

An Assessment of Statin Safety

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Abstract

Recently, statin safety and potential drug interactions have received close attention in the consumer and medical press. In particular, rosuvastatin, the most recent statin introduced into the US market, has been the object of much speculation. Many of these reports have lost sight of the proven efficacy of statins in coronary disease prevention at a time when coronary heart disease is the number one killer of adults, and have failed to frame the potential drug toxicity in the context of this benefit. Summarized here are the conclusions of the National Lipid Association's Statin Safety Assessment Task Force, which reviewed extensive new drug application (NDA) and postmarketing data for all the currently marketed statins regarding their effect on the liver, muscle, renal, and neurologic systems.

The task force found that, overall, hepatic, renal, or neurologic function does not appear to be compromised by statin use. They do not recommend routine monitoring of these systems but do recommend ongoing surveillance of symptomatic patients. With respect to muscle toxicity, the task force's Muscle Expert Panel concluded that the incidence of myopathy and rhabdomyolysis is low and appears to be dose-related, rather than associated with the degree of low-density lipoprotein cholesterol lowering and also appears to be related to the individual statin used. For example, from the rosuvastatin NDA database and additional postmarketing data, the overall incidence of myopathy was found to be lower than that observed with other statins.

Administrative claims data of hospitalization rates for adverse events in statin patients confirm the task force conclusion that, overall, statins are safe and well tolerated when used as monotherapy.

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Concern over the safety of statins has flourished since the removal of cerivastatin from the market in 2001. Cerivastatin was associated with more than 100 deaths from rhabdomyolysis, with most cases of muscle toxicity occurring in patients cotreated with the fibric acid derivative gemfibrozil.¹

Since then, statin safety and potential drug interactions have received close scrutiny in the consumer and medical press. The most recent statin introduced into the US market—rosuvastatin—has been the object of much speculation regarding its potential role in kidney failure as a result of an association with proteinuria. Other concerns raised have been potential effects of statins on the liver and on cognition.

The news media emphasis on potential severe side effects has influenced many patients to refuse to initiate therapy or withdraw from long-term treatment. The attention has caused many physicians to lose confidence in the benefit-safety profile of these agents as well. Frequent references to potential adverse events have pervaded the doctor-patient relationship. Unfortunately, many of these reports have lost sight of the proven efficacy of statins in coronary disease prevention at a time when coronary heart disease is the number one killer of adults, and have failed to frame the potential drug toxicity in the context of this benefit.²

To address the concerns over statin safety, the National Lipid Association's Statin Safety Assessment Task Force issued its conclusions and recommendations recently in a supplement to the *American Journal of Cardiology*.³ The task force commissioned expert reviews, carried out analyses of the major sources of adverse reaction information (the US Food and Drug Administration [FDA] Adverse Event Reporting System [AERS], administrative claims databases from managed care organizations, new drug applications [NDAs], cohort studies, and clinical trials), and appointed 4 independent

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teams of medical subspecialists to assess the effect of statins on the liver,⁴ muscle,⁵ renal,⁶ and neurologic⁷ systems. Following is a summary of the report.

Liver Toxicity

All statins are associated with asymptomatic elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >3 times the upper limit of normal (ULN) at a rate of <1% at starting and intermediate dosages.⁴ This rate increases up to 2% to 3% in those receiving 80 mg/day of any statin.⁴ From an analysis of 180 000 patients who participated in 21 major statin trials lasting an average of 3 years, the incidence of a liver function test (LFT) elevation >3 times the ULN on 1 occasion was found to be 300 cases per 100 000 person-years, whereas that for 2 consecutive elevations was 110 cases per 100 000 person-years (the incidence of similar elevations among placebo patients was 200 and 40 cases per 100 000 person-years, respectively).⁸ These elevations are most often transient and resolve spontaneously even with continued statin use and without dose reduction. Although there is a dose relationship to LFT elevations, data from clinical trials indicate that increases are unrelated to the degree of low-density lipoprotein cholesterol (LDL-C) lowering with a statin.⁹

In a “real-life” evaluation of 23 000 patients treated with statins in a health maintenance organization,^{9,10} 17 of 62 cases of markedly elevated ALT levels were thought to be statin-related, 13 of which were associated with potential drug interactions. Of the other 4 cases, 3 patients had heart disease, diabetes, or both. The remaining case was a 71-year-old woman on the highest marketed dose (80 mg) of atorvastatin. These data confirm that marked sustained elevations in liver enzymes are rare and may be affected by potential drug interactions and comorbidities or use of the highest dose of a statin.

