

THE AUTHORS REPLY: With respect to the comments of Chocair and Duley: although azathioprine has not been approved for the treatment of lupus nephritis in the United States, the drug was administered in accordance with the package insert, which recommends dose adjustment according to body weight.¹ Contrary to their assertion, TPMT testing was not omitted. Although in our study as in other studies,² such testing was not mandated by the protocol, it was allowed according to local clinical practice, and patients with known TPMT deficiency were excluded from the study. TPMT testing might confer protection against toxicity but would not directly affect the efficacy of azathioprine. In our study, although some patients withdrew because of neutropenia, such patients were not considered to have had treatment failure according to the protocol. Rather, data for these patients were censored at the time of withdrawal and did not necessarily contribute to the primary end point.

The FDA recommends but does not require TPMT testing for the administration of azathioprine.³ The label clearly states that TPMT testing cannot substitute for monitoring of the complete blood count, which was performed in our study.¹ We believe that a convincing case for routine TPMT monitoring does not yet exist in lupus nephritis, and it remains unusual in rheumatologic practice to guide the administration of azathioprine by measuring metabolites. Not all studies, including those involving patients undergoing organ transplantation, have shown a correlation between measured metabolites and outcomes of immunosuppression.⁴

With respect to our reporting of deaths in the azathioprine group: the outcomes of an intention-to-treat analysis must be reported in full, regardless of whether the investigator believes an adverse event was associated with the drug

being evaluated. Death was also an element of the prespecified definition of treatment failure, which is not unusual in a survival analysis.

In response to the comments of Arnaud et al. regarding the lack of pharmacokinetic monitoring in our study: we do not agree that this represents a major limitation. Mycophenolate mofetil was administered in accordance with the label for patients undergoing transplantation, and pharmacokinetic testing is currently being performed on samples obtained during the study. There is some evidence to support routine therapeutic drug monitoring for mycophenolate mofetil in patients undergoing transplantation, but no definitive guidance yet exists, and the benefit remains to be proved in patients with lupus nephritis.

Mary Anne Dooley, M.D., M.P.H.

University of North Carolina
Chapel Hill, NC

David Jayne, M.D.

Addenbrooke's Hospital
Cambridge, United Kingdom

Neil Solomons, M.D.

Vifor Pharma
Victoria, BC, Canada
neil.solomons@viforpharma.com

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

1. Imuran (azathioprine). San Diego, CA: Prometheus Laboratories, May 2011 (package insert) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016324s034s035lbl.pdf).

2. Houssiau FA, D'Cruz D, Sangle S, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Ann Rheum Dis* 2010;69:2083-9.

3. Pharmacogenomics Knowledge Base. FDA label — azathioprine, TPMT (<http://www.pharmgkb.org/drug/PA448515#tabview=tab0&subtab=32>).

4. Jun JB, Cho DY, Kang C, Bae SC. Thiopurine S-methyltransferase polymorphisms and the relationship between the mutant alleles and the adverse effects in systemic lupus erythematosus patients taking azathioprine. *Clin Exp Rheumatol* 2005;23:873-6.

Systemic Lupus Erythematosus

TO THE EDITOR: In the Mechanisms of Disease article on systemic lupus erythematosus (SLE), Tsokos (Dec. 1 issue)¹ notes that a lack of C1q leads to deficient clearance of waste material. I would like to add the role of C1q in the regulation of interferon- α production in response to immune complexes. Recently, Santer and colleagues

found that interferon- α production of purified plasmacytoid dendritic cells increased after the addition of C1q to SLE immune complexes.² In contrast, in the presence of CD14+ monocytes, almost the whole immune complex adhered to monocytes rather than to plasmacytoid dendritic cells *in vitro*.² C1q inhibited interferon- α produc-

tion induced by immune complexes indirectly through a monocyte-dependent mechanism. Exploration of the linkage between C1q and interferon- α production may be important when developing new therapeutic strategies to suppress the activated plasmacytoid dendritic cells in patients with SLE.

Eun Chun Han, M.D.

Korea Advanced Institute of Science and Technology
Daejeon, South Korea
f1849@kaist.ac.kr

No potential conflict of interest relevant to this letter was reported.

1. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med* 2011;365:2110-21.
2. Santer DM, Hall BE, George TC, et al. C1q deficiency leads to the defective suppression of IFN- α in response to nucleoprotein containing immune complexes. *J Immunol* 2010;185:4738-49.

