Decreased HLA (human leucocyte antigen)-DR expression on peripheral blood monocytes predicts the development of organ failure in patients with acute pancreatitis

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ABSTRACT

Immune suppression plays an important role in the pathogenesis of acute pancreatitis. Monocyte expression of HLA (human leucocyte antigen)-DR, a cellular marker of immune suppression, was determined in relation to the development of organ dysfunction in patients with acute pancreatitis. A total of 310 consecutive patients with acute pancreatitis, admitted to a university hospital within 72 h of pain onset, were studied; 194 (63%) had mild disease (group I), 87 (28%) had severe disease without organ dysfunction (group II), and 29 (9%) had severe disease with organ dysfunction (group III). HLA-DR expression, defined both as the proportion of monocytes that were HLA-DR-positive and as monocyte HLA-DR fluorescence intensity, was determined at admission, using whole-blood flow cytometry. Of the patients in group III, 13 (45%) developed organ dysfunction within 24 h of admission. The proportion of HLA-DR-positive monocytes and monocyte HLA-DR density were both related to the severity of pancreatitis (P < 0.001 for linear trend). In predicting organ dysfunction, the sensitivity, specificity and positive-likelihood ratio for the proportion of HLA-DR-positive monocytes were 83 % [95 % CI (confidence interval) 64–94 %], 72 % (67–77 %) and 3.0 respectively, and for monocyte HLA-DR density the respective values were 69 % (49–85 %), 84 % (79–88 %) and 4.3. In conclusion, monocyte HLA-DR expression predicts the development of organ dysfunction that occurs early in patients with acute pancreatitis.

INTRODUCTION

AP (acute pancreatitis) is usually a self-limiting disease of short duration. Some patients, however, develop fulminating systemic inflammation and multiple organ dysfunction. Organ failure affects approximately half of patients with severe AP, as defined by the Atlanta criteria [1], and is the major cause of mortality in AP [2–6]. Systemic
inflammation is considered to contribute to the development of organ failure [7,8]. It is characterized by systemic release of pro-inflammatory cytokines [9] and activation of blood neutrophils and monocytes [10]. The systemic inflammation is accompanied by development of an anti-inflammatory counter-reaction that results in high circulating levels of IL-10 (interleukin-10) and other anti-inflammatory cytokines [11,12], and a decrease in the monocyte surface expression of HLA (human leucocyte antigen)-DR antigens [13–15]. Monocytes with low HLA-DR density show impaired antigen presentation capacity [16,17] and low pro-inflammatory cytokine production in response to bacterial cell wall structures [18], while their IL-10 production capacity may be increased, decreased or unaltered [19,20].

Although there is currently no specific treatment for AP, strong evidence supports the view that patients may benefit from a variety of non-specific, often costly, treatment modalities [21–23]. To help in predicting the hospital course, several scoring systems have been developed, including the Ranson criteria [24], the multiple organ dysfunction score [25] and APACHE II (acute physiology and chronic health evaluation II) [26,27]. Also, several humoral mediators of inflammation [28,29] and immune suppression [30,31], and acute phase reactants, such as CRP (C-reactive protein) [32,33], are related to the severity of AP. However, none of them seem to be sufficient as a single marker to predict patient outcome [34], and, therefore, a search for novel predictors is necessary.

More than 10 years ago, Garcia-Sabrido et al. [35] found that patients with severe AP show impaired responses to recall antigens in skin testing carried out within 72 h of admission, denoting a state of cellular immune suppression. In accordance with this, we [36] and others [37,38] found that the presence of a low proportion of HLA-DR-positive monocytes in the blood is associated with the severity of AP. Here we evaluate monocyte HLA-DR expression as a predictor of organ dysfunction in 310 consecutive patients with AP.

METHODS

Subjects

This prospective study includes analysis of 314 consecutive patients with AP, all admitted within 72 h of pain onset to the Emergency Unit at the Helsinki University Central Hospital between September 1998 and July 2001. The study protocol was approved by the local institutional ethics committee. Informed consent was obtained from all patients. The diagnosis of AP was based on elevated serum amylase levels (more than three times the upper reference limit) and characteristic clinical findings, including acute onset of epigastric pain, nausea and vomiting. In cases of lower serum amylase levels, computed tomography was used to confirm the diagnosis.