Most important, the expert panel of hepatologists who examined this adverse effect was unable to find a link between changes in LFTs and outright episodes of liver failure. They concluded that isolated elevations of aminotransferase are not linked with acute or chronic liver injury.⁴

Few cases of liver failure have been reported in statin users. According to the FDA AERS database through 1999, 1 case of liver failure was reported per 1 million statin prescriptions; this is the same prevalence as the 1 case of liver failure per million reported in nonstatin-taking populations.⁸ Furthermore, only 1 patient of 51 741 who received a liver transplant between 1990 and 2002 was taking a currently marketed statin.⁴

According to the Liver Expert Panel, “...liver failure may occur very rarely with statin therapy...the risk of liver failure is present with any statin, but the risk is quite remote.”⁴ The Statin Safety Assessment Task Force concludes from the data mentioned that routine monitoring of LFTs in asymptomatic statin users does not appear warranted (**Table 1**).³ The task force recommended obtaining liver transaminase levels in the general evaluation of patients who are being considered for a statin, and continuing periodic measurement of transaminase levels only for medical-legal reasons, taking into consideration that the FDA-approved package labeling calls for monitoring of LFTs.⁴

A more sensible approach to detecting hepatotoxicity in statin recipients, in the view of the task force, is to carry out ongoing surveillance of significant symptoms of hepatic dysfunction, including jaundice, malaise, fatigue, and lethargy, and when symptoms are found, to obtain a fractionated bilirubin level, rather than periodic monitoring of aminotransferase levels.⁴

The Liver Expert Panel further stated that neither chronic liver disease nor compensated cirrhosis should be considered contraindications to statin therapy, but believes that decompensated cirrhosis or acute liver failure should remain a contraindication.⁴

Kidney Toxicity

Proteinuria and hematuria have rarely been described with all of the statins.⁹ The proteinuria is probably not a toxic effect but a physiologic effect that is central to the mechanism of lowering cholesterol.

Despite the mild proteinuria that has been reported most prominently with rosuvastatin but also with all statins, short- and long-term renal function is not compromised with the use of statins. In fact, the

Table 1. Recommendations to Healthcare Professionals Regarding the Liver and Statin Safety

1. During the routine general evaluation of patients, including those receiving statin therapy, it is advisable to obtain liver transaminase levels. If these tests are found to be abnormal, further investigation should be performed to determine the etiology of the abnormal test results.
2. Until there is a change in the FDA-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.
3. The clinician should be alert to patient reports of jaundice, malaise, fatigue, lethargy, and related symptoms in patients taking statin therapy as a signal of potential hepatotoxicity. Evidence for hepatotoxicity includes jaundice, hepatomegaly, increased indirect bilirubin level, and elevated prothrombin time (rather than simple elevations in liver transaminase levels).
4. The preferred biochemical test to ascertain significant liver injury is fractionated bilirubin, which, in the absence of biliary obstruction, is a more accurate prognosticator of liver injury than isolated aminotransferase levels.
5. Should the clinician identify objective evidence of significant liver injury in a patient receiving a statin, the statin should be discontinued. The etiology should be sought and, if indicated, the patient referred to a gastroenterologist or hepatologist.
6. If an isolated asymptomatic transaminase level is found to be elevated 1-3 times the ULN, there is no need to discontinue the statin.
7. If an isolated asymptomatic transaminase level is found to exceed 3 times the ULN during a routine evaluation of a patient administering a statin, the test should be repeated and, if still elevated, other etiologies should be ruled out. Consideration should be given to continuing the statin, reducing its dose, or discontinuing it based on clinical judgment.
8. According to the Expert Liver Panel, patients with compensated cirrhosis, chronic liver disease, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis may safely receive statin therapy.

