Chapitre 10 Le génotype du récepteur LDL est un déterminant significatif du rebond dans les concentrations de cholestérol LDL après l'aphérèse des lipoprotéines chez des patients avec hypercholestérolémie familiale homozygote

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The LDL receptor genotype is a significant determinant of the rebound in LDL-C concentration following lipoprotein apheresis among patients with homozygous familial hypercholesterolemia

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Résumé

Contexte et objectif : L'AL est la thérapie de référence pour diminuer les concentrations de C-LDL et de Lp(a) chez les patients avec HFHo. Limiter le rebond dans les concentrations de lipoprotéines dans les jours suivants un traitement d'AL est une stratégie reconnue qui permet d'améliorer l'efficacité à long terme de cette thérapie. Les déterminants du rebond dans les concentrations de C-LDL et de Lp(a) restent à identifier. L'objectif de cette étude était d'évaluer l'association entre le génotype du R-LDL et le rebond dans les concentrations de C-LDL et de Lp(a) suivant l'AL chez des patients avec HFHo.

Méthodes : Les données de 1999 traitements d'AL réalisés entre 2008 et 2016 chez des patients avec HFHo porteurs de doubles mutations récepteur-défectueux (RD, n=3), récepteur-nul (NR, n=8) ou porteurs d'une mutation récepteur-défectueux et d'une mutation récepteur-nul (RDRN, n=4) ont été compilées et analysées. Ces données incluent les concentrations de lipides pré- et post-AL, le volume de plasma filtré à chaque traitement, le système utilisé et l'intervalle de temps entre les traitements.

Résultats : Le génotype du R-LDL était associé au rebond dans les concentrations de C-LDL (*P*=0,005). Les patients avec HFHo porteurs de mutations récepteur-nul (RN) présentaient un rebond dans les niveaux de C-LDL plus élevé que les patients avec HFHo porteurs de mutations récepteur-défectueux (RD) (+233 ± 11% vs +141 ± 20% ; *P*=0,004). Cette différence était indépendante de la diminution aiguë induite par l'AL dans les niveaux de C-LDL, les concentrations de C-LDL post-AL, l'intervalle de temps entre les traitements, le nombre cumulatif de traitements reçus et l'intervalle de temps depuis le premier traitement compilé. Le génotype du R-LDL n'était pas associé au rebond dans les concentrations de Lp(a).

Conclusions : Le génotype du R-LDL est significativement associé avec le rebond dans les concentrations de C-LDL suivant les traitements d'AL. Les patients avec HFHo porteurs de mutations RN pourraient bénéficier de traitements plus fréquents afin de réduire le rebond dans les concentrations de C-LDL et leur exposition à ces lipoprotéines athérogènes.

Title page

The LDL receptor genotype is a significant determinant of the rebound in LDL-C concentration following lipoprotein apheresis among patients with homozygous familial hypercholesterolemia

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Running title

LDLR genotype and post-apheresis LDL-C rebound

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Research letter

In homozygous familial hypercholesterolemia (HoFH) caused by mutations in the LDL receptor (*LDLR*) gene, patients with two receptor-negative mutations have higher cholesterol concentrations and coronary heart disease (CHD) risk than patients with double receptor-defective mutations.[1]

Pharmacological treatment is insufficient to achieve an efficient reduction in LDL-cholesterol (C) or lipoprotein (a) (Lp(a)) concentrations in HoFH patients, and repetitive long-term lipoprotein apheresis (LA) remains the gold-standard therapy. LA induces an acute decrease in LDL-C and Lp(a) concentrations, which is then followed by a rebound in the following days. The post-LA rebound constitutes a major determinant of LA efficacy as it directly affects the average concentrations between treatments, considered the best estimate of the physiological effects of long-term LA.[2] However, our understanding of the determinants of post-treatment rebound in LDL-C and Lp(a) is very limited.[2]

This study aimed to determine the extent to which the *LDLR* genotype modulates the post-LA rebound in LDL-C and Lp(a) concentrations among HoFH patients. We hypothesized that the rebound in LDL-C and Lp(a) concentrations is greater among receptor-negative HoFH patients than among receptor-defective HoFH patients.

