidism like in Graves…This is less than in earlier pilot studies…and none of the alemtuzumab patients discontinued based on thyroid adverse events."
- **ITP in nearly 3% of treated patients.**
- **Profound T-cell depletion.** Dr. Hauser speculated that this is "likely to increase the risk of serious bacterial, fungal, and viral infections, and…there was a trend toward more infections in the alemtuzumab-treated group, including one case of listeria meningitis that might have been related to therapy." Prof. Alastair Compston of the University of Cambridge, U.K., said, "This was an extremely mild illness…The patient had a great response to antibiotics, and the patient was well within 24 hours."

Will alemtuzumab turn out to be a successful treatment for chronic, progressive MS? Dr. Hauser said the significance of the improvement in the progression of sustained disability associated with alemtuzumab remains an "open question." He added, "Such improvement was almost certainly due to a reduction in disability resulting from relapses and not from any effect on secondary progression. However, given the magnitude of the effects…one would be optimistic that with longer durations of therapy, an effect on the risk of chronic, progressive multiple sclerosis might also be found…However, if long-term therapy is required to sustain the clinical benefit, would the risk of toxicity then outweigh the benefit? A more hopeful scenario might presume that a relatively short course of alemtuzumab can restore immune homeostasis, which would eliminate the need for retreatment for many years."

The CAMMS-223 results, Dr. Hauser suggested, "point the way toward a rethinking of therapy for multiple sclerosis, akin to standard models of cancer therapy, in which an intensive induction is followed by a less-intensive maintenance regimen."

During a Genzyme-sponsored teleconference, investigators and company officials discussed the data. Among the key points they made were:

- **Efficacy excellent.** Prof. Alasdair Coles, also of the University of Cambridge and the lead author, emphasized the efficacy.
  - "The most striking and unprecedented effect is the mean disability of patients actually improved over three years of treatment, in contrast to a worsening on interferon-beta…This suggests treatment with alemtuzumab in some way allows or permits brain repair …and this conclusion is supported by MRI, showing an increase in brain volume with alemtuzumab in contrast to continued brain shrinkage for those on interferon."

3-Year Results in Phase II CAMMS-223 Trial

Measurement	Rebif 44 µg TIW n=111	Alemtuzumab 12 mg (n=113) Alemtuzumab 24 mg (n=110)	p-value
Primary endpoint #1: Rate of sustained accumulation of disability (SAD)	26.2%	9.0%	<0.001 (71% reduction)
Primary endpoint #2: Annualized relapse rate (ARR) at 3 years	0.36	0.10	<0.001 (74% reduction)
ARR with 2 cycles (n=161)	0.34 in Months 24-36	0.07 in Months 0-12 0.16 in Months 24-36	---
ARR with 3 cycles (n=45)	---	1 patient in Months 24-36	---
Secondary endpoint #1: Patients relapse free	52%	80%	<0.001
Secondary endpoint #2: T2 lesion burden	---	Down	0.005
Secondary endpoint #3: Brain volume (T1 MRI) in Months 12-36	Down	Up	0.02
Mean EDSS change	Down 0.38 points	Up 0.39 points	<0.001
Number needed to treat (NNT) to prevent one relapse	---	3.5 patients	---
NNT to prevent one SAD	---	5.8 patients	---
Adverse events			
Serious adverse events	0.3	0.2	---
Thyroid disorders	2.8%	22.7%	---
Idiopathic thrombocytopenic purpura (ITP)	0.9%	2.8%	---
Infections	46.7%	65.7%	---
Cancer	1 patient	3 patients	---

- "The headline results are that alemtuzumab reduced the risk of relapse by 74% and fixed disability by 71% compared to active drug. No other drug has achieved this magnitude of treatment before…Alemtuzumab can…perhaps prevent long-term conversion to disease progression."

➢ **Extension study underway.** Dr. Christoph Pohl, senior medical director at Bayer, announced an extension study of CAMMS-223 patients. Patients in both arms will be permitted two additional cycles of low dose (12 mg) alemtuzumab, either annually as in original protocol or, if the patient has a relapse or new brain lesions on MRI. Patients who do not opt for additional treatment and the Rebif patients will be observed in the extension study.

➢ **No off-label use.** Dr. Susan Moran, a medical director at Genzyme and the local safety officer for the program, emphasized strongly that alemtuzumab should ***not*** be used off-label – outside of a clinical trial. Dr. Compston added, "We would be keen to discourage (off-label use) …This is a drug which does not work in advanced or progressive MS, and we would be very keen that patients at that stage not be exposed to the drug…We are very opposed to any off-label use."

➢ **ITP is treatable.** Dr. Moran pointed out that ITP is treatable, "Genzyme has developed a safety monitoring plan to identify cases of ITP in a timely manner to allow for prompt management…Of the 5 cases since (the initial cases)…One did not require treatment, and the other four were successfully treated…This program would be considered mandatory to safe use of alemtuzumab."

