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ORIGINAL ARTICLE

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Serum bile acids in liver transplantation – early indicator for acute rejection and monitor for antirejection therapy

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Abstract We studied the course of serum bile acids to investigate its reliability in the diagnosis of acute rejection after liver transplantation in relation to pathohistological findings. Serum bile acid concentration, bilirubin and transaminases were measured in 41 patients who underwent liver transplantation. Their course was correlated to liver biopsy. Group I ($n = 19$) patients were without acute rejection, whereas group II ($n = 22$) patients showed acute rejection. Bile acid concentrations in group II showed a statistically highly significant ($P \leq 0.001$) threefold increase 3 days prior to biopsy. Successful antirejection treatment was correlated with a statistically significant ($P = 0.008$) decrease of serum bile acid 1 day after initiation of therapy. Patients without acute rejection showed a baseline bile acid concentration at the time of biopsy. Bilirubin and transaminases did not show any statistically significant correlation to acute rejection. Infection did not lead to a significant bile acid increase. Our study shows that serum bile acids monitored after liver transplantation can easily be used to detect acute rejection and at the same time they reflect the success of antirejection therapy.

Keywords Acute rejection · Serum bile acid · Liver transplantation

Abbreviations *ACR* Acute cellular rejection · *SBA* Serum bile acid · *OLT* Orthotopic liver transplantation

Introduction

Synthesis and secretion of bile acids belong to the most important functions in hepatic metabolism [13]. Information about liver function after liver transplantation can be obtained by measuring the bile acid concentration in the bile drained from the T-tube [15, 24]. The determination of bile acid kinetics in serum drawn from patients after liver transplantation also provides information about liver function [18]. Therefore bile acids represent an excellent parameter of liver function in patients after orthotopic liver transplantation (OLT). Together with bilirubin and the transaminases (GOT, GPT) they constitute a panel of liver biochemistry that characterizes graft functioning very well.

Graft dysfunction is a common problem in the early post-transplant period and acute cellular rejection (ACR) is one of the frequent causes [17, 31]. Since none of the routine serological biochemistries (bilirubin, transaminases) is specific for allograft rejection

[26, 30] there has been a need for more specific parameters other than an invasive biopsy.

We have been focusing on the serum bile acids (SBAs) as a reliable, specific and easily detectable marker for ACR. Bile acids have strong interactions with the immune system. They change the HLA expression in the liver [6, 12], and influence the concentration of cytotoxic T-lymphocytes [21] and of cytokines such as Interleukin-2 [19] in the peripheral blood. Our study was based on the measurement of SBA concentration and its variation from a baseline obtained in the first 24–48 h after transplantation. Our hypothesis was that a persistent increase in the SBA concentration is specifically correlated with an episode of ACR.

The aim of the study was (1) to assess the predictive value of an increase in SBA concentration for the early detection of ACR in the first 4 weeks post-transplant in comparison with total bilirubin and transaminases, (2) to compare the efficacy, specificity and sensitivity of SBA in the detection of ACR with the gold standard liver biopsy, bilirubin and transaminases, (3) to compare the reliability of SBA with that of bilirubin and transaminases in monitoring the efficacy of antirejection therapy, and (4) to determine whether the SBA concentration is influenced by viral, bacterial or fungal infection.

Patients and methods

A total of 41 consecutive patients enrolled after primary OLT were studied during a period over a maximum of 28 days after transplantation. Patient data are described in Table 1. The immunosuppressive regimen was based on CSA, FK-506, Azathioprine, Mycophenolate Mofetile, ATG and steroids in different combinations. ACR diagnosed by biopsy was treated with a total of 1 g prednisolone over a period of 3 days.

Liver biopsy was performed in the case of increased or ongoing high values of bilirubin and/or transaminases with lack of mechanical obstruction, ongoing elevated transaminases, fever and deterioration of clinical status. Histopathological diagnosis of ACR was made according to the criteria of Kemnitz [16] with mixed cellular infiltration of the portal tracts, venous endothelialitis of portal/central locations, degenerative hepatic parenchymal changes up to necrosis and mononuclear infiltration of the bile duct epithelium. Return of transaminases to normal values was interpreted as resolution of the ACR episode and a confirmatory biopsy was not obtained.

