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Metformin alleviates side effects and supports the resumption of interferon therapy in polycythemia vera and essential thrombocythemia

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Short Running Title: Metformin improves tolerance of interferon-α

Authorship Contributions

BNR, designed the study, drafted the manuscript and contributed 4 subjects; JS , critically evaluated possible physiological actions of metformin and designed follow up laboratory studies after metformin; AL, critically evaluated possible physiological actions of metformin; AS, analyzed data; SJK, analyzed data; SC, extracted medical records for 4 subjects; TT analyzed data and drafted the manuscript; JTP, designed the study after first person experienced metformin benefit, drafted the manuscript and contributed 8 subjects. All authors approved the final version.

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Abstract

Interferon-α is emerging as the preferential cytoreductive therapy for polycythemia vera (PV) and essential thrombocythemia (ET) due to improved long-term outcomes over alternatives such as hydroxyurea. Historically, interferon-α therapy has been marked by high rates of adverse events and subsequently poor adherence. Long-acting formulations of interferon-α, i.e., ropeginterferon-α-2b (ropeg), improve tolerability. However, nearly half of ropeg-treated patients experience fatigue, arthralgias, or myalgias and 10-20% discontinue treatment or cannot tolerate maximal ropeg doses, due to adverse events. Herein, we report our retrospective experience of adjunct metformin therapy in 11 PV and ET patients who were intolerant of ropeg. Metformin improved ropeg-related fatigue and/or myalgias in 10 of 11 patients. A complete hematologic response (CHR) was maintained in all 6 patients who had already achieved this prior to starting metformin, and a deepened hematologic response was observed in 3 of 4 patients after the addition of metformin. These encouraging results merit further evaluation in a randomized clinical study. Further, additional investigations are needed to elucidate the mechanism of interferon-α-mediated fatigue and myalgias and the mechanism of putative beneficial interaction between interferon-α and metformin.

Introduction

Interferon-α is used to treat myeloproliferative neoplasms (MPNs), but enthusiasm for this treatment has been limited due to adverse events, which are both dose- and frequency-dependent; longer-acting pegylated formulations improve tolerability.[1, 2]

Biweekly monopegylated ropeginterferon alfa-2b (ropeg) is increasingly used in MPNs, not only to induce hematologic responses but also for achieving molecular remissions.[3] It is the first agent shown to reduce transformation of PV and ET to myelofibrosis or acute leukemia.[1] The National Comprehensive Cancer Network guidelines recommend ropeg as a preferred cytoreductive therapy for PV.

Despite its advantages, 47% of PV patients treated with ropeg experience fatigue or arthralgias and 41% experience musculoskeletal pain.[3] Ten to twenty percent of patients discontinue ropeg due to adverse events.[3] Adverse events are most frequent in the first 3 months of therapy and are usually mild, most commonly presenting as fatigue, depression, pruritus, arthralgias, headache, diarrhea, influenza-like illness, and vertigo.[3] These side effects have been associated with elevated levels of pro- and anti-inflammatory cytokines, including IL-6 and IL-10.-Additionally, mitochondrial dysfunction has been implicated in Interferon-α-induced inflammation.[4] These findings suggest that the pro-inflammatory properties of Interferon-α may underlie its adverse effects. A prospective clinical trial demonstrated that ruxolitinib—a JAK1/2 inhibitor with anti-inflammatory activity—improved the tolerability of pegylated Interferon-α therapy.[5] These findings suggest that managing the heightened inflammatory response may mitigate the adverse effects of interferon therapy.

A physician with *JAK2*^{V617F}-mutated ET (see Table, patient #1) was unable to tolerate even low doses of pegylated Interferon-α-2a (Pegasys) due to disabling fatigue and depression. Despite warnings from one of the authors of this report that ropeg would likely be similarly intolerable, she was determined to try it. Drawing on recent studies demonstrating that metformin, a low-cost oral biguanide used to treat type 2 diabetes mellitus, has anti-inflammatory properties and can support mitochondrial function, she hypothesized that metformin might mitigate Interferon-α-associated side effects. At her own direction, she started taking metformin 500mg/day alongside ropeg 50mcg, once every 2 weeks (q2w). Remarkably, with adjunct metformin the patient not only tolerated ropeg well but also achieved a complete and ongoing hematologic response and remained asymptomatic. It is not known whether the patient would have tolerated ropeg without metformin; however, word of her positive experience spread among our patients, prompting 10 additional individuals with PV and ET to adopt the same approach. Below, we report the outcomes of these individuals who chose to add metformin to improve the tolerability of ropeg.

