

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

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## Abstract

Interferon- $\alpha$  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- $\alpha$  therapy has been marked by high rates of adverse events and subsequently poor adherence. Long-acting formulations of interferon- $\alpha$ , i.e., ropeginterferon- $\alpha$ -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 ten of 11 patients. A complete hematologic response (CHR) was maintained in all six patients who had already achieved this prior to starting metformin, and a deepened hematologic response was observed in three of four 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- $\alpha$ -mediated fatigue and myalgias and the mechanism of putative beneficial interaction between interferon- $\alpha$  and metformin.

## Introduction

Interferon- $\alpha$  is used to treat myeloproliferative neoplasms (MPN), but enthusiasm for this treatment has been limited due to adverse events (AE), which are both dose- and frequency-dependent; longer-acting pegylated formulations improve tolerability.<sup>1,2</sup>

Biweekly monopegylated ropeginterferon  $\alpha$ -2b (ropeg) is increasingly used in MPN, not only to induce hematologic responses but also for achieving molecular remissions.<sup>3</sup> It is the first agent shown to reduce transformation of polycythemia vera (PV) and essential thrombocythemia (ET) to myelofibrosis or acute leukemia.<sup>1</sup> The National Comprehensive Cancer Network guidelines recommend ropeg as a preferred cytoreductive therapy for PV.

Despite its advantages, 47% of PV patients treated with ropeginterferon- $\alpha$ -2b (ropeg) experience fatigue or arthralgias and 41% experience musculoskeletal pain.<sup>3</sup> Ten to 20% of patients discontinue ropeg due to AE.<sup>3</sup> AE 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.<sup>3</sup> These side effects have been associated with elevated levels of pro- and anti-inflammatory cytokines, including interleukin (IL)-6 and IL-10. Additionally, mitochondrial dysfunction has been implicated in interferon- $\alpha$ -induced inflammation.<sup>4</sup> These findings suggest that the pro-inflammatory properties of interferon- $\alpha$  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- $\alpha$  therapy (Pegasys).<sup>5</sup> These findings suggest that managing the heightened inflammatory response may mitigate the adverse effects of interferon therapy.

A physician with *JAK2*<sup>V617F</sup>-mutated ET (see Table 1, patient #1) was unable to tolerate even low doses of 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- $\alpha$ -associated side effects. At her own direction, she started taking metformin 500 mg/day alongside ropeg 50  $\mu$ g, 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 ten 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 [IRB] approval number: 00017665), and the University of North Carolina's Basnight Cancer Hospital (IRB approval number: 25-1214). Ropeg is Food and Drug Administration-approved for the treatment of both low- and high-risk PV but is not labeled for use in ET though shorter-acting Pegasys 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 50-100  $\mu$ g q2w and increasing by 50 mcg up to a maximum of 500  $\mu$ g 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 1,000 mg daily (range, 500-1,000 mg daily) with most patients taking the extended-release formulation (Table 1). Metformin subjectively improved tolerability of ropeg in ten of 11 patients (Table

1; Figure 1) with nine remaining on ropeg therapy. One PV subject (#2) experienced disabling fatigue on 100  $\mu$ g 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 150  $\mu$ g 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 450  $\mu$ g 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 1,000 mg daily and was not able to tolerate even 50  $\mu$ g ropeg q2w.

### Hematological response

Eight of 11 subjects achieved or had continued CHR, as defined by white blood cell count  $< 10 \times 10^9/L$ , hematocrit  $< 45\%$  without phlebotomy, and platelet count  $< 400 \times 10^9/L$ . 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  $\alpha$ -2b therapy. In particular, statins were recently associated with both improved CHR and partial molecular response.<sup>6</sup> Only one (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.<sup>7</sup> Only one 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*<sup>V617F</sup> mutant cells.<sup>8</sup> 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 Food and Drug Administration only in 1994.<sup>9</sup> Beyond its glucose-lowering

properties, metformin has been shown to inhibit inflammation<sup>10</sup> and may contribute to weight loss in some patients.<sup>11</sup> It is overall well-tolerated; possible adverse effects include diarrhea, nausea, and abdominal pain.<sup>12</sup>

