Assessing the efficacy of protein farnesyltransferase inhibitors in mouse models of progeria

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Abstract Hutchinson-Gilford progeria syndrome (HGPS) is caused by the accumulation of a farnesylated form of prelamin A (progerin). Previously, we showed that blocking protein farnesylation with a farnesyltransferase inhibitor (FTI) ameliorates the disease phenotypes in mouse model of HGPS (Lmna<sup>HG/+</sup>). However, the interpretation of the FTI treatment studies is open to question in light of recent studies showing that mice expressing a nonfarnesylated version of progerin (Lmna<sup>HG/-</sup>) develop progeria-like disease phenotypes. The fact that Lmna<sup>HG/+</sup> mice manifest disease raised the possibility that the beneficial effects of an FTI in Lmna<sup>HG/+</sup> mice were not due to the effects of the drug on the farnesylation of progerin, but may have been due to unanticipated secondary effects of the drug on other farnesylated proteins. To address this issue, we compared the ability of an FTI to improve progeria-like disease phenotypes in both Lmna<sup>HG/+</sup> and Lmna<sup>HG/-</sup> mice. In Lmna<sup>HG/-</sup> mice, the FTI reduced disease phenotypes in a highly significant manner, but the drug had no effect in Lmna<sup>HG/+</sup> mice. The failure of the FTI to ameliorate disease in Lmna<sup>HG/+</sup> mice supports the idea that the beneficial effects of an FTI in Lmna<sup>HG/-</sup> mice are due to the effect of the drug on the farnesylation of progerin.—Yang, S. H., S. Y. Chang, D. A. Andres, H. P. Spielmann, S. G. Young, and L. G. Fong. Assessing the efficacy of protein farnesyltransferase inhibitors in mouse models of progeria. J. Lipid Res. 2010. 51: 400–405.

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Hutchinson-Gilford progeria syndrome (HGPS) is caused by a point mutation in LMNA that alters splicing of the prelamin A transcript and leads to the deletion of 50 amino acids within the carboxyl-terminal portion of prelamin A (1, 2). The 50-amino acid deletion does not alter the molecule’s CaaX motif; consequently, the mutant prelamin A in HGPS (commonly called progerin) undergoes farnesylation, endoproteolytic trimming of the last three amino acids of the protein, and carboxyl methylation of the newly exposed farnesylcysteine (3, 4). However, the internal deletion prevents the subsequent cleavage of the carboxyl terminus by ZMPSTE24, the step that would ordinarily release mature lamin A (1–3). Because the ZMPSTE24 processing step does not occur, progerin retains a farnesylcysteine methyl ester at its carboxyl terminus. Progerin is targeted to the nuclear rim (5–7), interfering with the integrity of the nuclear lamina and causing misshapen cell nuclei (1, 2, 5). The farnesylation of progerin and the frequency of misshapen nuclei can be reduced by inhibiting protein farnesylation with a protein farnesyltransferase inhibitor (FTI) (6, 8–11).

The fact that several different FTIs improved nuclear shape in fibroblasts prompted interest in testing the efficacy of an FTI in a mouse model of HGPS (12, 13). Yang et al. (12, 14) found that an FTI improved progeria-like disease phenotypes (e.g., rib fractures, body weight curves, reduced bone density) in a gene-targeted mouse model of HGPS (Lmna<sup>HG/+</sup>) mice; the beneficial effects of the drug were highly significant and were identified in two independent studies. However, the amelioration of the disease phenotypes in Lmna<sup>HG/+</sup> mice was incomplete. Even with FTI treatment, all of the Lmna<sup>HG/+</sup> mice ultimately developed severe disease and died.

To further explore the concept that protein farnesylation is relevant to the pathogenesis and treatment of disease, Yang et al. (15) generated gene-targeted mice that synthesized a nonfarnesylated version of progerin (Lmna<sup>HG/-</sup>). This article is available online at http://www.jlr.org

Abbreviations: AG, 8-anilinogeraniol; FTI, farnesyltransferase inhibitor; HGPS, Hutchinson-Gilford progeria syndrome.
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mice). These mice were genetically identical to \( Lmna^{HG/+} \) mice except that the carboxyl-terminal cysteine in progerin was replaced with a serine (this substitution eliminates the CaaX motif that triggers protein farnesylation). Interestingly, the \( Lmna^{nHG/+} \) mice developed all of the same progeria-like disease phenotypes identified in \( Lmna^{HG/+} \) mice (e.g., abnormal body weight curves, rib fractures, reduced bone density), although the severity of disease was somewhat milder (15).