Methods

We conducted a retrospective chart review of ropeg-treated patients with PV or ET at the Huntsman Cancer Institute at University of Utah, the Veterans Hospital in Salt Lake City (Institutional Review Board approval number: 00017665), and the University of North Carolina's Basnight Cancer Hospital (IRB 25-1214). Ropeg is FDA-approved for the treatment of both low- and high-risk PV but is not labeled for use in ET though shorter-acting pegylated interferon alfa 2a is commonly used and endorsed as a recommended agent for ET in the National Comprehensive Cancer Network guidelines version 2.2025. Patients taking metformin for ropeg intolerance were identified by their treating clinician. Ropeg intolerance was defined as one or more grade $\geq$3, or more than two grade 2 events of fatigue, myalgias, arthralgias, persistent headache not limited only to 2 days after ropeg administration, and depression as per Common Terminology Criteria for Adverse Events (CTCAE) version 5. Our clinical practice follows a "low and slow" ropeg up-titration, starting at a dose of 50-100mcg q2w and increasing by 50mcg up to a maximum of 500mcg biweekly, depending on hematologic response and tolerability. We collected data on patient disease characteristics, ropeg-related adverse effects, maximum tolerated ropeg dose, metformin dosing, and disease control outcomes.

Results

Symptoms and Ropeginterferon dose

The median metformin dose was 1000 mg daily (range 500mg to 1000mg daily) with most patients taking the extended-release formulation (**Table 1**). Metformin subjectively improved tolerability of ropeg in 10 of 11 patients (**Table 1, Figure 1**) with 9 remaining on ropeg therapy. One PV subject (#2) experienced disabling fatigue on 100mcg of ropeg that slightly improved but was not resolved with adjunct ruxolitinib therapy, prompting the patient to stop both ropeg and ruxolitinib therapy. The patient learned of metformin to improve ropeg tolerance from a PV support group and began taking extended-release metformin 1,000 mg daily and resumed ropeg. With concomitant metformin, the patient had no fatigue with ropeg which was titrated to 150mcg q2w. One subject (#8) with severe fatigue and moderate depression attributed to ropeg had significant improvement in symptoms with metformin and was able to titrate ropeg to 450mcg q2w but discontinued ropeg when hospitalized for previously diagnosed severe depression with suicidal thoughts. One patient (#11) had no improvement in ropeg-mediated fatigue with the addition of extended-release metformin 1000mg daily and was not able to tolerate even 50mcg ropeg q2w.

Hematological response

Eight of 11 subjects achieved or had continued CHR, as defined by white blood cell count <10 x 10^9/L, hematocrit <45% without phlebotomy, and platelet count <400 x 10^9/L. Three subjects had CHR prior to starting adjunct metformin therapy which was

sustained thereafter. Five subjects attained CHR after metformin commenced (**Figure 1**), occurring between 2 to 22 months of combined metformin plus ropeg.

We also considered concomitant medications that may impact response to ropeginterferon alfa 2b therapy. In particular, statins were recently associated with both improved CHR and partial molecular response.[6] Only 1 (subject #9) of the 11 subjects was confirmed to be taking a statin. Angiotensin converting enzyme (ACE) inhibitors and angiotension receptor blocker (ARB) medications have similarly been reported to reduce the need for cytoreductive agents in MPN.[7] Only 1 of 11 subjects (subject #8) was confirmed to be taking an ARB. Finally, leukotriene inhibitors such as montelukast have been shown to induce cell death of *JAK2* V617F mutant cells.[8] None of our 11 subjects were taking a leukotriene inhibitor.

Discussion

The extract of French lilac, which contains metformin, was used in Europe for centuries to treat symptoms such as frequent thirst and urination, now recognized as classic signs of diabetes. Metformin itself was isolated in the late 1800s and synthesized by several groups in 1920s. In the 1950s, French physician Jean Stern conducted the first clinical tests of metformin in humans and observed its glucose-lowering effects. The drug was approved for diabetes in Europe in 1958, and but by the FDA only in 1994.[9] Beyond its glucose-lowering properties, metformin has been shown to inhibit inflammation[10] and may contribute to weight loss in some patients.[11] It is overall well-tolerated; possible adverse effects include diarrhea, nausea, and abdominal pain.[12]

Biodistribution studies identified the liver, kidney, marrow and circulating leukocytes, and gastrointestinal tract as the organs with the highest metformin uptake.[13] Metformin modifies the activity of cells of both the innate and adaptive immune system, and peripheral blood mononuclear cells.[14] This suggests that metformin and Interferon-α are distributed and target similar tissues, including the liver, hematopoietic, and immune system.