TO THE EDITOR: In his recent review, Tsokos comprehensively describes the mechanisms underlying SLE, including T-cell signaling aberrations. Defective signaling along the p21 ras–MAP kinase pathway plays a central role in SLE development and should be included among these mechanisms. This notion is supported by a number of findings. First, lymphocytes in patients with SLE are characterized by down-regulated early signaling of the p21 ras–MAP kinase pathway, resulting in unsuppressed enhanced constitutive activity of its downstream elements.¹ Second, T cells and B cells in SLE-prone NZB×NZW mice have defective ras signaling, which disappears on reversal of their disease by immune modulation.² Third, the activity of two downstream key elements of the p21 ras pathway — namely, ERK and JNK — correlates with disease activity in patients with SLE.³ It should also be pointed out that various aberrations along this pathway have been detected in various autoimmune diseases, including type 1 diabetes mellitus, celiac disease, and chronic idiopathic urticaria.⁴ Thus, it is conceivable that signaling defects along this key pathway constitute a common denominator of several autoimmune diseases.

Micha Rapoport, M.D.

Olga Bloch, Ph.D.

Assaf Harofeh Medical Center
Zerifin, Israel
mrapoport@asaf.health.gov.il

No potential conflict of interest relevant to this letter was reported.

1. Rapoport MJ, Bloch O, Amit-Vasina M, Yona E, Molad Y. Constitutive abnormal expression of RasGRP-1 isoforms and low expression of PARP-1 in patients with systemic lupus erythematosus. *Lupus* 2011;20:1501-9.
2. Rapoport MJ, Sharabi A, Aharoni D, et al. Amelioration of

SLE-like manifestations in (NZB×NZW)F1 mice following treatment with a peptide based on the complementarity determining region 1 of an antibody is associated with a down-regulation of apoptosis and of the pro-apoptotic factor JNK kinase. *Clin Immunol* 2005;117:262-70.

3. Molad Y, Amit-Vasina M, Bloch O, Yona E, Rapoport MJ. Increased ERK and JNK activities correlate with disease activity in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2010;69:175-80.

4. Rapoport MJ, Bloch O, Amit-Vasina M. “Something is wrong in the Ras kingdom” — evidence for the involvement of p21Ras/MAP kinase in autoimmune diseases. *Curr Rheumatol Rev* 2011;7:301-5.

THE AUTHOR REPLIES: It is true that many important contributions could not be included in the synoptic review article. I should have asked for the understanding of hundreds of colleagues whose work was not mentioned explicitly.

Indeed, C1q modulates several aspects of the immune response, and besides the article by Sander et al. cited by Han, earlier articles had identified C1q as being important in the regulation of dendritic-cell function and the pathogenesis of SLE¹ and specifically as a suppressor of interferon- α production.²

With regard to the letter by Rapoport and Bloch: I would like to note that the laboratory of Richardson³ detected abnormalities in the ras–MAP kinase and linked it to DNA hypomethylation in T cells, whereas the laboratory of Datta⁴ linked ERK activity to increased CD40 ligand expression in T cells.

A large number of articles such as those mentioned by the correspondents and others were not mentioned in the review article but have made important contributions to our understanding of SLE.

George C. Tsokos, M.D.

Harvard Medical School
Boston, MA
gtsokos@bidmc.harvard.edu

Since publication of his article, the author reports no further potential conflict of interest.

1. Ghebrehiwet B, Peerschke EI. Role of C1q and C1q receptors in the pathogenesis of systemic lupus erythematosus. *Curr Dir Autoimmun* 2004;7:87-97.
2. Lood C, Gullstrand B, Truedsson L, et al. C1q inhibits immune complex-induced interferon-alpha production in plasmacytoid dendritic cells: a novel link between C1q deficiency and systemic lupus erythematosus pathogenesis. *Arthritis Rheum* 2009;60:3081-90.
3. Deng C, Kaplan MJ, Yang J, et al. Decreased Ras-mitogen-activated protein kinase signaling may cause DNA hypomethylation in T lymphocytes from lupus patients. *Arthritis Rheum* 2001;44:397-407.
4. Yi Y, McNerney M, Datta SK. Regulatory defects in Cbl and mitogen-activated protein kinase (extracellular signal-related kinase) pathways cause persistent hyperexpression of CD40 ligand in human lupus T cells. *J Immunol* 2000;165:6627-34.