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Systemic liberation of interleukin-1β and interleukin-1 receptor antagonist in the perioperative phase of liver transplantation

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Abstract We measured systemic serum levels of interleukin-1 receptor antagonist (IL-1ra), interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α), and interleukin-6 (IL-6) during the preoperative, anhepatic, and postreperfusional phases up to the 7th postoperative day in 60 patients undergoing orthotopic liver transplantation (LTx). In contrast to IL-1β, IL-1ra, TNF-α, and IL-6 showed a significant elevation in relation to the early phase after reperfusion, while TNF-α displayed a high grade of scatter. In addition, IL-1ra levels were significantly elevated during the anhepatic phase. Maximum serum levels were found at 15 min after reperfusion, 120 min after reperfusion, and on the 1st postoperative day, respectively. Serum levels decreased considerably at 24 h and 7 days after reperfusion. The comparative monitoring of systemic cytokine and cytokine antagonist levels, in particular the liberation of IL-1ra and IL-6 may provide useful parameters for the development of new liver preservation theories for LTx.

Key words Liver transplantation, interleukins · Interleukins, liver transplantation

Introduction

The replacement of Euro-Collins preservation solution with the University of Wisconsin (UW) solution [23] has resulted in considerable improvements in the outcome of liver transplantation (LTx). However, liver injury during preservation and reperfusion is still associated with organ dysfunction in the early post-transplantation course. Various alterations in graft function, including the syndrome of primary nonfunction (PNF), which occurs in 3 %–8 % of LTx [43], are the cause of clinical problems. As a consequence, this problem is currently being addressed by several research groups working on the further development of preservation theories.

For comparative studies of these novel preservation theories, data describing the outcome of organ preservation are essential. The possibility of bleeding makes biopsies taken in the early postoperative phase dangerous. In addition, standard histology of biopsies mainly provides information about hepatocytes, while preservation injury most often appears to be associated with the nonparenchymal cells [30]. Investigation of blood samples would be a much less invasive method. However, for the assessment of potential organ damage during the perioperative period, only a few sensitive serum markers have been clinically established thus far.

During the perioperative phase of LTx, cytokines may play a central role in regulatory processes. The liver is described as a major target organ for interleukins. Tu-

mor necrosis factor (TNF)-α and interleukin-6 (IL-6) are among the interleukins that interact with blood cells and nonparenchymal liver cells such as Kupffer and sinusoidal endothelial cells [51]. The following cell types of the liver express cytokine genes: sinusoidal endothelial cells [38], other vascular endothelial cells [15], Ito cells [27], Pit cells [35], hepatocytes [1], hepatic fibroblasts [13], Kupffer cells [20], and epithelial bile duct cells [20]. Cytokines usually act in picomolar concentrations through specific, high-affinity cell surface receptors and work in a network that may produce either synergistic, additive, or antagonistic effects [39]. None of the cytokines alone is able to induce the complete set of acute phase proteins. When IL-6 is combined with either IL-1β or TNF-α, it generates several mediators, while IL-1β, IL-6, and TNF-α together induce the full range of acute phase proteins. In contrast to IL-1β and TNF-α, IL-6 and IL-4 also have anti-inflammatory properties. Cytokines are thought to directly damage the transplanted graft parenchyma. In addition, they promote induction of adhesion molecules [44] and, thus, the nonspecific recruitment of cells to allografts as a result of communication between endothelial cells and blood cells [3].

As suggested by Soulillou [42], cytokines are able to influence transplantation immunology in different ways: they may cause cellular lesions in donor organs before harvesting, as demonstrated for IL-6 [41], during reperfusion, and in the early phase of transplantation. Committed cells may attract nonspecific inflammatory cells such as activated macrophages, leading to organ injury.

IL-1β and TNF-α are known to be early mediators within the cytokine cascade. IL-1β induces a general inflammatory response, including neutrophil accumulation and activation, which may result in the progression of hepatic reperfusion injury. IL-1 production can be stimulated by IL-1 itself or by other mediators, including TNF-α [47]. IL-1 is predominantly formed by monocytes and macrophages but also by endothelial cells [38]. It may trigger endothelial cells [21] and hepatocytes [26] to release IL-6 and, subsequently, acute phase proteins. Interestingly, IL-1 levels are not elevated under hypoxic conditions but rather following reoxygenation [18].

