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Real world experience with ropeginterferon alpha-2b (Besremi) in essential thrombocythaemia and polycythaemia vera following exposure to pegylated interferon alfa-2a (Pegasys)

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ABSTRACT

Despite widespread use of Pegylated forms of Inteferon in the management of Myeloproliferative Neoplasms (MPN), most clinicians have experience predominantly with peginterferon alfa-2a (Pegasys). Third generation pegylated IFNα, ropeginterferon alfa-2b (ropegIFN; Besremi), was recommended by the European Medicine Authority (EMA) for treatment of Polycythaemia Vera (PV) following a Phase III trial (PROUD-PV / CONTINUATION-PV). FDA approval for PV, regardless of treatment history, was subsequently granted in November 2021. We hereby demonstrate the safety and tolerability of ropegIFN in a series of MPN patients at variable doses. It corroborates reports of efficacy of ropegIFN in patients with PV and use in pregnancy.

1. Introduction

For over 30 years interferon-alfa (IFNα) has been recognised as an effective treatment in the management of myeloproliferative neoplasms (MPNs), inducing clinico-haematological and symptoms response in a significant proportion of patients [1,2]. However, adverse effects and variable tolerability limits widespread use [1,2]. Pegylated forms of IFNα with improved toxicity and tolerability profiles have been developed. Most recently, third generation pegylated IFNα, ropeginterferon alfa-2b (ropegIFN; Besremi), was recommended by the European Medicine Authority (EMA) for treatment of PV following a Phase III trial (PROUD-PV / CONTINUATION-PV) and remains a potential therapeutic option in other MPNs [3]. FDA approval for PV, regardless of treatment history, was granted in November 2021. We hereby review 5 patients who have been treated with ropegIFN following previous exposure to pegylated IFNα (pegIFN) to share real world experience (Table 1), including a report of treatment in pregnancy.

1.1. Case 1

A 28-year-old male with *JAK2* V617F-mutated ET was referred in April 2018 for therapeutic review. He initially presented in 2013 with Budd-Chiari syndrome managed with a transjugular intrahepatic portosystemic shunt (TIPS) procedure. Following recurrent shunt thrombosis despite anticoagulation and emergent thrombocytosis (platelet peak 800 $\times$ 10^9/L), cytoreduction was initiated with pegIFN. After 11 months, therapy was changed to ropegIFN, 250 mcg fortnightly, due to refractory thrombocytosis. He tolerated treatment well with no adverse effects reported. However, his thrombocytosis was refractory despite 5 months of therapy and he hence switched to anagrelide (ANA) 2.5 milligrams (mg) achieving a partial response (PR; Fig. 1).

1.2. Case 2

A 15-year-old male was diagnosed with ET in 2005, later defined as *CALR* Type 2-mutated ET. He was initially managed with anagrelide and aspirin due to a profound thrombocytosis (platelets 1773 $\times$ 10^9/L) but

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switched to interferon- alfa (IFN) due to lack of response. He remained on IFN for many years but, due to significant fatigue and erratic compliance, there was variable control of thrombocytosis and hence he commenced pegIFN. Despite improved compliance, his previous platelet response was lost with a peak of 1169 × 10^9/L on maximum pegIFN dose of 275 mcg fortnightly. Reluctant to commence hydroxycarbamide (HC) due to age, ropegIFN was initiated at a dose of 350 mcg fortnightly. He tolerated ropegIFN well, apart from fatigue which was longstanding. However, despite 9 months of treatment his platelet count was persistently >1000 × 10^9/L (Fig. 1). Concomitant treatment with ANA has been commenced and response assessment awaited.

1.3. Case 3

A 47-year-old female, diagnosed with *JAK2* V617F-mutated ET following disequilibrium episodes associated with isolated thrombocytosis (platelet count 509 × 10^9/L), was referred in 2013. At first review, HC commenced locally, was stopped due to her intermediate thrombotic risk (International Prognostic Score for Thrombosis in Essential Thrombocythemia (IPSET) score 2) and her disequilibrium attributed to migraine-associated vertigo, rather than cerebrovascular disease, following extensive neurological assessment. After 4 years on expectant management, progressive thrombocytosis (platelet 1195 × 10^9/L) with a concomitant haematocrit (Hct) rise was noted. Red cell mass studies reported absolute erythrocytosis and her diagnosis revised to PV. She was commenced on venesections and pegIFN followed by HC and achieved a PR. However, due to adverse symptoms of cold intolerance and recurrent episodes of cystitis respectively, these were stopped. RopegIFN was commenced at 50 micrograms fortnightly. Successful resolution of thrombocytosis and Hct control was achieved with ropegIFN without concomitant venesection (Fig. 1). Other than stable grade 2 neutropaenia (neutrophil 1.3 × 10^9/L), she has been tolerating ropegIFN well.

