Metformin: interferon's new dancing partner?

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Introduction

In this issue of Haematologica, Reeves *et al*. report a seminal case series of 11 patients with myeloproliferative neoplasms (MPN) (Polycythemia vera [PV]=6 and essential thrombocythemia [ET]=5), who were intolerant of pegylated interferon-α2b (ropeg) (BESREMI®). Adjunct metformin treatment improved ropeg-related fatigue and/or myalgias in ten of the 11 patients. Indeed, in four of them the side effects completely resolved and in some patients metformin also improved the hematological response.[1] This elegant clinical observation may have paradigm-shifting and practice-changing implications. For decades, interferon-α (IFN) has been recognized as a disease-modifying therapy in MPN, capable of inducing molecular remissions and normalizing hematopoiesis.[2] Yet, treatment-limiting side effects have prevented many patients from realizing its full potential. Recently, Danish studies have shown that combination therapy with pegylated interferonα-2a (Peg-IFN-α2a) and ruxolitinib (RUX) is safe and efficacious in patients with PV and myelofibrosis (COMBI I). Most patients in this study were intolerant or refractory to Peg-IFN-α2a monotherapy, and the majority were also refractory or intolerant to hydroxyurea.[3] This combination therapy improved cell counts, reduced bone marrow cellularity and fibrosis, decreased *JAK2*^{V617F} burden, alleviated IFN-side effects and accordingly reduced symptom burden in a substantial proportion of the patients.[3] A prospective study of this combination therapy (COMBI II) in 25 newly diagnosed PV patients confirmed the highly encouraging effects of this doublet therapy with rapid normalization of blood cell counts, low-burden *JAK2*^{V617F} and even normalization of the bone marrow in a subset of patients.[4] However, this combination therapy implies an increased risk of infections, which are well-known during treatment with ruxolinib monotherapy and recorded in the COMBI trials as well.[3,4] Therefore, an inexpensive, safe and efficacious combinatorial approach with IFN is urgently needed to rescue the large number of patients, who are intolerant or refractory to IFN monotherapy. This excellent report by Reeves *et al*. opens the door to reintroducing IFN in thousands of patients worldwide who were previously deemed intolerant, by combining it with metformin - a simple, inexpensive, and well-tolerated drug with pleiotropic metabolic and anti-inflammatory effects[5] in addition to potent anti-leukemic effects in *JAK2*^{V617F}-positive MPN.[6]

Metformin: an unexpected ally

Metformin, a cornerstone in the management of type 2 diabetes, exerts broad systemic effects beyond glucose control.[5,6] It activates AMP-activated protein kinase (AMPK), reduces oxidative stress, inhibits mTOR signaling, and dampens chronic inflammation - all of which are relevant to MPN pathophysiology and interferon tolerance. Importantly, metformin improves mitochondrial bioenergetics and may counteract the flu-like, fatigue-related, and metabolic side effects of IFN. It also exerts antiproliferative and anti-neoplastic properties in MPN cells, potentially synergizing with IFN's immunomodulatory and differentiation-inducing mechanisms. These effects may explain why metformin also has been shown to protect against development of MPN in the background population.[7] Given this dual impact - mitigating toxicity and possibly enhancing efficacy - metformin should be considered not only as a rescue agent for IFN-intolerant patients but as a rational up-front partner.

Statins: the second partner in the dance?

Recent Danish registry-based and translational studies have shown that statins - similar to metformin - reduces the risk of developing MPN,[8] thereby potentially reducing disease progression and improving survival in MPN - likely through anti-inflammatory, endothelial-protective, and JAK2-signaling modulating mechanisms. Even more intriguing, statins appear to potentiate the efficacy of IFN,[9] possibly by lowering the inflammatory drive and thereby normalizing the bone marrow microenvironment. In this context, it is most intriguing that both metformin and statins possess anti-fibrotic capabilities[10] and therefore, in

the best of all scenarios, might also favorably and synergistically impact the development of bone marrow fibrosis in patients with MPN.

Together, IFN, metformin, and statins may form a triad of anti-inflammatory, anti-clonal, and anti-aging agents targeting key nodes in MPN pathogenesis - oxidative stress, inflammation ("inflammaging"), and metabolic dysfunction. Such a combinatorial potent triplet approach would converge on cholesterol-driven hematopoietic activation via complementary mechanisms - metformin enhancing cholesterol efflux capacity[11] and statins reducing low-density lipoprotein-driven input,[12] thereby dampening inflammatory myelopoiesis and atherosclerotic inflammation. At the same time, IFN would be even more engaged and beloved by both partners and by our patients.

