Cleveland Clinic Pharmacotherapy Update
From the Department of Pharmacy

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Update: Erythropoiesis-Stimulating Agents

Part 1: Evaluation of the Cleveland Clinic Health System Erythropoiesis-Stimulating Agents Therapeutic Interchange Program

by Amy T. Sekel, Pharm.D.

The Cleveland Clinic Health System (CCHS) is comprised of 10 hospitals including Cleveland Clinic, Euclid, Fairview, Florida, Hillcrest, Huron, Lakewood, Lutheran, Marymount, and South Pointe in addition to multiple family health and ambulatory surgery centers. Formulary integration has been a goal for the CCHS hospitals since the inception of the health system. With that, in 2004, the Cleveland Clinic Pharmacy and Therapeutics Committee approved a therapeutic interchange (TI) program for erythropoiesis-stimulating agents (ESAs) allowing the automatic conversion by pharmacists of epoetin alfa (Procrit®, EPO) to darbepoetin alfa (Aranesp®, DARB) for chronic kidney disease (CKD), chronic anemia of cancer, and chemotherapy-induced anemia (CIA). Subsequently, the TI program was adopted by the other hospitals within CCHS in 2005 as an effort to begin integrating the formularies and incurring cost savings associated with this program across the health system. After the TI had been in place for approximately 1 year, a drug use evaluation (DUE) was initiated. The DUE was reviewed and approved under the expedited review process by the investigational review board (IRB) at each institution.

The purpose of the DUE was to assess: 1) adherence to the TI program for ESAs within CCHS, 2) appropriate conversion of EPO to DARB based on TI criteria, 3) outcomes including hemoglobin and transfusions, and 4) iron studies. Medical records of inpatients and outpatients from seven of ten CCHS hospitals (Cleveland Clinic, Euclid, Hillcrest, Huron, Lakewood, Marymount, and South Pointe) who received EPO or DARB were reviewed between May 2006 and May 2007. Demographic data, ESA, dose, route, frequency, and indication were collected along with naïve or non-naïve ESA status, hemoglobin, iron studies, and concomitant therapies. In planning the DUE, the goal sample size was 250 patients (Cleveland Clinic, n=100; Euclid, Hillcrest, Huron, South Pointe, n=100; Lakewood, n=25; and Marymount, n=25 patients).

**Note: This DUE was conducted prior to the new safety data and black box warning for ESAs.*

Overall, data were collected for 279 patients (172 inpatients and 107 outpatients). Females comprised 53%

of the patient population. The mean age was 70±13.7 years (range 10-100 years), and the mean weight was 79.6±21.9 kg.

For inpatients, the most common indication, dose, route, and frequency for ESA was CKD (n=125), 100 mcg, subcutaneous, and once weekly (QW), respectively; 57% of patients were ESA naïve. Other frequent indications for inpatients included CIA (n=16) and miscellaneous indications (n=56) such as anemia of critical illness, anemia of blood loss, anemia of chronic disease, and anemia of unknown origin. Some patients had multiple indications for ESA (n=25). Additionally, other common doses and frequencies dispensed for inpatients were 60 mcg (n=31), 200 mcg (n=20) and one-time-only (OTO) (n=36).

For outpatients, the most common indication, dose, route, and frequency for ESA was CIA (n=65), 200 mcg, subcutaneous, and every 2 weeks (Q2W), respectively; 71% of patients were ESA naïve. Other frequent indications for outpatients included CKD (n=25), myelodysplastic syndrome (MDS) (n=18), and miscellaneous indications (n=8) such as Jehovah's Witnesses, anemia of chronic illness, and post allogeneic bone marrow transplant. Some patients had multiple indications for ESA (n=9). In addition, other common doses and frequencies dispensed for outpatients were 60 mcg (n=15), 100 mcg (n=101), every 3 weeks (Q3W) (n=15), and OTO (n=15).

The majority of patients evaluated met criteria for interchange from EPO to DARB (86%). It is important to note that each hospital had slightly different exclusion criteria for the TI; however, the investigator from each hospital made the determination as to whether the patient met criteria (See Table 1 for exclusion criteria for each facility). Accordingly, of the patients reviewed during the DUE (n=279) when the investigator answered the question as to whether the dose and frequency were converted according to the TI, the answer was "yes" 64% of the time, "no" 13% of the time, and data were missing 23% of the time.

Table 1: Exclusion criteria for ESA TI during time of DUE data collection:

Cleveland Clinic:
- Anemia of Critical Illness
- Jehovah's Witnesses
- HIV
- Hepatitis C
- Myelodysplastic Syndrome (MDS)
- Multiple Myeloma
- Pediatric Patients

Euclid/Hillcrest/Huron /South Pointe:
- Jehovah's Witnesses
- HIV
- Hepatitis C
- MDS
- Multiple Myeloma

Lakewood:
- Surgical patients with significant anticipatory blood loss or preoperative anemia

Marymount:
- Any indication other than CKD± Dialysis or Malignancy Induced Anemia or CIA

Inpatients received a mean of 1.97±1.72 doses during a mean length of stay of 13.78±9.18 days. These data can be seen in Figures 1 and 2 in comparison with data specific for Cleveland Clinic (CC) and the community hospitals.

