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Quick Pulse

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BIOGEN'S ANTEGREN

Antegren (natalizumab) is being developed jointly by Biogen and Elan, with trials ongoing in both multiple sclerosis (MS) and Crohn's Disease. The companies hope to file for FDA approval in Crohn's in late 2003 or early 2004 and in MS by year-end 2004 or early 2005. Antegren is the first in a new class of humanized monoclonal antibodies (selective adhesion molecules). It is an alpha4 integrin inhibitor which blocks immune cell adhesion to blood vessel walls and subsequent migration of lymphocytes into tissue. Antegren binds to the surface of alpha4beta1 receptors. Five gastroenterologists and two neurologists were questioned about the outlook for Antegren, particularly in Crohn's Disease.

CROHN'S DISEASE

Approximately one million people worldwide have Crohn's Disease, a chronic inflammatory relapsing-remitting disease of the GI tract, which commonly affects both men and women. The onset of disease is in young adults. The disease usually causes diarrhea, crampy abdominal pain, often fever, and at times rectal bleeding. Loss of appetite and subsequent weight loss also may occur. Complications include narrowing of the intestine, obstruction, abscesses, and fistulas (abnormal channels connecting the intestine and other organs, including the skin), malnutrition and decreased growth rate in children. Patients with Crohn's Disease fluctuate between periods of active disease and remission. The disease can result in frequent hospitalizations, and 70% of patients will undergo surgery at least once, and 30% will need additional operations.

A 244-patient, randomized, double-blind, placebo-controlled, parallel group, multinational, Phase II study completed in 2001 studied Antegren in moderate-to-severely Crohn's patients. Patients were randomized to one of four treatment groups: a single 3mg/kg Antegren infusion; two 3mg/kg Antegren infusions at a 4-week interval; two 6mg/kg Antegren infusions at a 4-week interval; or placebo. Patients were followed for 12 weeks after the first infusion and were assessed using the CDAI and changes in quality of life [using the Inflammatory Bowel Disease Questionnaire (IBDQ)].

The trial missed its primary endpoint: remission (CDAI score of ≤150) at six weeks in the 6 mg/kg dose group. The highest rate of remission was in the 3 mg/kg dose group at Week 6. A significant difference in clinical responses (drop of >70 points in CDAI) was seen as early as week 2 and was maintained through week 12. There was also a statistically significant difference in the change from baseline IBDQ score in patients receiving two infusions of Antegren as compared to those receiving placebo at both week 6 and week 12. The drug was well-tolerated, with the most common side effects headache and abdominal pain

Antegren Phase II Results in Crohn's Disease

Measurement	Placebo n=63	Antegren 3 mg/kg. 1 infusion n=68	Antegren 3 mg/kg 2 infusions n=66	Antegren 6 mg/kg 2 infusions n=51
Primary endpoint: Remission (CDAI ≤150) at Week 6	27% n=17	N/A	44% n=29	No statistically significant difference from placebo
Clinical response (decrease of >70 in CDAI) at Week 12	38% n=24	N/A	71% n=47	N/A
Secondary endpoint: IBDQ change from baseline at Week 6	Up 15 points	N/A	N/A	Up 32 points

Two Phase III trials are currently underway in Crohn's, ENACT-1 and ENACT-2. The 850-patient ENACT-1, which was fully enrolled by January 2003, will evaluate the clinical response and ability to induce remission with Antegren. ENACT-2, which was fully enrolled shortly after that, will evaluate the duration of effect of Antegren.

Sources are not very optimistic about the outlook for Antegren in Crohn's. One expert said, "I was surprised when it hit the New York Times...There was a buzz in the lay community, but it's lukewarm in the GI community." A California doctor said, "It is possible it will work. Preliminary studies indicate there is some effect, but perhaps it is not as effective as we had hoped." Another expert said, "There have been three independent studies using similar agents to block this pathway of inflammation -- one in England and two in Canada. The Canadian results were mostly negative. The European study showed some short term benefit, but not much. Their study assessed disease activity a few weeks after dosing. There was no re-treatment phase to the study. Thus, long term efficacy is unknown. In summary, the current evidence does not suggest that this will have major impact on treatment of this disease. More studies are required, however, until we can be sure."

Antegren is likely to find a role in Crohn's – if the pivotal Phase III trials are positive – but that still may be a niche role. An expert said, "Conceptually, it is likely to find a place in the market for IBD (inflammatory bowel disease) and will likely be most efficacious when used with other agents."