The proinflammatory potential and synergism of IL-1 with other cytokines require potent mechanisms that can limit or antagonize the effects of IL-1. Several years ago, a potent and specific inhibitor of IL-1 was isolated and later characterized. It displayed considerable homology to IL-1α and IL-1β [8]. This molecule, however, does not exert agonist effects. Instead, it acts as a specific IL-1 receptor antagonist [4] and was thus called IL-1ra. IL-4, interferon-α (IFN-α), IFN-γ, and other mediators have been shown to induce IL-1ra synthesis [37]. The major sources of IL-1ra are monocytes, macrophages [5], and neutrophils [28].

In order to determine whether selected cytokines and cytokine antagonists may serve as noninvasive parameters for the evaluation of new preservation theories, the systemic levels of IL-1ra, IL-1β, TNF-α, and IL-6 were investigated during the preoperative, anhepatic and postreperfusional phases of 60 patients undergoing LTx.

Materials and methods

Liver allograft recipients

Sixty adult patients consecutively underwent orthotopic LTx at our unit. The patients' age ranged from 20 to 62 years, twenty-eight of the patients were male. Indications for LTx included chronic active hepatitis, alcoholic cirrhosis, fulminant hepatitis, cryptogenic cirrhosis, primary biliary cirrhosis, Budd-Chiari syndrome, hepatocellular carcinoma, autoimmune hepatitis, and PNF. The mean cold ischemia time (starting from interruption of the blood circulation during organ harvesting until the beginning of the anastomosis) was 654 ± 29 min, the median 671 min, and the range 240–1138 min. The mean anastomosis time was 76.2 ± 3.2 min. Patients were randomized [34] to treatment with cyclosporin A (CyA) or FK 506-based immunosuppression prior to transplantation.

Liver transplantation and concomitant treatment

The surgical procedure was performed as reported elsewhere [33], including preservation with University of Wisconsin (UW) solution and the use of venovenous bypass in all cases. Aprotinin administration, i.v. antibiotic treatment, selective bowel decontamination, and further prophylaxis were performed as previously described [32].

Immunosuppressive protocol

Patients in both the FK 506 and CyA groups were treated according to an immunosuppressive regimen described elsewhere [22]. This included methylprednisolone (MP), azathioprine, and antithymocyte globulin (ATG; Fresenius, Bad Homburg, Germany). MP was administered by i.v. bolus injection at a dosage of 500 mg before and 6 h after reperfusion. MP treatment was commenced on postoperative day (POD) 1 with 20 mg and reduced to 15 mg/day after 4 weeks.

Collection of samples

Heparinized arterial blood samples were obtained through a radial artery catheter and collected aseptically. In rare cases, samples from the organ donor at day 7 postoperatively were taken from a central venous catheter. Plasma was collected following blood centrifugation at 4 °C and immediately frozen at –80 °C.

Time points of sampling were immediately prior to explantation in the donor, immediately preoperatively, and at the end of the anhepatic phase in the recipient. After reperfusion, serum was sampled 15, 30, 60, and 120 min after reperfusion and at 24 h and 7 days postoperatively.

