Transpl Int (2000) 13 [Suppl 1]: S147–S149
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RANTES in the postoperative course after liver transplantation

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Abstract RANTES (regulated upon activation, normal T-cell expressed and secreted), an inflammatory cytokine, promotes accumulation and activation of leukocytes. In 67 liver transplantations, systemic concentrations of RANTES were correlated to graft survival and incidence of rejection. RANTES levels either increased to highly elevated levels at day 14 (84 ± 64 ng/ml; group 1; $n = 43$) or remained within the limit of healthy controls (19 ± 11 ng/ml at day 14; group 2; $n = 24$). The 100-day graft function rate was 0.91 in group 1 and 0.63 in group 2 ($P = 0.002$). The risk ratio for rejection during the first 100 days was increased 2.2-fold in group 2 compared to group 1 ($P = 0.02$). High postoperative release of RANTES after liver transplantation, a beneficial factor, may reflect a general systemic immunological activation. It can be concluded that high early systemic RANTES levels may play a role in immunological recognition leading to a tolerance of the liver graft.

Key words RANTES · Liver transplantations · Graft survival · Rejection

Introduction

The chemokine RANTES (regulated upon activation, normal T-cell expressed and secreted), a member of the CC-chemokine family [10], was shown to be essentially involved in different kinds of immunological processes [4, 11]. Controlling the immunological activation directed towards the graft leading to its rejection is still a challenge of modern transplantation medicine. Therefore, the intragraft expression of RANTES in the context of rejection was intensively studied in various systems [5, 8]. In this study the role of the systemic RANTES concentration was determined in the early period after liver transplantation. We evaluated the correlation of the RANTES concentration to rejection risk and graft function.

Patients and methods

In a series of 67 liver transplantations from May 1994 to June 1997 with a graft survival of at least 10 days, the serum concentration of RANTES was determined prior to transplantation and daily for the first 2 weeks posttransplant by an ELISA procedure (BioSource International, Camarillo, Calif., USA). Sixty-three recipients (30 males, 33 females) were included. The age of recipients ranged from 12 to 67 years (median 43 years). Within the study there were 13 retransplantations due to acute graft failure or chronic rejection. The other main reasons for transplantation were biliary cirrhosis, sclerosing cholangitis, posthepatic (B/C) cirrhosis, alcoholic cirrhosis, and acute liver failure. Liver biopsies of these patients were taken on suspicion and the incidence and grading of rejection was recorded. No protocol biopsies were taken. Graft survival and risk of rejection were calculated (Kaplan-Meier, Cox model). Significance was assessed by a Wilcoxon test and by a Pearson test for cross-tables.

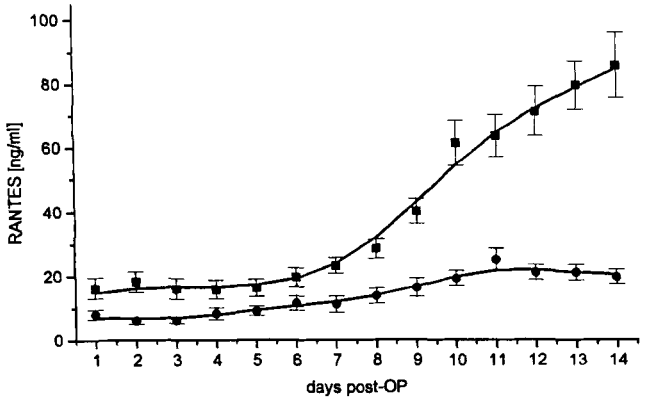

Fig. 1 Serum RANTES concentrations during the first 2 weeks after liver transplantation. Group 1 (■; $n = 43$) reached a maximum concentration above 40 ng/ml (normal value); the concentrations in group 2 (●; $n = 24$) remained below (*filled symbols* indicate $P < 0.05$)

Table 1 Portions of different leukocyte types

Type of cells	Group 1 [%]	Group 2 [%]	P (Wilcoxon)
Neutrophils	83.5 ± 8.5	86.4 ± 5.8	0.2
Lymphocytes	7.5 ± 6.5	5.7 ± 3.0	0.6
Monocytes	5.0 ± 2.0	5.2 ± 2.8	0.9
Eosinophils	2.0 ± 1.4	1.1 ± 0.7	0.001
Basophils	0.6 ± 0.4	0.5 ± 0.4	0.2
Unclassified	1.5 ± 0.8	1.2 ± 0.7	0.06

Results

During the first 2 postoperative weeks, serum RANTES levels in the recipients developed in two different ways which could be separated by the fact of reaching healthy control values or not. In group 1 ($n = 43$), serum RANTES levels started from low concentrations at day 1 (16 ± 19 ng/ml) to highly elevated levels at day 14 (84 ± 64 ng/ml). In group 2 the release remained low (8 ± 7 ng/ml at day 1, 19 ± 11 ng/ml at day 14; $n = 24$). The RANTES levels in healthy controls were 40 ng/ml (Fig. 1).

