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Soluble CD163 from activated macrophages predicts mortality in acute liver failure

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Abstract

BACKGROUND—Soluble CD163 (sCD163) is a scavenger receptor shed in serum during inflammatory activation of macrophages. We investigated if sCD163 was increased and predicted outcome in acute liver failure (ALF).

METHODS—Samples from 100 consecutive patients enrolled in the U.S. ALF Study Group for whom sera were available were collected on days 1 and 3, and clinical data were obtained prospectively. sCD163 levels were determined by ELISA.

RESULTS—The median level of sCD163 was significantly increased in ALF (21.1 mg/l (range 3.6 – 74.9)) as compared to healthy controls (2.3 mg/l (0.65 – 5.6), $p < 0.0001$) and patients with stable liver cirrhosis (9.8 mg/l (3.6 – 16.9), $p = 0.0002$). sCD163 on day 1 correlated significantly with ALT, AST, bilirubin, and creatinine. sCD163 concentrations on day 3 were elevated in patients with fatal outcome of disease compared to spontaneous survivors, 29.0 mg/l ((7.2 – 54.0) vs. 14.6 mg/l (3.5 – 67.2), respectively ($p = 0.0025$)). Patients that were transplanted had intermediate levels. Sensitivity and specificity at a cut off level of 26 mg/l was 62 % and 81 % respectively.

CONCLUSIONS—Activated macrophages are involved in ALF resulting in a 10-fold increase in sCD163. A high level (> 26 mg/l) of sCD163 was significantly correlated with fatal outcome and might be used with other parameters to determine prognosis.

Keywords

acute liver failure; prognostic score; anti-inflammatory markers

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INTRODUCTION

Macrophages and other cells of the immune system are involved in the pathogenesis of acute liver failure (ALF), as reflected by activation of both pro- and anti-inflammatory cascades of the innate immune system (1–4). Recent findings suggest that changes in the inflammatory balance may be important for the disease course, and that a shift towards an immunosuppressive, anti-inflammatory state may be deleterious (1,3).

CD163 is a macrophage lineage-specific scavenger receptor regulated by IL10 and known to be involved in several anti-inflammatory functions of the immune system (5). The receptor is significantly up-regulated on liver CD68+ macrophages during acute hepatitis (6). Highly elevated levels of a circulating form of the receptor (soluble CD163, sCD163) have recently been described in sera from patients with ALF (7), indicating that CD163 positive macrophages could be involved in the pathogenesis and clinical course of ALF.

The difficult decision whether to perform a liver transplantation in ALF must be made early in the disease course (8), and new marker molecules that could be incorporated into robust prognostic models would have important clinical value. In the present work we investigated whether levels of sCD163 were related to clinical outcome when measured early in patients with ALF.

MATERIALS AND METHODS

Study design and patients

One hundred patients with ALF were prospectively enrolled in the U.S. ALF Study Group (9). Patients met ALF criteria of coagulopathy (International Normalized Ratio > 1.5) and any degree of hepatic encephalopathy. On admission, 45 patients had hepatic coma grade I or II, and 55 patients had grade III or IV hepatic encephalopathy; maximum hepatic encephalopathy was I or II in 37 patients, whereas 63 patients had maximum grade III or IV hepatic encephalopathy. Consecutive patients for whom sera were available were chosen. After informed consent was obtained from next of kin, detailed prospective clinical and laboratory data were entered in anonymous fashion into case report forms at admission to study and 3 weeks later, or at time of death or liver transplantation. The aetiologies were established by the site investigators using standard criteria. Blood samples for sCD163 analyses were taken at the day of enrolment (day 1) and two days later (day 3). Seventy-five samples were obtained at day 1, and 77 samples at day 3. Samples from both days were available from 52 patients. Clinical and biochemical data are summarised in table 1. The study met all requirements of institutional review boards at the respective study sites. One-hundred age and sex-matched controls without known hepatic or biliary disease were selected from 240 samples obtained from the NOBIDA biobase (<http://www.furst.no/norip/nobida/index.htm>). Seven patients with chronic alcoholism (without clinical symptoms of liver cirrhosis) and 13 patients with stable liver-cirrhosis due to chronic alcoholism (without ascites or esophageal varices) were also included as pathological controls.