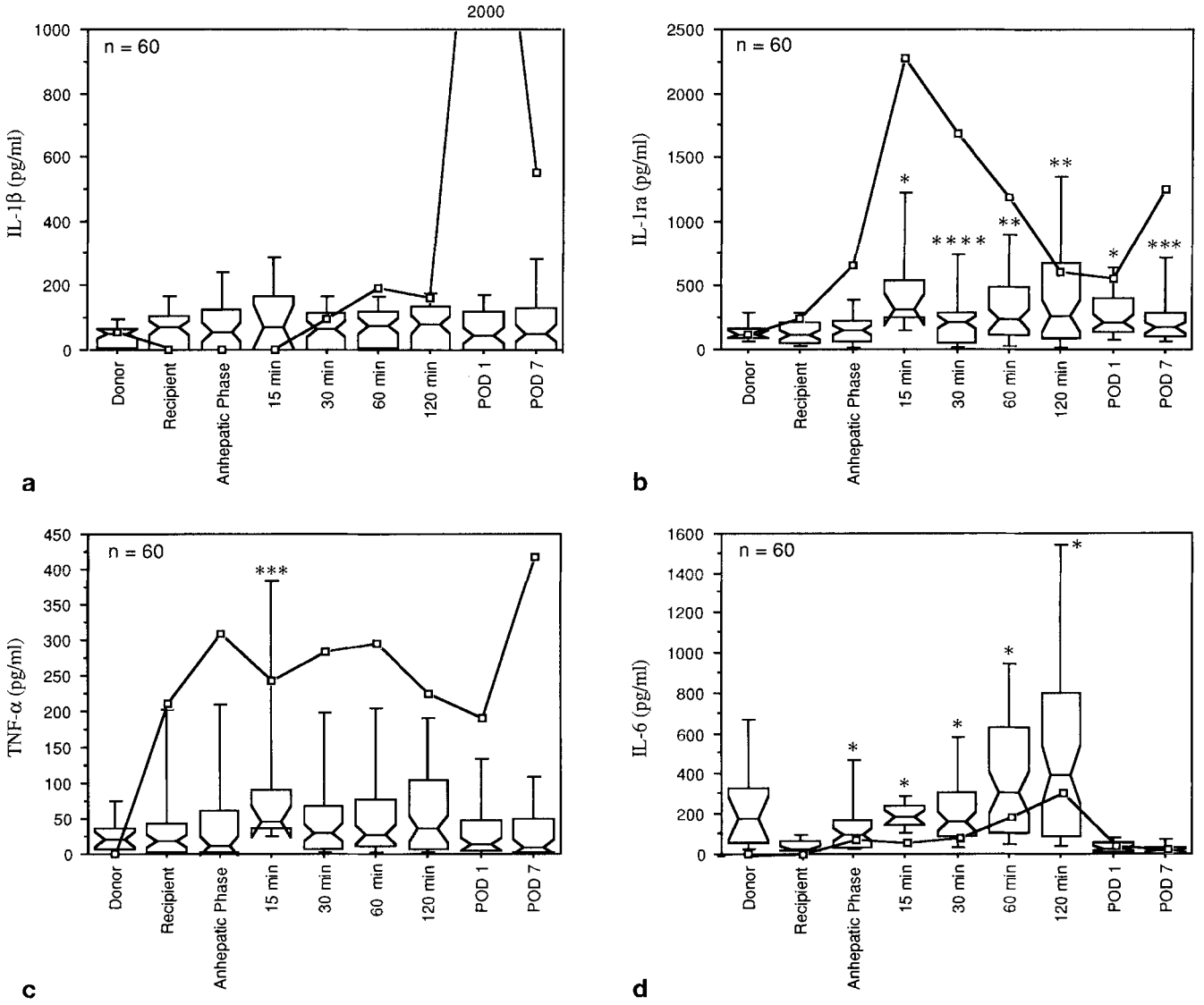

Fig. 1a–d Time course of systemic cytokine levels in pg/ml of 60 patients during the perioperative phase of LTx: **a** systemic IL-1β concentrations; **b** systemic IL-1ra concentrations; **c** systemic TNF-α concentrations; **d** systemic IL-6 concentrations. In addition, the values of one patient with PNF (included in the box plot) are drawn as a line chart. Time points of measurement were: immediately prior to explantation in the donor (*donor*), immediately before LTx (*recipient*), at the end of the anhepatic phase (*anhepatic phase*), 15 min, 30 min, 60 min, and 120 min after reperfusion, 24 h after reperfusion (*POD 1*), and on the 7th postoperative day (*POD 7*). Significance was calculated by comparing values with those from the recipients before LTx. * $P < 0.0001$; ** $P < 0.001$; *** $P < 0.01$; **** $P < 0.05$

