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Original article

High plasma levels of the pro-inflammatory cytokine IL-22 and the anti-inflammatory cytokines IL-10 and IL-1ra in acute pancreatitis

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ABSTRACT

Background/objectives: Pancreatic acinar cells are major targets of IL-22. Our aim is to study early plasma levels of IL-22, of pro- and anti-inflammatory cytokines in acute pancreatitis, and their association with severity or necrosis infection.
Methods: Consecutive patients admitted to the Department of Hepato-Gastroenterology at Poitiers University of Medicine Hospital (France) with a diagnosis of AP were prospectively enrolled. Plasma concentrations of IL-22, IL-6, IL-8, IL-1 α, IL-1β, TNF- α, IFN-γ, IL-17A, IL-10, IL-1ra and IL-4 were assessed by multiple immunoassay at the admission time. A thoracoabdominal contrast-enhanced CT scan was performed at day 2.
Results: Sixty-two patients were included; 13 patients (21%) had a severe acute pancreatitis, 5 patients (8%) developed necrosis infection and 29 patients (47%) had pleural effusion. Plasma levels of IL-22 were high in AP (135 ± 31 vs 4.2 ± 1.8 pg/ml for controls, $p < 0.05$), but did not correlate with the severity of the disease, whereas IL-6, IL-10 and IL-1ra where enhanced in patients with severe acute pancreatitis and with pleural effusion. Patients who further developed necrosis infection had higher levels of IL-1ra at admission ($p = 0.0004$).
Conclusion: In acute pancreatitis, high plasma levels of IL-22 are observed, regardless the severity of the disease. In contrast, severe forms were associated with increased levels of IL-6, IL-10 and IL-1ra. The beneficial or deleterious role of IL-22 in AP remains to be further studied.

Introduction

During acute pancreatitis (AP), early prediction of severity is crucial as mortality reaches up to 30% in severe forms [1,2]. The early-phase mortality is related to organ dysfunctions, whereas necrosis infection is a critical complication that mainly occurs after 15 days of evolution [3]. Pro-inflammatory cytokines play a central role in amplifying both pancreatic and systemic inflammation, as shown by animal models of AP [4,5] and reflected by high circulating levels of IL-6, IL-8, IL-1β and TNF-α in severe acute pancreatitis (SAP) [6,7]. Among the pro-inflammatory cytokines, IL-22, mainly produced by T helper 17 (Th17) cells and Th22 cells, is implicated in multiple tissue inflammation and defenses, especially against bacterial infections [8]. IL-22 signals through a dimeric receptor comprising the broadly expressed IL-10R β chain associated to the IL-22R chain which exhibits a restricted expression pattern. Following IL-22 discovery, pancreatic acinar cells were identified as one of the first targets. IL-22 induces pancreatic associated protein 1 secretion in pancreatic acinar cells [9], suggesting its involvement in pancreatic inflammation. Relative to other human tissues, the highest IL-22R mRNA expression was reported in pancreas [10]. Nevertheless, to the best of our knowledge, IL-22 plasma levels have never been studied during AP.

Abbreviations: AP, acute pancreatits; SAP, severe acute pancreatitis; IL, interleukine.

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On another hand, in most acute inflammatory responses including severe acute pancreatitis (SAP), the systemic inflammatory response syndrome is associated with a compensatory anti-inflammatory response, mediated by IL-10 and IL-1 receptor antagonist (IL-1ra). These cytokines correlate to the severity of AP [7] and may promote immunosuppression and infections [11].

Our objective was to measure circulating IL-22, IL-10 and IL-1ra, in parallel to other pro-inflammatory cytokines, at the admission of AP patients, and to assess their association with severity, lung injury and necrosis infection.

Materials and methods

Patients

Consecutive patients admitted from November 2009 to July 2011 to the Department of Hepato-Gastroenterology at Poitiers University of Medicine Hospital (France) with a diagnosis of AP were prospectively enrolled. AP was defined as the association of characteristic abdominal pain with a three times increase of serum lipase. The Regional Ethics Committee approved the study; all the patients provided written informed consent. The exclusion criteria were an age under 18 years, pregnancy or breastfeeding, diagnosis of AP more than 72 h after the onset of symptoms and patients with past history of mixed connective tissue disease, pneumotoxic treatment (D-penicillamine, bleomycin, cordarone), toxic exposure, recent lung infection or pulmonary embolism, considering the possibility of radiological confounding lesions. Patients were treated according to American and European guidelines [12–14] and did not receive antibiotic prophylaxis of necrosis infection.

