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Re: New drug application 021825, Ferriprox (Deferiprone); Proposed indication (use) for this product is for the treatment of patients with transfusional iron overload, when current chelation therapy is inadequate; September 14, 2011

Introduction

At the request of Cooley's Anemia Foundation, we are writing in support of the new drug application (#021825) for the oral chelator Ferriprox, which is to be discussed at the September 14 ODAC meeting. As the medical director (EY) and primary physician (RW) of the Red Blood Cell Disorders Program (RBCDP) at Toronto General Hospital, University Health Network, we represent the largest adult Hemoglobinopathy program in Canada. For the past 2 years, we have gained considerable experience in the safe and effective prescribing of Ferriprox to our patients. Also included in this package are personal testimonies from a few of our patients who have been treated with this drug, outlining their personal stories and perspective.

We cannot state how strongly we support this initiative and our positive clinical experience with Ferriprox when followed within accepted guidelines. Our experience is similar to that reported in the literature in European, Mediterranean and Asian countries (eg England, Italy, Cyprus and Greece, Thailand) where the drug is used in a similar medical population.

As the largest comprehensive Hemoglobinopathy program in Canada, we are aware that smaller centres across the country look to us for a lead in clinical care expertise. We are

aware, that since our change in chelation practice in summer 2009, a number of other patients across Canada, who would greatly benefit from Ferriprox, have now been prescribed it, based on the positive experience we have had, and our ability to offer expert advice to other physicians.

Background to RBCDP

The RBCDP is situated at the Toronto General Hospital and works closely with the pediatric program at the Hospital for Sick Children, Toronto. Together, we care for >80% of Canada's Hemoglobinopathy patients, providing comprehensive and lifelong care. At the present time we have 500 adult patients Sickle Cell Disease and Thalassemia Syndromes. The healthcare team comprises: 4 Hematologists, 2 Nurse Practitioners, 1 Social Worker and clerical support. We also run a Hemoglobinopathy fellowship training program supported in part by an award from the American Society of Hematology. Specialty Hemoglobinopathy clinics are run 5 days per week in dedicated space within the Toronto General Hospital, and care provided involves managing all aspects of iron chelation management. Although the program has been in existence for more than 20 years, the current clinic director and team have been in place since January 2009. Prior to this time the majority of patients where prescribed iron chelation with subcutaneous or intravenous Desferal and with Exjade, although 3 patients had chosen to independently source Ferriprox from overseas. Other patients had received Ferriprox at various times as participants in clinical studies under the responsibility of another Hematologist. In 2009, we moved to regularize Ferriprox for these three patients by obtaining Health Canada SAP approval. At the same time we initiated approval to address the addition of chelation with Ferriprox to our pharmacopeia for all of our chelated patients (see indications below).

RBCDP Indications for Ferriprox

Exjade is the first line iron chelation medication in the RBCDP. The RBCDP uses the following criteria as indications for commencing a patient on Ferriprox:

1. Severe cardiac iron overload whilst chelating with Exjade, Desferal or combination of Exjade and Desferal
2. Severe cardiac iron overload with a cardiac MRI T2* <10msec; Left Ventricular Ejection Fraction <50%; or >10% fall in EF
3. Severe hepatic iron overload unresponsive to Desferal, Exjade or combination of Exjade and Desferal
4. Intolerance, significant adverse event, or refusal to use Exjade or Desferal

Cardiac events are the leading cause of death in patients with β Thalassemia Major. Ferriprox has been reported in many studies to reduce cardiac siderosis, cardiac events, and deaths in this patient population. The decision to commence Ferriprox for a cardiac indication is taken in conjunction with a specialist heart failure cardiologist who is directly allied to the Program.

Amongst our cohort of 160 patients (both thalassemics and sickle cell) on any chelator, 23 patients were prescribed Ferriprox because of severe cardiac iron overload, 4 for

severe hepatic iron unresponsive to all other chelators, 10 who were intolerant of or had significant adverse events with other chelators, and 3 for other reasons.

RBCDP Experience

In the last 2 years we have prescribed Ferriprox to 40 patients with β Thalassemia Major (39) and Sickle Cell Disease (1) who have complications of transfusion related iron overload, for a total in excess of 30 patient years of Ferriprox therapy. These numbers represent approximately 25% of our chelated population, a proportion in line with that in other major Hemoglobinopathy centres across the World (excluding USA). Half of our patients received standard dose Ferriprox at 75mg/kg/day, the remainder (predominantly those with severe cardiac siderosis) at the higher dose of 100mg/kg/d. 18 patients were prescribed Ferriprox in combination with Desferal or Exjade, and 22 as monotherapy. Of patients still receiving Ferriprox, the longest duration of continuous exposure has been 25 months in a patient with severe cardiac iron overload. Six of 40 patients are no longer taking Ferriprox, three because they have had resolution of their cardiac siderosis and normalisation of cardiac MRI T2* values, 1 moved out of province, 1 had mild but persistent gastrointestinal upset, and 1 was non-compliant with taking the drug. Of note, 5 patients commenced on Ferriprox in the past year have been transitioned from the HSC pediatric program, highlighting the ongoing need for effective alternative iron chelators.