Total SBA was analyzed using an enzymatic photometrical method described by Mashige [22]. Primary bile acids (3-alpha-hydroxy-bile acids) were measured by this test independently of whether they were conjugated or unconjugated. Daily collected fasting serum samples were measured by Merckotest Bile Acids 14352 from E. Merk, Germany. Normal range values in the fasting serum were considered from 3 to 10 μM. All patients showed a slightly elevated course of SBA level after liver transplantation in comparison with the normal range. This was taken into account in the definition of the patient's individual baseline of SBA level. A threefold increase of SBA over the individual baseline during three consecutive days was considered as ACR. SBA was measured commencing on day 1 postoperatively and daily thereafter.

Table 1 Patients' demographic data from group I and group II

	Group I	Group II
Hepatitis B	3	2
Hepatitis C	4	3
Autoimmune hepatitis	1	1
Hepatocellular carcinoma	1	1
PSC	1	4
PBC	3	2
Alcoholic cirrhosis	4	5
Acute hepatic failure	1	–
M. Wilson	–	1
Cryptogenic cirrhosis	–	2
Hepatopulmonary syndrome	1	–
Congenital liver fibrosis	–	1
Age (years)	33–66	21–67
Mean age (years)	50	42

In group I nine patients had a T-tube, and in group II ten patients. An open or closed T-tube did not influence the course of the SBA level.

The patients were divided into two groups according to the histological occurrence of ACR: group I included patients who had no histological confirmation of ACR in the biopsy; group II included patients with histologically confirmed ACR in the biopsy. Furthermore the incidence of bacterial, fungal or viral infections in each group was recorded and related to the SBA concentration.

Data are expressed as means with standard deviation and were analyzed by means of the Mann–Whitney U test to demonstrate statistical significance. The level of significance was a P value < 0.05.

Results

Group I

Nineteen patients were included and 19 liver biopsies were performed between the third and 19th day after OLT. The indication for biopsy to exclude or confirm ACR resulted from individual clinical and biochemical findings according to the criteria mentioned above. All biopsies performed amongst this group showed no histological signs of ACR. Figure 1 shows the course of SBA, total bilirubin and transaminases 4 days around biopsy in patients of group I. During the observation period SBA levels ranged between mean values of 16 μM ± 10 on the third day prior to biopsy and 17 μM ± 14 on the day of biopsy. SBA levels in this group were almost normal, with the patient's individual baseline not showing any increase at the time of biopsy.

The course describing total bilirubin distinctly shows that hyperbilirubinemia persisted with mean bilirubin levels between 5.1 mg/dl ± 2.7 and 7.4 mg/dl ± 4.7 during the period around biopsy. While SBA and bilirubin showed a stable level, transaminases revealed a different course. GOT and GPT decreased from 60 U/L ± 42 and 152 U/L ± 96 to 25 U/L ± 21 and 62 U/L ± 57, respectively, 4 days after biopsy. The course of SBA levels

