EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Kinetic Characteristics of Biochemical Parameters during Consupren Therapy after Allogenic Transplantation of the Kidney

N. A. Denisova, T. V. Pletneva, V. N. Baikova, and T. T. Berezov

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Changes in biochemical and common clinical parameters of the blood were detected in patients treated with consupren (cyclosporin) as the main immunosuppressant after allogenic transplantation of the kidney. Kinetic model for evaluation of treatment adequacy was based on therapeutic drug monitoring and monitoring of blood biochemistry in recipients of the primary kidney transplant. The k_1, $t_{1/2}$, C_0, clearance (for hemoglobin), conditioned volume of distribution (for cyclosporin) of processes of biochemical parameters (toxicity markers) stabilization within the framework of a single-part kinetic model were determined.

Key Words: *cyclosporin; biochemical parameters; biokinetics*

Cyclosporin (CsA) is now a drug of choice in immunosuppressive therapy after organ transplantation. Its introduction into clinical practice in 1983 improved survival of transplanted kidneys during the first year after the operation by 30-35%. On the other hand, high doses of CsA during the postoperative period cause damage to the liver, kidneys, and other target organs. The kinetic monitoring of diagnostic markers of toxicity and correction of the drug dose help to reduce the incidence of such side effects as nephro- and hepatotoxicity. Since the original drug is expensive, evaluation of the safety and efficiency of CsA-based generic drugs becomes more and more important.

Here we analyzed kinetic characteristics of some biochemical parameters of the blood for quantitative prediction of body functions recovery after allogenic transplantation of the kidney (ATK) followed by treatment with CsA-based generic drug consupren (Ivax), a new drug for the Russian pharmaceutical market. The results of this study can be used for optimizing the doses of consupren when evaluating the treatment adequacy.

Russian University of Peoples' Friendship, Moscow

MATERIALS AND METHODS

Biochemical parameters of the blood and CsA pharmacokinetics were monitored in 26 patients (men and women aged 18-60 years, mean age 40.7±13.3 years). The measurements were carried out 1 day before the operation, every 3 days during the first 2 weeks postoperation, and during weeks 4, 7, 10, 13, 19, and 24 after ATK.

CsA in the whole blood was assayed on a TD_X automated analyzer (Abbott Laboratories S.A.) by the fluorescent polarization immunoanalysis using enzyme immunoassay with monoclonal antibodies.

The concentrations of the urea and creatinine were measured on a Hitachi-917 device. Total blood count was determined on a Cell-Dyn 1700 device (Abbott).

The kinetic parameters of biochemical markers were calculated using a single-compartment model admitting that the studied markers were evenly dis-

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tributed in the compartment (homogeneous system). The velocities (rate constants) of decreases in the content (k_e) of some biochemical markers (creatinine, urea) and velocities of increase in the content (k_a) of other markers (hemoglobin) were thus determined.

Evaluation of the kinetic order of the process showed that the time course of concentrations of some parameters conformed to zero ($dC/dt=kC^o=const$) and first ($dC/dt=kC$) order kinetics.

First-order equations ($y=a\pm bx$) were derived from the kinetic linear plots in the semilogarithmic coordinates with specification of the error in evaluation of coefficients of regression equations *a* and *b* and the standard deviation in evaluation of the range of values of direct regression. In accordance with the coefficient *a* value, the initial concentration of the biochemical marker C_0 ($a=\ln C_0$ at $t=0$) was calculated. The first-order rate constant k_1 was estimated by the coefficient *b* of regression equation (straight line slope angle tangent in the lnC—*t* coordinates). The period of half-transformation (half-recovery of physiologically normal value; $t_{1/2}$) was calculated by the formula: $t_{1/2}=\ln 2/k_1$.

For evaluation of hemoglobin clearance, the volume of distribution was considered equal to the real blood volume (5 liters) of an individual weighing 70 kg [2].