A new era of combination therapy

Although the combination of IFN and RUX has been shown to be promising in patients with PV and MF,[2,3] it needs to be validated in well-designed prospective studies to confirm its superiority to monotherapy, which has not been confirmed in patients with myelofibrosis. The combination of IFN with metabolic modulators such as metformin and statins could represent the next major therapeutic advance in the field. These agents are safe, inexpensive, and globally available, and their pleiotropic effects align perfectly with the chronic inflammatory and metabolic hallmarks of MPN. It is now imperative to design prospective trials to validate metformin's ability to rescue IFN-intolerant patients, evaluate its potential as a first-line adjunct to IFN and explore synergistic regimens combining IFN, metformin, and statins for optimal molecular and clinical outcomes.

Conclusion and perspectives

The work by Reeves *et al*. reminds us that scientific progress often begins with clinical observation. Metformin's capacity to make interferon tolerable again could transform MPN therapy, enabling more patients to receive a treatment capable of deep molecular remissions and potential cure. Future studies should map the molecular crosstalk between metabolism, inflammation, and the malignant clone. In this regard, it is highly intriguing to note that metformin possesses strong anti-atherosclerotic effects and suppresses mobilization of hematopoietic stem cells and progenitors, thereby dampening myelopoiesis, which is a key driver of atherosclerotic inflammation and plaque formation. Metformin exerts these effects by upregulating the cholesterol transporter Abca1 in hematopoietic cells. By these effects metformin may act in synergy with statins, which reduce hematopoietic stem cells and progenitors by lowering low-density lipoprotein and modulating mobilizing cytokine pathways.[11,12] The time has come to explore "the right partners for interferon to dance with" - and both metformin and statins may truly be great companions (Figure 1). It is prime time for revisiting these two old drugs for the treatment of MPN.

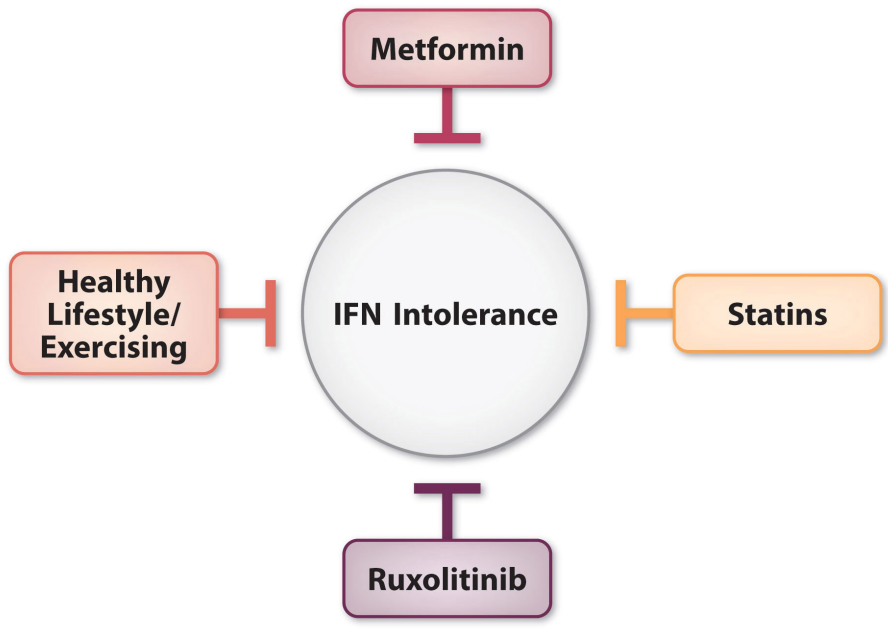

Figure 1. The interferon "dancing partners" in myeloproliferative neoplasm therapy. Schematic illustration showing pegylated interferon-α2 (IFN) at the center of a square of combination partners. Left: a healthy lifestyle with exercise to improve metabolism and immune fitness is the key preventive medicine across all disciplines to dampen chronic inflammation, thereby enhancing IFN-tolerability, reducing fatigue and prohibiting accelerated immune-and inflammaging. Top: metformin improves metabolic resilience, reduces oxidative stress, and enhances IFN tolerance. Right: Statins exert anti-inflammatory and endothelial-stabilizing effects, potentially enhancing IFN efficacy. Bottom: the malignant clone and inflammatory microenvironment are the targets of the synergistic triad as shown in the combination trials with IFN and ruxolitinib. Together, the combination reduces "inflammaging," restores hematopoietic homeostasis, and hopefully will improve long-term outcomes.

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