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Commentary

Targeting inflammation in progeria – insights from combined baricitinib and lonafarnib treatment in a mouse model of progeria

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Abstract

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare and fatal premature aging disorder caused by progerin accumulation, leading to nuclear abnormalities, systemic inflammation, and early cardiovascular decline. Lonafarnib, a farnesyltransferase inhibitor (FTI), improves nuclear shape and extends lifespan, but its efficacy is limited and accompanied by pro-inflammatory effects. Here, we discuss preclinical findings from a combination therapy using the JAK1/2 inhibitor baricitinib (BAR) with FTI in a progeria mouse model. This approach produced synergistic improvements in lifespan and physical condition. Importantly, BAR counteracted the pro-inflammatory STAT1 hyperactivation induced by FTI. Combination treatment also reduced levels of senescence-associated secretory phenotype (SASP), a hallmark of senescent cells characterized by the secretion of inflammatory cytokines. Histological analysis revealed improved aortic wall thickness and reduced fibrotic remodeling (excessive buildup of connective tissue), suggesting better vascular integrity. Despite these benefits, growth impairment, lipodystrophy, and metabolic disturbances persisted, underscoring the need for further therapeutic refinements.

Keywords: HGPS, Baricitinib, Lonafarnib, Inflammation

Abbreviations: FTI: Farnesyltransferase Inhibitor; HGPS: Hutchinson-Gilford Progeria Syndrome; JAK/STAT: Janus Kinase / Signal Transducer and Activator of Transcription; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; NLRP3: NOD-, LRR-, and Pyrin Domain-Containing Protein 3; SASP: Senescence-Associated Secretory Phenotype

Introduction

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare and fatal genetic disorder characterized by features of accelerated aging in children. It is caused by a *de novo* point mutation in the *LMNA* gene, which encodes prelamin A, the precursor of lamin A, a key structural protein of the nuclear lamina [1,2]. Under normal conditions, prelamin A undergoes several post-translational modifications, including farnesylation and subsequent cleavage to produce mature lamin A [3]. In HGPS, the mutation activates a cryptic splice site, resulting in the production of progerin, a truncated form of prelamin A that retains its farnesyl group [1,4]. As a result, progerin remains permanently anchored to the nuclear envelope, disrupting nuclear architecture, altering chromatin organization, inducing DNA damage, and promoting cellular senescence [4–7]. Children with HGPS experience growth failure, loss of subcutaneous fat (lipodystrophy), joint contractures, bone abnormalities, alopecia, and sclerotic skin [8,9]. The most serious complication is progressive atherosclerosis, which frequently leads to myocardial infarction or stroke [9]. Most patients die from cardiovascular events in their early teens [10].

While there is no cure for HGPS, the FDA approval of lonafarnib, a farnesyltransferase inhibitor (FTI), has marked a significant therapeutic milestone [4,11]. By preventing farnesylation, FTI reduces the aberrant anchoring of progerin to the nuclear envelope, thereby partially restoring nuclear architecture and improving cellular functions [4,12]. Clinical trials have shown that FTI extended lifespan by an average of 1.6 years and improvements in vascular stiffness and bone integrity [10,13]. However, FTI is not curative and does not fully prevent progerin formation [14]. Its intake has also been associated with gastrointestinal symptoms, cellular abnormalities and inflammation, underscoring the need for additional therapies [15–17]. In response, several clinical studies have explored combination therapies to enhance the benefits of FTI and to reduce associated side effects. One approach combined FTI with pravastatin and zoledronate to block compensatory prenylation routes [14,18]. However, this regimen offered no cardiovascular benefit, raised safety concerns, and as such, this combination was ultimately not recommended for clinical use [18]. More recently, combinations with everolimus, an mTOR inhibitor, and progerinin, a small molecule that disrupts progerin-lamin A interactions, have entered clinical evaluation, though results are not yet available [19–21]. Collectively, these efforts reflect a growing clinical trend toward combination therapies, with FTI serving as the therapeutic backbone.