Using the clinical classification of the Atlanta Symposium [1], the patients were divided into two groups: mild AP (group I) and severe AP. In that classification AP is classified to be severe if one or several local complications are present (pancreatic necrosis, an abscess, a pseudocyst) or if systemic organ dysfunction (shock, renal failure, respiratory insufficiency, disseminated intravascular coagulation) develops. These patients were divided further into two groups: patients with severe AP who recovered without organ dysfunction (group II) and patients with severe AP who developed organ dysfunction (group III). In the present study, organ dysfunction was defined as the development of respiratory failure necessitating mechanical ventilation and/or renal failure necessitating haemodialysis. The criteria for initiating mechanical ventilation were tachypnea (respiratory rate > 35 breaths/min) and/or the need for an inspiratory oxygen fraction > 0.6 in order to maintain the arterial partial pressure of oxygen > 8.0 kPa. Haemodialysis was started in patients with a significant reduction of renal function, indicated by increased levels of serum creatinine (> 300 µmol/l) and serum urea (> 40 mmol/l) and progressive metabolic acidosis (pH < 7.28) in serial measurements with or without anuria or oliguria (urine output < 500 ml/24 h). The time interval from symptom onset to hospital admission was obtained retrospectively from patient records. A Ranson score [24], determined 48 h after admission, and APACHE II [26] and multiple organ dysfunction [25] scores, determined both at admission and 24 h later, were used to validate the patient groups.

Blood samples

Peripheral blood samples for determination of HLA-DR were taken by venipuncture on admission to the hospital. Pyrogen-free acid/citrate/dextrose was used as an anticoagulant. Samples were cooled immediately in ice/water and then kept at 0°C until stained for two-colour flow cytometry. Serum samples for determination of CRP were collected concurrently.

Reagents

mAbs (monoclonal antibodies) were as follows: anti-CD14 FITC-conjugated mAb (IgG2a; clone MFP9), anti-HLA-DR PE (phycoerythrin)-conjugated mAb (IgG2a; clone L243) and mouse IgG2a,PE-conjugated mAb. FACS lysing solution was used for cell washing and lysing of red blood cells. All reagents were purchased from Becton Dickinson (San Jose, CA, U.S.A.).

Flow cytometry

Two 25 µl aliquots of each sample were stained, one with saturating concentrations of FITC-conjugated anti-CD14 mAb and PE-conjugated anti-HLA-DR mAb, and the other with FITC-conjugated anti-CD14 mAb and PE-conjugated irrelevant mouse IgG2a mAb. After...
staining, the non-bound mAb molecules were removed by washing, then red blood cells were lysed with FACS lysing solution and the cell pellet was resuspended in ice-cold 0.5 % formaldehyde in saline.

Flow cytometric analysis was performed using a FACSort flow cytometer (Becton Dickinson) and CellQuest software. Monocytes were identified on the basis of their CD14-positive fluorescence and light scatter properties. An HLA-DR histogram and a mouse IgG2a (control) histogram were developed for 2000 monocytes. The HLA-DR expression of monocytes was evaluated by determining the HLA-DR fluorescence intensity of monocytes and the proportion of positively fluorescing monocytes. The latter was done in two different ways. First, a threshold method was used, as described previously [36]. Briefly, an electronic gate was set manually so that it included the brightest 3–5 % of the cells stained with mouse IgG2a mAb. Then the same gate was used to determine the proportion of positively fluorescing cells in the sample stained with the HLA-DR-specific mAb. This was done by laboratory technicians who were unaware of the patients’ clinical status. Secondly, a modified histogram subtraction method was used, as described previously [39,40]. Briefly, the IgG2a histogram was smoothed and then subtracted, using a CellQuest software program, from the respective HLA-DR histogram (Figure 1). The histogram differential represents HLA-DR-positive monocytes, whose proportion is calculated by the software program. Monocyte HLA-DR fluorescence intensity, expressed as RFU (relative fluorescence units), was obtained by subtracting the median channel number of the IgG2a histogram from the median channel number of the respective HLA-DR histogram.

CRP levels
The reagents for the immunoturbidimetric measurement of the serum CRP concentration were purchased from Orion Diagnostica (Espoo, Finland). The detection limit was 2 mg/l.

