Antidrug Antibodies in Patients Treated with Alirocumab

CORRESPONDENCE

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TO THE EDITOR: Immunogenicity led to the discontinuation of clinical development of bococizumab, a murine-derived, humanized antibody to proprotein convertase subtilisin–kexin type 9 (PCSK9), as now described by Ridker et al.[1] in the *Journal*. Evidence suggests increased immunogenicity potential for murine-derived antibodies humanized by artificially engineering them in vitro, as compared with fully human antibodies that are produced with the use of mice with genetically humanized immune systems.

Very low rates of immunogenicity were observed in clinical trials of alirocumab, a fully human PCSK9 antibody derived from VelocImmune mice (in which the murine genes in the heavy-chain and light-chain immunoglobulin variable region are replaced with their human counterparts).[2-4] We evaluated the effect of antidrug antibodies on the safety and efficacy of alirocumab with respect to reductions in levels of low-density lipoprotein (LDL) cholesterol using data from 10 trials involving 4747 patients (Tables S1 and S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Antidrug antibodies were assessed with the use of a validated assay with positivity set to maximize sensitivity, which resulted in false positives in a low percentage of baseline and control samples.

Antidrug antibodies were observed in 155 of 3039 patients (5.1%) in the alirocumab group and in 17 of 1708 (1.0%) in the control group. Persistent antidrug antibodies (i.e., ≥2 consecutive positive samples over ≥12 weeks) were found in 44 patients (1.4%) in the alirocumab group and in 3 (0.2%) in the control group (Table S3 in the Supplementary Appendix). To evaluate the potential effect of antidrug antibodies on efficacy, we compared patients without antidrug antibodies with those who had persistent or transient antidrug antibodies using a mixed-effect model with repeated measures (Fig. 1, and the Methods section in the Supplementary Appendix).

According to regulatory guidance,[5] we reasoned that the presence of persistent antidrug antibodies would most likely influence efficacy. However, we found that substantial reductions in LDL cholesterol levels were maintained over the course of the studies, regardless of antidrug-antibody status, although for some time points, nominally significant differences (not adjusted for multiple testing) were noted (Fig. 1, and Table S4 in the Supplementary Appendix). In a trend analysis, no late loss in the LDL-cholesterol response was seen in patients with antidrug antibodies. Mean reductions in LDL cholesterol were also maintained over time in patients with neutralizing antibodies (antidrug antibodies that inhibit binding), which were observed in 1.3% of the patients (Table S5 and Fig. S1 in the Supplementary Appendix). Among the patients who received alirocumab, adverse events occurred at similar frequencies regardless of antidrug-antibody status, although injection-site reactions

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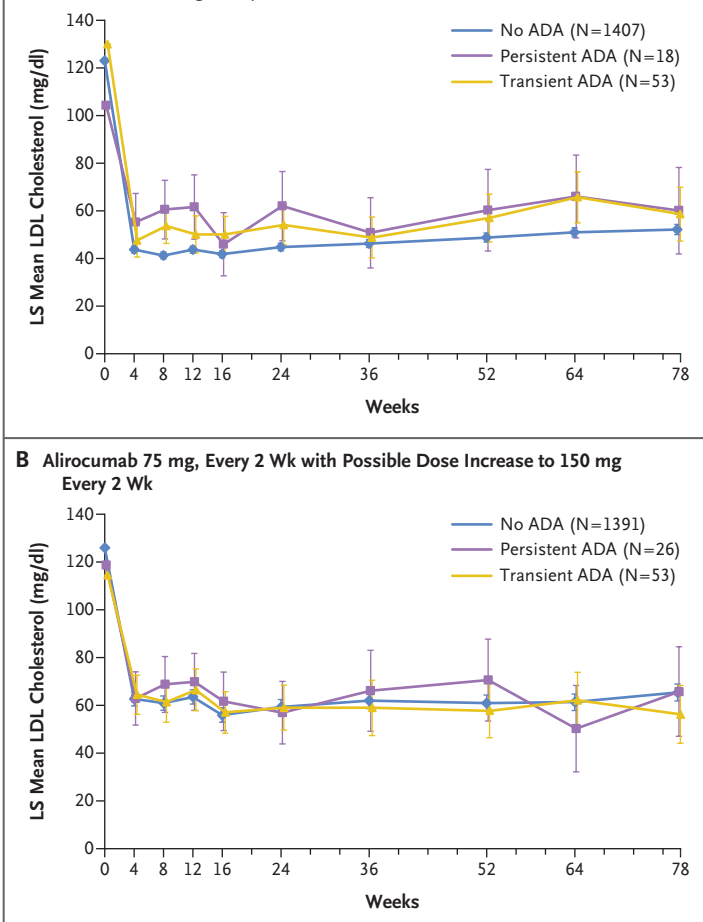

