Efficacy of alfa-2b Treatment in Reducing Red Blood Cell Counts in Polycythemia Vera Patients

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Abstract

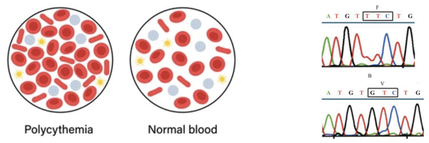
Polycythemia Vera(PCV) puts thousands of seniors at risk for blood clots and cardiovascular issues every year. Few treatments exist for this understudied cancer. Ropeginterferon alfa-2b (alfa-2b) is a novel drug that can treat the effects of PCV. The treatment works by attaching to receptors called interferons, which produces immunomodulatory effects that slows the production of red blood cells. In this double-blinded, randomized control trial, we analyzed the efficacy of alfa-2b in lowering hematocrit and instances of splenomegaly. After 12 months, 84% of participants treated with alfa-2b saw an improved hematocrit whereas only 1(0.8%) of the participants in the control group improved. Additionally, the number of participants in the experimental group with splenomegaly decreased by 12.8%. Common side effects of this treatment included pruritus, headaches, fatigue, and arthralgia. Overall, alfa-2b was found to be an effective treatment in reducing the red blood cell count in PCV patients.

Background

Every year, Polycythaemia Vera (PCV) affects thousands of adults primarily between the ages of 50 and 75. Polycythaemia Vera is a specific type of myeloprolific neoplasm (MPN) that causes an increased and uncontrollable production of red blood cells (RBC). PCV leads to an increased risk of blood clots and puts patients at higher risk of heart attacks, strokes, and pulmonary embolisms. PCV can also lead to liver and spleen enlargement in some patients. If left untreated, PCV can be fatal.

The mutation responsible for PCV was determined to be caused by a valine to phenylalanine substitution at position 617 (V617F) of the JAK2 gene (James et al. 2005). This mutation causes a faulty JAK2 protein to ignore termination signals and continue producing red blood cells. PCV was initially considered a Myeloproliferative disease and was reclassified as cancer in 2008 after the discovery of the V617F mutation. There is a critical need for novel treatments for PCV because many JAK2 inhibitors are still in clinical trials or just reaching the market. Bone marrow transplantation is currently the only treatment for PCV, but the majority of patients with PCV are unable to receive this procedure because of their age.

In this study, we proposed a drug to treat PCV. The active chemical in the drug is ropeginterferon alfa-2b, which binds to receptors called interferon alfa/beta receptors (IFNAR). This binding triggers a chain reaction that results in the activation of JAK1 and transcription (STAT) signaling pathways, producing a series of anti-proliferative and immunomodulatory effects that slows the production of red blood cells in the bone marrow. In our drug, the interferon has been 'pegylated' (attached to the polyethylene glycol chemical) so that it can stay in the body longer and thus be given less frequently.

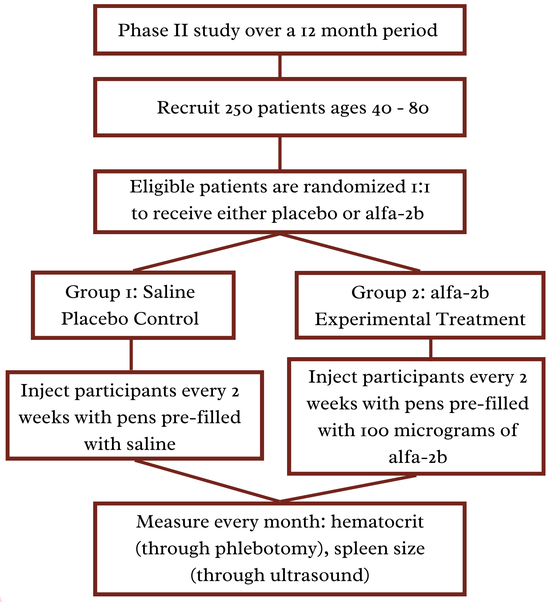


Polycythemia Normal blood

Hypothesis

We hypothesize that ropeginterferon alfa-2b will reduce the effects of Polycythemia Vera by lowering hematocrit levels down to normal levels. This additionally helps manage the enlarged spleens found in PCV patients, lowering the number of patients affected by splenomegaly.