CCHS outpatients received a mean of 7.61±6.25 doses during a mean of 23.9±18.42 weeks of therapy. Outpatients from the community hospitals received a mean of 8.82±7.40 doses. Outpatients from the Cleveland Clinic received a mean of 5.57±2.57 doses over 11.23±5.82 weeks of therapy.

Figure 1

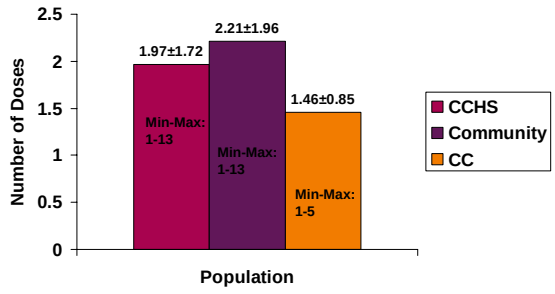
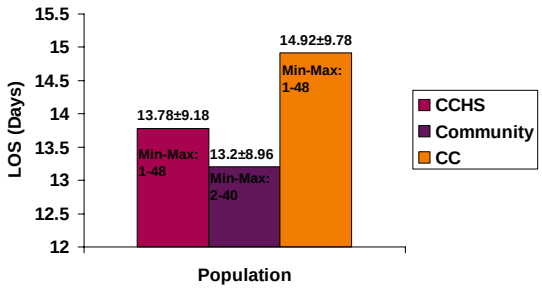


Figure 2



Target hemoglobin (defined as ≥12 g/dl or ≥2 g/dl above baseline) was achieved in 34% of patients during the course of treatment (46 inpatients on darbepoetin, two inpatients on epoetin and darbepoetin, one inpatient on epoetin, and 45 outpatients on darbepoetin). The mean hemoglobin values at various time periods for CCHS in comparison to Cleveland Clinic are shown in Figures 3 (inpatients) and 4 (outpatients).

Figure 3

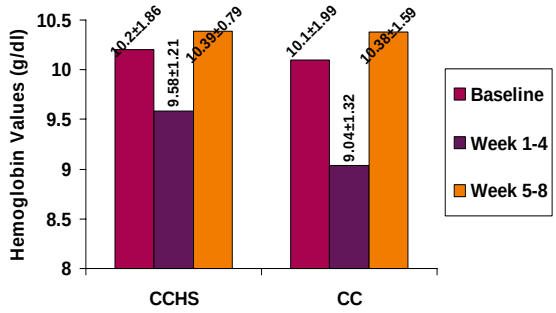
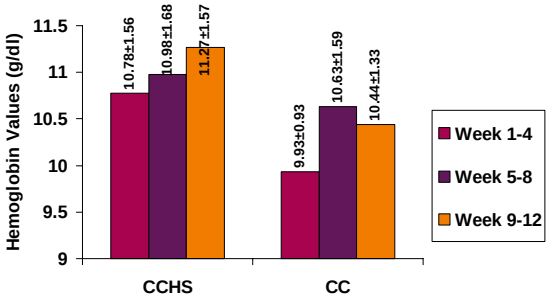
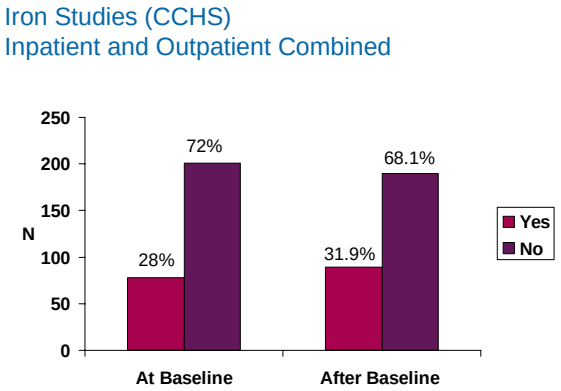


Figure 4



During ESA treatment, 71 inpatients and 16 outpatients received blood transfusions. At baseline four inpatients received 2±1.4 units of blood (Min-Max 1-4 units). Seventy-one inpatients received 1.84±0.83 units during weeks 1-4 (Min-Max 1-6 units). No inpatients received transfusions after week 4. No outpatients received blood transfusions at baseline. During weeks 1-4, 11 outpatients received 1.97±0.38 units of blood. During weeks 5-8 and 9-12, three and two patients, respectively, received 2 units of blood (Min-Max 2-2 units). Overall, the majority of CCHS patients evaluated did not have iron studies performed at baseline (72%) or after baseline (68.1%), see Figure 5. This remained true when looking at inpatients and outpatients from the community hospitals: iron studies obtained at baseline (76.1%=No) and iron studies obtained after baseline (56%=No). There was a slightly higher number of inpatients at Cleveland Clinic with iron studies performed at baseline (43.6%=No), but after baseline (i.e. during admission only) the trend continued to favor a lack of iron studies (89.1%=No). The majority of Cleveland Clinic outpatients also did not have iron studies performed at baseline (92.5%= No) or after baseline (95%= No).