Metformin's biochemical actions are complex, remain incompletely understood, and are subject to debate due to contradictory findings. Nonetheless, it is well established that metformin can inhibit mitochondrial respiratory chain complex I,[15] thereby triggering adenosine monophosphate (AMP)-activated protein kinase (AMPK) activation. AMPK is a regulator of metabolism and cellular homeostasis, with over 100 distinct substrates across various biological pathways.[16] Additionally, AMPK has anti-inflammatory and immune-modulatory effects, such as suppressing nuclear factor κB (NF-κB), and epigenetic effects by reducing DNA methyltransferase 1 (DNMT1) and histone deacetylase (HDAC) activities. Its complex I inhibition decreases oxidative phosphorylation and lowers reactive oxygen species (ROS) production[16]. Metformin has several other complex I- and AMPK-independent actions, it inhibits signal transducer

and activator of transcription 3 (STAT3),[17] a key regulator of the immune response; suppresses NF-κB signaling,[18] thereby reducing the pro-inflammatory cytokines; induces histone modifications, micro RNA expression, and long noncoding RNAs alterations that impact inflammation, metabolism, and cancer progression[19] and modulates the gut microbiome, promoting bacteria that contribute to its therapeutic effects.[20]

Metformin may also be beneficial in MPNs. A Danish population study found that individuals taking metformin had a lower risk of developing MPNs than those who did not.[21] In a *JAK2* V617F mouse model of MPNs, metformin improved splenomegaly and reduced viability in a *JAK2*V617F-mutant cell line.[22] In the Phase II FibroMet study of metformin in myelofibrosis, metformin treatment did not reduce bone marrow fibrosis, but did reduce JAK-STAT signaling and inflammatory cytokines.[23]

We reported that non-responders to ropeg, those who did not achieve complete hematologic response (CHR), exhibited higher expression levels of inflammatory and hypoxia-inducible factor (HIF)-regulated genes.[24] HIF is a key regulator of inflammatory and thrombotic gene expression in both PV and ET.[25] Several studies have demonstrated that metformin suppresses HIF-1 transcriptional activity in hepatocellular carcinoma[26] and multiple myeloma.[27] This suggests that reduced HIF-1 activity may contribute to decreased inflammation, leading to improved responses to ropeg and enhanced tolerability.

Metformin may provide the additional benefit of attenuating the excessive ROS production.[28] Interferon-α has been shown to downregulate genes involved in oxidative stress and upregulate genes responsible for antioxidative defense in patients with MPNs, indicating its potential to alleviate oxidative stress.[29] ROS levels in erythroid progenitors are significantly higher in PV and ET patients receiving hydroxyurea compared to those treated with ropeg or healthy controls. Interferon-α reduces ROS production in MPNs; however, if metformin further decreases ROS levels, it could provide additional benefit to patients with PV and ET. Further studies measuring ROS levels in ropeg-tolerant and -intolerant patients, as well as the intolerance to ropeg and its reversal by metformin and their relationship to evolutionary evolved polymorphism of NFKB1 are needed to better elucidate metformin's potential effect.[30]

Therefore, it stands to reason that metformin can actively mitigate interferon-α side effects through multiple mechanisms, including anti-inflammatory effects, neuroprotection, restoration of mitochondrial integrity and reduction of mitochondrial ROS, and protection against hepatotoxicity, among others.

To our knowledge, this is the first report of metformin improving the subjective tolerability of Interferon-α therapy for ET and PV. Our study has substantial limitations including its retrospective nature, the fact that these patients were motivated to continue

ropeg therapy and actively seeking strategies to improve tolerance, and lack of placebo control. However, the results remain very intriguing, with 10 out of 11 patients reporting improved tolerance of Interferon-α therapy with concomitant metformin use. Ongoing studies of high dose accelerated titration of ropeg are evaluating a starting dose of 250mcg with uptitration to maximal 500mcg q2 weeks by the third dose.[31] If this dosing strategy proves to induce more rapid hematologic responses and better protection from early thrombotic events, mitigation of ropeg side effects will become even more clinically important.