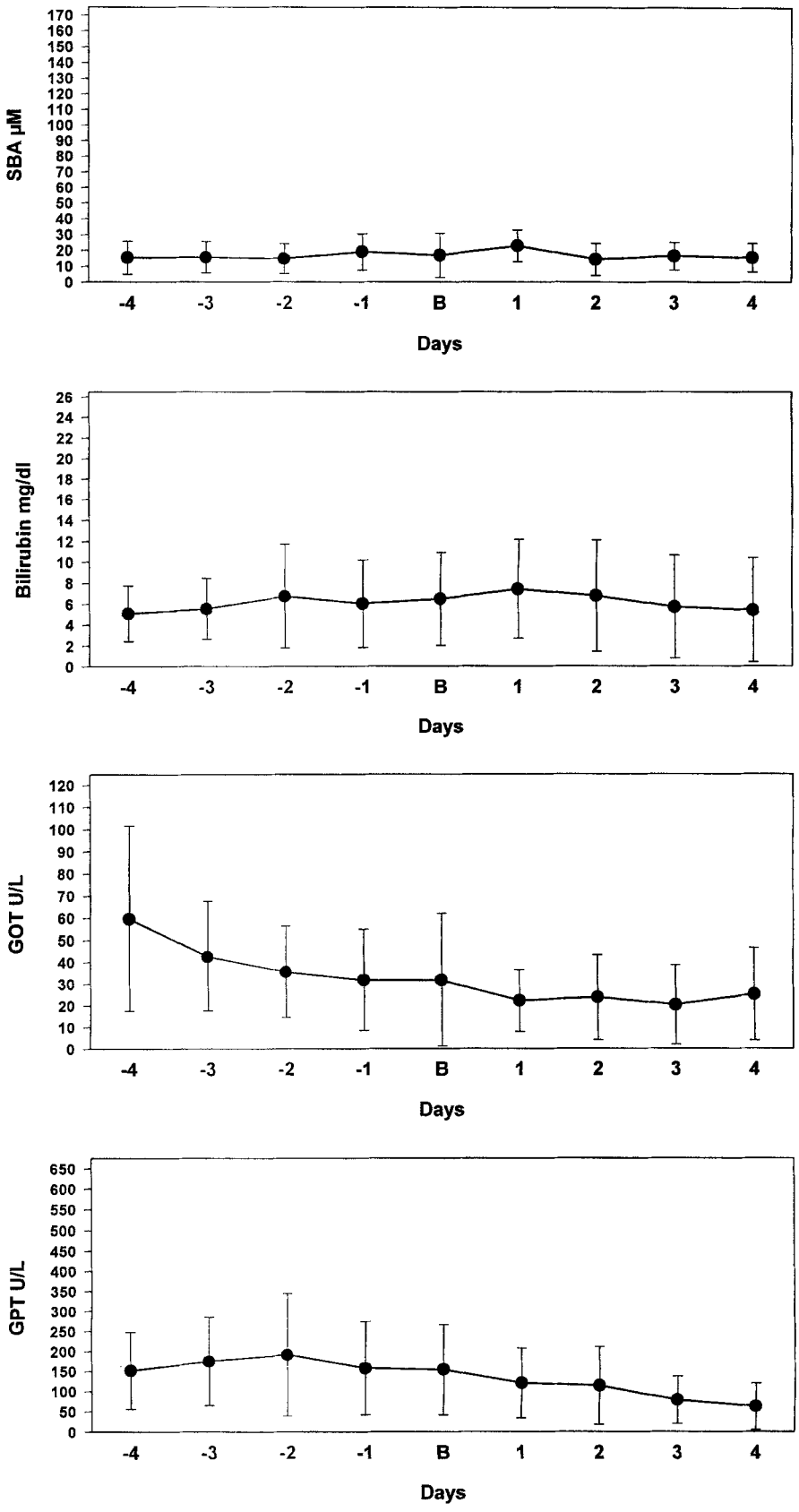

Fig. 1 SBA, total bilirubin and transaminases 4 days before biopsy, at the time of biopsy (*B*) and 4 days after biopsy (mean ± SD) in patients ($n = 19$) of group I without ACR