Data on all consecutive LA treatments performed between August 2008 and February 2016 among HoFH patients with genetically-defined defective/defective LDLR mutations (n=3), negative/negative LDLR mutations (n=8) and defective/negative LDLR mutations (n=4), treated at the CHU de Québec-Université Laval were collected. For each patient, the compiled data included: 1) date of LA, 2) cumulative number of LA treatments received, 3) interval between LA treatments, 4) LA system used, 5) volume of filtered plasma per treatment, 6) duration of treatments, 7) pre- and post-LA lipoprotein concentrations and 8) the cumulative interval since the first compiled LA treatment. Data on LDL-C and Lp(a) rebound covered 1999 and 1567 treatments, respectively. The rebound was calculated as the percentage difference between post-LA and pre-LA concentrations of the subsequent LA treatment. Mixed models for repeated measures with patients as a random effect were used for statistics. The study was approved by the Laval University Medical Center ethical review committee, and informed consent was obtained from each patient.

At baseline, patients (34.2 ± 14.3 years; women, n=8/15; CHD history, n=8/15) were treated with maximally tolerated dose of statin (atorvastatin: 80 mg, n=7; 40 mg, n=1; rosuvastatin: 40 mg, n=6; 5 mg, n=1) and ezetimibe and had cutaneous and tendinous xanthomas. Patients were French-Canadians (n=13), Lebanese (n=1) and Hondurian (n=1).

The *LDLR* genotype was significantly associated with LDL-C rebound (*P*=0.003). Negative/negative patients had a greater mean rebound in LDL-C concentrations compared with defective/defective patients and defective/negative patients, independent of the interval since the last treatment and drug therapy (**Figure, A**). Similar observations were obtained when the analysis was conducted with the rebound in absolute LDL-C levels in mmol/L. No interaction was observed between the *LDLR* genotype and the interval between treatments for the rebound in LDL-C ($P_{genotype*interval}$ =0.06). Therefore, differences in the rebound in LDL-C levels between *LDLR* genotypes were maintained over time. Moreover, weekly treatments were associated with significantly lower rebound in LDL-C levels compared with treatments conducted at longer intervals, independent of the *LDLR* genotype and drug therapy (**Figure, B**).

No difference was found in the rebound in Lp(a) concentrations according to the *LDLR* genotype. Nonetheless, the rebound in Lp(a) associated with weekly treatment was significantly lower than the rebound associated with bi-monthly treatments (117 ± 37% vs 166 ± 36%, *P*=0.0002).

This retrospective longitudinal study demonstrates that the *LDLR* genotype is a significant determinant of the rebound in LDL-C concentration following LA among HoFH patients. It was estimated that the receptor-negative HoFH patients treated every 3 to 5 days would exhibit a rebound in LDL-C concentrations similar to one of the receptor-defective HoFH patients treated at an interval of 7 to 14 days. Mechanisms underlying the greater rebound in LDL-C observed in receptor-negative patients than in receptor-defective patients remain unclear, but are likely to rely on the impact of *LDLR* deficiency on apoB metabolism. Indeed, several studies have reported a direct inverse association between *LDLR* functionality and apoB secretion.[3] In addition, it is likely that the efficacy of statins to inhibit cholesterol synthesis, which differs between receptor-negative and receptor-defective patients, could modulate post-LA LDL-C rebound.[4, 5] Nevertheless, receptor-negative HoFH patients may benefit from more frequent LA to reduce their exposure to apoB-containing lipoproteins.

The number of treatments and the ~8 year follow-up are major strengths of the present study. However, these observations are reported from a limited number of mutations in the *LDLR* gene highly prevalent among the French-Canadians. A similar assessment among patients carrying other common *LDLR* mutations is warranted.

This study demonstrated that the rebound in LDL-C levels was markedly greater among receptor-negative than among receptor-defective HoFH patients. In order to optimize long-term benefits of LA in an era of precision medicine, this study underscores the importance of the screening for the *LDLR* mutation, the relevance of adapting LA therapy to the severity of the disease and the benefits associated with more frequent treatments.