RESULTS

The optimal immunosuppressive effect can be attained if blood concentration of CsA is maintained at 200-300 ng/ml [6]. Hence, during the first 10 days after ATK high doses of the drug were used (Fig. 1, *a*, *b*). Subsequent reduction of CsA dose did not change its optimal therapeutic concentration in the blood. Moreover, despite a decrease in the dose, the dose/concentration ratio became constant on days 12-14 (Fig. 1, *c*), which suggests that CsA was present mainly in the blood and there was no acute intoxication.

The most serious side effect of CsA is its nephrotoxic effect, which acquires special significance in

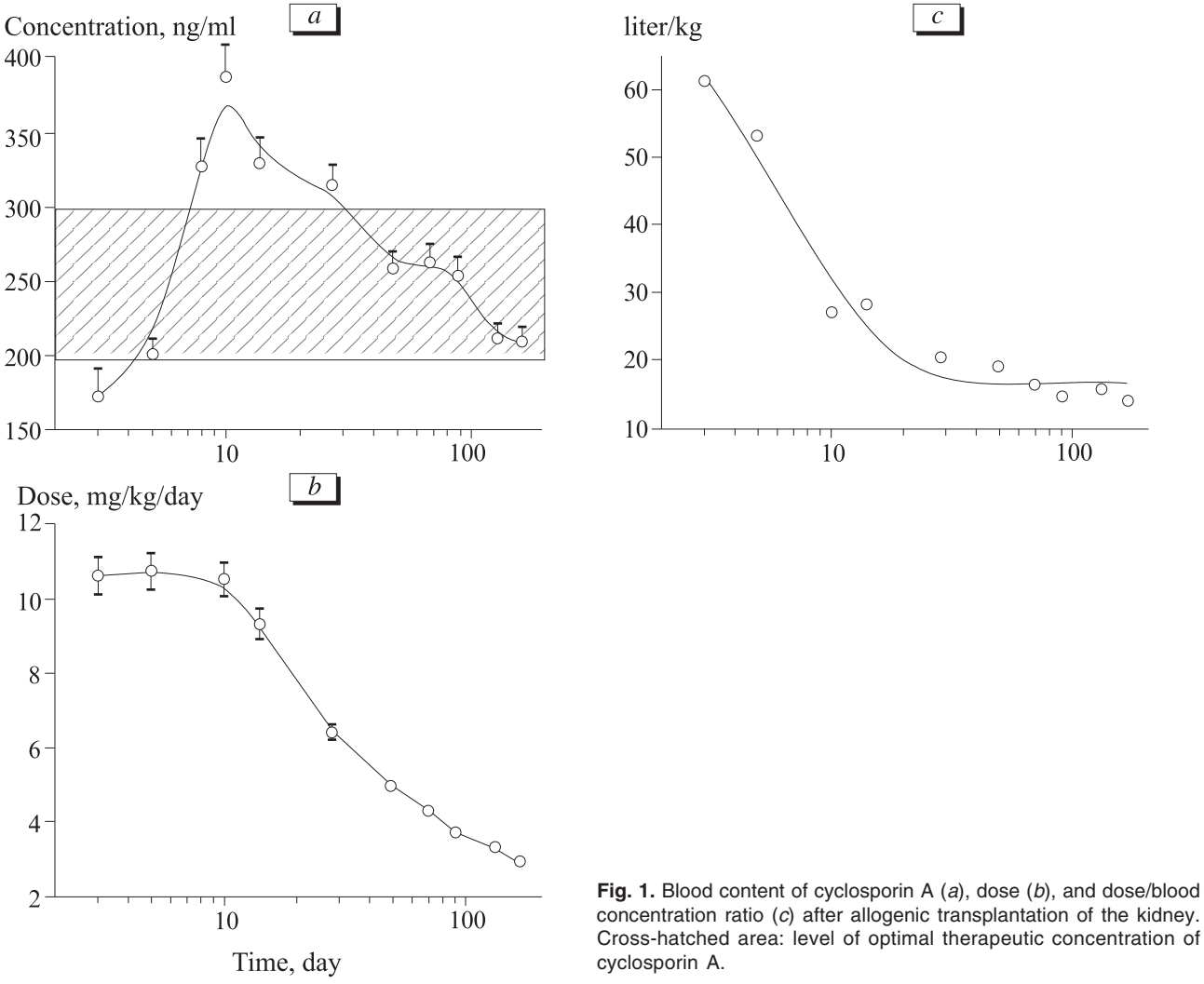

Fig. 1. Blood content of cyclosporin A (*a*), dose (*b*), and dose/blood concentration ratio (*c*) after allogenic transplantation of the kidney. Cross-hatched area: level of optimal therapeutic concentration of cyclosporin A.