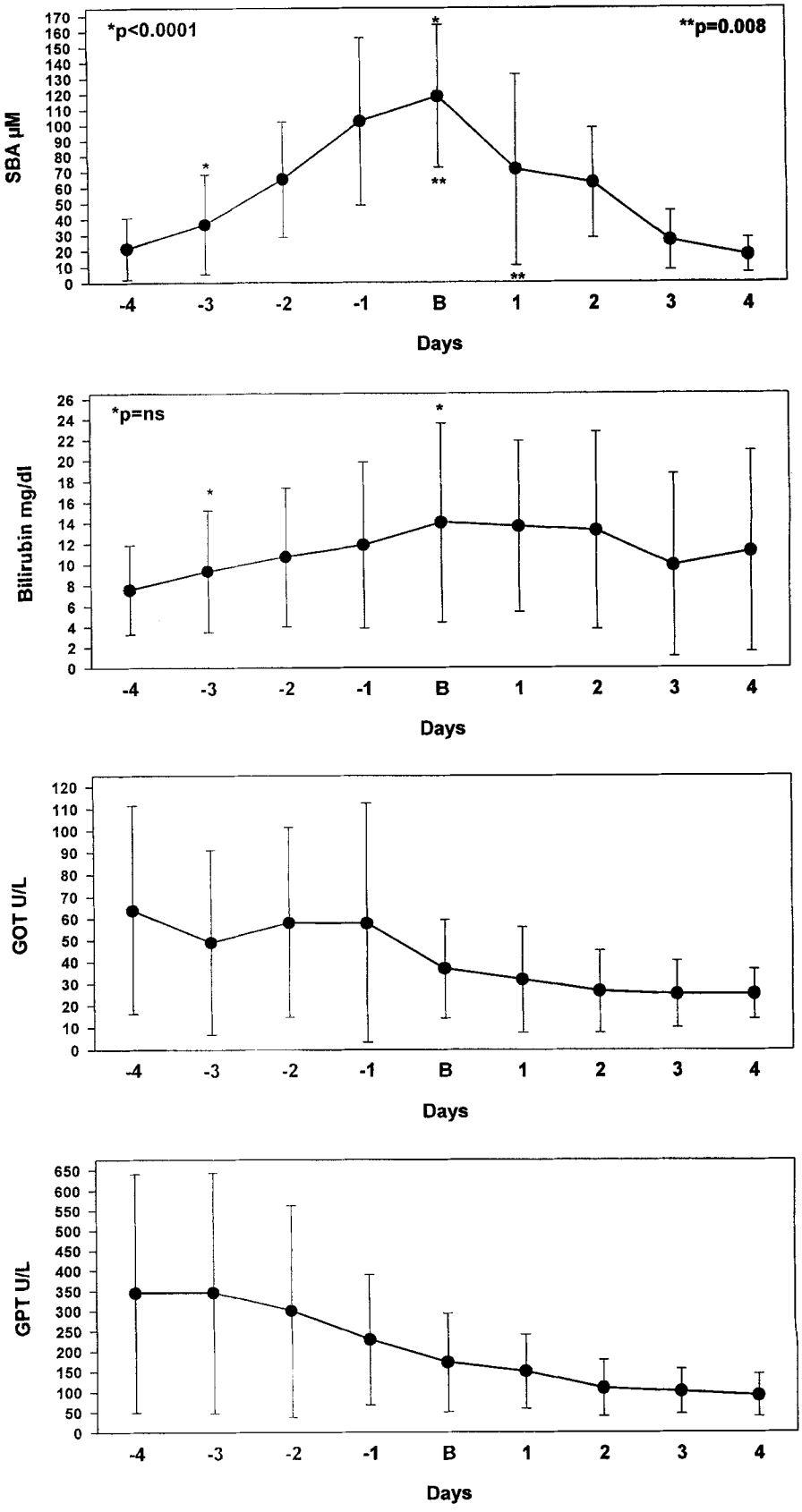

Fig. 2 SBA, total bilirubin and transaminases 4 days before biopsy, at the time of biopsy (*B*) and 4 days after biopsy (mean ± SD) in patients ($n = 22$) of group II with ACR