Statistical analysis
The data are presented as median and interquartile range (IQR). For comparison of the time from onset of symptoms to hospital admission between the groups, we used the Kruskal–Wallis test. For comparisons of the severity of AP and the proportion of HLA-DR-positive monocytes between groups I, II and III, we used Cuzik’s test for trend, and adjusted P values with Hommel’s modification of the Bonferroni method. Agreement of values for the proportion of HLA-DR-positive monocytes between repeated measurements using the threshold method and that between the threshold method and the channel-by-channel subtraction method was evaluated using the intraclass correlation coefficient and its 95 % CI (confidence interval). The relationship between the proportion of HLA-DR-positive monocytes and HLA-DR fluorescence intensity was determined using the Spearman rank correlation coefficient (r). Sensitivity, specificity and positive-likelihood ratio, and their 95 % CI values, were calculated for admission data, including the proportion of HLA-DR-positive cells, HLA-DR fluorescence intensity and APACHE II score. ROC (receiver-operating characteristic) curves were used for determination of thresholds for the organ dysfunction group compared with the group without organ dysfunction, and the respective areas under the curve were calculated with a bias-corrected accelerated bootstrap confidence interval.

RESULTS
Clinical findings
Of the 314 patients included in the study, 197 (63 %) had mild AP (group I), 87 (28 %) had a severe AP without organ failure (group II) and 30 (9.6 %) had severe AP complicated by organ failure (group III). A total of four patients were excluded from the data analysis. Three were members of group I for whom samples were lacking, and one belonged to group III and presented with monocytopenia, which rendered the HLA-DR measurement unreliable.

Among the remaining 310 patients, APACHE II score, multiple organ dysfunction score, Ranson score and length of hospital stay all increased with increasing severity of AP (Table 1). The aetiology of AP was alcohol in 193 (62 %) patients, biliary disease in 68 (22 %), unknown in 46 (15 %), endoscopic retrograde
Table 1  Characteristics of patient groups defined by severity of AP

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>3 (2, 5)</td>
<td>8 (5, 9)</td>
<td>8 (7, 11)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>24 h</td>
<td>3 (2, 4)</td>
<td>6 (4, 8)</td>
<td>8 (4, 10)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>MODS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>0 (0, 1)</td>
<td>1 (0, 2)</td>
<td>4 (1, 5)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>24 h</td>
<td>0 (0, 0)</td>
<td>0 (0, 1)</td>
<td>7 (2, 9)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Ranson score</td>
<td>1 (1, 2)</td>
<td>3 (2, 4)</td>
<td>6 (3, 7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>5 (4, 6)</td>
<td>9 (6, 12)</td>
<td>24 (12, 40)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 2  Characteristics of the 29 patients with organ failure

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from hospital admission to organ dysfunction (h)</td>
<td>26 (14, 78)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>25 (86)</td>
</tr>
<tr>
<td>Duration (days) [median (IQR)]</td>
<td>12 (2, 24)</td>
</tr>
<tr>
<td>Haemodialysis [n (%)]</td>
<td>14 (48)</td>
</tr>
<tr>
<td>Multiple organ dysfunction score [median (range)]</td>
<td></td>
</tr>
<tr>
<td>On admission (n = 29)</td>
<td>4 (0, 8)</td>
</tr>
<tr>
<td>Day 1 (n = 28)</td>
<td>6 (0, 13)</td>
</tr>
<tr>
<td>Day 7 (n = 25)</td>
<td>6 (2, 14)</td>
</tr>
<tr>
<td>Day 14 (n = 21)</td>
<td>5 (0, 11)</td>
</tr>
<tr>
<td>Day 21 (n = 14)</td>
<td>5 (0, 11)</td>
</tr>
<tr>
<td>Deaths [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Early (⩽ 7 days after admission)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Late (&gt; 7 days after admission)</td>
<td>5 (17)</td>
</tr>
</tbody>
</table>

cholangiopancreatography in two (0.6%) and pancreas divisum in one (0.3%) patient. The time from the onset of symptoms to hospital admission was significantly longer in the 29 patients with organ failure than in patients in groups I and II [group III, 48 h (IQR 21–72 h); group I, 24 h (IQR 8–48 h); group II, 24 h (IQR 8–48 h); P = 0.040, Kruskal–Wallis test]. Ten patients (3.2%) died during the hospital stay. Death was related to AP in nine patients, all of whom were members of group III, and to acute myocardial infarction in a member of group I.