Biochemical analyses

sCD163 was measured in ELISA as described in detail (10). In brief, rabbit anti-CD163, 4 mg/l was coated onto micro-titer wells. After wash, 100 µl of sample (diluted 1:50 in PBS with albumin, pH 7.2) was added and incubated for 1 h. The wells were washed and 100 µl of monoclonal anti-CD163 (GHI/61, diluted 1:500) was added and incubated for 1 h. After wash, 100 µl of peroxidase-labeled antibody (goat anti-mouse immunoglobulins, DAKO P447, diluted 1:4000) was added and incubated for 1 h. The wells were washed, and 100 µl of a H₂O₂/1,2-phenylenediamine dihydrochloride substrate solution was added. After 15 min 50

μL of 1 mol/l H_2SO_4 was added, and the plates were read at 492/620 nm. Control-samples and standards of purified CD163 were co-analysed in each run. The inter-assay imprecision was 6.2 and 9.7 % CV at levels of 1.8 and 3.9 mg/l respectively ($n=15 \times 2$).

Statistics

Non parametric tests were used for comparison of groups (Mann-Whitney test for unpaired data and Wilcoxon signed rank test for paired data) and for correlation analyses (Spearman Rho). 95 % confidence intervals (95 % CI) for the area under curve (AUC) in Receiver Operating Characteristics (ROC curves) were calculated nonparametrically.

All statistical analyses were performed using GraphPad Prism Version 4.02.

RESULTS

The study population is described in table 1. The levels of sCD163 were measured on day 1 and day 3 of entrance. There was no difference in sCD163 levels between men and women ($p=0.08$ and $p=0.95$ for Day 1 and Day 3 respectively), and levels were not related to age ($r=0.16$, $p=0.17$ and $r=-0.01$, $p=0.94$ for day 1 and 3 respectively).

Highly increased sCD163 in acute liver failure

The median sCD163 levels were highly increased in patients with AFL on both day 1 (21.1 mg/l (range 3.6 – 74.9)) and day 3 (19.2 mg/l (2.6 – 67.2)) as compared to healthy controls (2.3 mg/l (0.65 – 5.6)) ($p < 0.0001$). Patients with chronic alcoholism and patients with stable alcoholic liver cirrhosis had intermediate levels (4.7 mg/l (2.9 – 11.0) and 9.8 mg/l (3.6 – 16.9) respectively) (Figure 1A). There was no statistical difference between CD163 levels day 1 and day 3 ($p=0.68$).

Grouping patients according to aetiology revealed that sCD163 in the acetaminophen group at day one was significantly lower than in patients with non-acetaminophen induced ALF ($p=0.016$). This difference, however, was levelled out at day 3. The highest concentrations were found at day one in patients with indeterminate causes ($p=0.009$ as compared to acetaminophen) (Figure 1B).

Significant correlations were found between sCD163 and ALT ($r=-0.40$, $p=0.0004$), AST ($r=-0.33$, $p=0.005$), bilirubin ($r=0.41$, $p=0.0003$), and creatinine ($r=-0.23$, $p=0.046$) at day 1, however these correlations were absent at day 3. No correlation was observed between sCD163 and INR. Patients with ascites at day 1 had higher CD163 levels ($p=0.029$), however no increase was seen in patients with peripheral oedema ($p=0.53$). Infected patients did not have increased levels of sCD163 ($p=0.20$). There was no correlation between the levels of sCD163 and the duration of icterus or the duration of symptoms. Patients with grade III or IV hepatic encephalopathy did not have higher levels of sCD163 than patients with lower grade encephalopathy.

Prediction of survival by sCD163

The levels of sCD163 were compared between patients with spontaneous survival, patients who died (without transplantation), and patients who underwent liver transplantation. At day 1 the median levels in non-survivors were slightly increased as compared to survivors (23.5 mg/l (range 3.6 – 57.1) vs. 16.2 mg/l (5.6 – 74.9), $p=0.087$), and this difference was significantly expanded at day 3 (29.0 mg/l (7.2 – 54.0) vs. 14.6 mg/l (3.5 – 67.2), $p=0.002$) (Figure 2AB). When comparing the groups using the maximum sCD163 value for each patient who had both samples taken, the difference between non-survivors and survivors became even more

pronounced (43.5 mg/l (7.2 – 57.1) vs. 21.1 mg/l (6.6 – 74.9), $p=0.0009$) (Figure 2C). Patients that were transplanted had intermediate levels.

The ability of sCD163 to distinguish between non-survivors and survivors was described by generating Receiver Operating Characteristics (ROC curves) for sensitivity and specificity using different cut-off levels. At a cut-off level of 26 mg/l the sensitivity and specificity was 40.6 % and 75.0 % respectively at day 1 (Figure 3A) and 61.5 % and 81.3 % respectively at day 3 (Figure 3B). Using the maximum value of day 1 and 3, the sensitivity and specificity was 80.0 % and 72.7 % respectively (75 % and 81.8 % at a cut-off level of 27.5 mg/l) (Figure 3C).