FDA indicates US Food and Drug Administration; ULN, upper limit of normal. Source: Adapted with permission from Reference 3.

evidence indicates that statin therapy may be associated with an improvement in renal function. In a meta-analysis of 13 clinical trials in which the effect of lipid-modifying drugs on renal function was examined, these therapies preserved glomerular filtration rate and reduced the level of proteinuria in patients with existing renal disease.^{9,11}

Cases of renal failure occur with the same frequency in patients taking and not taking statins. In placebo-controlled, randomized trials with pravastatin, more cases of renal

failure and other renal diseases occurred in patients randomized to placebo.¹² Therefore, statin therapy does not appear to cause acute renal failure or insufficiency in the absence of rhabdomyolysis.⁶ The Statin Safety Assessment Task Force concludes that during the management of patients with statin therapy, it is not necessary to routinely carry out serum creatinine and proteinuria monitoring for the purpose of identifying an adverse effect, although an assessment of renal function is advisable before initiating statin therapy (Table 2).³

Nevertheless, rosuvastatin has come under increased public scrutiny for its potential relationship to kidney failure and proteinuria, probably as a result of its development after cerivastatin was withdrawn. The task force found that these concerns are unwarranted. In a retrospective comparison of rosuvastatin with atorvastatin, simvastatin, pravastatin, and placebo, using the rosuvastatin 12 500-patient NDA database, there was no significant difference in the incidence of combined proteinuria and hematuria (0%-0.3%) between the statins or between doses of the statins, and urine dipstick protein results comparing baseline with values at the final visit were not different between any of the statins and placebo.^{9,13} Further, no decline in renal function was observed in patients with or without diabetes who were treated with rosuvastatin for up to 3.8 years.

In a 2005 Public Health Advisory,¹⁴ the FDA stated that there is no evidence that renal injury/failure could be linked causally to rosuvastatin or any other statin. The conclusion with respect to rosuvastatin was reached on a premarketing experience that included more than 12 000 patients and “a substantial number of study participants with mild-to-moderate renal impairment.”⁹

Neurologic Toxicity

Case reports and a few small cohort studies suggest that statins may have neurologic adverse effects on the central nervous system (CNS).^{9,15-17} Findings from larger clinical trials do not support a cause for concern, and in fact, some even point to a possible favorable effect of statins on CNS disorders such as Alzheimer's disease and dementia.^{18,19}

In 2 large clinical trials of statins—the Heart Protection Study (HPS)^{8,20,21} and the Prospective Study of the Elderly at Risk (PROSPER)^{8,22}—in which more than 26 000 patients were randomized to either placebo or simvastatin (HPS) or pravastatin (PROSPER), there was no decline in cognitive function among the patients allocated to a statin compared with those assigned placebo.

In studies of statin use and incident dementia and/or Alzheimer's disease, statins have had either a neutral or beneficial effect on these end points.²³ Other studies suggest potential improvement in various cognitive scales in patients with Alzheimer's disease who were taking statins.^{18,19,23}

Statin use has had a pronounced favorable effect on the risk of thrombotic stroke in clinical trials. In a meta-analysis of 58 clinical trials, the relative reduction in nonhemorrhagic stroke risk with statin use was as great as 17% compared with placebo.²⁴

Statin use and peripheral nervous system adverse events has also been examined. Literature reviews indicate that any such risk of peripheral neuropathy with statin use and idiopathic peripheral neuropathy is very small.⁷ In an examination of an electronic pharmacy claims database that included 17 219 persons who had received at least 1 prescription for lipid-lowering drugs, no significant association between idiopathic peripheral neuropathy and statin use could be identified.²⁵

Routine neurologic monitoring of patients administered statin therapy for changes indicative of peripheral neuropathy or impaired cognition is not recommended.⁷ However, if the patient experiences either of these problems while receiving statin therapy, it is appropriate to first look for other etiologies, and if none are found, to withdraw the statin for 1 to 6 months. If improvement is not seen, statin therapy should be restarted based on a risk-benefit analysis (Table 3).³

Muscle Toxicity

The effect of statins on creatine kinase (CK) levels and muscle pain, weakness, or cramps and their association with rhabdomyolysis have received the most attention of the potential statin toxicities. In

clinical trials, rates of muscle complaints are similar in statin and placebo recipients.^{9,26} The rates observed in clinical trials should be viewed with caution, however, given that clinical trials include patients who have a low risk of statin-induced muscle injury.