Characteristics of group III patients are shown in Table 2. Of the 29 patients, 13 (45%) developed organ failure within 24 h of admission (Figure 2). Of the nine patients with fatal AP, seven developed organ failure within 26 h of admission.

Measurement of HLA-DR expression

The reproducibility of the threshold method has been criticized if considerable overlap exists between positive and negative distributions of test histograms [41]. To evaluate the reproducibility of the measurement, specimens from 138 consecutive patients were analyzed further. The intraclass correlation coefficient of the two measurements was 0.98 (95% CI 0.97–0.99). Next, we evaluated the agreement between the threshold method and the channel-by-channel subtraction method. In the present study of 170 consecutive patients, the intraclass correlation coefficient for the two assays was 0.96 (95% CI 0.95–0.97). The channel-by-channel subtraction method was preferred to the threshold method, because it lacks the element of subjectivity and because considerable overlap was frequently seen between the negative control histogram and the test histogram, and, by using this method, the proportion of HLA-DR-positive monocytes was related to HLA-DR fluorescence intensity (r = 0.89; 95% CI 0.86–0.91; Figure 3). The two variables were used in the further analysis.

HLA-DR expression in relation to the severity of AP

The proportion of HLA-DR-positive monocytes and HLA-DR fluorescence intensity both decreased significantly with increased severity of AP (Table 3).

In predicting organ failure, the ROC curves for the proportion of HLA-DR-positive monocytes (Figure 4A), HLA-DR fluorescence intensity (Figure 4B), APACHE II score (Figure 4C) and CRP levels (Figure 4D) were calculated on the basis of the admission data. Areas under the ROC curve were 0.78 (95% CI 0.66–0.87), 0.81 (0.71–0.89), 0.79 (0.69–0.86), and 0.80 (0.69–0.88) respectively. The optimal cut-off level for HLA-DR-positive monocytes was ⩽ 78%, for HLA-DR fluorescence intensity ≤ 33 RFU, for APACHE II ⩾ 7, and for CRP ⩾ 57 mg/ml (Table 4).
Figure 3  Relationship between proportion of HLA-DR-positive monocytes and HLA-DR fluorescence intensity of monocytes from 310 patients at admission to hospital

The channel-by-channel subtraction method was used to define HLA-DR-positive cells. ● Patients with organ dysfunction (n = 29); ○, patients without organ dysfunction (n = 281).

### Table 3  HLA-DR expression on monocytes from 310 patients with AP at admission to hospital

Values are median (IQR). P values were obtained using Cuzik’s test for trend and were adjusted using Hommel’s method.

<table>
<thead>
<tr>
<th>HLA-DR expression</th>
<th>Group I (n = 194)</th>
<th>Group II (n = 87)</th>
<th>Group III (n = 29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive monocytes (%)</td>
<td>90 (80, 95)</td>
<td>84 (66, 91)</td>
<td>62 (49, 76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Density (RFU)</td>
<td>90 (53, 143)</td>
<td>65 (24, 115)</td>
<td>20 (13, 49)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

When the patients were classified according to the original Atlanta classification (groups II and III compared with mild AP), the optimal cut-off level for HLA-DR-positive monocytes was ≤78%, for HLA-DR fluorescence intensity ≤54 RFU, for APACHE II ≥6, and for CRP ≥24 mg/ml at admission. Sensitivities were 52%, 55%, 65% and 68% respectively, specificities were 77%, 74%, 88% and 61% respectively, and positive-likelihood ratios were 2.3, 2.1, 5.4 and 1.7 respectively.

Figure 4  ROC curves for the prediction of organ dysfunction on the basis of the proportion of HLA-DR-positive monocytes (A), HLA-DR density (B), APACHE II score (C) and CRP concentration (D)

Analyses were done on the basis of data obtained on admission to hospital.
Predicting organ failure in patients with AP at admission to hospital