ATK [4,5]. Nephrotoxicity of consupren was evaluated by measuring urea and creatinine in the blood [2].

The kinetics of normalization of the blood urea concentration is complex (Fig. 2, *a*, *b*) with pronounced peak corresponding to days 10-12 after ATK. The descending branch of the kinetic curve, originating from the extreme point, corresponded to the first-order equation after week 7 of observation, judging from

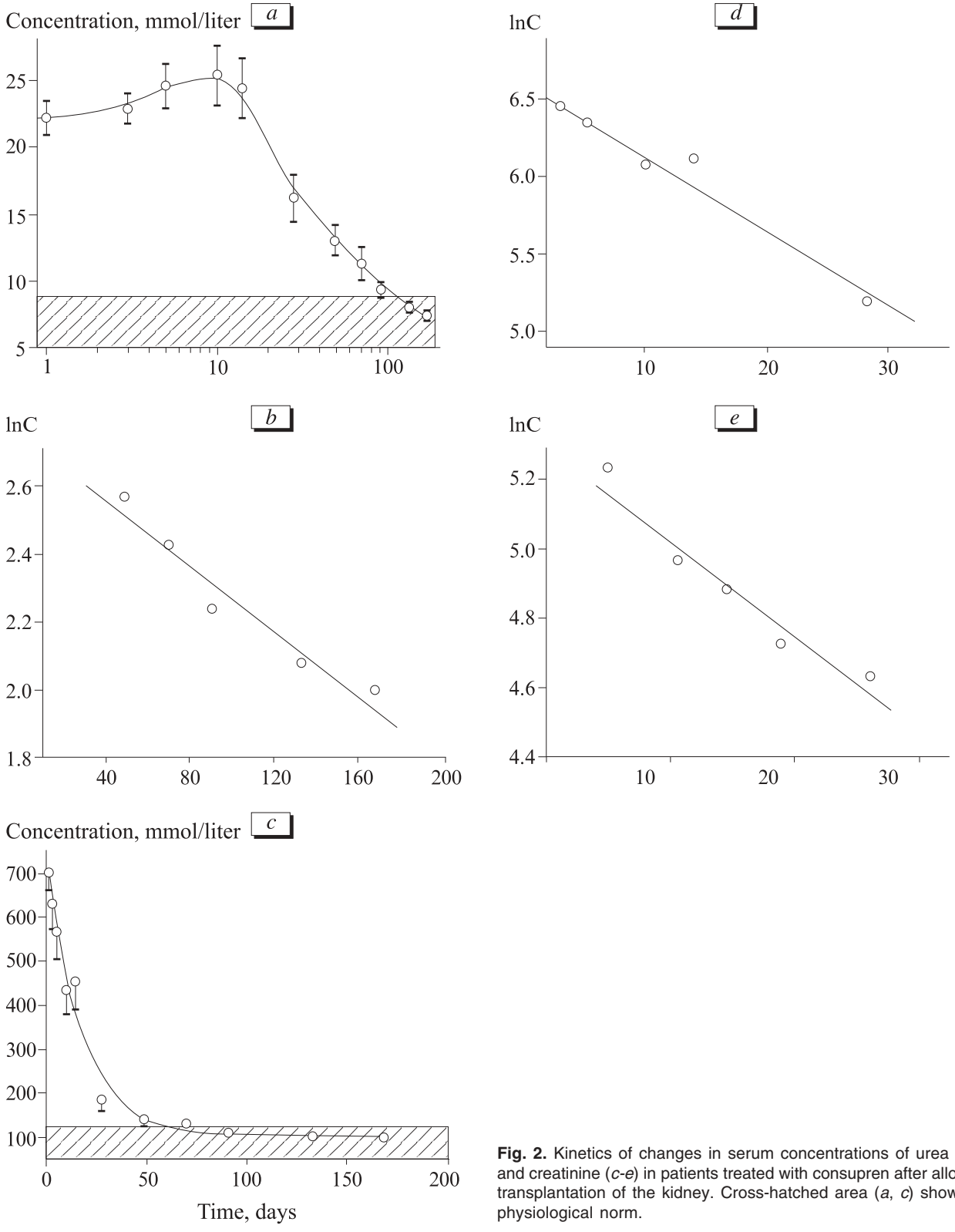

Fig. 2. Kinetics of changes in serum concentrations of urea (*a*, *b*) and creatinine (*c*-*e*) in patients treated with consupren after allogenic transplantation of the kidney. Cross-hatched area (*a*, *c*) shows the physiological norm.

linear plot obtained in semilogarithmic lnC—t coordinates (Fig. 1, *c*).

Hence, urea concentration in the blood is half-restored 3 months after ATK. This parameter stabilized by month 6 after surgery in only 70% patients.

The kinetics of creatinine is quite different (Fig. 2, *c-e*) and is characterized by the presence of two phases. The kinetics of phase 1 (fast) and 2 (slow) conforms to a first-order equation: $y=a+bx$. Results of analysis of kinetic equation of linear plot in semilo-