That nonfarnesylated progerin would elicit progeria-like disease phenotypes was unexpected, and this result naturally raised questions about the mechanism by which an FTI had reduced disease in \( Lmna^{HG/+} \) mice (12, 14). One possibility was that the FTI improved disease phenotypes directly, by interfering with the prenylation of progerin and reducing the intrinsic toxicity of the protein. Another was that the FTIs acted indirectly, by interfering with the processing of other farnesylated proteins in cells aside from progerin. An indirect effect was not farfetched in our opinion. For example, one could imagine that blocking the farnesylation of a signaling protein might reduce bone turnover and stabilize bone disease, leading indirectly to improved growth and survival of \( Lmna^{HG/+} \) mice. The concept that FTIs could act in an unanticipated fashion is not novel. FTIs were developed to inhibit cancer cell growth by blocking the farnesylation of the Ras proteins (16), but it is now widely assumed that the anticancer effects of these drugs are mediated mainly by their effects on other proteins in cells (17).

We reasoned that it would be possible to gain insights into whether the beneficial effects of the FTI in \( Lmna^{HG/+} \) mice were direct or indirect by simultaneously assessing the effects of the drug in \( Lmna^{nHG/+} \) and \( Lmna^{HG/+} \) mice. If the FTI were to improve disease phenotypes in both \( Lmna^{nHG/+} \) and \( Lmna^{HG/+} \) mice, that would favor an indirect mechanism of action (because a direct effect of an FTI on nonfarnesylated progerin is not possible). On the other hand, finding that the beneficial effects of the FTI were confined to \( Lmna^{HG/+} \) mice would favor the view that the drug ameliorates disease directly by inhibiting the farnesylation of progerin. To explore this issue, we compared, side-by-side, the effects of an FTI on disease phenotypes in both \( Lmna^{HG/+} \) and \( Lmna^{HG/+} \) mice.

**MATERIALS AND METHODS**

**Knock in mice expressing progerin**

Male and female \( Lmna^{HG/+} \), \( Lmna^{nHG/+} \), and \( Lmna^{HG/+} \) mice were bred as described (12, 15). Genotyping of mice was performed by PCR with genomic DNA from tail biopsies (12, 15). Mice were fed a chow diet and housed in a virus-free barrier facility with a 12 h light-dark cycle. UCLA’s Animal Research Committee approved all protocols.

**Treatment with a protein farnesyltransferase inhibitor**

An FTI, ABT-100 (18), was administered to groups of male and female \( Lmna^{HG/+} \), \( Lmna^{nHG/+} \), and \( Lmna^{HG/+} \) mice (\( n = 12 \) mice/group). ABT-100 was mixed in drinking water containing 0.4% hydroxy methyl propyl cellulose and 1.0% ethanol at a concentration of 0.4 mg/ml, so as to deliver an approximate dose of 52 mg/kg/day. Vehicle-treated mice were given drinking water with 0.4% hydroxy methyl propyl cellulose and 1.0% ethanol. The FTI was initiated at 4 weeks of age and was continued for up to 38 weeks of age (at that time point, any mouse that had not yet succumbed to the disease was euthanized). Plasma FTI levels were measured as described (12–14).

**Analysis of disease phenotypes**

Body weights were assessed weekly, and body weight curves were compared with repeated-measures ANOVA and the log rank test. The number of surviving mice was recorded weekly and expressed as a percentage of the total number of mice. Differences in survival curves were assessed by the Kaplan-Meier method. Body fat depots (reproductive, inguinal, and mesenteric) were measured when each mouse died or was euthanized. Differences were assessed with a two-tailed Student’s \( t \)-test.

The number of spontaneous rib fractures in \( Lmna^{HG/+} \) and \( Lmna^{HG/+} \) mice was documented when each mouse died. After opening the thoracic cavity and removing the heart and lungs, the interior of the thorax was photographed and rib fractures were counted (12, 15). Numbers of rib fractures in FTI- and vehicle-treated \( Lmna^{HG/+} \) and \( Lmna^{HG/+} \) mice were compared with a two-tailed Student’s \( t \)-test.

**Fig. 1.** Western blot testing the effect of ABT-100 on the farnesylation of the B-type lamins and progerin in \( Lmna^{HG/+} \) and \( Lmna^{nHG/+} \) fibroblasts. For these studies, we used the same concentration of ABT-100 that we achieved in the plasma of mice (0.5 \( \mu \)g/ml). The top panel shows the merged images of Western blots with an antibody specific for lamin A/C (red) and an antibody specific for the farnesol analog AG (green); the middle panel shows the signal for the antibody against AG; the bottom panel shows a loading control (actin). In this experiment, \( Lmna^{HG/+} \) and \( Lmna^{nHG/+} \) fibroblasts were incubated with AG (100 \( \mu \)M) in the presence (+) or absence (−) of ABT-100. The electrophoretic mobility of progerin, lamin B1, and lamin B2 are virtually identical, and all are farnesylated; hence, the antibody against AG detected a farnesylated protein in both cell lines (in the absence of an FTI). When progerin and lamin A/C were immunoprecipitated with an antibody against lamin A/C, the progerin in \( Lmna^{HG/+} \) fibroblasts, but not \( Lmna^{nHG/+} \) fibroblasts, stained with the antibody against AG.
Western blots and metabolic labeling studies