Future prospective, double-blinded, placebo-controlled studies are needed to validate our observation that metformin mitigates interferon-α AEs and to better delineate the mechanisms underlying interferon-α toxicities. Molecular analyses, including assessments of inflammatory signaling, HIF transcriptional activity, mitochondrial function, and correlation with Aymara *NFKB1* polymorphism,[30] will be pursued to further investigate how metformin may reduce ropeg intolerance and even improve response to ropeg therapy. If confirmed, it may be extended to patients with more aggressive forms of MPNs, including primary myelofibrosis and post-PV, and post-ET myelofibrosis. These conditions are characterized by even higher levels of inflammation than PV and ET and represent clinical settings in which ropeg is increasingly utilized, yet often poorly tolerated.

We conclude that metformin, an inexpensive and generally well-tolerated therapy, may improve tolerance of ropeg therapy. In light of these encouraging results, we have designed a prospective, blinded phase 2 multicenter study of metformin treatment for patients with PV and ET who are intolerant of ropeg.

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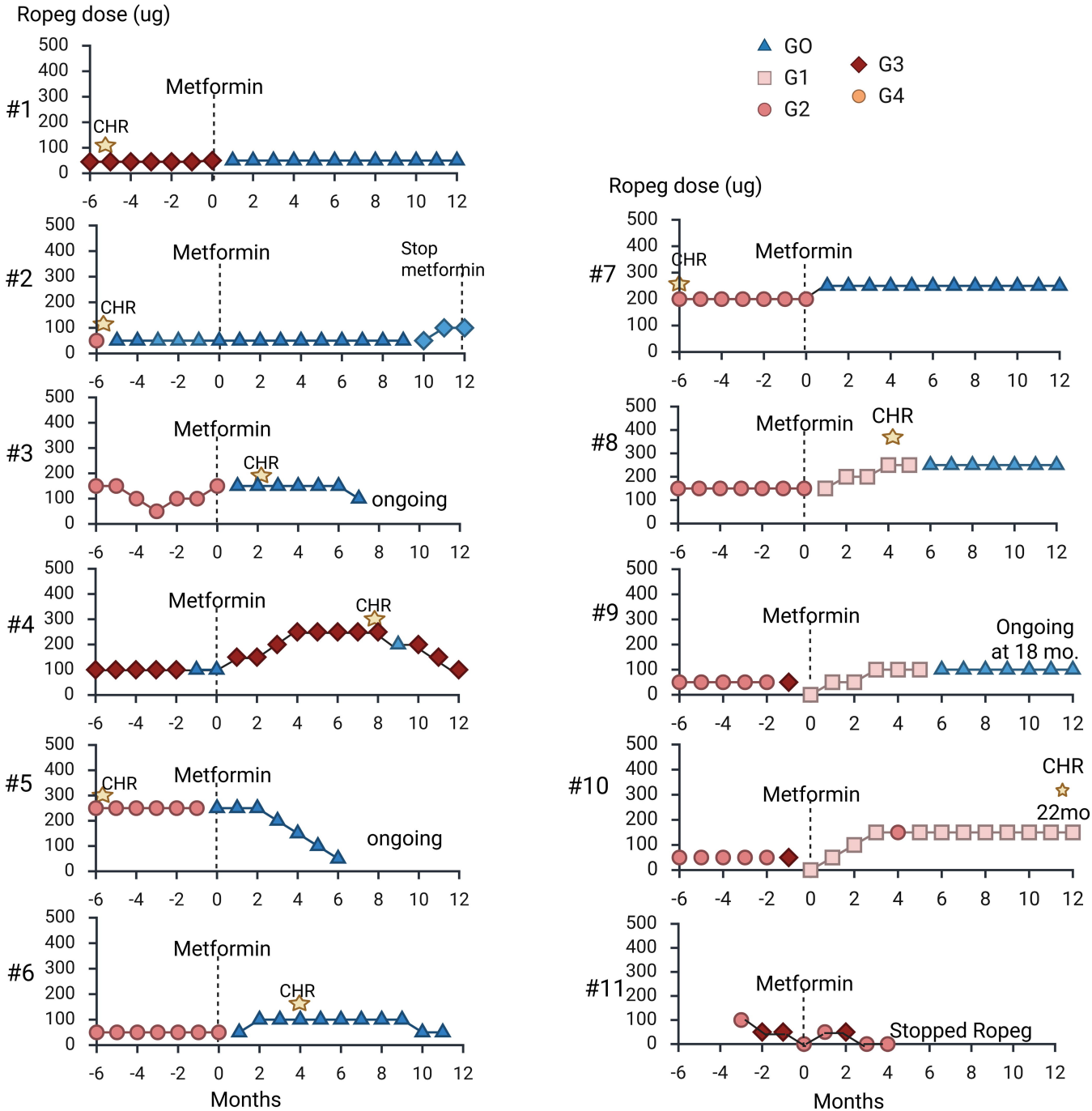
Table 1. Enhanced tolerability of ropeginterferon alfa-2b with adjunct metformin therapy

