Serum Amyloid A Protein Monitoring for Early Prediction of Kidney Allograft Rejection

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Dear Sir,

Early recognition of allograft rejection remains a major problem in clinical renal transplantation. Monitoring of inflammatory responses in the postgrafting period [1-3] provides valuable information on the rejection process. Although some 30 plasma proteins increase in concentration during inflammation, only two of them are suitable markers of acute-phase response: serum amyloid A protein (SAA) and C-reactive protein (CRP) [4-6]. Both are quick to respond and both increase substantially in severe inflammation, SAA being the more sensitive parameter [4, 6-8]. Routine assays for SAA were not available until recently, mainly due to the difficulty in producing useful antisera against human SAA. A new micro-ELISA test [9] with commercially available sequence-specific antibody obtained from Ti-noLab Co., Zagreb, Croatia [10] now enables one to measure SAA quickly and routinely. We used this micro-ELISA assay for everyday monitoring of SAA in 17 patients (4 females and 13 males) with kidney allografts in order to facilitate an early diagnosis of rejection. Altogether 43 SAA peaks were observed and 19 of them were caused by allograft rejections. The results are presented in figure 1. During the first 3 of 4 days, the initial SAA peaks (caused by surgical trauma) 400-1 a

Fig. 1. Serum amyloid A protein (■) and C-reactive protein (○) values in three patients, a Patient with no signs of kidney allograft rejection, b Patient with kidney allograft rejection in postsurgical period (during first 4 days after surgery), c Patient with kidney allograft rejection in a later period (5th day after surgery or later). Arrow (↓) and RD denote clinically diagnosed rejection and the start of anti-rejection therapy in the form of methylprednisolone. The clinical diagnosis of rejection was based on the rise in serum creatinine, diminution of urine output, urine cytology, rise in CRP and confirmed by needle biopsy.

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reached a mean value of 306 mg/l (range 222-412). Later they decreased close to the baseline (9 + 5 mg/l) between days 7 and 9, in patients who showed no signs of rejection (fig. 1a). When

allograft rejection occurred in the postsurgical period (first 4 days; fig. 1b), SAA levels rose to a mean value of 705 mg/l (range 478-1,000) and decreased to their baseline value 7 days after initiation of antirejection therapy. The statistical significance was very high, $p < 0.0001$. In all 8 rejection episodes in this period, SAA peaks were higher than 400 mg/l, so we chose this level as a reference limit for this period: it gave an extremely high sensitivity and predictive value for rejection (in our cases 100%). SAA peaks caused by allograft rejection at a later time were also markedly higher (mean value of 460 mg/l, range 232-800, fig. 1c) than those caused by infections or other complications (gastrointestinal hemorrhage, acute pancreatitis, wound hematoma or fever of unknown origin with a mean value of 141 mg/l, range 42-400, $p < 0.0001$). In all 11 rejection episodes in this period, SAA peaks were higher than 200 mg/l, so we chose this level as a reference limit for this period: it gave an extremely high sensitivity (100% in our cases) and reasonable predictive value for rejection (65%). Since all 'false-positive' results were caused by obvious infections or surgical complications, they were false positive only with respect to rejection. One week after successful antirejection therapy was applied, SAA levels were decreased to

baseline level. SAA values in the control group (30 healthy adults) were below 1.2 mg/l, while we observed elevated SAA levels (up to 10 mg/l) in all patients for several months after transplantation, which suggests that mild responses to an allograft occur persistently for several months or even years after successful kidney transplantation (Ogata et al. [3] named this 'latent acute rejection').

In 18 out of 19 rejection episodes (95%), SAA elevation predicted rejection and in only 1 case it was concomitant with clinically diagnosed rejection. On the other hand, CRP predicted rejection in only 12 out of 19 episodes (68%), while in 5 out of 19 episodes (26%) CRP elevations came after clinically diagnosed rejection. SAA usually started to rise sharply 2 days before clinical rejection. There was no rejection episode in which SAA was not strongly elevated while it did not happen in all cases with CRP.

An excellent correlation between kidney allograft rejection and SAA reaction was found in this study (much better than with CRP reaction) so we strongly recommend every-day monitoring of SAA concentrations in patients with kidney allograft as a valuable aid in the early diagnosis and prediction of acute allograft rejection. The new micro-ELISA assay [9] with commercially available sequence-specific antibody will give results within 3.5 h with a cost of only 4 \$ per patient a day and with only 10 min of technician's time.

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