The Muscle Expert Panel⁵ concluded that myopathy and rhabdomyolysis are likely a class effect with the statins. The potential to cause adverse muscle experiences, however, probably differs with the individual statins and depends on the blood level achieved. In the case of cerivastatin monotherapy, more deaths due to rhabdomyolysis occurred at the highest marketed dose, 0.8 mg, than with the lower doses.¹ Gemfibrozil coadministration, which increases cerivastatin blood levels, was a factor in many cerivastatin-related deaths.

The relative muscle toxicity between therapies is unknown because comparisons between statins (or other lipid-lowering therapies) are absent, wrote the Muscle Expert Panel, which also found an evaluation of the data with respect to muscle toxicity to be difficult because no standard definitions of myopathy or rhabdomyolysis exist.⁵

Table 2. Recommendations to Healthcare Professionals Regarding the Kidney and Statin Safety

1. During the management of patients with statin therapy, it is not necessary to routinely monitor serum creatinine and proteinuria levels for the purpose of identifying an adverse effect, although an assessment of renal function is advisable before initiating statin therapy.
2. If serum creatinine becomes elevated in a patient without rhabdomyolysis while receiving statin therapy, there is generally no need to withdraw the statin, but in some cases, according to prescribing information, an adjustment in the statin dose may be required.
3. If unexpected proteinuria develops in a patient receiving a statin, there is no need to withdraw statin therapy, or to alter the dose of the statin. An investigation into the cause of the proteinuria is warranted, as is consideration of a change in the statin dose as guided by the prescribing information for each statin.
4. Chronic kidney disease does not preclude the use of a statin. However, the dose of some statins should be adjusted in cases of moderate or severe renal insufficiency (see Kasiske et al⁶ or prescribing information for each statin).

Source: Adapted with permission from Reference 3.

Table 3. Recommendations for Healthcare Professionals Regarding Neurologic Disorders and Statin Therapy

1. Routine neurologic monitoring of patients administered statin therapy for changes indicative of peripheral neuropathy or impaired cognition is not recommended.
2. Patients experiencing symptoms consistent with peripheral neuropathy while receiving a statin should be evaluated to rule out secondary causes (ie, diabetes, renal insufficiency, alcohol abuse, cancer, hypothyroidism, acquired immunodeficiency syndrome, Lyme disease, or heavy metal intoxication).
3. If another etiology of the neurologic symptoms is not identified, it is appropriate to withdraw statin therapy for a period of 3 to 6 months to establish whether an apparent association with statin therapy exists.
4. If the patient's neurologic symptoms improve after statin therapy is discontinued, a presumptive diagnosis of statin-induced peripheral neuropathy might be made. However, because of the proven benefit of statin therapy, reinitiation of statin therapy should be considered.
5. If the patient's neurologic symptoms do not improve after statin therapy has been withdrawn for the specified period, statin therapy should be restarted based on a risk–benefit analysis.
6. If the patient experiences impaired cognition while receiving statin therapy, it is appropriate to follow a similar course of evaluation as suggested above for peripheral neuropathy—ie, first rule out other etiologies, and if none are found, then withdraw the statin for 1 to 3 months. If improvement is not seen, statin therapy should be restarted based on a risk–benefit analysis.

Source: Adapted with permission from Reference 3.

In a review of the statin NDAs, additional studies were required for rosuvastatin after an increase in awareness of safety issues generated by the experience with cerivastatin and rhabdomyolysis. With the additional studies, 12 569 patients were included in the revised NDA for rosuvastatin in 2003.²⁷ About 4000 patients in this database were treated with 40 mg of rosuvastatin, the highest dose that was eventually approved. This number was greater than the number of patients treated with any dose of any other statin. Also, recipients of the 40-mg dose were treated for at least 1 year, and 1100 patients received it for 2 years, representing a high level of exposure compared with the patients in the NDA databases for the other statins. The rosuvastatin NDA database included many high-risk patients with significant comorbidities to better reflect the actual users of the drug. The review for rosuvastatin was therefore more critical than it was for the other statins in light of the cerivastatin experience.