1.4. Case 4

A 43-year-old female diagnosed with *JAK2* V617F-mutated ET in 1998 attended our centre for review in 2018 following development of splenomegaly. Bloods on attendance revealed Hb 152 g/L, Hct 45.9, WCC 8.02 × 10^9/L and platelets 1017 × 10^9/L. Disease reassessment demonstrated evolution of ET to Post ET (PET)-MF. She commenced fortnightly pegIFN 45 mcg with platelet count falling to a nadir of 507 × 10^9/L after 11 months of treatment. Following episodic ophthalmic discomfort, pegIFN was temporarily withheld due to concern of possible IFN-induced optic neuritis, subsequently excluded following neurology review. Due to a rising platelet count (808 × 10^9/L), she recommenced pegIFN at 3-weekly intervals but stopped due to adverse effects (flu-like symptoms, hair loss). RopegIFN was commenced at 25 mcg monthly and up-titrated to 50 mcg fortnightly. Platelet count is down trending (Fig. 1) with a stable Hb 133 g/L and WCC 4.25 × 10^9/L. Previous symptoms of hair loss and pruritus have resolved. Out with mild flu-like symptoms peri-administration, she is tolerating ropegIFN well.

1.5. Case 5

A 32-year-old female with *JAK2V617F*-mutated PV was referred for consideration of cytoreduction in March 2019. She initially presented in December 2018 with intermittent right-sided paraesthesia; no thrombotic event was identified but bloods revealed WCC 25.2 × 10^9/L, Hb 175 g/L, Hct 0.57 and platelet count 859 × 10^9/L. She was initially managed with venesection and aspirin. Due to thrombotic risk profile, she commenced pegIFN 45 mcg 2-weekly. Despite escalating pegIFN to 225 mcg weekly, leucocytosis and thrombocytosis remained persistent with progressive splenomegaly (23 cm from baseline 16 cm at diagnosis). *Re*-assessment bone marrow biopsy remained consistent with PV. Given sub-optimal response after 11 months of pegIFN, she switched to ropegIFN at 300mcg fortnightly. Soon after initiation of ropegIFN she became pregnant and the dose was increased to 350 mcg to optimise cytoreduction. She remained on ropegIFN throughout pregnancy with no adverse effects reported. She successfully delivered a healthy baby girl and has breastfed since birth. After 14 months, she remains on ropegIFN 350 mcg every two weeks, with improved counts (Fig. 1) and reduction in spleen size to 20.3 cm.

2. Discussion

Management of patients with MPNs who are intolerant or refractory to conventional treatments can be challenging. Interferon-based approaches offer an effective, alternative treatment option. Recently, ropegIFN has been shown to be efficacious in the management of patients with PV [2,3]. Our small case series of previously treated ET and PV patients demonstrates variable haematological responses in a real-world setting. It must be noted that outwith PV, this is 'off-label use'.

RopegIFN consists of a single positional isomer facilitating an extended half-life and less frequent administration (fortnightly initially

Table 1
Summary of patient characteristics.

Diagnosis	Case 1 ET	Case 2 ET	Case 3 PV	Case 4 PET MF	Case 5 PV
Driver mutation (Allele burden)	*JAK 2 V617F* (21.8%)	*CALR* (35%)	*JAK2 V617F* (not recorded)	*JAK2 V617F* (26%)	*JAK2 V617F* (not recorded)
Sex	Male	Male	Female	Female	Female
Previous treatment, maximum dose, total duration	PegIFN, 180 mcg weekly 11 months	Anagrelide 4.5 mg daily 5 months; IFNα 4.5 million units daily 140 months pegIFN 275 mcg weekly, 19 months	HC 1 g daily, 16 months, pegIFN 45 mcg weekly, 10 months	PegIFN 45 mcg 3–weekly	PegIFN 225 mcg –weekly, 11months
Age- at start of ropegIFN (yrs)	27	30	54	41	31
Disease duration when ropegIFN commenced (months)	19	177	88	252 (from ET diagnosis) 15 (from PET-MF diagnosis)	14
Maximum dose of ropegIFN	250 mcg, fortnightly	500 mcg fortnightly	50 mcg, fortnightly	50 mcg, fortnightly	350 mcg, fortnightly
Duration of ropegIFN treatment (months)	5	9	9	16	14
Adverse effect	Nil	Disturbed sleep Fatigue	Grade 2 neutropaenia	Mild flu-like symptoms	Nil
Response	Refractory thrombocytosis	Refractory thrombocytosis	Complete haematological response	Partial response	Stable disease