Case #	Diagnosis	At the time of intolerance				Metformin dose	Ropeg + metformin combination			
		Ropeg dose	Duration of therapy (months)	CHR achieved	AEs causing intolerance (grade)		Tolerated ropeg dose	Duration of combined therapy (months)	CHR achieved	Ropeg-related AEs
Case 1	*JAK2 ET*	Pegasys 45 μg/q1w	18	Yes	Neutropenia(G2), fatigue(G3), depression(G2)	500mg BID	50μg/q6w	19	Yes	All Resolved
Case 2	*JAK2 PV*	100μg/q2w	32	Yes	Fatigue(G2), depression(G2)	1000mg daily	50μg/q3w	12	Yes	All Resolved
Case 3	*CALR ET*	100μg/q2w	16	Yes	LE pruritus(G2)	500mg daily	150μg/q2w	7	Yes	All Resolved
Case 4	*JAK2 PV*	250μg/q2w	34	Yes	Fatigue(G2), myalgia(G1), depression(G3)	1000mg daily	250μg/q2w	9	Yes	All Resolved
Case 5	*CALR ET*	250μg/q2w	19	Yes	Fatigue(G3)	1000mg daily	250μg/q2w	6	Yes	Fatigue(G1)
Case 6	*JAK2 ET*	150μg/q2w	22	Yes	Fatigue(G3), depression(G2)	500mg daily	150μg/q2w	12	Yes	Fatigue(G1) depression(G0)
Case 7	*JAK2 PV*	200μg/q2w	16	Yes	Fatigue(G3), depression(G2)	500mg daily	250μg/q2w	11	Yes	Fatigue(G0) depression (G3)
Case 8	*JAK2 PV*	150μg/q2w	23	No	Fatigue(G2), myalgia(G2)	500mg BID	250μg/q2w	12	Yes	Fatigue(G1), myalgia(G2)
Case 9	*JAK2 PV*	50μg/q2w	6	No	Fatigue(G3)	500mg BID	100μg/q2w	18	No	Fatigue(G1)
Case 10	*CALR ET*	50μg/q2w	6	No	Fatigue(G3), myalgia(G2)	500mg BID	150μg/q2w	20	No	Fatigue(G2), myalgia(G1)
Case 11	*JAK2 PV*	50μg/q2w	2	No	Fatigue(G3)	500mg BID	50μg/q2w	Off therapy	No	Fatigue(G3)

q1w: once every 1 week; q2w: once every 2 weeks; q6w: one every 6 weeks; BID: twice a day; CHR: complete hematological response (sustained hematocrit <45% without phlebotomy plus white blood cell count <10 x 10^9/L and platelet count <400 x 10^9/L)

FIGURE LEGENDS

Figure 1. Individual subject adverse event (AE) profile before and after starting metformin for ropeginterferon alfa 2b intolerance. AE severity was according to the Common Terminology for Adverse Events (CTCAE) v5.0 grading. Timelines indicate dose of ropeginterferon alfa 2b (ropeg) and AE severity before after starting metformin. Complete hematologic response (CHR) indicated by a star and was defined as sustained hematocrit <45% without phlebotomy for ≥3 months, white blood cell count <10x10^9/L, and platelet count <400 x 10^9/L.


Ropeg dose (ug)
GO
G1
G2
G3
G4
#1
Metformin
CHR
#2
Metformin
Stop metformin
CHR
#3
Metformin
CHR
ongoing
#4
Metformin
CHR
#5
CHR
Metformin
ongoing
#6
Metformin
CHR
Months
Ropeg dose (ug)
#7
CHR
Metformin
#8
Metformin
CHR
#9
Metformin
Ongoing at 18 mo.
#10
Metformin
CHR
22mo
#11
Metformin
Stopped Ropeg
Months