From the rosuvastatin NDA database, the incidence of myopathy (defined as CK >10 times the ULN, with muscle symptoms) ranged from 0.1% at 10 mg to 0.4% at 40 mg, a lower incidence than that observed with the other statins. With an additional 6 months of postmarketing data, which brought the total patient population to 13 395 for analysis, only 1 case of rhabdomyolysis was documented with rosuvastatin, for an overall incidence of 0.01%, which is consistent with the rate observed in the overall statin NDA and AERS databases.^{27,28}

In pooling the databases from all of the statin NDAs, increases in CK concentrations were not found to be related to the degree of LDL-C lowering but rather to the dose (or serum concentration) of the statin.^{8,29-41} The threshold serum concentration level for increases in CK elevation is higher than the currently approved doses for the statins still being marketed, although other factors, such as drug–drug interactions, may elevate statin concentrations to myotoxic levels.

An analysis of 468 statin users from a managed care organization who were identified as having myopathy provides some insight into the true risk of muscle symptoms in a real-world setting.⁴² Of these 468 cases, only 61 had received a statin before their diagnosis and only 41 had a confirmed myopathy on the basis of CK levels. The authors estimated that the risk of myopathy with statins is 0.12% when used without a fibrate and 0.22% when used in combination with a fibrate.

The choice of fibrate will affect blood levels of statins, and thus the risk of muscle symptoms. Gemfibrozil interferes with statin metabolism through inhibition of glucuronidation, and does so to a greater degree with cerivastatin than other statins (except fluvastatin, which is not affected by concurrent gemfibrozil).⁴³ In contrast, fenofibrate appears to affect statin concentrations only minimally. It does, however, cause myotoxicity and rhabdomyolysis when used alone and has an additive effect on the incidence of muscle injury when combined with a statin. A key to reducing muscle toxicity when a statin and fibrate are combined is being alert to risk factors for muscle prob-

lems and counseling patients to report any related muscle symptoms.

The Muscle Expert Panel made several recommendations to healthcare professionals (Table 4).³ It did not advocate routine measuring or monitoring of CK levels in asymptomatic statin recipients, but did recommend measuring CK levels in symptomatic patients to guide decisions about continuing statin therapy. In the panel's view, severe persistent muscle symptoms warrant discontinuation of the statin regardless of CK level. When the patient becomes asymptomatic after stopping their statin because of muscle symptoms, the same or another statin can be restarted at the same or a lower dose; with recurrence of symptoms to multiple statins, use of a lipid-lowering agent from another class is advised. An additional measure to reduce risk is appropriate patient education regarding the signs and symptoms of potential adverse experiences.⁹

Statin Safety From an Administrative Claims Database

Using administrative claims data, Cziraky et al⁴⁴ evaluated the rates of hospitalization for myopathy, renal events, and hepatic events among 473 343 users of statins and other lipid-modifying drugs, representing 490 988 person-years of monotherapy and 11 624 person-years of combination therapy for dyslipidemia. The data presented include all reports of potential adverse events. Because these reports had not been validated with chart review, the data may represent an overestimate of the true incidence of adverse events associated with statin use. However, the relative rates of the occurrence of adverse events may allow a valid comparison between statins.

The study authors found a similar rate of muscle abnormalities requiring hospitalization among the users of the currently marketed statins, whereas cerivastatin was associated with a nearly 7-fold increase in myopathy compared with atorvastatin. Furthermore, being treated with a lipid-modifying drug concomitantly with an agent metabolized via the cytochrome P450 3A4 enzyme was associated with a 6-fold increased risk of myopathy. Another risk fac-

tor for myopathy was the presence of comorbidity, such as hypertension or diabetes.