Biodistribution studies identified the liver, kidney, marrow and circulating leukocytes, and gastrointestinal tract as the organs with the highest metformin uptake.<sup>13</sup> Metformin modifies the activity of cells of both the innate and adaptive immune system, and peripheral blood mononuclear cells.<sup>14</sup> This suggests that metformin and interferon- $\alpha$  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,<sup>15</sup> 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.<sup>16</sup> Additionally, AMPK has anti-inflammatory and

immune-modulatory effects, such as suppressing nuclear factor  $\kappa$ B (NF- $\kappa$ B), 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.<sup>16</sup> Metformin has several other complex I- and AMPK-independent actions, it inhibits signal transducer and activator of transcription 3 (STAT3),<sup>17</sup> a key regulator of the immune response; suppresses NF- $\kappa$ B signaling,<sup>18</sup> thereby reducing the pro-inflammatory cytokines; induces histone modifications, microRNA expression, and long non-coding RNA alterations that impact inflammation, metabolism, and cancer progression<sup>19</sup> and modulates the gut microbiome, promoting bacteria that contribute to its therapeutic effects.<sup>20</sup>

Metformin may also be beneficial in MPN. A Danish population study found that individuals taking metformin had a lower risk of developing MPN than those who did not.<sup>21</sup> In a *JAK2*<sup>V617F</sup> mouse model of MPN, metformin improved splenomegaly and reduced viability in a *JAK2*<sup>V617F</sup>-mutant cell line.<sup>22</sup> In the phase II FibroMet study of metformin in

**Table 1.** Enhanced tolerability of ropeginterferon  $\alpha$ -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	AE causing intolerance (grade)		Tolerated ropeg dose	Duration of combined therapy, months	CHR achieved	Ropeg-related AE (grade)
1	<i>JAK2</i> ET	Pegasys 45 $\mu$ g/q1w	18	Yes	Neutropenia (2), fatigue (3), depression (2)	500 mg BID	50 $\mu$ g/q6w	19	Yes	All resolved
2	<i>JAK2</i> PV	100 $\mu$ g/q2w	32	Yes	Fatigue (2), depression (2)	1,000 mg daily	50 $\mu$ g/q3w	12	Yes	All resolved
3	<i>CALR</i> ET	100 $\mu$ g/q2w	16	Yes	Pruritus (2)	500 mg daily	150 $\mu$ g/q2w	7	Yes	All resolved
4	<i>JAK2</i> PV	250 $\mu$ g/q2w	34	Yes	Fatigue (2), myalgia (1), depression (3)	1,000 mg daily	250 $\mu$ g/q2w	9	Yes	All Resolved
5	<i>CALR</i> ET	250 $\mu$ g/q2w	19	Yes	Fatigue (3)	1,000 mg daily	250 $\mu$ g/q2w	6	Yes	Fatigue (1)
6	<i>JAK2</i> ET	150 $\mu$ g/q2w	22	Yes	Fatigue (3), depression (2)	500 mg daily	150 $\mu$ g/q2w	12	Yes	Fatigue (1) depression (0)
7	<i>JAK2</i> PV	200 $\mu$ g/q2w	16	Yes	Fatigue (3), depression (2)	500 mg daily	250 $\mu$ g/q2w	11	Yes	Fatigue (0), depression (3)
8	<i>JAK2</i> PV	150 $\mu$ g/q2w	23	No	Fatigue (2), myalgia (2)	500 mg BID	250 $\mu$ g/q2w	12	Yes	Fatigue (1), myalgia (2)
9	<i>JAK2</i> PV	50 $\mu$ g/q2w	6	No	Fatigue (3)	500 mg BID	100 $\mu$ g/q2w	18	No	Fatigue (1)
10	<i>CALR</i> ET	50 $\mu$ g/q2w	6	No	Fatigue (3), myalgia (2)	500 mg BID	150 $\mu$ g/q2w	20	No	Fatigue (2), myalgia (1)
11	<i>JAK2</i> PV	50 $\mu$ g/q2w	2	No	Fatigue (3)	500 mg BID	50 $\mu$ g/q2w	Off therapy	No	Fatigue (3)