Targeting Inflammation in Progeria

While many therapies have primarily focused on correcting defective prelamin A processing, accumulating evidence suggests that inflammation is a key pathological driver in HGPS [22]. Progerin not only disrupts nuclear architecture but also activates multiple pro-inflammatory signaling pathways, including the JAK/STAT, NF-κB, and NLRP3 inflammasome pathways, leading to an enhanced senescence-associated secretory phenotype (SASP) and systemic tissue dysfunction [23–26]. These pathways may not act independently but rather interact through cross-talk. JAK/STAT can act upstream of NF-κB, promoting NF-κB signal transduction [27]. In turn, NF-κB drives production of cytokines such as IL-6, which feedback to activate STAT signaling [28]. Moreover, NF-κB is crucial for the priming phase of NLRP3 activation [29]. STAT3 has also been shown to promote NLRP3 inflammasome activation by mediating mitochondrial translocation of NLRP3 [30]. In addition, chronic inflammation is a well-established driver of cellular dysfunction, tissue degeneration and cardiovascular disease, which is the primary cause of death in individuals with HGPS [31]. Consequently, several anti-inflammatory treatments have been tested in preclinical models of HGPS, as detailed in **Table 1**. Across these studies, all compounds have shown beneficial effects on key disease features, including improvements in cellular homeostasis,

Table 1. Data summarized from studies using HGPS mouse models and human fibroblasts.

Drug / Compound	Pathway / Target	Model	Mono / Combi-Treatment	Observed Improvements	Efficacy Summary	Ref
Baricitinib	JAK/STAT pathway	HGPS fibroblasts	Monotherapy	· Reduced cellular senescence and inflammation · Enhanced proteostasis and mitochondrial function	↓ Inflammation ↑ Cellular health	[23]
		HGPS fibroblasts	Combined with FTI	· Prevented FTI-induced cGAS-STING-STAT1 activation and inflammation · Improved cellular homeostasis	↓ Inflammation ↑ Cellular health	[16]
		Lmna$^{G609G/G609G}$ mice	Monotherapy and Combined with FTI	· Reduced progerin levels, SASP and inflammation · Improved skin, vascular, muscle and liver structure · Lifespan extension with improved physical condition	↓ Inflammation ↑ Tissue/vascular integrity ↑ Lifespan ↑ Healthspan ↑ Efficacy with FTI	[32]
Ruxolitinib		*Zmpste24*$^{-/-}$ mice	Monotherapy	· Improved musculoskeletal health · Prolonged survival	↑ Bone Health ↑ Lifespan	[33]
Sodium salicylate	NF-κB pathway	*Zmpste24*$^{-/-}$ mice *Lmna*$^{G609G/G609G}$ mice	Monotherapy	· Preserved skin and bone structure · Increased body weight and extended lifespan	↑ Tissue Integrity ↑ Bodyweight ↑ Lifespan	[24]
Tocilizumab	IL-6 neutralization	HGPS fibroblasts *Lmna*$^{G609G/G609G}$ mice	Monotherapy	· Decreased progerin accumulation and DNA damage · Delayed onset of progeroid features including lipodystrophy, kyphosis and functional decline	↓ Progerin ↓ DNA damage ↓ Lipodystrophy ↑ Vascular and functional health	[34]

MCC950	NLRP3 inflammasome pathway	HGPS fibroblasts *Zmpste24*$^{-/-}$ mice	Monotherapy	· Inhibited NLRP3 inflammasome activity and reduced IL-1β levels · Improved nuclear morphology · Increased body weight and extended lifespan	↓ Inflammation ↑ Bodyweight ↑ Lifespan	[25]
Dapansutrile		HGPS fibroblasts *Lmna*$^{G609G/G609G}$ mice	Monotherapy and Combined with FTI	· Reduced progerin levels, SASP and inflammation · Improved skin, vascular, muscle and liver structure · Lifespan extension with improved physical condition	↓ Progerin ↓ Inflammation ↑ Bodyweight ↑ Lifespan ↑ Efficacy with FTI	[35]

reduction of inflammatory markers, preservation of tissue structure, or extended survival. These findings underscore the therapeutic relevance of inflammation in HGPS and support the continued development of multi-targeted treatment approaches.

Insights from Combined Baricitinib and Lonafarnib Treatment in a Mouse Model of Progeria

Motivated by the consistent benefits observed with anti-inflammatory strategies, we investigated whether combining the JAK1/2 inhibitor baricitinib (BAR) with lonafarnib (FTI) could offer synergistic therapeutic effects in *Lmna*$^{G609G/G609G}$ mice, a well-established preclinical model of HGPS [32,36]. We focused on BAR because it inhibits both JAK1 and JAK2, thereby broadly reducing pro-inflammatory signaling [37]. Importantly, BAR is an orally available drug already approved for use in children as young as two years old to treat inflammatory conditions such as juvenile idiopathic arthritis and atopic dermatitis [37,38]. This pediatric approval is a critical consideration for HGPS, where treatment must begin early in life.