Methods

At admission (day 0) and at day 2, clinical and biological data were recorded in order to assess organ failure, APACHE-II score and Ranson score. A thoracoabdominal contrast-enhanced computed tomography (CT) scan blindly reviewed by 2 radiologists (JS, JPT) was performed at day 2 in order to evaluate pancreatic necrosis, local complications and lung injury. Severity of AP was defined according to Atlanta symposium [15]. Pancreatic necrosis infection was diagnosed either by CT-guided needle aspiration or by the association of bacteriemia with the presence of air in the necrotic tissues on imaging studies. Lung injuries on CT scan attributed to AP were pleural effusion, atelectasis and diffuse pulmonary infiltrates.

Peripheral blood samples obtained at day 0 were centrifuged and stored at −20 °C until measurement. The levels of the pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, Tumor Necrosis Factor-α), of anti-inflammatory cytokines (IL-10 and IL-1ra), Th1 cytokine Interferon γ, Th2 cytokine IL-4 and Th17 cytokine IL-17A were measured in plasma using the MILLIPLEX *MAP* Human Cytokines/Chemokine magnetic bead panel kit (Millipore) coupled to the LUMINEX 200™ xPONENT™ software. IL-22 was detected by direct ELISA (Peprotech), according to manufacturer's instructions. Concentrations below the detection limit were considered undetectable.

Statistical analysis

Data were analyzed using GraphPad Prism (GraphPad software, San Diego, CA). Results are presented as median ± interquartile range (IQR). Comparisons between 2 groups used the nonparametric Mann–Whitney *U* test; comparisons between 3groups used the nonparametric Kriskal–Wallis test and the Dunn's post-test when applicable. Correlational analysis used the Pearson test. A $p < 0.05$ was considered statistically significant.

Results

Patients' characteristics

The study included 62 patients (43 males and 19 females), and none of them were further excluded. The mean age was 51 years (range 20–89 years). Alcohol ($n = 24$) and biliary gallstones ($n = 20$) were the main etiologic factors (71%). According to Atlanta classification, 13 patients (21%) developed a SAP, including 4 (6.5%) with respiratory failures and 3 (4.9%) with renal failures. Five patients developed necrosis infection; all were diagnosed after ten days of hospitalization. Four patients developed other bacterial infections (3 biliary infections and 1 prostatitis). Of the 51 patients (82.2%) who had lung injury, 29 had pleural effusion, 40 had atelectasia and one developed acute respiratory distress syndrome (Table 1).

Circulating cytokines levels

Circulating levels of IL-22 were highly elevated during acute pancreatitis when compared with controls. At the admission, the mean plasma concentration was 135 ± 31.2 pg/mL while IL-22 was detected in only one healthy donor ($p = 0.0001$). Among the other measured cytokines, levels of IL-6 ($p < 0.0001$), IL-8 ($p = 0.037$), TNF-α ($p = 0.0003$) and IL-10 ($p = 0.021$) were elevated compared to healthy donors. Levels of IL-1ra were non-significantly increased (Table 2).

In SAP patients, among the pro-inflammatory cytokines measured at admission, plasma levels of IL-6 were twice as much increased ($p = 0.0088$) as compared to mild AP; as well as the anti-inflammatory cytokines IL-10 ($p = 0.0032$) and IL-1ra ($p = 0.0068$). Levels of IL-22 did not differ significantly in SAP ($p = 0.57$) (Fig. 1A). Likewise, IL-6 ($p = 0.0007$, $r = 0.42$) and IL-10 ($p = 0.009$, $r = 0.33$) levels correlated with C-reactive protein (CRP) concentrations at admission, whereas IL-22 levels did not correlate with CRP ($p = 0.75$) (Fig. 2).

When compared with uninfected patients, patients who further developed infections showed at admission a significant increase of plasma IL-1ra ($p = 0.0004$), IL-10 ($p = 0.008$), IL-6 ($p = 0.026$) and IL-8 ($p = 0.023$), and a non-significant increase of plasma IL-22 ($p = 0.33$). Early levels of IL-6, IL-8 and IL-10 did not differ significantly in patients with necrosis infection or other infections; whereas IL-1ra ($p < 0.05$) levels were specifically increased in necrosis infection (Fig. 1B).