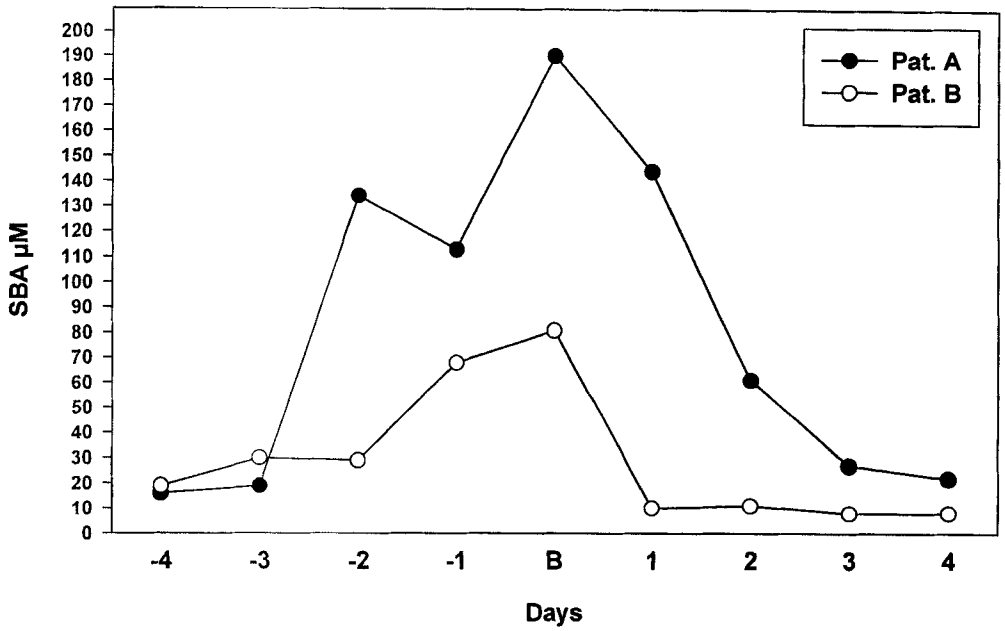

Fig. 3 Individual course of two patients with ACR in group II during the time of biopsy with antirejection therapy

in group I was almost in the normal range. Bilirubin and transaminases showed a slight but continuous decrease during the time before and after biopsy. Nevertheless in comparison with SBA, total bilirubin and transaminases were continuously elevated and out of the normal range.

Group II

Twenty-two patients were included and 22 liver biopsies were performed. Patients in this group experienced a histologically proven ACR episode between the fourth and 15th postoperative day. As shown in Fig. 2 the concentration of SBA increased 3 days prior to biopsy more than threefold from a mean of 37 µM ± 31 to 118 µM ± 46, measured on the day of biopsy. The concentration of SBA decreased rapidly and statistically significantly ($P = 0.008$) to a mean SBA value of 71 µM ± 61 immediately after the first treatment with steroids. At the end of antirejection therapy SBA levels returned to a normal range with a mean value of 17 µM ± 11.

In comparison, the total bilirubin concentration increased only very slightly over a period of 3 days from a mean value of 9.4 mg/dl ± 5.9 to a mean of 14.0 mg/dl ± 9.6 on the day of biopsy without any statistical significance (P = n.s.). Again, also in this group persistent hyperbilirubinemia was observed during the whole period. After commencing antirejection therapy the amount of total bilirubin decreased only very slightly to a mean value of 11.2 mg/dl ± 9.7 on the fourth day after biopsy.

Even though both parameters (SBA and bilirubin) showed a continuous increase, only the increase of SBA was statistically highly significant ($P < 0.001$) in confirming ACR. Furthermore the reversed course could be seen after antirejection therapy. SBA levels decreased significantly ($P = 0.008$) after the first treatment with steroids and normalized rapidly.

To demonstrate the meaning and importance of the individual course of SBA after OLT in the diagnosis of ACR the development of SBA was compared in two patients with histologically confirmed ACR. As shown in Fig. 3 the slope of SBA increase before biopsy was much higher in patient A than in patient B. Furthermore the maximum SBA value and the slope of decrease after the successful antirejection therapy showed a higher level in patient A. This also explains the high

Table 2 Sensitivity, specificity and predictive value of individual SBAs in the detection of ACR versus total bilirubin and transaminases

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SBA	86	100	100	86
Total bilirubin	59	53	59	53
GOT	14	89	60	47
GPT	14	84	50	46