Figure 5



In conclusion, CCHS pharmacists are appropriately adhering to the ESA TI, with opportunity for improvement in dosing and frequency conversion as the program continues. Co-morbid conditions and unknown iron status may have contributed to the lower than expected efficacy. Education for providers regarding the importance of adequate iron stores for ESA efficacy is planned. Standardization of the exclusion criteria for the TI throughout CCHS is under consideration. These data will also be used to assess the impact of the new Centers for Medicare and Medicaid Services (CMS) reimbursement for ESAs. A review of the new CMS National Coverage Determination will be in the next issue of the Pharmacotherapy Update newsletter (November/ December 2007).

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Lakewood: John Remchick, RPh.

Marymount: Joan Cook, Pharm.D.

Formulary Update

The Cleveland Clinic Pharmacy and Therapeutics Committee met on Tuesday, October 9, 2007, and the following decisions were made:

Formulary Additions:

1. Aripiprazole Intramuscular Injection (Abilify® IM): Aripiprazole is an antipsychotic agent FDA-approved for the treatment of agitation associated with schizophrenia or bipolar disorder, manic or mixed. It can also be used to achieve immediate control of agitated patients. The recommended initial dose of aripiprazole IM for agitation is 9.75 mg (dose ranges of 5.25-15 mg have been evaluated). Repeated doses may be administered at ≥2 hour intervals to a maximum of 30 mg/day. Aripiprazole IM is available as 9.75 mg/1.3 mL vials. It is ***restricted*** to the Departments of Psychiatry and Emergency Medicine. Aripiprazole tablets will remain on Formulary.

2. Darunavir (Prezista™): Darunavir is a protease inhibitor used in combination with ritonavir (Norvir®) and other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor. The recommended oral dose of darunavir is 600 mg twice daily taken with ritonavir 100 mg twice daily and with food. Darunavir is available as 300 mg tablets.

3. Hydroxocobalamin (Cyanokit®): Hydroxocobalamin is the activated form of vitamin B_{12} that avidly binds to intracellular cyanide forming cyanocobalamin. It is used to treat cyanide intoxication after intravenous and inhalational/topical exposure. Compared to other antidotes used in treating cyanide poisoning, hydroxocobalamin does not induce hypotension or methemoglobinemia to the same extent as nitrites (e.g., amyl or sodium nitrite) and has a more rapid onset of action compared to sodium thiosulfate. Each kit contains two vials of 2.5 grams hydroxocobalamin. The recommended starting dose is 5 grams administered intravenously over 15 minutes. If necessary, a second dose of 5 grams may be administered. Kits will be stored in the Emergency Department.

4. Maraviroc (Selzentry™): Maraviroc is a CCR5 antagonist indicated for the treatment of CCR5-tropic HIV-1 infection in combination with other antiretroviral agents in patients with evidence of viral replication and HIV strains resistant to multiple antiretroviral therapies. Due to drug interactions, the dose of maraviroc depends upon other concomitant medications the patient is receiving (e.g., CYP3A inducers or inhibitors). It is available as 150 mg and 300 mg tablets.

5. Tranexamic Acid Mouthwash (Cyclokapron®): Tranexamic acid mouthwash is used to control postoperative bleeding in anticoagulated patients requiring dental surgery. It acts as a local antifibrinolytic. Tranexamic acid is commercially available as a 10% injection. A 5% solution can be made by diluting 100 mL of the injection with 100 mL of saline (total volume = 200 mL). Patients should rinse and expectorate 10 mL of the 5% solution every 6 hours until the solution is gone.

6. Zolendronic Acid Injection (Reclast®): Reclast® is a bisphosphonate that contains the same active ingredient as Zometa®; however, Reclast® is a 5 mg/100 mL infusion whereas Zometa® is a 4 mg injection. Reclast® is FDA-approved for the treatment of Paget's disease and postmenopausal osteoporosis. In Paget's disease, a single 5 mg infusion is recommended. A single 5 mg intravenous infusion once a year is recommended for osteoporosis treatment. Patients receiving Reclast® should take supplemental calcium and vitamin D. Reclast® infusions should be administered over at least 15 minutes. It should be avoided in patients with CrCl ≤35 mL/min. It is ***restricted*** to outpatient use only.

Formulary Restriction Changes:

1. The olanzapine IM (Zyprexa® IntraMuscular) restriction has been changed to include both the Departments of Psychiatry and Emergency Medicine.

Therapeutic Interchanges:

1. Zolpidem CR (Ambien® CR): Zolpidem CR tablets are non-formulary. Beginning November 20, 2007, all orders written for zolpidem CR tablets will be automatically interchanged by a pharmacist to an appropriate dose of zolpidem immediate-release (Ambien®) tablets. Additional information about this therapeutic interchange will be communicated in the near future.

For more detailed information on the above medications, please consult the Formulary on the Intranet (under Clinical Resources/Drug Information), specifically under Lexi-Drugs Online. Furthermore, please call the Drug Information Center at 4-6456, option #1 if you have any questions.