In this commentary, we discuss findings from our recent preclinical study, where we identified several key findings that underscore the therapeutic potential of this combination approach [32]. Most notably, dual treatment with BAR and FTI significantly extended lifespan beyond either agent alone. Average survival was 114.4 days in untreated mice, 138.4 days with BAR (+21.0%), 131.3 days with FTI (+14.8%) and 142.4 days with the combination (+24.6%). Furthermore, mice were scored weekly based on predefined objective criteria and combination treated animals maintained better overall physical condition throughout life. Health improvements were evident in delayed onset of kyphosis, improved fur condition (assessed by alopecia, fur density and grooming), lower frequency of ocular symptoms (cataracts and eye discharge), reduced incidence of hearing loss and milder dysgnathia (malocclusions). Notably, the combination treatment also produced a stronger reduction in progerin levels than either drug alone. Our earlier *in vitro* work suggested that this effect may arise from complementary actions [16]. BAR enhanced both autophagy and proteostasis while FTI blocks progerin farnesylation [16,23]. This may also explain the stronger reduction seen in the mouse model, though further studies are needed to confirm this mechanism *in vivo*.

From a mechanistic perspective, we found that FTI monotherapy led to STAT1 hyperactivation, a pro-inflammatory response that may limit its overall therapeutic benefit. Importantly, this effect was robustly suppressed by BAR, which restored STAT1 and STAT3 signaling across multiple affected tissues (aorta, skin, liver and lung), as determined by Western blot analysis. In addition, BAR reduced the expression of SASP factors and inflammatory markers. These findings highlight the critical role of JAK/STAT inhibition not only in dampening disease-associated inflammation, but also in counteracting inflammatory side effects induced by FTI. By dampening upstream cytokine signaling, BAR may also attenuate NF-κB and NLRP3 activity, although these pathways were not directly assessed in our study and should be examined in future work.

Importantly, these benefits translated into improved tissue integrity, particularly within the vascular system, a central contributor to morbidity and mortality in HGPS [9]. Histological analysis of the aorta (H&E staining) showed that media thickness increased from 46.9 µm in untreated HGPS mice to 60.6 µm with FTI and 64.0 µm with BAR + FTI. Cell density in the aortic media rose from 0.014 cells/µm² in untreated *Lmna*$^{G609G/G609G}$ mice to 0.018 with FTI and 0.033 with BAR + FTI, approaching the wild-type value of 0.037. Fibrosis, assessed by Masson's trichrome, was markedly reduced with the combination (4.7%) compared to FTI monotherapy (18.5%) and untreated *Lmna*$^{G609G/G609G}$ mice (10.5%). As reported in the original study, these effects were consistent across animals ($n \geq 6$ per group) and not driven by outliers. These improvements in vascular integrity support the idea that targeting inflammation is essential for preserving cardiovascular function in HGPS.

Taken together, these findings provide strong preclinical evidence supporting a combination therapy that targets both progerin accumulation and its inflammatory consequences. Although FTI monotherapy provides clear clinical benefits and remains the current standard of care, it does not fully address the diverse and progressive pathology of HGPS. Building on its established efficacy, we demonstrated that adding the anti-inflammatory agent BAR produces a synergistic effect by suppressing JAK/STAT-driven inflammation and addressing pathological features not corrected by FTI alone.

Persistent Challenges and Considerations

Despite the therapeutic benefits of combined baricitinib (BAR) and lonafarnib (FTI) treatment, critical aspects of the disease remain. One of the most prominent is growth impairment with reduced body weight, a feature also observed in the *Lmna*$^{G609G/G609G}$ mouse model [9,36]. In our study, BAR and FTI, whether given individually or in combination, did not result in any measurable improvement in body weight. Interestingly, previous studies in progeria mouse models have reported inconsistent effects of FTI on body weight, with some showing modest improvements and others finding no significant change [35,39,40]. Clinical data reflect a similarly mixed

picture. A clinical study evaluating FTI treatment in HGPS patients reported that nine individuals exhibited an increased rate of weight gain, six showed reduced gain, and ten experienced no change [13]. Moreover, anorexia and weight loss are listed as common side effects of FTI [17]. The addition of BAR did not improve this phenotype, highlighting growth dysfunction as an important aspect of HGPS pathology that remains unaddressed by this therapeutic intervention.

