Journal of Rare Cardiovascular Diseases 2019; 4 (2): xx–xx
www.jrcd.eu

REVIEW ARTICLE
Rare diseases

Current views on the use of interferons in the treatment of polycythaemia vera (RCD code: VIII)

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Abstract

Interferon alpha is a molecule associated with stimulation of immune system cells, resulting in an anti-proliferative and immunomodulatory effect. It has been demonstrated that interferon reduces the number of platelets, leukocytes, and erythrocytes in patients suffering from chronic myeloproliferative diseases. In this paper, we present an overview of selected research evaluating the efficacy and adverse effects of various recombinant interferons used in the treatment of polycythaemia vera. We have analysed previously reported studies on the use of interferon. Interferon alfa-2a was the first interferon approved for standard treatment of polycythaemia vera, while the next was pegylated interferon alfa-2a. We also present recent results from studies on a newly modified molecule, ropeginterferon, a mono-pegylated form of interferon alfa-2b. Interferons reduce the number of phlebotomies required in patients with polycythaemia vera, accompanied by a resolution of typical disease symptoms. Treatment is well tolerated by the majority of patients. JRCD 2019; 4 (2): x–x

Key words: rare disease, interferon alfa-2a, pegylated interferon alfa-2a, ropeginterferon, polycythaemia vera

Background

Sixty years ago, interferon was discovered as a cytokine which inhibited viral replication [1]. After 30 years, clinical trials were initiated on its use in the treatment of myeloproliferative disorders. The action of interferon alpha is associated with stimulation of immune system cells, resulting in an antiproliferative and anti-angiogenic effect [2]. In the 1980's, interferon was shown to be effective in reducing platelet counts in patients with myeloproliferative neoplasms. [3]. Subsequent studies have shown a reduction in the number of phlebotomies needed in patients with polycythaemia vera along with a resolution of other disease symptoms such as pruritus, normalisation of leukocyte count and spleen size [4].

Polycythaemia vera (PV) is a Ph-negative myeloproliferative neoplasm and its incidence is 2–3 cases per 100 000 persons [5]. In the pathogenesis of PV, a key role is played by the activation of signal transduction pathways dependent on tyrosine kinases, especially the JAK-STAT pathway. The V617F mutation in the JAK2 tyrosine kinase gene appears in nearly 100% of PV cases, leading to constitutive tyrosine kinase phosphorylation, which induces cytokine hypersensitivity. This pathway transmits extracellular chemical signals to the cell nucleus, where it initiates the transcription of specific genes. This results in an increased production of erythrocytes, sometimes accompanied by increased production of leukocytes and platelets [6,7,8].

Major functions of interferon alpha include exerting a strong influence on JAK signal transducers and activating the STAT signal pathway. Interferon alpha binds to type I interferon receptors (IFNAR1 and IFNAR2c), which upon dimerisation, activate tyrosine kinases. This leads to autophosphorylation and phosphorylation of the receptors. The phosphorylated INFAR receptors then bind to STAT1 and STAT2 (signal transducers and activators of transcription), which dimerise and activate multiple immunomodulatory and antiviral proteins [9].

As molecular tests have become available in clinical practice, researchers began to evaluate the effect of treatment on the suppression of the malignant clone. In 2006, the first studies on molecular remission were published involving JAK2-positive polycythaemia vera patients treated with interferon-alfa 2a [10]. There have been reports of long-lasting remissions which persist even after interferon discontinuation [11,12].

Please cite this article: Prochwicz A, Szczepanek E, Krochmalczyk D. Current views on the use of interferons in the treatment of polycythemia vera (RCD code: VIII). J Rare Cardiovasc Dis. 2019; 4 (2): …; doi: https://doi.org/10.20418/jrcd.vol4no2.363

Conflict of interest: none declared Dorota Krochmalczyk was subinvestigator in the PROUD study and she is principal investigator in the CONTINUATION study, conducted with AOP Orphan Pharmaceuticals AG. Submitted: January 1, 2019. Accepted: February 15, 2019.

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In this paper, we present an overview of selected research evaluating the efficacy and adverse effects of various recombinant interferons used in the treatment of polycythaemia vera.

Interferon alfa-2a

Interferon alfa-2a was the first interferon approved for the standard treatment of polycythaemia vera.

In 1998, Professor Foa and co-authors published a report on the long-term efficacy and safety profile of recombinant interferon alfa-2a. Thirty-eight patients with polycythaemia vera participated in the study. From this group, 28.9% of patients achieved complete remission (CR), defined as maintaining a correct haematocrit without phlebotomy. Partial remission (PR) was obtained in 21% of the patients, which was described as a reduction in frequency of phlebotomy by 50%. In patients who achieved response, leukocyte and platelet counts normalised. Spleen size also returned to normal. Interferon alfa-2a also led to resolution of pruritis in all cases in which it was present at the beginning of the disease. Toxicity analysis showed a flu-like syndrome occurring in 23.6% of patients, while severe weakness was observed in 13.1% of cases. Among patients treated only with interferon, there was no progression to acute myeloid leukaemia (AML). One patient who was previously treated with an alkylating agent developed AML [13].

Silver et al. presented results from a long-term observation of polycythaemia vera patients treated with interferon alfa-2a (median 13 years). All patients required less frequent phlebotomy, with 96% of patients not requiring phlebotomy at all. In addition, the number of platelets and the size of the spleen were reduced. Thromboembolic complications were not observed and toxicity was acceptable [4].

