SERUM LEVELS OF β2 MICROGLOBULIN AND INTERLEUKIN-6 TO DIFFERENTIATE MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

To the Editor:

We would like to comment on the recent letter from Greco et al.[1] They mistakenly claim that we[2-4] presented serum levels of β2 microglobulin (β2M) and of interleukin-6 (IL-6) as clinically useful parameters to discriminate individuals with monoclonal gammopathy of undetermined significance (MGUS) from those with early multiple myeloma (MM). About β2M, we clearly stated that (1) "it was impossible to separate normal individuals, patients with benign monoclonal gammopathy and patients with low mass MM" (ie, using β2M)[2]; (2) "serum β2M cannot clearly distinguish MGUS from early MM in an individual patient"[3]; and (3) "serum β2M cannot be used as a discriminant test to differentiate the two conditions" (ie, MGUS from early MM).[5] We made no specific comments about IL-6,[4] but clearly noted that both β2M and IL-6 were related to disease severity and had strong prognostic value in patients with overt MM.[4,5] These data are confirmed by the large studies from the Medical Research Council (UK) and the Southwest Oncology Group (United States) for β2M, and by Ludwig et al[6] and Reibnegger et al[7] for IL-6. Finally, the prognostic value of IL-6 was recently confirmed by discovery of the strong prognostic value of C-reactive protein (CRP), an IL-6–dependent acute phase protein, in patients with overt MM.[8,9] Like β2M and IL-6, CRP does not discriminate between benign monoclonal gammopathy and early MM.[9] It is clear for all experts that the problem of differentiating MGUS from early MM is difficult. Measurement of the plasma cell labeling index[10] and evaluation of plasma cell-induced bone changes[11] or of plasma cell phenotype (CD56 expression)[12] may help, but no single technique really differentiates benign from malignant plasma cell proliferation (see Kyle[13] for a recent review).

Another point in the letter of Greco et al[1] is that 81.5% of their patients with MGUS had neoplastic disease. It is now well documented that several epithelial tumors can produce or use IL-6 as a tumor growth factor.[14] The best example is renal cell carcinoma for which IL-6 is an autocrine growth factor, CRP a strong prognostic factor, and anti–IL-6 therapy a currently investigated treatment.[15-17] More importantly, the associated MGUS status can be greatly improved by nephrectomy.[18] Thus, their MGUS population is not the usual one that could account for its increased IL-6 and CRP serum levels, similar to the increased β2M serum levels which commonly occur in patients with cancer.

RÉGIS BATAILLE
BERNARD KLEIN
Laboratoire d'Oncogénèse immuno-hématologique
Institut de Biologie
Nantes, France

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Serum levels of beta 2 microglobulin and interleukin-6 to differentiate monoclonal gammopathy of undetermined significance [letter; comment]

R Bataille and B Klein

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