With respect to adverse events, we recognise that total duration of exposure is such that rare adverse effects would not be expected to have been detected to date in our patient cohort. 75-80% of patients are adherent to the prescribed dose more than 90% of the time. Neutropenia (ANC < 1.5), has been observed in 4 patients on 11 occasions, but with no episodes of agranulocytosis (ANC <0.5). All have recovered with close attention or drug at altered dosage. Patients have complied with requests for a CBC every 5-10 days. Consideration could be given to relaxing monitoring to every month after 6-12 months of therapy as this is beyond the period of highest risk for agranulocytosis. Four patients had an asymptomatic transient increase in alanine transaminase (> 5x upper limit of normal), which settled either spontaneously or with transient interruption of Ferriprox. Two of these patients were referred to a Hepatologist who did not definitively implicate Ferriprox in the etiology of the hepatitis's. None of the patients required a liver biopsy as part of further investigation. Four patients had arthralgias, which resolved with dose reduction or interruption. All of our patients on chelation have MRI Ferriscans every 3-6 months. We have no data to support an effect on liver fibrosis as liver biopsy and histological examination is no longer performed as part of routine clinical care, and liver MRI assessment is unable to comment on tissue architecture. However, none of our patients have had clinical or biochemical evidence of cirrhosis or worsening liver function whilst taking Ferriprox.

A recent analysis of serial cardiac MRI T2* and EF measurements in 22 patients from this cohort has demonstrated a mean change in T2* of +2.6 ms/year and also improvement in EF +1.5%/year after an average of 425 days of therapy. These are statistically significant results. To date, the improvements in cardiac T2* in the total patient group ranges from -0.9ms to +25.6ms. There have been no episodes of cardiac failure requiring admission to hospital/CCU. It is important to note these improvements

have been achieved, in the main, without the need for insertion of an intravenous line for continuous IV Desferal (and its attendant risks and toxicities), which is the only other proven effective method for removing cardiac iron.

Canadian Access to Ferriprox

Since 2004 APOTEX ARE CHECKING THIS DATE AND WILL GET BACK TO US, Ferriprox has been available via a compassionate use program (CUP) from Apopharma Inc (a division of Apotex) in conjunction with Section A approval from Health Canada's Special Access Programme. This provides access to non-marketed drugs for practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable, or unavailable. As part of this process, we gain informed consent from patients informing them as to the status of the drug in Canada, and its published efficacy and safety/toxicity data. A stipulation of approval to supply the drug by Apopharma is the careful logging of regular Complete Blood Counts and other measures to ensure safe use of the drug and drug accountability. Advice is followed to monitor for neutropenia on a weekly basis (every 5-10 days) for the duration of therapy, with reporting of these results to Apopharma as part of pharmacovigilance. The drug is delivered to a single pharmacy (at Toronto General Hospital) and thereafter collected in person by patients or shipped to their home address.

Monitoring of Ferriprox

It is recognised that the time required in preparing, and maintaining the documentation for the CUP (Apopharma) and SAP (Health Canada) is incredibly burdensome and time consuming. We have heard anecdotal reports that this has been a barrier to some US based physicians attempting to access the drug.

We have allocated this role to a single administrative individual under the supervision of a physician (RW). In addition to pre-approval applications to Health Canada and Apopharma, there are ongoing weekly CBC results to monitor and quarterly reporting of these and any adverse events to Apopharma. As well, every 6 months, a renewal request is required from Health Canada. The administrative role includes checking CBC results, reminding patients to attend their community blood lab for blood draws, liaising with patients as to when their supply of medication will need renewing, and liaising with Apopharma for timely delivery of drug to the hospital pharmacy. A shadow chart is kept by the administrator to facilitate all this data collection.

An internal review of the Ferriprox access process, described above, was undertaken by our Institution in 2011. UHN's medical and legal auditors were satisfied that the process and documentation undertaken to obtain and monitor patients receiving Ferriprox was of the standard expected by the institution, and comparable to that required as part of Good Clinical Practice in the setting of research studies.

In Winter 2010/11, an external review of the RBCDP took place. Amongst its findings was that INCLUDE QUOTE ON L1 USAGE HERE.

Concluding Comments

We believe that the RBCDP currently has the largest active population of patients receiving chelation with Ferriprox in North America. Our experience is much in line with that seen in other centres across the World (excluding USA). We have had no reason to abandon the use of Ferriprox and continue to use where indicated. As our understanding of the basic science of iron homeostasis improves, along with our ability to closely monitor its effect on vital organs, it is essential that patients and their physicians have access to the full range of iron chelation options, in order to tailor chelation to the individual's personal circumstances and needs.

Disclosure Statement

None of the physicians in the RBCDP have received personal funding of any sort from, nor hold stocks or ownership in Apopharma/Apotex. The RBCD Program and the Division of Hematology have received unrestricted educational grants from Apotex (Ferriprox) and Novartis (Exjade, Desferal). The physicians do not consider there to be any relevant personal conflicts of interest.

Respectfully
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