Assays

Enzyme immunoassays were performed in microtiter strips (Nunc, Roskilde, Denmark) as previously described for IL-6 and TNF-α [22]. The following antibodies were used: for the IL-1ra assay, polyclonal anti-IL-1ra antibody (R + D Systems, Bad Nauheim, Germany); for the IL-1β assay, monoclonal anti-IL-1β antibody (Biogenesis, Bournemouth, UK); for the IL-6 assay, mouse monoclonal anti-human IL-6 antibody (Serva, Heidelberg, Germany); and for the TNF-α assay, mouse monoclonal anti-human TNF-α IgG antibody [Saxon Biochemicals (formerly Bissendorf Biochemicals), Hannover, Germany]. After staining with 3,3',5,5'-tetramethyl benzidine (TMB) substrate buffer, absorbance was measured using a plate reader (Dynatech, Denkendorf, Germany). Detection limits were 20 pg/ml for TNF-α, 50 pg/ml for IL-1β, 20 pg/ml for IL-6, and 50 pg/ml for IL-1ra.

Statistics

Data analysis was performed by notched box-and-whisker plot analysis [29]. The boxes in Fig. 1a–d show the range from 25 % to 75 % quartiles. The bars represent the 10 % and 90 % percentiles. A notch is added to each box corresponding to the width of a confidence interval for the median. In addition, the values of one pa-

tient with PNF, included in the box plot, are drawn as a line chart. The results given in the text are expressed as mean ± SEM. Differences between values were calculated using the Mann-Whitney U-test. Significance was determined in the recipient values before LTx. Differences were considered significant when P was less than 0.05.

Results

In a study of 60 patients undergoing LTx, we measured selected systemic cytokines at the end of the anhepatic phase, 15, 30, 60, and 120 min after reperfusion of the graft, and 24 h and 7 days after LTx. We compared these values to preoperative and postoperative levels. The results are summarized in Fig. 1a–d. The results in the text are given as mean ± SEM, the results in the figures as the median.

IL-1β

Figure 1a shows the course of systemic IL-1β levels. A maximum mean concentration of 114 ± 39 pg/ml was seen 24 h after LTx. In the donors, the mean was 43 ± 7 pg/ml, and preoperatively in the recipients the mean was 77 ± 12 pg/ml. None of the values differed significantly from the recipients' values.

IL-1ra

Figure 1b shows the course of systemic IL-1ra levels. A maximum mean concentration of 568 ± 113 pg/ml was measured 120 min after reperfusion. The donors had a mean of 144 ± 23 pg/ml, the recipients a mean of 141 ± 15 pg/ml preoperatively. Apart from the samples taken at the end of the anhepatic phase, each value differed significantly from the recipient level. The time course of liberation showed a single-peak curve. In comparison to donor and preoperative values, IL-1ra was significantly enhanced between 15 and 120 min after reperfusion. The 15 min value followed a different course. IL-1ra decreased after 24 h postoperatively and remained low at day 7. At both time points, however, mean levels differed significantly from the recipient levels.

TNF-α

Figure 1c shows the course of systemic TNF-α levels. The highest level (maximum mean) was detected 15 min after reperfusion at 115 ± 39 pg/ml. The means for donors and recipients were found to be 27 ± 7 pg/ml and 55 ± 13 pg/ml, respectively. With the exception of the 15-min value, differences compared to the recipients did not reach statistical significance. A high grade of scatter was observed, especially in the 15-min values.

IL-6 levels

Figure 1d shows the course of systemic IL-6 levels. A maximum mean serum concentration of 572 ± 85 pg/ml was found 120 min after reperfusion. The mean for the donors was 265 ± 74 pg/ml and for the recipients 51 ± 13 pg/ml. The course displays a continuous rise up to the 120-min value. In contrast to the other values, plasma concentrations measured on the 1st and 7th postoperative days were not statistically significant when compared to the recipient values.

Patients were divided into three groups according to the cold ischemia times. group 1, cold ischemia time 240–500 min; group 2, ischemia time 501–800 min; and group 3, ischemia time to 1138 min. While significant differences in the cytokine response were calculated for IL-1β and IL-1ra, no valid distinction occurred for IL-6 and TNF-α. Differences with P below 0,05 were calculated for IL-1ra between groups 1 and 3 on POD 7; differences with P below 0,05 were calculated for IL-1β between groups 1 and 2 120 min after reperfusion.