The present results show that APACHE II, CRP and proportion of HLA-DR-positive monocytes at admission predicted organ dysfunction equally well, when compared on the basis of sensitivity (76 %, 83 % and 83 % respectively), specificity (73 %, 74 % and 72 % respectively) and positive-likelihood ratio (2.8, 3.2 and 3.0 respectively). The findings support previous results indicating that, in the prediction of severe AP, the APACHE II score at the time of admission had a sensitivity of 63 % and a specificity of 81 % with a cut-off value of ≥10 [43]; in another study [27] these values were 95 % and 54 % respectively, with an optimal cut-off value of ≥6. The APACHE II score is composed of as many as 12 clinical and laboratory variables [26] and may therefore be difficult to accomplish in clinical practice on admission to a hospital [48]. In addition, comparison of the APACHE II score between different centres is hampered by differences in the aetiology of AP and the timing of presentation. Monocyte HLA-DR expression might provide an alternative means to predict the hospital course of AP. Flow cytometric measurement of the plasma membrane glycoproteins, such as HLA-DR molecules, can be used as a routine clinical test [49–51] and provides results within 30–60 min of sampling. In addition, it is likely that the results obtained in different centres are comparable. Both HLA-DR and CRP are clearly associated with the severity of AP, indicating that they are, in terms of the pathophysiology of AP, relevant markers. However, optimal cut-offs for both HLA-DR and CRP at admission were far from their nadir [36] and peak [46] levels respectively, which are reached not infrequently after, and not before, the occurrence of organ failure. Due to their relatively slow time course, HLA-DR and CRP may not be ideal markers in terms of predicting the development of organ failure.

Monocyte HLA-DR expression has been analysed in a variety of clinical studies of conditions other than AP [52–58]. At present, however, it is uncertain which of the different ways used to measure the monocyte surface density of HLA-DR molecules correlates best with the clinical findings. The threshold method, commonly used to determine the proportion of HLA-DR-positive monocytes with flow cytometry, is subjective because the lowest level of positive fluorescence is set manually.

DISCUSSION

This prospective study shows that monocyte HLA-DR expression, a cellular marker of immune suppression, provides a novel means of predicting organ dysfunction in patients with AP admitted to a hospital emergency unit within 72 h of the onset of symptoms. While the present study was in progress, Johnson et al. [6] reported that 44 % of the patients with predicted severe AP developed failure of one or more organs within 72 h of the onset of symptoms. This new finding is corroborated by our results indicating that 45 % of the patients in group III had already developed organ dysfunction within 24 h of admission. The very early development of organ failure has important implications for the current use of severity markers of AP, the search for novel predictors of organ dysfunction and the design of therapeutic studies aimed at altering the course of systemic inflammation in AP to interfere with the development of organ failure.

The prognostic system APACHE II [26] and its modification APACHE III [42] are both related to the severity of AP [27,43–45]. CRP concentration is the most widely used single marker for determining the severity of AP, although it reaches its peak value 48–72 h after disease onset [46]. Because organ failure is the major cause of mortality, morbidity and hospital costs in patients with AP [3,4], we analysed the data in the present study, as we did in our previous studies [36,47], in terms of the development of organ dysfunction. We used the Atlanta classification, the major scoring system presently available, as a reference method to allow comparison with other studies. The Atlanta classification is problematic because it is retrospective and its definition of severe AP is very broad. Patients with local complications only have a favourable outcome, no mortality and a short hospital stay (Table 1) [47]. Further, the definition of organ failure in the Atlanta classification places patients with transient, clinically insignificant hypotension or a low arterial partial pressure of O2 into the severe group, which in our view is somewhat misleading. Therefore we applied clinically more relevant and widely accepted criteria for organ failure, i.e. the need for mechanical ventilation or haemodialysis.

### Table 4 Predicting organ failure in patients with AP at admission to hospital

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Cut-off point</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>LR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DR expression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive monocytes</td>
<td>≤ 78 %</td>
<td>83 (64–94)</td>
<td>72 (67–77)</td>
<td>3.0 (2.2–3.8)</td>
</tr>
<tr>
<td>Density</td>
<td>≤ 33 RFU</td>
<td>69 (49–85)</td>
<td>84 (79–88)</td>
<td>4.3 (2.9–6.1)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>≥ 7</td>
<td>76 (56–90)</td>
<td>73 (67–78)</td>
<td>2.8 (2.0–3.6)</td>
</tr>
<tr>
<td>CRP</td>
<td>≥ 57 mg/l</td>
<td>83 (64–94)</td>
<td>74 (68–79)</td>
<td>3.2 (2.5–4.1)</td>
</tr>
</tbody>
</table>

