

Deliverable 1 – Health Analytics Project Proposal

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CLINICAL QUESTION

In patients undergoing treatment for thrombocytopenia, does those that have been treated with Anagrelide has a higher risk of thrombosis, compared with a more conventional alternative, Hydroxyurea?

Thrombocytopenia represent in various myeloproliferative disorders, including chronic myeloid leukaemia, agnogenic myeloid metaplasia, and essential thrombocytopenia (ET) (Sanchez & Ewton, 2006), which is characterized by platelet production increase, and elevated platelet counts (Spencer & Brogden, 1994). Thrombocytopenia is usually seen in elderly patients, and could be dangerous, as the increased number of platelets might cause dangerous complications such as systemic thrombosis (Xiong et al., 2017). Thus, there is an essential need for drug development to limit the patient's platelet count in normal range, in order to minimize the risk of the potential cardiovascular adverse effects.

BACKGROUND

Anagrelide is an orally active quinazolin, which is known for causing thrombocytopenia, and has thus been evaluated for treating thrombocytopenia (Spencer & Brogden, 1994). Anagrelide is approved by FDA in 1997 in order to treat essential thrombocytopenia, under then commercial name of AGRYLIN by Roberts Pharmaceutical. In the associated clinical trial, among a total of 551 patients, the most frequently reported adverse reactions were headache, palpitations, diarrhea, and abdominal pain (Solberg Jr et al., 1997). Patient thrombosis data was not included in this clinical trial.

Hydroxyurea is a time-tested older drug, which has been widely used to treat sickle cell disease in 1980s (although FDA has not approved its usage until 1998)

(Okam, Shaykevich, Ebert, Zaslavsky, & Ayanian, 2014). Compared with newer drugs, hydroxyurea is also cost-effective. The cost for hydroxyurea oral capsule 500 mg is around \$78 for a supply of 100 capsules, while the cost for Anagrelide oral capsule 0.5 mg is around \$273 for a supply of 100 capsules (Drugs.com, 2019).

In 2012, a clinical trial compared 122 patients treated with Anagrelide and 137 treated with Hydroxyurea suggest that both groups show similar risk of all kinds of thrombosis, including major/minor arterial/venous thrombosis, and concluded that “Anagrelide as a selective platelet-lowering agent is not inferior compared with hydroxyurea in the prevention of thrombotic complications.” (Gisslinger et al., 2013) However, a more recent research article published in 2019 checked the Anagrelide clinical trials back in the 1990s, and noticed that the thrombosis-free survival data for ET patients diagnosed before the 1997 FDA approval date is significantly better compared with that after the 1997 FDA approval date (Tefferi et al., 2019). In more recent literature review, transfusion experts suggest directly that the main indication for treatment in ET is to prevent thrombosis, and that “none of the newer drugs have been shown to be superior to the time-tested older drugs (e.g., hydroxyurea).” (Tefferi, Vannucchi, & Barbui, 2018). These works indicate that it is beneficial to compare Anagrelide with Hydroxyurea on the risk of thrombosis, using a broader data generated in actual clinical practice.

COHORTS

Target Cohort - The target cohort is patients who have taken Anagrelide to treat thrombocythemia with at least 60 days of follow-up, and are not affected by sickle cell disease.

Comparator Cohort - The target cohort is patients who have taken with Hydroxyurea to treat thrombocythemia with at least 60 days of follow-up, and are not affected by sickle cell disease.

Outcome Cohort – The outcome cohort is patients who have been diagnosed with thrombosis complications.

ADDITIONAL COMMENTS

As the patient groups of the Anagrelide and Hydroxyurea are not perfectly matching, the former is used majorly on ET patients, while the latter are widely

used for all kinds of thrombocythemia (including ET), as well as for sickle cell disease patients. Thus, I propose to exclude all patients that are affected by sickle cell disease. This decision could be due for change, as in the U.S., nearly all sickle cell disease patients are African-Americans (Hassell, 2010), which in general are easier to be affected by hypertension (Kramer et al., 2004), and thus might be exposed to a higher risk of thrombosis than other groups. Thus, including sickle cell disease patients might be helpful to expose the difference between Anagrelide and Hydroxyurea.

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