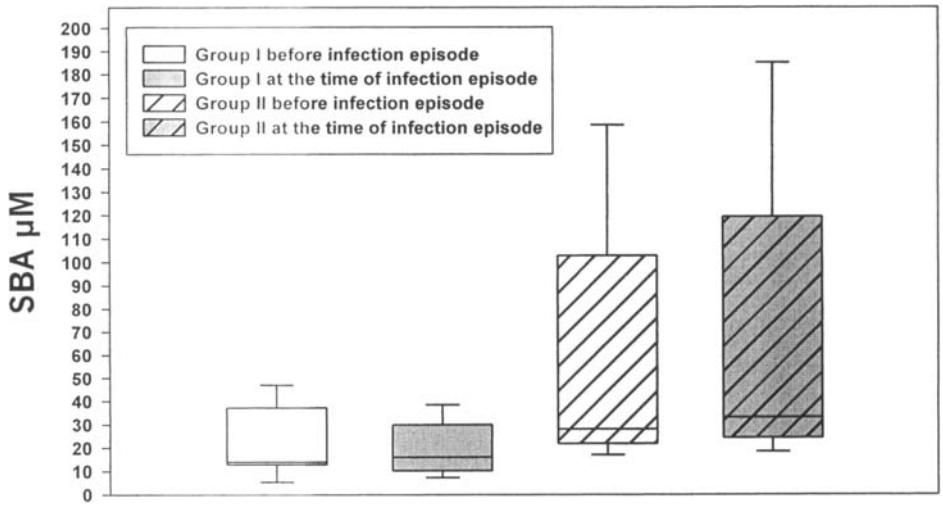

Fig. 4 Comparison of SBA concentration in group I and group II before and at the time of an infection episode (median, 5th/95th percentile)

standard deviation in the course of SBA of the patients with ACR in Fig. 2.

Analysis of transaminases at the time of biopsy did not show any correlation and no significant increase with the diagnosis of ACR (Fig. 2). Furthermore a similar course of GOT and GPT around biopsy was seen in comparison with patients without ACR. GOT and GPT decreased from 64 U/L ± 48 and 345 U/L ± 296 4 days prior to histological diagnosis of ACR to 25 U/L ± 11 and 91 U/L ± 52 4 days after biopsy, respectively. Only in the ACR group was GPT slightly higher during the days before biopsy than for the control group.

Sensitivity, specificity and predictive values of SBA

To confirm the need of SBA measurement in daily routine after OLT we analyzed the sensitivity, specificity and predictive value of this parameter in comparison with bilirubin and transaminases. As shown in Table 2 the sensitivity (the incidence of a threefold increase of SBA 3 days prior to histological confirmation of ACR; true positive) of SBA was 86% and the specificity (the incidence of the lack of SBA increase 3 days prior to biopsy without ACR; true negative) was 100%. Meanwhile all 22 patients with ACR showed an increase of SBA but only three of them did not reach a threefold increase 3 days prior to biopsy. On the other hand an increase of SBA was not seen in patients without ACR.

The analysis of the positive predictive value (which can give an idea of how well the threefold SBA increase 3 days prior to biopsy predicts the diagnosis of ACR correctly) and the negative predictive value (which can give an idea of how well the lack of a threefold increase in SBA 3 days prior to biopsy correctly predicts the absence of ACR) revealed 100% and 86%, respectively.

In comparison with SBA, the sensitivity, the positive predictive and negative predictive value for total bilirubin and transaminases only reached about 50% (14–60%). Only the specificity for GOT and GPT in the diagnosis of ACR lies in an acceptable range at 89% and 84%, respectively. Nevertheless none of the parameters reached the high level of predictive value of ACR, seen in SBA.