Depending on this grouping of high and low systemic RANTES levels, the graft function rate was assayed (Fig. 2, *left*). One year after transplantation, graft function probability was 0.86 in group 1 and 0.50 in group 2 ($P = 0.001$). Thus, the risk of graft non-function was elevated 4.5-fold in the lower RANTES group ($P = 0.002$). Six grafts in group 1 and 12 grafts in group II lost function during the observation time. Most grafts were lost due to septic complications (67%) in group 2 whereas, in group 1, two grafts were lost due to initial poor function and three grafts due to infections.

In order to assess the influence of RANTES on the risk of rejection, histologically proved rejection episodes during the first 100 days were compared in the established RANTES groups. The risk of rejection was increased 2.6-fold in group 2 compared to group 1 ($P = 0.006$). Whereas in 80% of the recipients of group 2 signs of rejection were found, evidence for rejection only was found in 44% of the grafts of group 1 (Fig. 2, right; $P = 0.005$). Regarding the portions of the different leukocyte types on the last 3 days of the period observed, in the distribution of most cell types no significant differences between the RANTES groups were observed (Table 1). However, the portion of the eosinophils was elevated nearly twofold in group 1 versus group 2.

Discussion

From the low incidence of rejection and the good graft function probability in the group with elevated RAN-

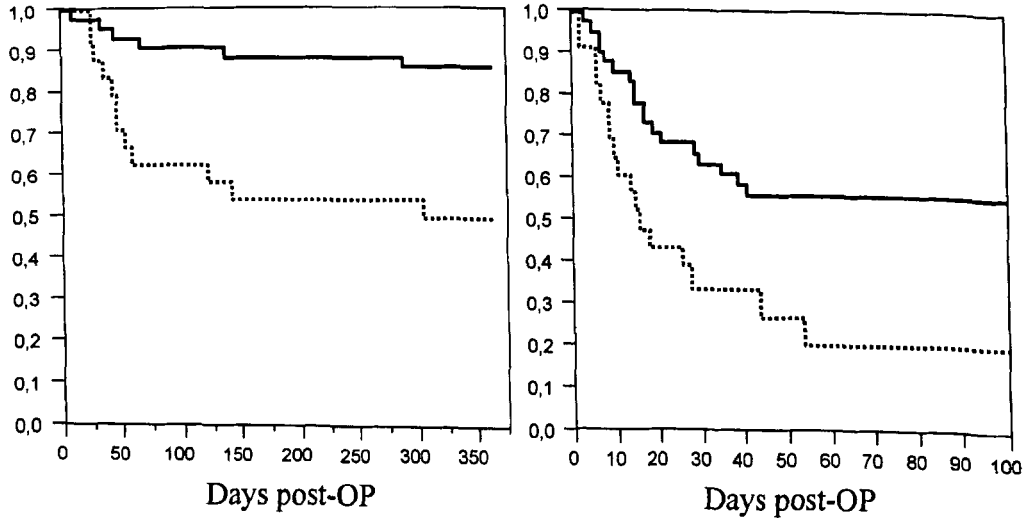

Fig. 2 Kaplan-Meier plot of the graft survival rate (*left*) and rejection free survival (*right*). *Solid line* Group 1 ($n = 43$), *dotted line* group 2 ($n = 24$)

TES concentrations after liver transplantation, it can be concluded that there is a beneficial influence of systemic RANTES to graft development in transplantation. Even though there were no protocol biopsies taken, the findings of a close relation of rejection to intragraft RANTES concentration in other systems [5, 8] indicate that, in our population, systemic RANTES concentration did not reflect the spill-over of the intrahepatic expression.

One recently reviewed [9] explanatory model for the inverse effect of high systemic RANTES is based on the fact that chemotactic molecules, probably including RANTES, induce leukocyte–endothelial cell adhesion by rapidly activating integrins [2]. Because this activation happened in the correct sequence in the case of leukocyte integrins activated by high RANTES concentrations in circulation before initial interaction with the endothelium, the leukocytes lost their ability to adhere and emigrate [3, 6, 12]. Therefore, an inactivation of leukocytes by the high RANTES levels in circulation may be one reason for the reduced incidence of rejection and may also lead to a desensitisation of eosinophils and basophils for RANTES itself and other chemokines [1].

In current opinion, RANTES is discussed as a preferred target for the suppression of inflammatory or immunological disorders. The main aim is to locally inhibit the chemokine expression or function, thereby limiting the degree of leukocyte infiltration [7]. Our data suggest another model. Because elevated systemic RANTES possibly inactivates certain leukocyte populations and prevents the eosinophils from transmigration, nothing should be done to decrease RANTES concentrations. In contrast, a way to elevate systemic RANTES could probably act as an immunsuppessive.

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