These data are congruent with findings from a similarly designed study by Graham et al⁴⁵ of 252 460 patients treated in a managed care organization with lipid-lowering

Table 4. Recommendations to Healthcare Professionals Regarding the Muscle and Statin Safety

1. Whenever muscle symptoms or an increased CK level is encountered in a patient receiving statin therapy, health professionals should attempt to rule out other etiologies, because these are most likely to explain the findings. Other common etiologies include increased physical activity, trauma, falls, accidents, seizure, shaking chills, hypothyroidism, infections, carbon monoxide poisoning, polymyositis, dermatomyositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, or PCP).
2. Obtaining a pretreatment, baseline CK level may be considered in patients who are at high risk of experiencing a muscle toxicity (eg, in older individuals or when combining a statin with an agent known to increase myotoxicity), but is not routinely necessary in other patients.
3. It is not necessary to measure CK levels in asymptomatic patients during the course of statin therapy, because marked, clinically important CK elevations are rare and are usually related to physical exertion or other causes.
4. Patients receiving statin therapy should be counseled about the increased risk of muscle complaints, particularly if the initiation of vigorous, sustained endurance exercise or a surgical operation is being contemplated, and advised to report such muscle symptoms to a health professional.
5. CK measurements should be obtained in symptomatic patients to help gauge the severity of muscle damage and facilitate a decision of whether to continue therapy or alter doses.
6. In patients who develop intolerable muscle symptoms with and without a CK elevation and in whom other etiologies have been ruled out, the statin should be discontinued. Once the patient is asymptomatic, the same or different statin at the same or lower dose can be restarted to test the reproducibility of symptoms. Recurrence of symptoms with multiple statins and doses requires initiation of other lipid-altering therapy.
7. In patients who develop tolerable muscle complaints or are asymptomatic with a CK <10 times the ULN, statin therapy may be continued at the same or reduced doses and symptoms used as the clinical guide to stop or continue therapy.
8. In patients who develop tolerable muscle complaints with a CK >10 times the ULN or who experience rhabdomyolysis (ie, develop a CK >10 000 IU/L with or without muscle complaints or have a CK >10 times the ULN with a change in renal function or require IV hydration therapy), statin therapy should be stopped. IV hydration therapy in a hospital setting should be instituted if indicated for patients experiencing rhabdomyolysis. Once the patient has recovered, the risk-benefit of statin therapy should be carefully reconsidered.

CK indicates creatine kinase; PCP, phencyclidine hydrochloride; ULN, upper limit of normal; IV, intravenous.

Source: Adapted with permission from Reference 3.

agents. These authors found that the rate of hospitalized rhabdomyolysis was 0.44 per 10 000 person-years for monotherapy with atorvastatin, pravastatin, or simvastatin, and about 10-fold higher when the statin was cerivastatin or when the statin was used in combination with a fibrate.

Cziraky et al concluded, “Our study corroborates previous findings that statin monotherapy as currently prescribed is generally well tolerated and safe.”⁴⁴

Safety Appraisal From the AERS Perspective

An examination of the AERS database was conducted to identify events that may influence the reporting of serious statin-associated side effects, particularly total and fatal rhabdomyolysis.⁴⁶ The data show a pronounced increase in reporting events for rhabdomyolysis and renal failure for all statins after the withdrawal of cerivastatin. The adverse event reporting rate for rosuvastatin was affected by 3 biases: the new drug reporting effect (the so-called Weber effect,⁴⁷ which describes an increased reporting rate of adverse events for any drug soon after it is released to the market), the withdrawal of cerivastatin from the market, and adverse publicity regarding the side effect profile of rosuvastatin. When taking these differential factors into account, rosuvastatin’s proportional reporting pattern did not differ from the other statins still on the market. Initial reporting rates for total and fatal rhabdomyolysis for rosuvastatin were consistent with the preapproval safety database for rosuvastatin and the results observed with the other available statins in the period after removal of cerivastatin from the market.

Conclusion

The NDAs, AERS reports, and clinical trials using “real-world” analysis based on managed care organization data for all approved statins demonstrate a very favorable benefit–risk relation with respect to liver, muscle, and renal issues.²⁷ With all of the statins, a threshold level of dose exists at which the risks exceed the benefits.

This latter point takes on new importance as LDL-C targets go lower, requiring higher doses of statin monotherapy and greater use

of combinations, thereby increasing the risk of adverse events. Nevertheless, the statins have a proven track record with regard to preventing death and major cardiovascular events, and, as a whole, have a good safety profile as demonstrated by extensive patient-years of treatment.

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