SBA and infection

The influence of bacterial, viral or fungal infections on SBA was investigated. The types of infection appeared to be equally distributed between both groups of patients after OLT. To clarify whether the infections had any interference with the SBA concentration, the values were compared prior to the infection episode and during specific antibiotic, antiviral or antimycotic therapy. The analysis differentiates between infectious episodes in patients without ACR and patients with histologically confirmed ACR. As shown in Fig. 4, median SBA concentration in patients without ACR was nearly equal with 14.0 µM (1–47 µM) prior to the infectious episode and 16.0 µM (7–44 µM) when therapy was begun. Also patients with histologically confirmed ACR did not show any significant differences of median SBA concentrations prior to and at the onset of the infectious episodes with 28.0 µM (16–168 µM) and 33.0 µM (17–196 µM), respectively.

Discussion

The early detection of postoperative graft dysfunction is of great importance for the patient's prognosis after liver transplantation. Results of conventional and routine

liver biochemistries are not specific and leave a wide spectrum of differential diagnosis, from technical complications to ACR [32]. An ideal parameter should have nearly normal values immediately after transplantation and show instant variation from baseline when a specific dysfunction occurs. This parameter should be obtained by a non-invasive method. Currently there is no proven, non-invasive test to diagnose ACR specifically. In view of the fact that SBA concentration changes when an immuno-mediated episode occurs, we decided to evaluate the sensitivity, specificity and the predictive value of SBA concentration in the event of ACR. A normal concentration of SBA is a result of the functional integrity of the graft. The pathophysiological causes of an increasing SBA concentration during an ACR are assumed to be dependent on many factors. One main factor is the attack of the immunocompetent cells against the endothelium and the intrahepatic bile ducts of the graft causing a deterioration of the microcirculation [33]. This leads to an important impairment of the absorption of the bile acids from the portal blood and their excretion into the bile ducts [20, 36]. The high rate of enterohepatic circulation of the bile acids, about 5 to 15 times daily [3], could also explain their early increase in the event of ACR. Due to this high turnover an increase of SBA could always be measured far earlier than any other liver biochemistries or before clinical symptoms become apparent. Hepatic damage caused by ischemia and reperfusion affects bilirubin and transaminases; serum concentrations of these therefore make the detection of a process like ACR difficult. In contrast SBA concentration returns to normal within hours of the anhepatic phase [7, 11]. This is a major advantage in the routine measurement of the SBA in comparison with bilirubin and transaminases in diagnosing ACR.

A further explanation for the higher response of SBA in the detection of ACR could be the multidrug resistant protein 2 (MRP2). This ATP-dependent conjugate export pump is localized in the canalicular apical membrane of hepatocytes [5] and is responsible for the transport of bile acids into the bile duct. This transport system is also involved in the excretion of bilirubin. Several studies revealed that endotoxins [4, 14, 28, 29] and cytokines [9, 23, 35] impaired the function and gene expression of MRP2. Both substances lead to a rapid decrease of MRP2 expression within 16 h and therefore attack the serum level and transport of bile acids very early [37], which is of importance due to the much higher circulation rate of SBA than bilirubin in the liver. This could explain the significant increase of SBA in contrast to bilirubin in the case of ACR with a high target level of cytokines from liver infiltrated lymphocytes, which induce the damage to the MRP2.

The analysis of SBA concentration in both groups of patients confirmed a nearly complete return to normal values during the first postoperative day except in the case of ACR (data not shown). In contrast, the bilirubin and transaminase concentrations in the early postoperative period all showed values above normal due to ischemia and reperfusion injury, which only improved over a period of several days [34]. In the study presented here we could confirm this course of transaminases around biopsy without any correlation to the diagnosis of ACR. The cause of slow reaction of the total serum bilirubin depends on the prolonged synthesis and elimination before and after a graft dysfunction [8]. For this reason, bilirubin subfractions that have a faster metabolism rate have been studied as a non-invasive test to diagnose ACR [38, 39]. Nevertheless esterified bilirubin as a possible marker of ACR [25] is extremely complex to measure, whereas the total SBA can be measured easily and cheaply with basic equipment in only 30 min.