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In general, the threshold method is considered to be reliable provided that the control and test histograms do not have considerable overlap [59]. Our findings show, however, that the overlap of histograms does occur, particularly in patients with greatly decreased HLA-DR density, which may distort the results [40, 41, 59]. The histogram subtraction method has been proposed as an alternative method [40], but this method has also been criticized [41]. More accurate methods have been developed that rely on the fact that histograms are symmetrical and show constant variance [59, 60], which is seldom the case for HLA-DR histograms. Thus the current methods used to define monocyte HLA-DR expression may not be perfect. However, the results show that fluorescence intensity and the proportion of HLA-DR-positive monocytes, determined by either the threshold method or the channel-by-channel subtraction method, are equally reliable in predicting the development of organ dysfunction in patients with AP.

To our surprise, the time from symptom onset to hospital admission was doubled among the patients with organ failure compared with the other patients. This may indicate that a delay in referral or presentation potentially increases the risk of systemic complications. Although the reason for this difference is not known, it may derive from alcohol consumption, the major cause of AP in the present study. Indeed, it is possible, but not shown, that alcohol intake alleviated the initial abdominal pain, so that the patient was able to continue drinking at home. It is also possible, but again not proven, that drinking alcohol during the initial disease process may increase susceptibility to the development of complications. These possibilities warrant further study.

In patients with severe AP in its early stages, the inflammation represents a body compartment where a strong inflammatory reaction takes place. The reaction is characterized by high levels of circulating pro-inflammatory cytokines (reviewed in [61]), such as tumour necrosis factor [62], IL-1β [29], IL-8 [63], IL-12 [64] and pro-calcitonin [47, 65], an acute-phase reactant [32, 33, 46]. Tumour necrosis factor and IL-1β are considered to stimulate the microvascular endothelium in end organs. IL-8 is notably a tissue chemokine which is barely detectable in healthy tissues, but is induced rapidly by a variety of infectious and non-infectious insults (reviewed in [66]). IL-12 induces Th1-type responses, which may play an important role in the pathogenesis of AP (reviewed in [67]). An activated endothelium promotes leucocyte end-organ sequestration, leucocyte activation and microvascular injury (reviewed in [7, 10, 68]), leading ultimately to organ dysfunction. The inflammatory reaction coincides at an early stage of AP with high circulating levels of anti-inflammatory cytokines, such as IL-10, [30, 31, 69]. Coincidence of the pro- and anti-inflammatory responses is evident also in patients with systemic inflammation triggered by sepsis [70]. Evidence has accumulated to show that low HLA-DR expression results from monocyte re-endocytosis and subsequent intracellular sequestration of MHC II molecules, an event mediated, at least partially, by IL-10 [71, 72]. Over time, a shift will occur in sepsis patients from inflammation towards immune suppression in the blood, but not in the end-organ tissues, where inflammation appears to remain dominant [19, 20].

At the time of co-occurrence of pro- and anti-inflammatory responses in the blood, neither HLA-DR density, as shown in the present study, nor any other single marker [34] may be sufficient to predict organ dysfunction. We are currently studying the possibility that a combination of clinical markers, inflammatory markers and anti-inflammatory markers may provide a marker profile that aids the identification of the patients with AP that are at risk of organ dysfunction. Such a marker profile is needed in selecting patients for clinical studies, which are expensive and not necessarily without side effects, on non-specific therapies [21–23] or targeted therapies [6, 73, 74] aimed at altering the natural course of systemic inflammation.

In conclusion, monocyte HLA-DR expression, a cell-associated marker of immune suppression, is a novel marker that predicts the development of organ dysfunction in patients with AP at the time of admission to hospital. In the present study, of 29 patients with organ dysfunction, 13 (45 %) developed it within 24 h of admission, indicating that HLA-DR expression, like other predictors of organ failure, needs to be measured within hours of admission. HLA-DR expression is not sufficient as a single predictor, but may aid in the creation of a set of markers of inflammation and immune suppression for the early identification of patients with AP that are about to develop organ failure.

ACKNOWLEDGMENTS

We are grateful for grants received from the Helsinki University Central Hospital Research Funds and the Paulo Foundation, Helsinki, Finland.

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Human leucocyte antigen-DR expression in early acute pancreatitis

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Received 5 February 2003; revised 2 March 2003; accepted 2 June 2003
Published as Immediate Publication 2 June 2003. DOI: 10.1042/CS20030058

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