Procedures for preparing liver extracts and Western blotting techniques have been described previously (12, 14, 15). To detect lamins A and C and progerin, we used a 1:400 dilution of a goat anti-lamin A/C IgG (Santa Cruz Biotechnology, Santa Cruz, CA) and a 1:5000 dilution for an IRdye800-conjugated donkey anti-goat IgG (Li-Cor; Lincoln, NE). Antibody binding was detected with an Odyssey infrared scanner (Li-Cor). To detect HDJ-2, we used a 1:5000 dilution for an IRdye800-conjugated donkey anti-rabbit IgG (Santa Cruz Biotechnology, Santa Cruz, CA) and a 1:5000 dilution of a mouse monoclonal antibody against HDJ-2 (NeoMarkers; Fremont, CA) and a 1:5000 dilution of an HRP-labeled anti-mouse IgG (GE Healthcare). For both prelamin A and HDJ-2 Western blots, antibody binding was detected with the ECL Plus chemiluminescence system (GE Healthcare) and exposure to X-ray film.

To assess protein farnesylation in fibroblasts, the cells were incubated for 48 h with an analog of farnesol, 8-anilinogeraniol (AG) (100 µM in DMSO) (19) in the presence and absence of ABT-100 (1 µM). AG is incorporated by cells into AG pyrophosphate, a farnesylphosphate analog, which is used by protein farnesyltransferase as a substrate to farnesylate CaaX proteins. AG incorporation into cellular proteins was detected by western blotting with a mouse monoclonal antibody specific for AG, diluted 1:5000 (19).

RESULTS

We administered an FTI, ABT-100 (52 mg/kg/day), or vehicle alone to groups of 12 male and female Lmna<sup>HG/+</sup>, Lmna<sup>HG/+</sup>, and Lmna<sup>HG/+</sup> mice, starting at 4 weeks of age. Our goal was to determine if the FTI would ameliorate progeria-like disease phenotypes in Lmna<sup>HG/+</sup> mice in addition to Lmna<sup>HG/+</sup> mice.

The plasma levels of ABT-100 in treated mice were similar to those in earlier studies (12–14), ranging from 0.3 to 0.7 µg/ml. When we incubated Lmna<sup>HG/+</sup> and Lmna<sup>HG/+</sup> fibroblasts with the same concentration of ABT-100 that we achieved in mice (0.5 µg/ml), the farnesylation of B-type lamins and progerin was inhibited, as judged by metabolic labeling experiments with a farnesol analog (8-anilinogeraniol) (Fig. 1). Also, we observed, as expected, an accumulation of prelamin A and nonfarnesylated HDJ-2 in liver extracts from FTI-treated mice (Fig. 2A). Interestingly, there were lower levels of mature lamin A, relative to actin, in liver extracts from FTI-treated mice (Fig. 2A). Long-term treatment of Lmna<sup>HG/+</sup> and Lmna<sup>HG/+</sup> fibroblasts with ABT-100 also lowered levels of mature lamin A, consistent with the findings in FTI-treated mice (Fig. 3).

Consistent with earlier studies by Yang et al. (12, 14), the FTI improved body weight curves in Lmna<sup>HG/+</sup> mice (P < 0.0001 for both males and females when compared with Lmna<sup>HG/+</sup> mice treated with vehicle alone) (Figs. 4A, B). In contrast, the body weight curves of FTI- and vehicle-treated Lmna<sup>HG/+</sup> mice were not different. This was the case for both male and female Lmna<sup>HG/+</sup> mice (P = 0.27 and 0.54, respectively). Also, there were no differences in the body weight curves of FTI- or vehicle-treated Lmna<sup>HG/+</sup> mice (P = 0.36 for males and 0.52 for females).

Kaplan-Meier survival curves revealed that the FTI improved survival in Lmna<sup>HG/+</sup> mice (P < 0.0001), extending survival by 6–8 weeks (Fig. 4C). In contrast, the FTI had no effect on survival of Lmna<sup>HG/+</sup> mice (P = 0.45) (Fig. 4C).
mice ($P < 0.0001$) (Fig. 6A). In contrast, the drug had no significant effect on the number of rib fractures in $Lmna^{HG/+}$ mice (Fig. 6A). The FTI improved mean bone density and bone cortical thickness in $Lmna^{HG/+}$ mice ($P < 0.0001$ for both males and females) (Fig. 6B, C). In contrast, the FTI had no effect on these bone phenotypes in $Lmna^{nHG/+}$ mice (Fig. 6B, C).