Similarly to cytokine profile in SAP, patients with pleural effusion showed at admission a significant increase of plasma IL-6 ($p = 0.0036$), IL-10 ($p = 0.027$) and IL-1ra ($p = 0.04$); whereas levels of IL-22 did not differ significantly ($p = 0.91$) (Fig. 1C). Considering the presence or absence of atelectasis or respiratory

Table 1
Patients' characteristics.

Characteristics	$n = 62$
Mean age (years)	51.2 (range 20–89)
Sex ratio (M/F)	43/19
Etiology (n, %)	
Alcohol	24 (38.7)
Cholelithiasis	20 (32.3)
Other	18 (29)
Necroziting pancreatitis (n, %)	15 (24.2)
Severe acute pancreatitis (n, %)	13 (21)
Necrosis infection	5 (8.1)
Lung injury	51 (82.2%)
Pleural effusion	29 (46.8%)
Atelectasis	40 (64.5%)
Respiratory failure	4 (6.5%)

Table 2
Early cytokines plasma levels during AP compared to healthy donors.

	Controls ($n = 14$) median (interquartile range)	Acute pancreatitis ($n = 62$) median (interquartile range)	p
IL-22 (pg/mL)	2.5 (2.5–2.5)	70.3 (27.1–128)	0.0001
IL-17A (pg/mL)	7.4 (1.5–21.5)	5.2 (1.9–14.3)	0.81
IL-1α (pg/mL)	0.6 (0.6–0.6)	0.6 (0.6–11.6)	0.68
IL-1β (pg/mL)	0.5 (0.5–0.5)	0.5 (0.5–0.5)	0.82
IL-6 (pg/mL)	0.6 (0.6–0.6)	13.8 (1.7–35.7)	<0.0001
IL-8 (pg/mL)	17.1 (11.2–32.7)	45.2 (16.7–87.6)	0.037
TNF-α (pg/mL)	4.0 (1.4–8.3)	10.4 (6.5–18.5)	0.0003
IFN-γ (pg/mL)	12.4 (1.9–28.1)	3.3 (1.6–16.2)	0.34
IL-4 (pg/mL)	1.8 (1.8–120)	11.8 (1.8–31.4)	0.81
IL-10 (pg/mL)	1.3 (1.3–1.3)	1.3 (1.3–12.3)	0.021
IL-1ra (pg/mL)	2.1 (2.1–2.1)	2.1 (2.1–7.5)	0.12

failure, none of the cytokines measured differed significantly (data not shown).

Discussion

Identifying patients at risk for SAP is crucial. Many predictive models based upon clinical, biological or radiological findings have been developed to predict the course of AP. Amongst them, CRP is one of the most reliable marker during the first 48 h after admission. However, its predictive value is rather low at admission [16] and may not help to discriminate between mild and necrotizing pancreatitis at this time. As CRP is produced secondarily to the release of pro-inflammatory signals, the knowledge of the early cytokine network involved in AP could be useful to predict complications from the admission. We confirm that IL-6 plasma concentration is elevated at admission in patients with SAP. In a recent meta-analysis, area under the curve (AUC) of IL-6 at admission for diagnosing SAP was 0.75 [17], which was comparable with the AUC of the different scores commonly used in AP. In the study of Mounzer et al., AUC of Ranson, Glasgow and Bedside Index for Severity in Acute Pancreatitis (BISAP) scores were 0.63, 0.74 and 0.69 respectively for predicting persistent organ failure at admission [18]. In this setting, IL-22 levels had never been studied. In addition to the well-studied triad of the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α, IL-22 has emerged as a powerful regulator of innate and adaptive inflammatory response, especially in non-immunologic organs. Pancreatic acinar cells express high levels of the IL-22 receptor subunit IL-22R [9]. In our study, we report high plasma IL-22 during the early phase of AP. IL-22 is a cytokine closely related with tissue repair and tissue response to microbes, and is mainly produced by Th17 and Th22 cells. Circulating levels of IL-22 are enhanced in acute infections such as acute hepatitis B [19] or abdominal sepsis [20], as in chronic inflammatory diseases such as psoriasis [21]. Interestingly, plasma IL-17A, also produced by Th17 lymphocytes, was not enhanced during AP, leaving open the question of IL-22 sources in this condition. Nonetheless, circulating lymphocytes during SAP indicate

