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by Lynne Peterson

Quick Pulse

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Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

ROCHE'S MIRCERA

New Phase III data indicate kidney dialysis patients can be switched directly from frequently dosed anti-anemia drugs to Roche's once-monthly Mircera and maintain stable hemoglobin (Hb). Mircera, a first-in-class agent, is the new name for CERA (continuous erythropoietin receptor activator). In three trials presented at the European Renal Association/European Dialysis and Transplant Association (ERA-EDTA) meeting in Glasgow, Scotland, earlier this month, Mircera performed very well and was found to be non-inferior – but not superior – to epoetin alfa/beta or darbepoetin alfa.

However, a number of questions remain about Mircera, including:

- **What is the safety profile?** The company claims it is fine, but adverse event data were not presented. A source said, "When we pool the results (from three Phase III trials)…there is no difference in any category (between Mircera and the comparator)…Our adverse event rate is slightly lower than the pooled comparator, and the serious adverse event rate is lower than comparator."
- **What Mircera dose was used?** Roche has declined to talk about that.
- **How does Mircera compare to Amgen's once-monthly Aranesp (darbepoetin alfa)?**
- **What dose adjustments are necessary with Mircera?** Roche officials said fewer dose adjustments are necessary with Mircera than other epoetins, but no details were available on this yet.
- **Will Mircera be found to infringe Amgen's patents?** Amgen filed suit against Roche in 2005 to block Mircera, claiming Mircera infringes six of its patents. Shortly after the ERA-EDTA meeting, Amgen emphasized that it will continue legal action over Mircera.

Roche claims Mircera, which activates the receptor sites involved in stimulating red blood cell production, has a distinct molecular interaction that helps it provide targeted, stable, and sustained control of anemia. Roche filed Mircera with the FDA and with European regulators in late April 2006 – and in Canada in May 2006 – for the treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients who are not on dialysis. Mircera is expected to be submitted in Japan in 2009.

The data presented at the ERA-EDTA meeting was the first public presentation of the results from three Phase III ***maintenance*** trials in renal anemia. Two of these studies used epoetin alfa as a comparator, and one study used Amgen's Aranesp. The studies were designed to demonstrate that both intravenous (IV) and subcutaneous (SC) Mircera can maintain hemoglobin concentration in dialysis patients who had been on prior epoetin alfa/beta or Aranesp at least as well as those existing therapies (based on their approved schedules).

Patients were randomized to continue their frequent treatment with epoetin alfa/beta or Aranesp – or they could convert directly to Mircera given once every two weeks

(Q2W) or once-monthly (QM). The primary endpoint was the mean change in Hb between baseline and the evaluation period. In these trials, dosage was adjusted to maintain Hb ±1.0 g/dL of the baseline level.

The results from three Phase III ***correction*** studies – RUBRA, AMICUS, and ARTCOS – will be announced later this year, probably at the American Society of Nephrology meeting, November 14-19, 2006, in San Diego.

BACKGROUND

- By 2010, it is estimated that there will be more than 2 million patients with chronic kidney disease (CKD) worldwide, with growth of 7% per year.
- In Europe, the incidence of patients receiving renal replacement therapy has grown 47% in the last eight years.
- The average weekly epoetin dose for anemia patients not on dialysis is about half that for dialysis patients.
- The U.S. is a large market, and Roche does not currently market an anemia product in the U.S., though it has a significant share of the worldwide anti-anemia market, which Roche estimated to be $6.56 billion in 2006.

2006 Estimated Anti-Anemia Market Share

Company	Drug	Market share
Amgen	Aranesp/Epogen (epoetin alfa)	57%
Roche/Chugai	NeoRecormon (epoetin beta)	21%
Johnson & Johnson	Procrit (epoetin alfa)	16%
Other	---	6%

Despite the availability of these anti-anemia agents, Roche officials suggested there is a need for another drug since:

- 2/3 of patients are not maintained within target Hb range.
- 90% of patients experience Hb "cycling" (fluctuations), which are associated with hospitalizations, iron use, and frequent changes in the dose of their current erythropoietin agent.
- Patients who are unable to maintain stable Hb within the target range experience the highest rates of hospitalization and mortality.
- The vast majority of patients still receive three times a week (TIW) or weekly (QW) dosing, though doctors have tried to extend dosing. There is no product currently indicated for once-monthly dosing in dialysis, though once-monthly Aranesp is in development.

MIRCERA PHASE III MAINTENANCE RESULTS

All three of these trials were a non-inferiority study design. A Roche official said that when these three trials are compared to each other, "Mircera's difference to the comparator was virtually always 0 or slightly greater than 0 but not less than 0. And these are very far away from the limits of non-inferiority, suggesting with high confidence we can assume there is no approach to the limit of non-inferiority, and the statistical test is positive with a p-value <0.0001 for all comparisons. In all studies, Hb is maintained at about 70% whether Mircera is dosed Q2W or Q4W."

The safety profile was described as "characteristic of the study population." An official said, "We have shown that dialysis patients treated with short-acting, frequently administered epoetins can be switched directly to once-monthly Mircera while maintaining stable Hb levels. Mircera once every 2 weeks and once-monthly is non-inferior to erythropoietin 1-3 times weekly, regardless whether Mircera is given IV or SC. Mircera once every 2 weeks is also non-inferior to Aranesp QW or Q2W."

A researcher cited two key benefits to Mircera – once-monthly dosing and stable hemoglobin levels, "It is a question of convenience and practical importance on costs – though we haven't analyzed that exactly…A great deal of discussion goes on about what to do with Hb during the month. Currently, many changes are made in the dose of epoetin…Once-monthly dosing and the ability to move to a stable and constant hemoglobin level with Mircera has been impressive."

MAXIMA study. Patients who had been on IV epoetin alfa/beta, dosed up to three times weekly (90% were on TIW), were converted to IV Mircera Q2W or Q4W or continued on the same therapy (a 3-arm trial). The study had 28 weeks of titration, then an 8-week evaluation period, followed by 16 weeks of long-term safety follow-up.

MAXIMA Study Results

Measurement	IV Mircera Q2W n=223	IV Mircera Q4W n=224	IV Epoetin 1-3x/wk n=226
Primary endpoint: Non-inferiority vs. epoetin in maintenance of Hb concentrations			
Intent-to-treat	0.031 *	0.025 *	---
Per protocol	0.004 *	0.051 *	---
Secondary endpoint			
Maintained average Hb within ±1 g/dL	70%	70%	70%

* p<0.0001

PROTOS study. This trial compared SC Mircera Q2W or QM to epoetin alfa/beta dosed up to three times weekly (in patients previously on SC epoetin alfa/beta dosed up to three times weekly). The 572-patient study was 28 weeks of titration, then an 8-week evaluation period, followed by 16 weeks of long-term safety follow-up. Mircera's mean change in Hb vs. epoetin was negligible (-0.02 g/dL), demonstrating non-inferiority and a steady maintenance of Hb. No additional details on the results were presented.

STRIATA study. This trial compared IV Mircera Q2W to Aranesp in dialysis patients previously maintained on IV Aranesp dosed QW or Q2W. The study was 28 weeks of titration, then an 8-week evaluation period, followed by 16 weeks of long-term safety follow-up. The difference between IV Mircera and Aranesp in the mean change in Hb was negligible (0.18 g/dL), demonstrating non-inferiority and steady maintenance of Hb. No additional details on these results were presented. ♦