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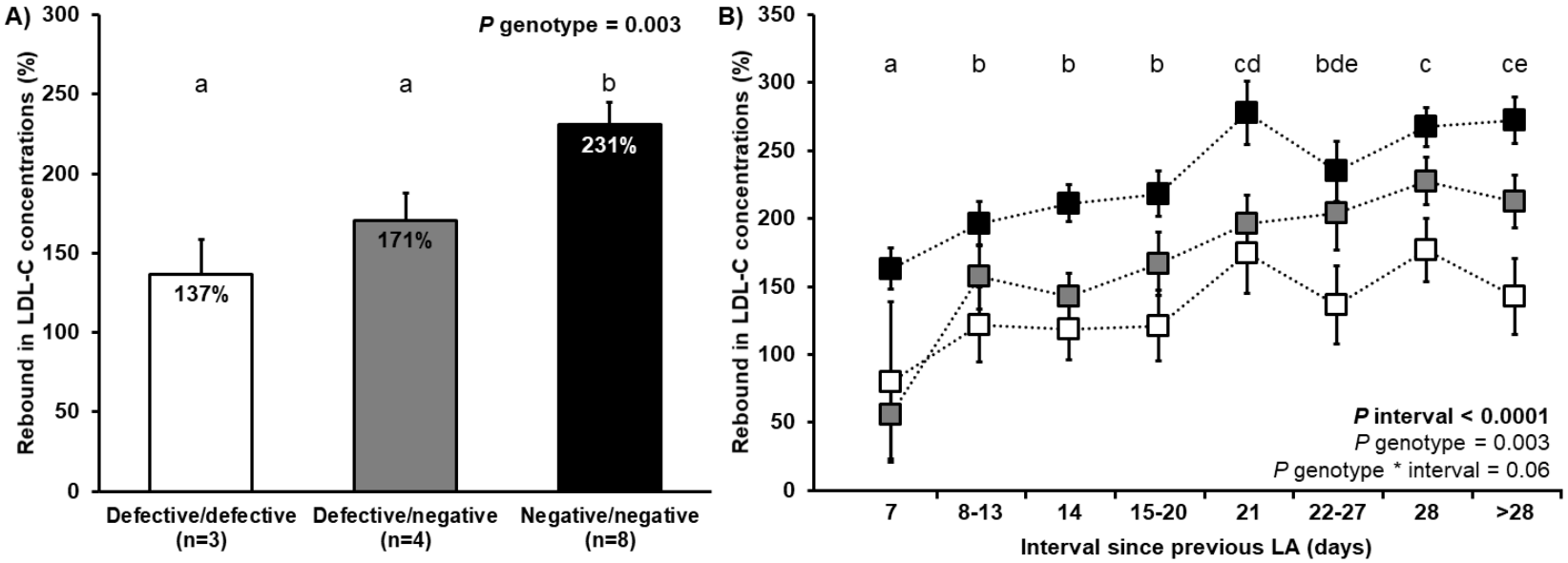
Figure

Figure 10-1 Rebound in LDL-C concentrations after lipoprotein apheresis according to the *LDLR* genotype



A, Mean rebound in LDL-C concentrations after lipoprotein apheresis according to the *LDLR* genotype among patients with homozygous familial hypercholesterolemia (HoFH) independent of the interval since previous treatment. Patients with receptordefective HoFH (defective/defective, n=3) were carriers of the W66G mutation in exon 3. Patients with receptor-negative HoFH (negative/negative, n=8) were carriers of the >15 kb deletion at the 5' end of the gene (del15kb, n=5), the splice site mutation in intron 7 (LDLR1061(-1) G to C, n=1), and the C660X Lebanese alleles (n=1), and 1 subject was a carrier of the del15kb and the C646Y mutation in exon 14. Patients with defective/negative LDLR mutations (n=4) were carriers of the del15kb and the W66G mutation. Different superscript letters (a, b) denote significant differences (P<0.05). **B,** Rebound in LDL-C concentrations after lipoprotein apheresis according to the interval since last LA treatment and the *LDLR* genotype among patients with HoFH. Interval points with different superscript letters (a, b, c, d, e) denote significantly different rebound independent of the LDLR genotype. White boxes signify patients with receptor-defective HoFH (defective/defective); black boxes signify patients with receptor-negative HoFH (negative/negative); and gray boxes signify patients with HoFH with defective/negative

LDLR mutations. Data are presented as the mean±standard error of the mean and were calculated using a mixed model that included the LDLR genotype, the interval between LA treatments, the LA-induced acute decrease in LDL-C, LDL-C concentrations after LA, the interval since the first LA, statin therapy and the cumulative number of LA treatments as independent fixed variables, and the study subjects as a random effect. Interval (days) since last LA were treated as the following categories in the models: 7, 8 to 13, 14, 15 to 20, 21, 22 to 27, 28, and >28 days. The patient-specific time interval since the first compiled LA for each treatment was treated as a repeated measure in the models. The spatial power covariance structure was used. Normality of the models was assessed by the distribution of the scaled residual values. The Tukey-Kramer adjustment was used for multiple comparison tests. LA indicates lipoprotein apheresis ; LDL-C, low-density lipoprotein cholesterol; and LDLR, low-density lipoprotein receptor.