The most common adverse effect was a flu-like syndrome, which occurred in a significant number of patients. Symptoms included fever, chills, joint and bone pain, headache, and weakness. These side effects were managed by paracetamol or by initiating treatment with lower doses of interferon Moreover, severity of these side effects decreases during the first few weeks of treatment. The treatment was usually discontinued due to severe fatigue and bone and muscle pain. Additionally, interferon can have a negative influence on mental condition. Cases of depression have been observed, which is why administration of interferon is contraindicated in patients with previously diagnosed depression. Another important issue is the effect of interferon on the immune system. As a result of the immunomodulatory effect of interferon, autoimmune disorders may develop during therapy, with Hashimoto's disease being the most common. Haemolytic anaemia, mixed connective tissue disease, and polyarthritis are much less common [9,13,14].

Pegylated interferon alfa-2a

Interferon alfa-2a showed significant toxicity, which often resulted in discontinuation of treatment. Because a less toxic form of interferon was needed, work on its pegylated form was initiated. Clinical trials were conducted using pegylated interferon alfa-2a in patients with Ph-negative myeloproliferative disorders. This more advanced variant of interferon was effective in inducing haematologic remission and reducing the level of JAK2 V617F-positive cells [15,16,17].

The pegylated form of interferon alfa-2a introduced for treatment is characterised by a prolonged half-life, lower toxicity, and greater stability and solubility. Therefore, it can be administered over longer time intervals. The effectiveness of the pegylated form of interferon is similar to the non-pegylated form [18].

Several studies have been conducted to evaluate the efficacy and safety of pegylated interferon alfa-2a. One of them was a phase 2 multi-center study which included 40 patients with polycythaemia vera. After 12 months of treatment, 8% of patients discontinued therapy, while all others achieved a haematological response, of which 94.6% achieved complete remission. A total molecular response was obtained in 7 patients lasting from 6 to 18 months. In addition, none of the patients experienced a thromboembolic episode [19].

In another phase 2 study, patients with polycythaemia vera and essential thrombocythemia were evaluated. Haematological responses were found in 80% of PV patients, including total remission in 70% of patients. A molecular response was obtained in 54% of patients, and from this group, JAK2 V617F was undetectable in 14%. High patient tolerance to pegylated interferon alfa-2a at a dose of 90 μg/week was demonstrated. While assessing the haematological response, haematocrit normalisation, platelet count, spleen size reduction, and leukocyte count normalisation were all taken into account. In the group of patients in which JAK2 V617F mutation had become undetectable, none experienced a molecular relapse in the 2-year observation period. The toxicity of treatment was low. Only 10% of patients had side effects, mainly after administration of higher doses (180–450 μg/week) in the initial phase of the study. The most common adverse effect was neutropenia. In addition, elevated liver function tests and weakness were observed [20].

Mono-pegylated interferon alfa-2b (ropeginterferon)

A new mono-pegylated form of interferon alfa is ropeginterferon alfa-2b. Due to a minor change in structure, an isoform with a longer half-life was obtained. This enabled the drug to be administered every two weeks, in contrast to less advanced forms, which needed to be administered several times per week.

Results from phase 1 and 2 studies using ropeginterferon alfa-2b in 51 polycythaemia vera patients after 1 year of treatment were published by Gisslinger et al. The dose was gradually increased until the optimal effective dose was determined. The effective dose varied between individual patients and ranged from 50 to 540 μg. None of the patients experienced dose-limiting toxicities. The total response rate was 90%, of which 47% had a complete response and 43% had a partial response. A total molecular response was obtained in 21% of patients, while a partial molecular response was obtained in 47% of patients. It was shown that ropeginterferon is effective even at low doses and that the percentage of responses obtained and their duration did not differ from the group with higher doses [21].

Results from the phase 3 study comparing the safety and efficacy of ropeginterferon and hydroxyurea (HU) were presented during the most recent European Haematology Association meeting. The groups were divided depending on their age: under 60 years of age and over 60 years of age, and observed for a period of 2 years. In the PROUD study, 254 patients with polycythaemia vera participated. They were randomised to two study arms: treatment with ropeginterferon or treatment with HU. After 12 months, 89.6% of patients in the ropeginterferon arm and 68.5% in the HU arm continued treatment in the CONTINUATION study. After 24 months, ropeginterferon resulted in a higher rate of haematological responses than HU in both age groups. For patients under 60 years of age, 77.6% responded to ropeginterferon and 55.9% responded to HU. Similar results were obtained in the of patients over 60 years of age: 63% responded to ropeginterferon and 42% responded to HU.

Assessment of molecular response showed higher response rates in the group of patients treated with ropeginterferon. A partial molecular response was observed in 78.1% of patients under 60 years of age and in 59.5% of patients over 60 years of age. For comparison, a partial molecular response in the group treated with HU was obtained in 33.3% of younger patients and in 25.0% of older patients. Ropeginterferon was also effective in improving the general symptoms associated with myeloproliferative disease. The number of adverse reactions in patients treated with ropeginterferon and hydroxyurea was comparable. The rate of adverse drug reaction in elderly patients treated with ropeginterferon was lower. These recent observations allow us to consider ropeginterferon as an effective drug which is safe for all patients with PV, regardless of age [22].

Conclusions

Many previous studies have demonstrated the efficacy of interferons. Non-pegylated forms are widely used in everyday clinical practice but they also have a problematic toxicity profile. Pegylated forms of interferon are better tolerated by patients and produce less adverse effects. Currently, much interest surrounds the mono-pegylated form of interferon alfa-2b, ropeginterferon, which can be administered subcutaneously less frequently (once every 2–4 weeks). Ropeginterferon possesses an acceptable toxicity profile, high efficacy, and the ability to achieve suppression of clonal haematopoiesis. All of these should lead to its wider use in haematology.

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