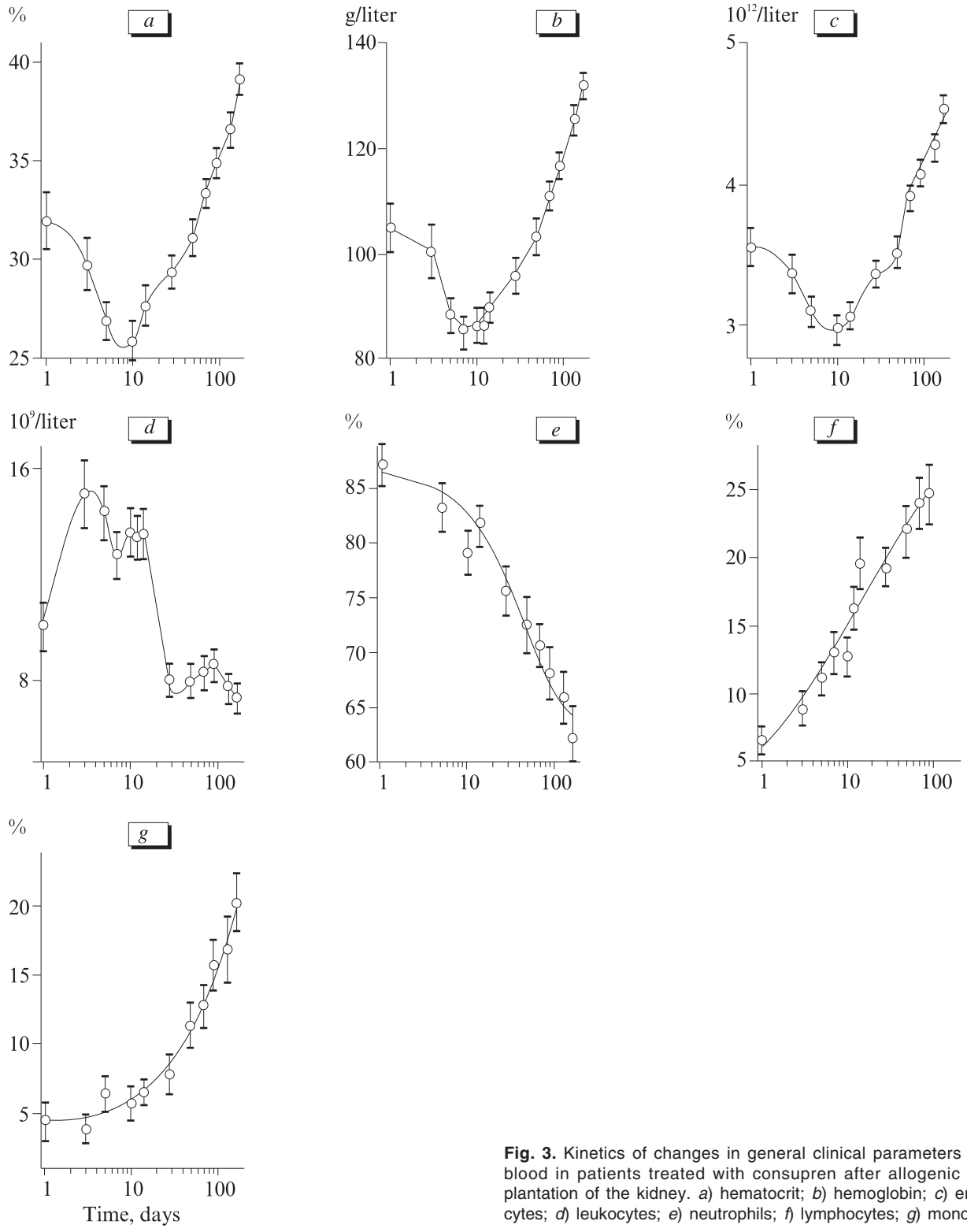

Fig. 3. Kinetics of changes in general clinical parameters of the blood in patients treated with consupren after allogenic transplantation of the kidney. *a*) hematocrit; *b*) hemoglobin; *c*) erythrocytes; *d*) leukocytes; *e*) neutrophils; *f*) lymphocytes; *g*) monocytes.

garithmic coordinates for the fast phase indicate high rate of normalization process: $k_e=(4.83\pm 0.416)\times10^{-2}$ day^{-1}.

Hence, at blood creatinine concentration of 1 μmol/liter the rate of attaining the level corresponding to the physiological norm is about 4.83×10^{-2} μmol/liter/day. The kinetic equation describing the process of stabilization of blood creatinine concentration during the rapid stage, with consideration for C_0=743.6 μmol/liter, is as follows: $C=743.6\times e^{-0.0483t}$.

The mean half-period of creatinine level normalization is 14.4 days:

$$t_{1/2}=0.693/(4.83\times10^{-2}),$$

that is, the stabilization process is to be half-over within about 2 weeks. Indeed, after 6 months blood creatinine content was normal in all patients. However, it is noteworthy that blood creatinine concentration was 66.4±3.46 μmol/liter as soon as after 50 days. This lower value (compared to expected) can be due to triggering phase 2 (slow) in the mechanisms of stabilization.

Hence, in contrast to urea, restoration of normal values of creatinine requires consideration for the kinetics of both stages of this process.

