

hand. The solution is not to abandon accountability, but rather to develop stronger auditing strategies with the use of methods such as video surveillance, computerized triggers, and unannounced, secret monitoring of compliance by hospital personnel. Clearly, we have much to learn here, and we agree that we must be careful to preserve the collegial exchange and openness that are so essential to organizational learning.

We recognize that finding the balance between accountability and “no blame” will be difficult. But, a decade into the safety movement, we now know that our present strategy guarantees lackluster adherence to a number of low-risk, universally accepted, and evidence-based safety prac-

tices such as hand hygiene. Without minimizing the challenges we face and fully recognizing the need to proceed slowly, it borders on magical thinking to believe that a strategy of “more of the same” will achieve the levels of safety and reliability that our patients deserve.

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Since publication of their article, the authors report no further potential conflict of interest.

Lovastatin in X-Linked Adrenoleukodystrophy

TO THE EDITOR: As reported previously in the *Journal*, lovastatin lowers levels of very-long-chain fatty acids in plasma in patients with X-linked adrenoleukodystrophy (X-ALD).¹ Further studies did not reproduce this finding with the use of simvastatin in patients or with the use of lovastatin in X-ALD–knockout mice.^{2,3} Still, many patients with X-ALD worldwide receive lovastatin.

We conducted a randomized, double-blind, placebo-controlled, crossover trial comparing lovastatin at a dose of 40 mg once daily with placebo (Current Controlled Trials number, ISRCTN31565393). Outcome measures were levels of hexacosanoic acid (C26:0) in plasma, low-density lipoprotein (LDL) particles, lymphocytes and erythrocytes, and plasma LDL cholesterol after 22 weeks of treatment. For some outcome measures, an intermediary analysis at 8 weeks was performed. A total of 14 men with X-ALD (adrenomyeloneuropathy phenotype) were enrolled in the study. Merck provided lovastatin for this study but did not participate in the trial design, data analysis, or drafting of the letter.

No patients dropped out of the study, and neither myopathy nor rhabdomyolysis or other adverse events were observed. Data on all major outcomes are summarized in Table 1. There were significant decreases of 1.44 mmol per liter in the level of LDL cholesterol in plasma at 8 weeks and 1.35 mmol per liter at 22 weeks. At 8 weeks, the levels of plasma tetracosanoic acid (C24:0) and C26:0 had decreased by 14.2 μ mol per liter and

0.39 μ mol per liter, respectively. However, even with this decrease, C26:0 levels remained above the control level (mean \pm SE) of 0.67 ± 0.13 μ mol per liter.⁴ Furthermore, the reduction in C26:0 was no longer significant at 22 weeks. There was a decrease of 0.38 mmol per liter in the level of oleic acid (C18:1) at 8 weeks and a decrease of 0.44 mmol per liter at 22 weeks. There was no change in levels of C26:0 in erythrocytes or lymphocytes at either measurement. Finally, the levels of C18:1, C24:0, and C26:0 in LDL lipoprotein particles remained unchanged.

This trial was designed to investigate whether lovastatin has a biochemical effect in vivo in patients with X-ALD and to provide pilot data for a possible large-scale trial with clinical outcome variables. We conclude that lovastatin leads to a small decrease in levels of C24:0 and C26:0 in plasma; this must be considered a nonspecific result of the decrease in the level of LDL cholesterol. Since very-long-chain fatty acids are virtually water insoluble, and only a small fraction binds to albumin,⁵ most of the very-long-chain fatty acids in plasma are transported as cholesterol esters in lipoprotein particles such as LDL. This finding is corroborated by the finding that the level of C18:1 was also reduced, and it is further supported by the lack of an effect on C26:0 levels in peripheral-blood lymphocytes and erythrocytes and in the content of very-long-chain fatty acids in the LDL lipoprotein fraction. Our data indicate that investment of substantial

Table 1. Major Outcome Measures after 8 Weeks (if Applicable) and 22 Weeks of Treatment with Lovastatin at a Dose of 40 mg Once Daily.*

Outcome	Plasma			Lipoprotein Fraction				Cells		
	Total Cholesterol mmol/liter	LDL mmol/liter	C18:1 mmol/liter	C24:0 μmol/liter	C26:0 μmol/liter	C18:1 in LDL pmol/mmol of ApoB	C24:0 in LDL pmol/mmol of ApoB	C26:0 in LDL pmol/mmol of ApoB	C26:0 in Lymphocytes nmol/mg of protein	C26:0 in Erythrocytes % of total fatty acids
Baseline	5.52	3.54	2.37	77.1	2.56	1540	64	9.7	0.35	0.18
8 wk of treatment										
Mean change	1.48±0.25	1.44±0.20	0.38±0.17	14.2±2.0	0.39±0.11	ND	ND	ND	-0.01±0.02	ND
95% CI	0.94 to 2.02	1.02 to 1.87	0 to 0.76	9.8 to 18.5	0.15 to 0.63	NA	NA	NA	-0.04 to 0.03	NA
P value	<0.001	<0.001	0.05	<0.001	0.004	NA	NA	NA	0.64	NA
22 wk of treatment										
Mean change	1.45±0.24	1.35±0.21	0.44±0.17	10.7±3.8	0.23±0.16	-84±69	3.4±2.5	-1.9±1.1	0.03	0.002±0.003
95% CI	0.92 to 1.98	0.89 to 1.82	0.06 to 0.82	2.4 to 19.0	-0.12 to 0.58	-240 to 80	-2.0 to 8.9	-4.3 to 0.6	-0.02 to 0.08	-0.01 to 0.01
P value	<0.01	<0.01	0.03	0.02	0.18	0.26†	0.19	0.12	0.22	0.53

* Plus-minus values are means ±SE. The mean reduction indicates the absolute change from baseline levels after treatment. P values were calculated with the use of a two-sided, unpaired Student's t-test. ApoB denotes apolipoprotein B, CI confidence interval, C18:1 oleic acid, C24:0 tetracosanoic acid, C26:0 hexacosanoic acid, NA not applicable, and ND not determined.

† Equal variances were not assumed.

resources and time in a trial with clinical end points seems unwarranted. Lovastatin should not be prescribed as a therapy to lower levels of very-long-chain fatty acids in patients with X-ALD.

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