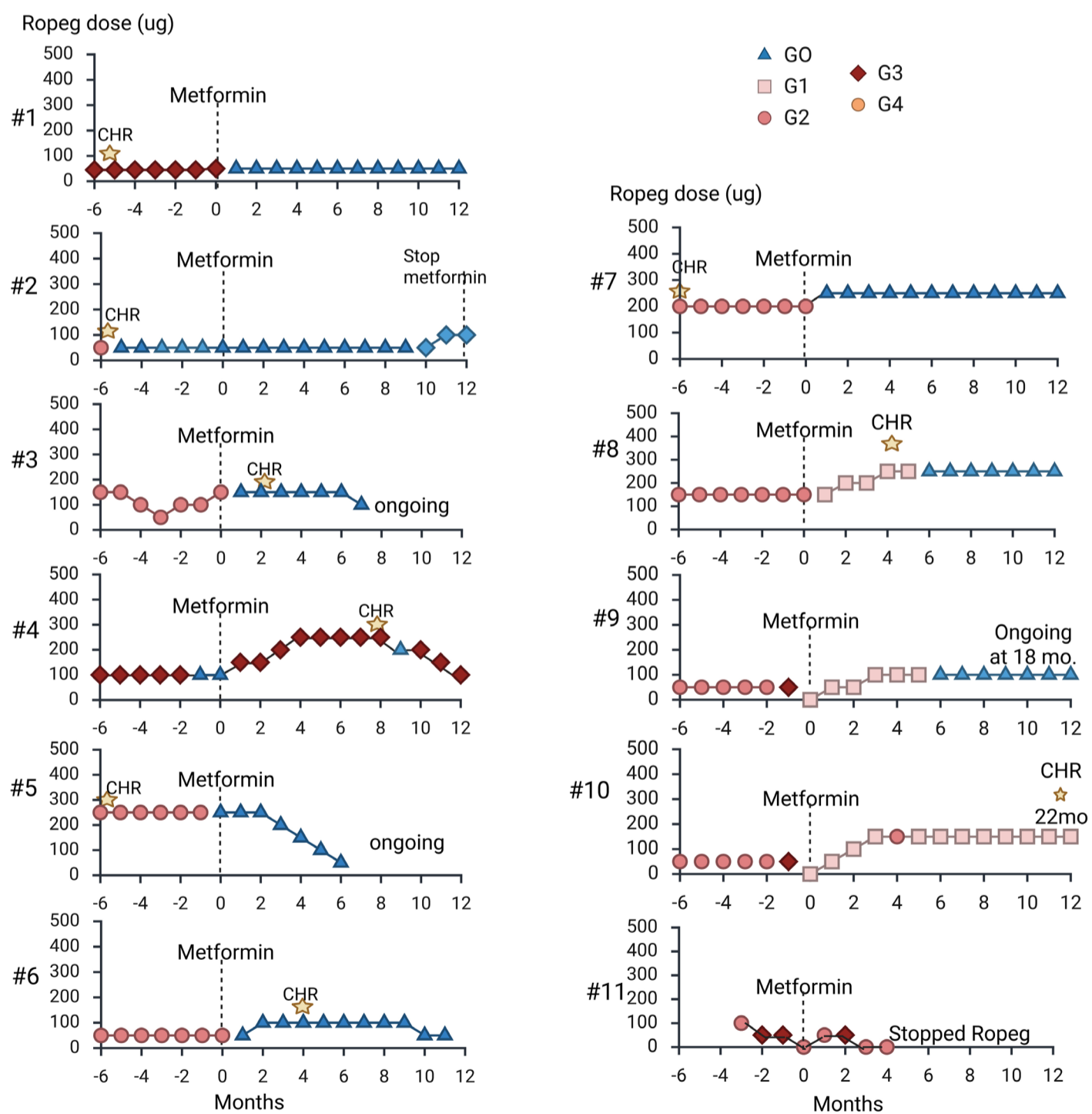
AE: adverse event; Pegasys: pegylated interferon- $\alpha$ -2a; ropeg: ropeginterferon  $\alpha$ -2b; q1w: once every 1 week; q2w: once every 2 weeks; q3w: once every 3 weeks; q6w: once every 6 weeks; BID: twice a day; CHR: complete hematological response (sustained hematocrit <45% without phlebotomy plus white blood cell count <10 $\times$ 10<sup>9</sup>/L and platelet count <400 $\times$ 10<sup>9</sup>/L); ET: essential thrombocythemia; PV: polycythemia vera.