In considering clinical translatability, it is also important to note that long-term use of JAK inhibitors such as BAR in children may carry risks, including immunosuppression and increased infection susceptibility [38]. While a long-term study of up to 9.3 years in adults with rheumatoid arthritis reported no new safety concerns beyond those already recognized, comparable studies in pediatric populations are not yet available [41]. These factors highlight the need for careful monitoring and rigorous clinical evaluation.

To further explore systemic metabolic alterations in HGPS, we conducted a comprehensive analysis of blood plasma and glucose metabolism. Progeria mice showed pronounced alterations in multiple parameters, including reduced levels of insulin, FGF21, glucose, triglyceride, total cholesterol, HDL, as well as elevated LDL and uric acid. None of the treatments produced significant improvements in these parameters. Notably, lipid disturbances (total cholesterol, HDL, LDL and triglyceride) were more severe in the male cohort, with stronger statistical significance, whereas comparable changes in females were weaker or not significant, as reported in the original study. Glucose tolerance was also impaired in progeria mice, as assessed by intraperitoneal glucose tolerance testing. While FTI treatment showed a trend toward improved glucose handling in males, no effect was observed in females. BAR alone or in combination did not produce improvements in glucose tolerance in either sex. These sex-specific differences may have important clinical implications, suggesting that therapeutic responses could vary between male and female patients. This underscores the need to consider sex as a biological variable in the design and interpretation of both preclinical models and clinical studies, particularly when translating therapies to pediatric populations. Overall, none of the tested treatments resulted in significant correction of these metabolic imbalances, underscoring the complexity of metabolic dysfunction in HGPS.

Another unresolved hallmark of HGPS is the pronounced lipodystrophy, which severely affects metabolic homeostasis and contributes to systemic energy imbalance [9,42]. *In vitro*, combined BAR and FTI treatment has been shown to ameliorate adipogenic differentiation in HGPS fibroblasts [43]. However, this encouraging cellular effect did not translate into improvements *in vivo*. $Lmna^{G609G/G609G}$ mice treated with BAR + FTI still displayed persistent body weight deficits together with altered plasma levels of lipid markers. These findings indicate that adipose dysfunction remains unresolved despite treatment. The lack of improvement may stem from the complex *in vivo* microenvironment, where systemic factors such as chronic inflammation, hormonal imbalances, and impaired mesenchymal stem cell function contribute to defective adipogenesis and lipid storage [44]. Moreover, potential irreversible changes in progenitor cell pools or altered extracellular matrix composition may impair the recruitment and differentiation capacity of adipocyte precursors, even under conditions that promote adipogenesis *in vitro*. Additionally, the pharmacokinetics and tissue distribution profiles of BAR and FTI may also be suboptimal in adipose tissue, further limiting their local efficacy. These findings highlight the need for a deeper mechanistic understanding of adipose dysfunction in HGPS. Addressing these challenges will likely require strategies beyond inflammation suppression and farnesylation blockage, such as metabolic modulators, stem cell-based approaches, and extracellular matrix remodeling.

Despite the promising outcomes, this study has several limitations. Cardiovascular analyses such as transthoracic echocardiographic and electrocardiography measurements were included but yielded inconclusive results due to the experimental setup and stress-related confounding. No systematic long-term follow-up of treated cohorts was performed beyond survival and physical condition. Finally, species-specific differences in drug metabolism and pharmacokinetics must be considered when translating these findings to human patients.

Conclusion

Lonafarnib remains the clinical backbone of HGPS treatment and has set the foundation for current combination strategies aimed at improving therapeutic efficacy. Building on this established standard, our findings suggest that targeting inflammation through JAK/STAT inhibition may provide added benefits. The combination of BAR and FTI was associated with improvements in lifespan, overall health, inflammation, and vascular integrity, but important challenges such as reduced body weight, pronounced lipodystrophy, and unresolved metabolic abnormalities remain. Overcoming these limitations will likely require complementary approaches, such as dietary interventions, metabolic modulators, or stem cell–based strategies. Ultimately, clinical validation will be essential, particularly given developmental, metabolic and pharmacokinetic differences between mice and humans.

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