Abbreviations: ET = essential thrombocytosis; PV = polycythaemia vera; PET MF = post essential thrombocytosis myelofibrosis; pegIFN = pegylated interferon alfa; HC = hydroxycarbamide; cm = centimetres; mcg = micrograms; ropegIFN = ropeginterferon alfa-2b.

and monthly in maintenance phase), potentially improving tolerability and subsequent long-term compliance [2]. A phase III trial (PROUD-PV /CONTINUATION-PV) [3], comparing ropegIFN to HC in patients with PV as first line therapy and those previously treated with HC for <3years, demonstrated efficacy in PV. The primary endpoint aimed to demonstrate non-inferiority of ropegIFN to HC in achieving complete haematological response (CHR) with spleen size reduction at 12 months. Although this endpoint was not met, likely limited by paucity of patients presenting with splenomegaly at baseline, it demonstrated that ropegIFN was effective at inducing haematological response without spleen response criteria in 43% patients in the ropegIFN cohort versus 46% in the HC cohort ($p = 0{\cdot}63$) at 12 months in the PROUD-PV study. However, CONTINUATION-PV showed that responses to ropegIFN continued to increase over time with a CHR of 71% versus 51% in HC cohort ($p = 0{\cdot}012$) at 36 months [3]. Additionally, molecular responses with reduction in *JAK2* V617F allele burden were reported. Whilst 1-year molecular responses between groups were not different (34% ropegIFN versus 42% HC cohort, $p = 0.19$), CONTINUATION-PV demonstrated that over a 3-year period molecular responses were significantly higher in the ropegIFN versus HC group (66% versus 27%, $p < 0.0001$) [3]. Recent data presented at the American Society of hematology in 2020, showed that at 5-years, the median ropegIFN dose was 499 mcg per 4- week period and ropegIFN treated paients were much more likely in the 4th/ 5th year of treatment to be phlebotomy free compared to best available therapy. Disease progression was rare during longterm therapy and no new safety concerns arose [4]. RopegIFN has additionally been evaluated in low-risk PV. Interim reports from a Phase II trial where ropegIFN with phlebotomy was compared to phlebotomy alone have reported superior Hct control in the ropegIFN cohort (84% vs 66%; $p = 0.008$) [5]. Although treatment- related adverse effects were significantly higher in the ropegIFN group (48% vs 6% $p=<0.001$), there was no significant difference in severe grade 3 adverse effects (6% vs 8%, $p = 1$) [5]. Currently, a Phase III trial is in progress evaluating ropegIFN compared with Anagrelide as second-line therapy for patients with ET who have had a suboptimal or failed response to HC [6].

Although trials have highlighted promising efficacy, there is a paucity of published real-world experience. In our series, ropegIFN was generally well tolerated with no treatment discontinuation due to adverse effects. However, haematological responses were heterogeneous. For PV, one patient had a CHR whilst the other a PR.