myelofibrosis, metformin treatment did not reduce bone marrow fibrosis, but did reduce JAK-STAT signaling and inflammatory cytokines.<sup>23</sup>

We reported that non-responders to ropeg, those who did not achieve CHR, exhibited higher expression levels of inflammatory and hypoxia-inducible factor (HIF)-regulated genes.<sup>24</sup> HIF is a key regulator of inflammatory and thrombotic gene expression in both PV and ET.<sup>25</sup> Several studies have demonstrated that metformin suppresses HIF-1 transcriptional activity in hepatocellular carcinoma<sup>26</sup> and multiple myeloma.<sup>27</sup> 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.<sup>28</sup> Interferon- $\alpha$  has

been shown to downregulate genes involved in oxidative stress and upregulate genes responsible for antioxidative defense in patients with MPN, indicating its potential to alleviate oxidative stress.<sup>29</sup> 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- $\alpha$  reduces ROS production in MPN; 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.<sup>30</sup>

Therefore, it stands to reason that metformin can actively



**Figure 1. Individual subject adverse event profile before and after starting metformin for ropeginterferon  $\alpha$ -2b intolerance.** Adverse event (AE) severity was according to the Common Terminology for Adverse Events (CTCAE) v5.0 grading. Timelines indicate dose of ropeginterferon  $\alpha$ -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  $<10 \times 10^9/L$ , and platelet count  $<400 \times 10^9/L$ . G: grade; #1-11: subjects 1-11; mo: months.

mitigate interferon- $\alpha$  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- $\alpha$  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 ten of 11 patients reporting improved tolerance of interferon- $\alpha$  therapy with concomitant metformin use. Ongoing studies of high dose accelerated titration of ropeg are evaluating a starting dose of 250  $\mu\text{g}$  with uptitration to maximal 500  $\mu\text{g}$  q2w weeks by the third dose.<sup>31</sup> 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- $\alpha$  AE and to better delineate the mechanisms underlying interferon- $\alpha$  toxicities. Molecular analyses, including assessments of inflammatory signaling, HIF transcriptional activity, mitochondrial function, and correlation with Aymara *NFKB1* polymorphism,<sup>30</sup> 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 MPN, 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 II multicenter study of metformin treatment for patients with PV and ET who are intolerant of ropeg.

### Disclosures

*BNR has received consulting fees from PharmaEssentia, Incyte, and Pint Pharma. All other authors have no conflicts of interest to disclose.*

### Contributions

*BNR designed the study, drafted the manuscript and contributed four 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 and SJK analyzed data. SC extracted medical records for four subjects. TT analyzed data and drafted the manuscript. JTP designed the study after first person experienced metformin benefit, drafted the manuscript and contributed eight subjects. All authors approved the final version.*

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### Data-sharing statement

*All the data presented in the manuscript will be shared upon the request to the corresponding authors.*

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