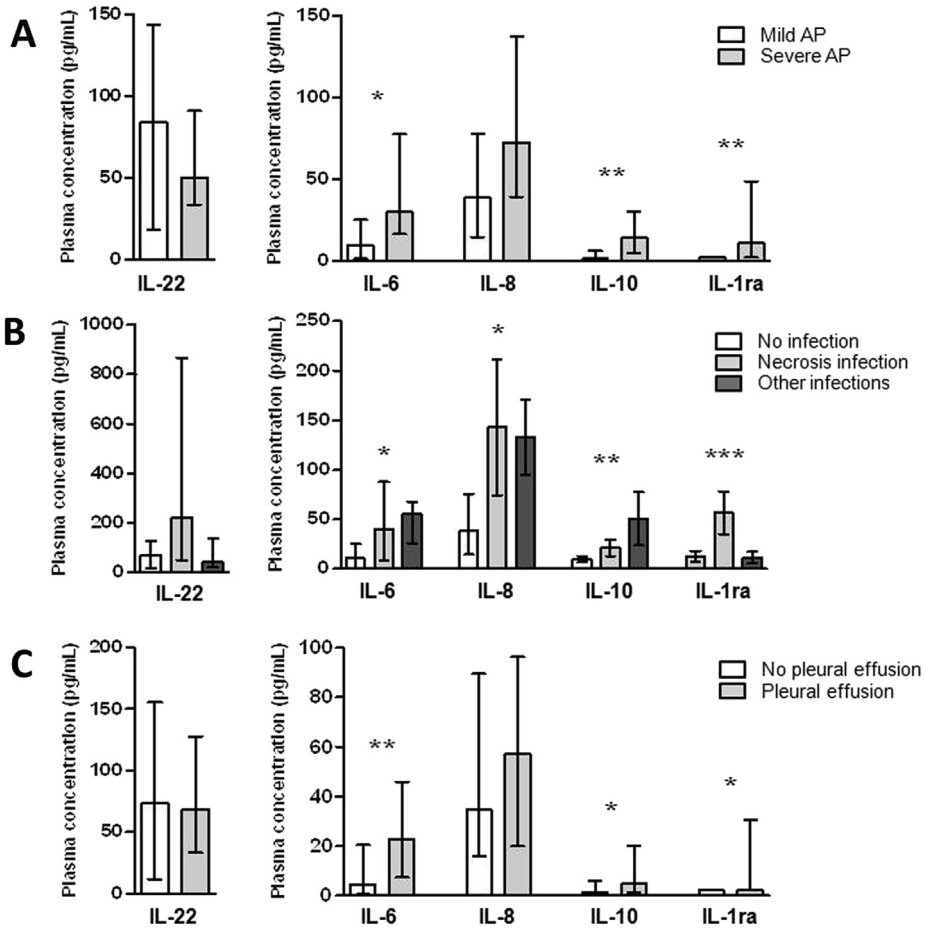

Fig. 1. Cytokines plasma levels at admission in acute pancreatitis. In patients with severe ($n = 13$) or mild acute pancreatits ($n = 49$) (A), in patients without infection ($n = 53$), with necrosis infections ($n = 5$) or with other infections ($n = 4$) (B), and in patients with pleural effusion ($n = 29$) or without pleural effusion ($n = 33$) (C). Results are presented as median ± IQR. Statistical comparisons were performed using Mann–Whitney and Kriskal Wallis tests ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).