The diagnostic validity of SBA in the diagnosis of ACR is clearly evident in the patients of group II. For a period of 3 days prior to liver biopsy and the confirmed diagnosis of ACR these patients had a steady increase (threefold) of the SBA concentration. This increase proved to be significant ($P < 0.001$). On the other hand, even if the bilirubin concentration increased, this increase was only slight and when compared with the baseline values not statistically significant. The major fact remains that SBA increases much more dramatically and in less time than bilirubin. This allows earlier diagnosis and faster initiation of rejection treatment.

Another point of great interest is the rapid decrease of SBA once an effective treatment has been started. This is shown in group II, where the SBA concentration returned to baseline values within 3 days of the beginning of the antirejection therapy. Immediately after initiation of rejection treatment the decrease of SBA was significant ($P = 0.008$). Although the bilirubin concentration also decreased, the course was not impressive (P = n.s.) and therefore made the interpretation of the antirejection therapy's effectiveness very difficult. This supports our thesis that the measurement of SBA is extremely precise and useful not only in allowing fast and reliable diagnosis of ACR but also in monitoring the response to treatment.

Special attention should be drawn to the definition of the individual baseline and course of SBA measurements after OLT. It is obvious that the SBA standard deviation in group II is much higher than that in group I and is caused by ACR. This was also confirmed by the data of Baumgartner et al. with a smaller group of patients [2]. As shown in Fig. 3 there are different patterns of SBA levels around the histological diagnosis of ACR, which lead to the high standard deviation in this group. This should always be kept in mind if a single SBA value should be interpreted and calculated for the occurrence of ACR. Our study revealed that there is no objective cut-off value for the diagnosis of ACR. Therefore single

SBA values should only be interpreted in the context of the entire postoperative course in which measurements were obtained daily.

Along with the advantage of being a non-invasive test, the measurement of SBA concentration also allows an earlier diagnosis of rejection, when compared with the biopsy, and therefore an earlier start of therapy [10]. Although the biopsy is still the gold standard for the diagnosis of acute graft rejection [27], we believe that measuring SBA concentrations is a valid and non-invasive alternative especially when biopsy cannot be performed in time due to clinical or logistical problems.

The specificity of SBA in the diagnosis of ACR is further proven by the analysis of its concentration in patients who suffered infections. Although patients experienced episodes of infections in both groups, an increase of SBA concentration was never detected. The different initial levels of SBA (14 μM versus 28 μM) prior to infection in both groups could explain the overlap of infection and rejection episodes in group II. The lack of a statistically significant increase in the event of infection clearly shows that a variation from the baseline of SBA is specific for ACR.

The sensitivity (86%), specificity (100%), the positive predictive value (100%) and the negative predictive value (86%) of SBA in the diagnosis of ACR revealed a very high level of diagnostic safety in comparison with measurements of total bilirubin and transaminases. Especially in the case of an early ACR after OLT, SBA is much more sensitive than other parameters. A major advantage of SBA is the return to normal values shortly after transplantation.

Moreover, studies of specific bile acid sub-groups showed an increase during ACR [1]. However, the measurement of these subgroups is technically very difficult, complex and therefore impractical for daily routine testing. In addition, the changes found in the bile acid subgroups during other complications make an interpretation and clinical relevance of these values very difficult compared with our study of the total SBA. In particular, the rise of specific subgroups of bile acids during transplant-relevant complications could not be verified in our study.

In conclusion, this study clearly demonstrates that the daily routine measurement of total SBA concentration is an excellent test for the early diagnosis of ACR and the monitoring of the response to antirejection therapy. In addition, we could confirm that there is no need for complicated estimation of specific bile acid subgroups to detect ACR. The inexpensive test is very easily performed in 30 min without major technical equipment, is non-invasive and specific. For the first time we are able to demonstrate that a threefold increase of SBA level prior to biopsy is a clinically useful, significant and safe cut-off level for the diagnosis of ACR. Again the validity of SBA measurements in the detection of ACR was confirmed by the gold standard liver biopsy. In most clinical circumstances measurement of SBA can therefore indicate not only the necessity of a liver biopsy to confirm the suspicion of ACR but also direct antirejection therapy without the need of histological diagnosis.

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