Figure 1. LDL Cholesterol Levels in Patients Who Received Alirocumab, According to Antidrug-Antibody (ADA) Status.

Panel A shows data from ODYSSEY LONG TERM, which involved patients who received 150 mg of alirocumab every 2 weeks. Panel B shows the results of a meta-analysis of eight phase 3 ODYSSEY trials (FH I, FH II, COMBO I, COMBO II, OPTIONS I, OPTIONS II, MONO, and ALTERNATIVE) in which patients received 75 mg of alirocumab every 2 weeks with a possible dose increase to 150 mg every 2 weeks, depending on the low-density lipoprotein (LDL) cholesterol level at 8 weeks. (References for all the trials cited here are provided in the Supplementary Appendix.) Although immunogenicity data were compiled from 10 studies involving all 4747 patients, the 10th trial (ODYSSEY HIGH FH) was not included in the efficacy analyses, since it did not have any patients with persistent antidrug antibodies (i.e., those occurring in ≥2 consecutive samples over ≥12 weeks). Transient antidrug antibodies include those that were defined as either indeterminate (present only at the last sampling time point) or transient (any positive antidrug-antibody response that was considered to be neither persistent nor indeterminate). Among the patients in whom no antidrug antibodies developed, the least-squares (LS) mean LDL cholesterol level at 78 weeks was 52.2 mg per deciliter in Panel A and 65.3 mg per deciliter in Panel B. Among the patients with transient antidrug antibodies, the values were 58.6 mg per deciliter and 56.2 mg per deciliter, respectively; among those with persistent antidrug antibodies, the values were 60.1 mg per deciliter and 65.7 mg per deciliter, respectively. The I bars denote 95% confidence intervals. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

(mostly mild) were more frequent among the patients with antidrug antibodies (Table S6 in the Supplementary Appendix).

In conclusion, antidrug antibodies developed in few patients who were treated with alirocumab, and even those patients had substantial and durable evidence of LDL-cholesterol lowering. However, these findings are limited by the small number of patients in whom antidrug antibodies developed. Since immunogenicity data are dependent on numerous factors, comparisons of antidrug-antibody incidence among different drugs (even in the same class) may be misleading.

Eli M. Roth, M.D.
Sterling Research Group
Cincinnati, OH
eroth@sterlingresearch.org

Anne C. Goldberg, M.D.
Washington University School of Medicine
St. Louis, MO

Alberico L. Catapano, Ph.D., M.D.
University of Milan Multimedica IRCCS
Milan, Italy

Albert Torri, Ph.D.
George D. Yancopoulos, M.D., Ph.D.
Neil Stahl, Ph.D.
Regeneron Pharmaceuticals
Tarrytown, NY

Aurélie Brunet, Pharm.D.
Sanofi
Bridgewater, NJ

Guillaume Lecorps, M.Sc.
Sanofi
Chilly Mazarin, France

Helen M. Colhoun, M.D.
University of Edinburgh
Edinburgh, United Kingdom

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