Methods



Double-blinded, randomized, placebo-controlled study with 125 male and 125 female participants

Inclusion Criteria:

- PCV Patient with JAK2 Mutation
- 40-80 years old

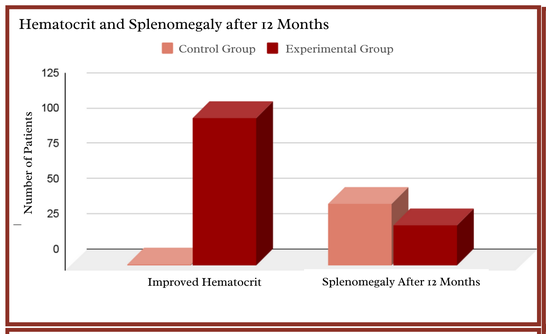
Exclusion Criteria:

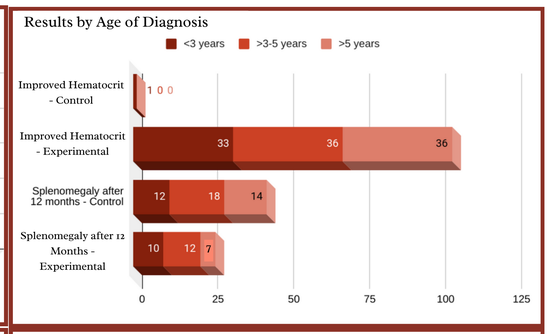
- History of severe psychiatric disorders, particularly depression
- Allergy to alfa 2b
- Suppressed Immune System
- Pregnant
- Diagnosed with liver diseases

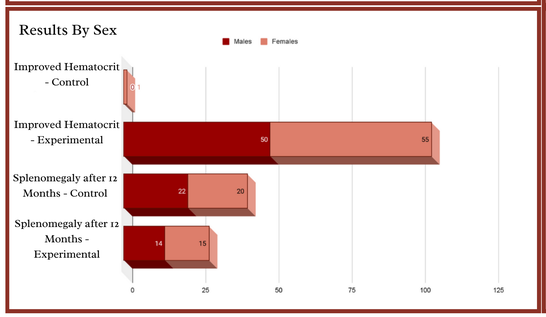
Patient Characteristics	Participants (N = 250)
Sex - no. (%)	
Male	125 (50)
Female	125 (50)
Age	
Median	65
Range	40 - 80
Time from Diagnosis to Entering Study	
Less than 3 years	175 (70)
3 - 5 years	50 (20)
More than 5 years	25 (10)

Results

Hematocrit: The percentage of red blood cells in the blood by volume
Splenomegaly: The condition of an enlarged spleen (400-500g)







Most Common Side Effects
Pruritus (Itchy Skin)
Headache
Fatigue
Arthralgia (Joint Stiffness)
Diarrhea
Vertigo

The results clearly show how alfa-2b can effectively reduce blood count, as 105 out of the 125 people (84%) in the experimental group saw their hematocrit improve back down to normal levels. In addition, alfa-2b helps treat the main secondary symptom of Polycythemia Vera, which is splenomegaly. 23.2% of patients in the experimental group had splenomegaly after 12 months, compared to 36% before treatment started.

Feasibility

There are several different ways to treat PCV that are currently being investigated. This study seeks to explore the efficacy of this particular technique but does not promise to be the best possible solution. PCV patients are also in relatively short supply, meaning that finding patients for the study can be difficult, which is compounded by the fact that competition must be proven to be less important than this study.

The distribution of this drug can be handled in a versatile number of ways, based on what is most convenient to the patient. This particular drug is injected into the bloodstream, so it can be handled in a similar manner to insulin shots where they are administered by the patient themselves. If the patient does not feel comfortable, and or capable of administering their own medication, then they can go to the local pharmacy to have it administered by the pharmacist.

Typically, a study such as this includes a control group that is robbed of any sort of treatment so that they can be compared to those who do. This study maintains these consistencies but makes it far less of a problem since PCV is a chronic problem. Many people live a very long time with diagnosed and untreated PCV since it does not put their life in immediate danger, which means that taking their treatment away does not have large implications on their life.

Conclusion

This was a phase II clinical trial assessing the efficacy of alfa-2b in treating Polycythemia Vera. In this study we found that:

- 84% (105) of participants treated with alfa-2b saw an improved hematocrit compared to 0.8% (1) of participants in the control group.
- The number of participants with splenomegaly decreased by 12.8% over the course of the 12 months.
- Common side effects included: pruritus, headaches, fatigue, arthralgia, diarrhea, and vertigo.
- It is worth noting that 2 participants developed moderate to severe depression as a result of this drug.

This demonstrates that our hypothesis was correct; when administered once every 2 weeks, alfa-2b successfully lowers the hematocrit of PCV patients to a normal range. In addition, it was able to alleviate the splenomegaly found in some patients.

Our use of a randomized placebo-controlled study eliminated potential result-affecting biases in patients. Additionally, our double-blinded study ensured that the physicians working with the patients were unbiased as well. The patient characteristics in the control and experimental groups were similar, which ensured that external factors did not cause the results.

In this study, only the hematocrit and spleen size were measured. For future studies, white blood cell counts should also be measured, and comprehensive blood exams can be taken. Additionally, the prevalence of depression should also be tracked, as it is uncertain what caused the depression in the 2 participants. Lastly, alfa-2b treatment is only viable in PCV patients that have the JAK2 VF mutation. Future studies should test treatments for the 20% of PCV patients that do not have this mutation.

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