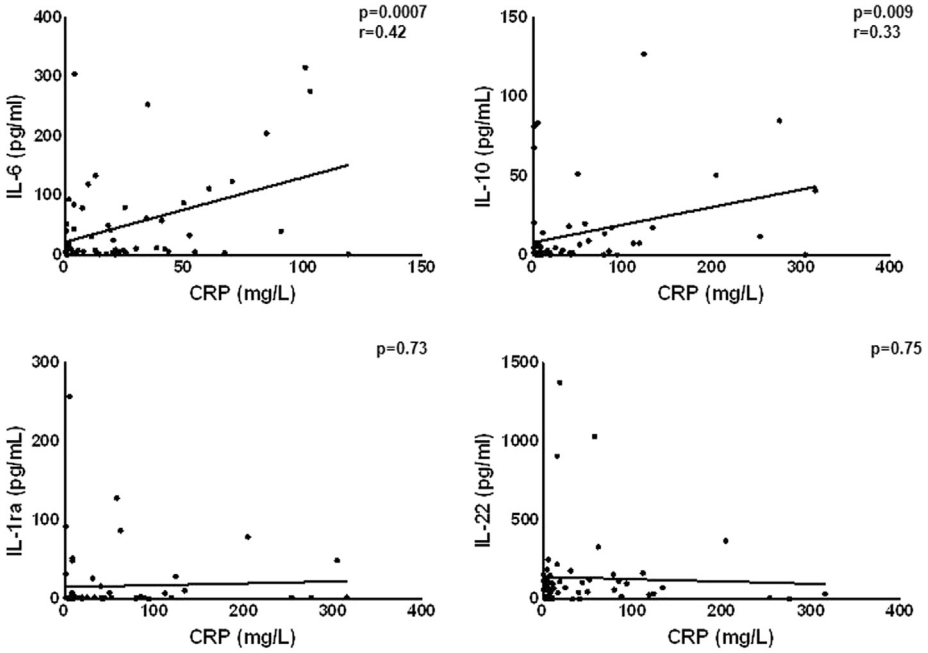

Fig. 2. Correlation of IL-22, IL-6, IL-10 and IL-1ra levels with C-Reactive Protein concentration at admission. Statistical comparisons were performed using Pearson test.

constitutive STAT3 activation, which is a marker of Th17 lymphocyte lineage [22].Three studies have reported protective effects of IL-22 in experimental models of AP. Whereas pancreatic IL-22 is reduced within the first hours, administration of exogenous IL-22 attenuates the severity of experimental AP and lung injury [23,24]. Moreover, attenuation of pancreatitis-associated lung injury is associated with upregulation of IL-22 in lung tissue [25]. In our present study, early plasma levels of IL-22 did not correlate with severity nor with lung injury. Contrary to circulating levels of IL-6 or IL-10, IL-22 concentrations were not associated with systemic inflammation as reflected by CRP levels. This observation suggests that IL-22 production during AP may be induced by pathways distinct from systemic inflammatory responses. When compared with uninfected patients and patients who developed biliary or urinary infections, patients with necrosis infection showed a significant increase of IL-1ra concentrations and a non-significant increase of IL-22 concentration at admission, even though the number of patients is rather low to draw definite conclusions. Development of an excessive compensatory anti-inflammatory response in SAP, as reflected by higher levels of IL-1ra, may favor immunosuppression and thus necrosis infection [11]. In the study of Mentula et al. [26], elevated plasma levels of IL-1ra in AP were correlated with a downregulation of human leukocyte antigen (HLA)-DR, which was associated with necrosis infection. Moreover, necrosis infection is associated with early enterocyte damage, increased gut permeability and bacteremia [27]. These phenomena could further induce a compensatory intestinal production of IL-22 by digestive lymphoid cells [28,29]. Up to now, although IL-22 and IL-1ra measurements do not appear to be useful in order to predict necrosis infection, they seem to be promising markers. Further studies are necessary to evaluate their putative predictive value.

We also confirm that the pro-inflammatory state in SAP is associated with an early anti-inflammatory response [7,30], as reflected by significantly higher plasmatic levels of IL-10 and IL-1ra. The early-phase mortality however mainly relies on a systemic inflammatory state. The major role played by cytokines in initiating this process is illustrated by genetic studies showing an association between IL-8 gene polymorphisms and the risk of AP [31,32]. After the activation of pancreatic enzymes, pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β and IL-8 are released and contribute to the early aggression by amplifying acinar cell injury and leukocyte recruitment [5]. Release of these cytokines via the portal vein to the circulation may explain remote organ complications [33], as in sepsis.

In conclusion, we show for the first time a strong elevation of plasma IL-22 during the early phase of AP. We confirm that SAP associates early systemic pro-inflammatory and anti-inflammatory responses characterized by higher plasma concentrations of IL-6, IL-10 and IL-1ra. Further studies will be necessary to precise the IL-22 cellular sources and the beneficial or deleterious role of IL-22 in AP.

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