➢ **Risk management program necessary.** If alemtuzumab is approved by the FDA, Genzyme and Bayer expect the risk management program to be similar to what they are doing in Phase III – weekly blood tests.

➢ **Side effects not barrier to use.** Dr. Compston said, "Times are changing. We've moved from an era in which there was no treatment for MS in the early 1990s to a phase in which there are treatments which make a modest impact and are pretty safe – the interferons and glatiramer acetate (Teva's Copaxone)…and now a new era in which drugs…for the individual patient will make a substantial difference in their life, but come at a substantial price in terms of the adverse event profile…So, in discussions with individual patients one has to weigh the increased efficacy vs. the possibility of serious adverse events – because there clearly is a trade-off at the moment…Of the many patients we have treated (with alemtuzumab), some have had adverse events…I can't think of a patient who regrets the course they took because for them the benefit of treating their core disease…outweighs any discomfort or transient difficulties they had through having one of the complications…So, the balance is in favor of efficacy in our own patients." Dr. David Margolin, senior medical director at Genzyme, urged people to wait for the Phase III safety data, "We suggest people wait to see the safety in Phase III and hope the efficacy/safety balance will make alemtuzumab the preferred therapy for first-line and follow-on use."

➢ **Biomarkers a possibility.** Dr. Compston said this is being explored, "We are hoping to understand the nature of the adverse events in enough detail to have accurate biomarkers to spot the patients most likely to develop (adverse events) and to understand the immunological basis."

➢ **Convenience a plus.** Dr. Margolin pointed out that alemtuzumab is more convenient than other currently available MS therapies, adding, "That has great significance on treatment compliance and probably quality of life. So, we think there are advantages beyond superior efficacy that weigh in alemtuzumab's favor."

➢ **Better efficacy than Biogen Idec/Elan's Tysabri (natalizumab).** Although there are no head-to-head data comparing Tysabri and alemtuzumab, Dr. Compston said an eyeball look at the data for each suggests a greater treatment effect with alemtuzumab and greater convenience, "I would say efficacy is perhaps a step up on Tysabri…(and) there is the convenience issue…On safety, we have different adverse event profiles…There are a whole list of opportunistic infections, of which PML is the prime example, with Tysabri…We have been treating patients since 1991 with alemtuzumab, and we've seen very few extra infections and no PML cases… Tysabri is associated with a whole range of opportunistic infections which we are not, at present, seeing with alemtuzumab."

Two Phase III trials of alemtuzumab are ongoing:

- **CARE-MS-1.** This trial is testing only the 12 mg dose, given for five days in Year 1 and three days in Year 2 vs. Rebif 44 µg TIW. Recruitment is ongoing in Australia, Europe, North America, and Latin America. About 250 patients had been enrolled as of mid-September, and investigators predicted it would be fully enrolled in 2009.

- **CARE-MS-2.** This is a superiority trial comparing alemtuzumab to Rebif. There are three arms: (a) 12 mg for five days in Year 1 and then 12 mg for three days in Year 2; (b) 24 mg for five days in Year 1 and 24 mg for three days in Year 2; (c) Rebif 44 µg TIW. An investigator said this is enrolling slower than CARE-MS-1. Genzyme's Dr. Margolin said the publication of CAMMS-223 should help boost enrollment in this and the CARE-MS-1 trial.

Asked about the possibility of Goodpasture's syndrome with alemtuzumab, Prof. Coles said there have been no cases of this serious disease of the lungs and kidneys – within a few weeks kidney function goes from normal to completely absent – in MS trials of alemtuzumab and only one case among the 150 patients treated in Cambridge outside of the trials. However, Goodpasture's syndrome is very serious. He explained, "There

is only a small window of opportunity to treat the disease…It is very difficult to put in a monitoring plan in sufficient time to introduce treatment." He said the one Goodpasture's patient is doing well, "She lost kidney function, went on to dialysis, and then a transplant, and is now well. She has not had signs of disability of MS and is living with a kidney transplant."

In a message to local chapters of the National MS Society, Dr. John Richert, executive vice president, said, "We are pleased to see potential new treatment options move positively through the MS pipeline. We look forward to results from the Phase III studies now getting underway, which will help determine if this treatment can be used safely and effectively in people with MS." The society's message noted that this trial does not mean that Rebif doesn't work: "This study compared alemtuzumab against Rebif in part so that no one would have to take inactive placebo. Those people who were in the Rebif group experienced reduced relapse rates, similar to what has been shown in the trials that led to Rebif's approval by drug agencies. Those who were in the alemtuzumab group experienced even fewer relapses, but also experienced some serious side effects."

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