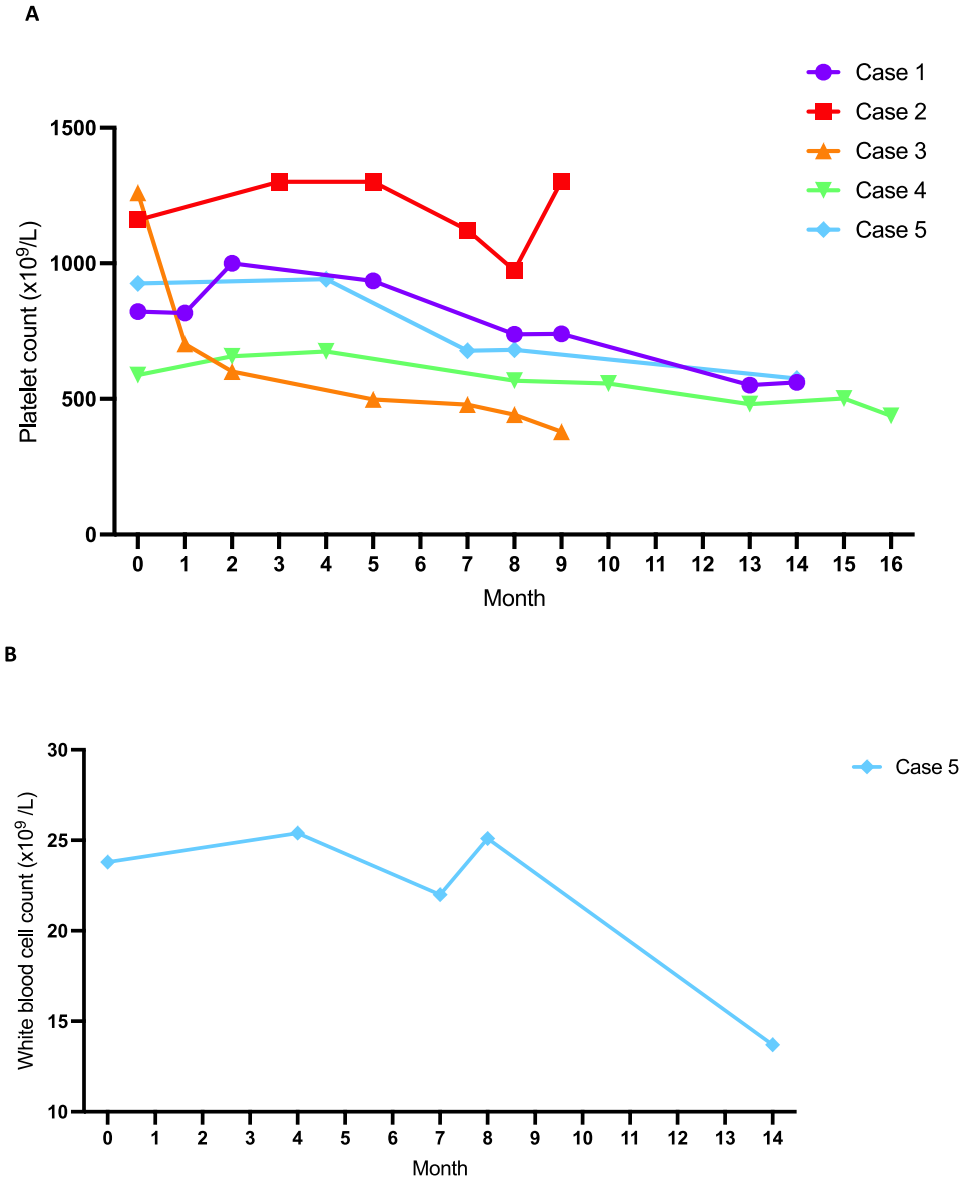

Fig. 1. Haematological response in RopegIFN treated patients, x axis represents the time in months following the initiation of ropegIFN treatment **A)** Platelet count response to RopegIFN and in case 1 from 5 months, platelet count response to ANA **B)** WCC response to RopegIFN in case 5.

Interestingly, the dose of ropegIFN in the patient with CHR was lower compared to doses reported in trials [4]. We have additionally reported on a successful case of ropegIFN use during pregnancy, resulting in delivery of a healthy baby with no obstetric complications.

Conversely, our 2 patients with ET showed no demonstrable response to ropegIFN with persistent thrombocytosis. Interestingly, both cases previously had poor responses to pegIFN suggesting that in ET, pegIFN failure may predict poor response, however clearly a larger cohort of treated patients is required. The observation of symptomatic benefit and improved tolerability of ropegIFN in the PET MF patient supports the potential role of ropegIFN in MF as previously reported [7].

In conclusion, our small case series demonstrates the safety and tolerability of ropegIFN in MPN patients at variable doses. It corroborates reports of efficacy of ropegIFN in patients with PV and potential use in pregnancy. Further examination of efficacy in both ET and MF is required.

Informed consent

No personal identifiable material is included.

Declaration of Competing Interest

Patrick Harrington: research funding from Bristol Myers Squibb, Honoraria and Incyte. Claire N. Harrison: Advisory board and speaker fees: AOP and Roche.

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