If Antegren is approved, sources do not expect it to replace Remicade, but an expert suggested Antegren and Remicade may be used in combination, "Comparing Antegren and Remicade (Johnson & Johnson, infliximab) is like comparing apples and oranges. I think we will be using 'anti-inflammatory cocktails' for many patients, deciding which immunoregulatory pathway to impact on for individuals based on response." Another source said, "Antegren may find a niche, especially in patients who don't respond to Remicade. At this point, with the biologics few people think of combination therapy because of cost and unfamiliarity. Remicade will still be used first…We still have good medicines for patients with mild disease. This would probably be used for more severe patients, patients who are refractory to Remicade." A third expert said, "Antegren appears to show promise as an agent to be used in complement to existing biologic therapy (infliximab) for Crohn's Disease, and, perhaps as a single biologic agent in ulcerative colitis. Since the immune system is being activated by several mechanisms, it is logical to reduce the excess activation by several mechanisms …It is likely in the future we will be using a "cocktail" of agents to treat IBD."

Gastroenterologists are not excited about Antegren, so what do they think is most promising? A California expert said, "Alpha4beta7 is what we ideally want to target…The results with alpha4beta7 are somewhat less impressive for Crohn's than for ulcerative colitis. That was a preliminary trial, but it is potentially more exciting than Antegren."

At least two alpha4beta7 antibodies are in development:

- **CELLTECH** reportedly has a humanized alpha4 integrin receptor program, and is doing preclinical studies in rheumatoid arthritis (RA), MS and IBD on a number of potent dual alpha4beta1/alpha4beta7 antagonists with oral bioavailability.
- **MILLENNIUM/GENENTECH'S** LDP-02 (MNL02), an IV anti-alpha4beta7 antibody which is in a Phase II trial in ulcerative colitis (UC) and a six-month, 180-patient Phase II trial in mild- to-moderate Crohn's. Reportedly, the drug led to remission in one-third of UC patients vs. 15% in placebo patients.

MULTIPLE SCLEROSIS

In preliminary findings in MS, which were published in January 2003 in the *New England Journal of Medicine*, Antegren showed fewer brain lesions (an 88%-93% reduction) and less relapses, with fewer side effects than existing drugs. The data from a six-month, 213-patient, randomized, double-blind, placebo-controlled Phase II trial of two doses (3 mg/kg and 6 mg/kg) vs. placebo in relapsing-remitting MS was positive. The trial showed 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.

Within a month of stopping this once-a-month IV therapy, patients worsened to the point placebo patients were 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."

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, though doctors did not appear concerned with this. Reportedly, all three patients with serum sickness 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. The significance of this is not yet clear.

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%
Number of relapses (6-12 months)	24	24	26
Number of of patients with relapses	21	21	23
Mean number of brain lesions	9.6	1.2	0.6

Generally, neurologists are fairly hopeful about Antegren, sources said. The early data has been very good, but they are anxious to see the pivotal trial data to see if the data holds up.

Two Phase III trials in relapsing-remitting MS are currently underway: AFFIRM and SENTINEL. Both are fully enrolled. AFFIRM is evaluating the ability of Antegren to slow the rate of disability in MS and reduce the rate of clinical relapses. SENTINEL in assessing the safety and efficacy of Antegren combination with Bigoen's Avonex (interferon beta-1a) in patients with relapsing-remitting MS vs. Avonex alone in slowing the rate of disability and reducing the rate of clinical relapses.

The FDA has agreed to consider an interim review of the MS data, and it is possible the FDA could approve Antegren, at least for limited use, based on the interim results. However, some experts do not believe the MS trial should be stopped early. A source warned, "I was very impressed with the safety, but 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 (Ares Serono, recombinant human beta interferon) and Betaseron (Schering AG/Berlex, beta interferon-1b), 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."

QUESTIONS ABOUT ANTEGREN

1. Antibodies.
2. Rebound.
3. Serum sickness.
4. Efficacy.
   a. The April 17, 2003, edition of the *New England Journal of Medicine* refers to a 1999 exploratory study at the University of Glasgow, which raised questions about the efficacy of Antegren in MS. That 72-patient 12-week study suggested that Antegren, like other MS therapies, may not have long-lasting benefits. An Elan official countered that the study was small, short and insufficient to determine clinical benefits.
   b. The Phase II Crohn's trial missed its primary endpoint.

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