**DISCUSSION**

During the past few years, Yang et al. (12, 13) showed that an FTI ameliorates disease phenotypes in a mouse model of HGPS. Although the results were significant and reproducible, putting the findings into perspective is challenging, particularly with the discovery that $Lmna^{nHG/+}$ mice develop disease (15). $Lmna^{nHG/+}$ have all of the same progeria-like disease phenotypes as $Lmna^{HG/+}$ mice, albeit somewhat milder, and they invariably succumb to the disease. The discovery that nonfarnesylated progerin elicits disease prompted us to consider the possibility that the beneficial effects of the FTI in $Lmna^{HG/+}$ mice might have little to do with a direct effect on the farnesylation of progerin. Instead, we wondered whether the effect of the FTI might be more indirect, perhaps secondary to inhibiting the farnesylation of other cellular proteins. If the effects of the FTI were indirect, one would predict the FTI might be equally efficacious in $Lmna^{HG/+}$ and $Lmna^{nHG/+}$ mice. This prediction was not borne out. FTI treatment had no effect on body weight, survival, the number of rib fractures, fat stores, bone cortical thickness, or bone density of $Lmna^{nHG/+}$ mice. In contrast, the FTI improved all of these phenotypes in $Lmna^{HG/+}$ mice, and did so in a highly significant fashion. The fact that the FTI improved disease in $Lmna^{HG/+}$ but not $Lmna^{nHG/+}$ mice suggests that the beneficial effect of the FTI in $Lmna^{HG/+}$ mice is likely a consequence of inhibiting the prenylation of progerin, rather than an indirect effect of the drug on other cellular proteins.

The beneficial effects of the FTI on disease phenotypes in $Lmna^{HG/+}$ mice were very apparent, and most of the different qualitative and quantitative changes seen in $Lmna^{HG/+}$ mice were also reproduced in $Lmna^{nHG/+}$ mice (Fig. 4B). Consistent with the improvement in body weight curves in FTI-treated $Lmna^{HG/+}$ mice, the FTI significantly increased body fat stores in $Lmna^{HG/+}$ mice, compared with vehicle-treated mice ($P = 0.002$) (Fig. 5). In contrast, the FTI had no effect on fat stores in $Lmna^{nHG/+}$ mice (Fig. 5).

We assessed the impact of the FTI treatment on spontaneous rib fractures in both male and female mice. The FTI clearly reduced the number of rib fractures in $Lmna^{HG/+}$ mice (Fig. 6A). In contrast, the drug had no significant effect on the number of rib fractures in $Lmna^{nHG/+}$ mice (Fig. 6A).
Genetic studies have suggested that lower levels of lamin A synthesis reduce the disease phenotypes elicited by a LmnaHG allele (20). The finding of lower lamin A levels in association with FTI treatment was also observed in earlier studies (8, 14, 15). The mechanism for the fall in lamin A levels is unclear but we suspect that sustained blockade of prelamin A farnesylation leads to the eventual turnover of nonfarnesylated prelamin A, reducing the production of mature lamin A.

The current study reinforces the idea that an FTI can ameliorate disease in LmnaHG/+ mice, but important questions remain about the utility of FTIs in the treatment of humans with HGPS. Indeed, questions were raised about whether an FTI is the most appropriate drug for inhibiting the prenylation of progerin (21). Varela et al. (21) reported data suggesting that progerin can be geranylgeranylated in the setting of an FTI, and they proposed that a combination of a statin and a bisphosphonate (which would theoretically inhibit both farnesylation and geranylgeranylation) might be more useful for treating HGPS. They went on to show that a statin/bisphosphonate combination improved progeria-like disease phenotypes in ZMPSTE24-deficient mice; however, they provided no evidence that the combination actually inhibited the prenylation of prelamin A (or any other protein) in mice. Until such evidence is in hand, doubts will remain about the rationale for the statin/bisphosphonate combination, and in particular, whether the combination ameliorates disease indirectly (perhaps secondary to the bone-strengthening properties of bisphosphonates) or more directly by inhibiting the prenylation of prelamin A. For those interested in investigating the utility of a bisphosphonate/statin combination, the approach outlined in the current study should be of interest. If a statin/bisphosphonate combination were to improve disease phenotypes in LmnaHG/+ mice, that would suggest that the mechanism for the combination was likely indirect, perhaps due to the bone-strengthening properties of the bisphosphonates, and not to a specific effect on the prenylation of prelamin A.

In summary, an FTI ameliorates disease phenotypes in LmnaHG/+ mice, but not LmnaHG/- mice. The failure of the FTI to improve disease in LmnaHG/- mice suggests that the beneficial effects of the drug in LmnaHG/+ mice are likely due to blocking the farnesylation of progerin.

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