The influence of the duration of the anastomosis time on the cytokine response was also calculated. For this, the patients were divided into two groups. In group A, anastomosis time ranged from 30 to 79 min; in group B, from 80 to 131 min. IL-1β was found to be sensitive for different anastomosis times. The 15-min postreperfusional value ($P < 0.05$) and the 30-min value ($P < 0.05$), as well as the 60-min ($P < 0.01$) and 120-min values ($P < 0.01$) measured, differed significantly.

Discussion

Since the outcome of organ preservation is still a problem in LTx, many groups are working on modified liver preservation methods. For clinical studies on liver preservation, noninvasive serum parameters that react quickly to consequences of preservation damage are rare.

With respect to the possibility of a relationship with rejection or infection, the systemic liberation of some interleukins after LTx has been monitored by other authors. Tilg et al. [48] found no increase in TNF-α following uncomplicated LTx of 20 patients, but they did not investigate the early postoperative phase. Pirenne et al. [36] investigated three time points in seven patients: preoperatively, before the anhepatic phase, and after reperfusion. Hamilton et al. [19] studied the same time points in 15 patients as well as during and at the end of the anhepatic phase. In contrast to IFN-γ and IL-2, IL-1, IL-6, and TNF-α were found to be elevated.

Whether systemic cytokine levels can serve as a marker of acute graft rejection is still unclear. Függer et al. [17] reported that intraoperatively elevated TNF-α and IL-6 were closely related to postoperative rejection. Steininger et al. discussed TNF-α as a predictor of liver dysfunction [45].

Surgical procedures alone influence systemic cytokine levels [40]. Baxevanis et al. [7] showed increased levels of IL-1β and TNF-α following major surgery. Di Padova et al. [12] found that systemic IL-6 increased postoperatively. Therefore, the question of whether perioperative systemic cytokine monitoring can predict the outcome of LTx should be considered carefully.

Perioperative systemic cytokine levels may be judged to be a general response to inflammation that accompanies surgery, including inflammation due to ischemia and reperfusion, rather than to specific organ alterations like graft rejection. Therefore, the additional data from a patient with PNF was included here, but only to give an impression of the cytokine levels in a preservation altered graft rather than to draw any conclusions about PNF.

We investigated the period 15–120 min after reperfusion for the measurement of systemic cytokine liberation because experimental data suggest that a response can be expected within this period [6, 25]. The recorded levels of IL-1β were rather low during the period of investigation. Despite the significant influence of anastomosis time, no significant elevation of general levels was seen. This may have been a consequence of its short half-life, the presence of binding proteins, or the presence of inhibitors. However, IL-1β may be produced locally [11] without appearing in the systemic blood circulation [31] and may act predominantly in a cytoplasmatic manner [46]. The low levels of IL-1 do not appear to be consistent with the demonstrated increase in IL-1ra concentrations. In contrast to the described action of soluble IL-1 receptors [9], IL-1ra works as a competitive inhibitor for IL-1 [10] and not as a binding protein. However, estimation of systemic IL-1 does not appear suitable for studies focussing on preservation. In contrast, we found a high elevation of IL-1ra, which is in accordance with previous experimental findings [49]. An estimation of the IL-1/IL-1ra ratio [50], its biological implications and the quantitative value of IL-1 inhibition is still under discussion [2]. However, since different cytokines contribute to this [16], our data do not enable quantification of IL-1 signal antagonism.

IL-1ra showed a significant elevation in relation to the early phase after LTx, while IL-1β differed according to different anastomosis times. In general, IL-6 showed a significant elevation in relation to the early phase after LTx, although the preservation times had no significant influence on the systemic concentrations. TNF-α displayed a high grade of scatter. Our data confirm that cytokine levels normalize within the 1st day after LTx [24], which may be influenced by the postoperative therapy [14].

The biological effects of cytokines cannot be argued on the basis of measured systemic levels. However, comparative monitoring of systemic IL-1ra and IL-6 levels might be an interesting tool for the testing of novel preservation theories and the development of new preservation solutions for LTx. In such instances, measurements of systemic IL-1ra and IL-6 should be conducted mainly in the perioperative phase.

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