By month 6 after ATK the counts of neutrophils, lymphocytes, and monocytes were completely stabilized in patients treated with consupren; the levels of hemoglobin and erythrocytes were restored in 92.3% patients; leukocyte count reduced to the norm in 77% patients. Evaluation of the kinetics of these parameters indicates their close relationship (Fig. 3), which, first of all, is seen from a drastic modulation of the kinetic curves on days 10-12 postoperation. Despite previous changes, hematocrit, hemoglobin level, counts of erythrocytes, monocytes, and lymphocytes start increasing, while leukocyte and neutrophil counts decrease.

These results indicate that the rate constant of the normal level restoration ("absorption" constant) for hemoglobin is $(2.3\pm0.14)\times10^{-3}$ day^{-1}. Half-period of this process is about 10 months: $t_{1/2}=0.693/(2.3\times10^{-3})=$ 301 days. From this value we can see that the process of restoration of physiological level of hemoglobin will be half-over within less than a year (0.83 year). Our results really indicate that as soon as by month 6 the content of hemoglobin reached the lower threshold normal level in 80% patients.

The kinetic data for some biochemical parameters in patients treated with CsA after ATK, summed up in this paper, can be used by transplantologists, as they help to predict the time of normalization of these parameters and correct the CsA-based drug doses at any stage of the postoperative period.

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