DISCUSSION

In acute liver failure, the decision to perform a liver transplantation is a critical but difficult one. It is particularly challenging during the early phase of disease when chances for survival are best but the outcome most uncertain (8). At present the Kings College criteria (11) are most widely used, however, they lack sensitivity for accurate selection of patients at an early stage (8). New marker molecules that might be incorporated into more robust prognostic models therefore may have important clinical value.

In this report we have shown that the serum levels of soluble CD163, originating predominantly from anti-inflammatory macrophages, are increased 10-fold in acute liver failure compared to age and gender matched controls in agreement with previous findings in a smaller group of patients (7). Furthermore we have demonstrated that very high levels of sCD163 (> 26 mg/L) are related to poor disease outcome and may be valuable in selection of patients for transplantation.

The accuracy of measuring sCD163 alone for prediction of fatal outcome does not exceed what is obtained by traditional scores such as Kings College criteria (8), however, addition of sCD163 to Kings College criteria or other criteria such as MELD may improve sensitivity and identification of patients early in the disease process, which should be prospectively validated.

sCD163 was also elevated in patients with chronic alcoholism (2 times) and in patients with stable alcoholic liver cirrhosis (4–5 times), however still far from the very high levels found in ALF. None of the controls reached the levels associated with a poor prognosis in ALF.

CD163 is a marker-molecule in the plasma membrane of alternatively activated macrophages that is up-regulated by IL10 and glucocorticoid (12–14). The primary role for CD163 is the scavenging of haptoglobin-hemoglobin complexes (15), but it also appears to have anti-inflammatory activity (5). CD163 is almost exclusively restricted to monocytes and macrophages (16), and strong expression has been demonstrated in CD68-positive liver macrophages during acute hepatitis (6). Increased levels of IL10 in ALF have been reported in several reports (3,4), which may contribute to the very high levels of sCD163 in ALF.

Besides its presence in the membrane of macrophages, CD163 is found in the extra-cellular fluids (soluble CD163, sCD163), due to proteolytic cleavage of the membrane form by metalloproteinase activity (17). This shedding of sCD163 is dependent on activation of toll-like receptors by inflammatory mediators (18), that gives rise to increased levels of sCD163 in serum in diseases involving activation (e.g. hemophagocytosis, sepsis) and proliferation (e.g. leukaemia, Gaucher disease) of macrophages (19–22).

In vitro, macrophages can take up different phenotypes dependent on the cytokine environment (23,24), which is reflected in vivo by pro- and anti-inflammatory activation states balancing the immune responses. The high CD163 levels in ALF may represent an anti-inflammatory

imbalance, especially in patients with a poor outcome of disease. This is supported by a recent report that describes a significant reduction in the expression of monocytic HLA-DR in patients with acute liver failure, and importantly, a correlation between monocytic deactivation and poor survival (3). The cells have impaired ability at presenting antigen and at producing TNF- α (3,23), and may represent a possible target for intervention.

A relation between high levels of sCD163 and mortality has also been described in patients with sepsis and hemophagocytosis (19,20). In sepsis, the levels of sCD163 are considerably lower than in ALF (e.g. 4.6 mg/l in pneumococcal bacteremia vs 21.1 mg/l in ALF (19)), but interestingly the relatively few sepsis-patients with very high sCD163 levels had increased mortality (19). Hemophagocytic syndrome is a clinicopathologic entity characterized by a generalized activation of macrophages with hemophagocytosis throughout the reticuloendothelial system, and clinical manifestations resulting from the overproduction of cytokines (25). The levels of sCD163 in hemophagocytosis are comparable to the very high levels found in ALF, whereas the levels seen in other situations of macrophage activation (infections, autoimmune disease, cancer) are considerably lower. This suggests that in ALF a large proportion of liver macrophages are activated and may contribute significantly to the pathogenesis of ALF.

Our study supports that sCD163 may be valuable as a disease marker. At day three of enrolment to the study, high levels of sCD163 were significantly associated with mortality. It is clear, however, that the time of sampling is crucial since the levels at day one was only marginally significant, and that the maximum level of sCD163 had the highest sensitivity and specificity for prediction of fatal outcome. Serial measurements of sCD163 should therefore be performed to evaluate if a continuous increase in sCD163 levels or a certain threshold may contain most information. It is interesting that sCD163 at day one correlated significantly to several biochemical liver-parameters, while this correlation was lost by day three, indicating an independent pathophysiological role for sCD163. Whereas the physiological roles for sCD163 in inflammatory diseases are poorly understood, the membrane bound sCD163 seems to strengthen the anti-inflammatory response by fueling heme oxygenase-1 and by upregulating its expression (5,26).

It is important to consider that the sequence of sCD163 concentrations may be different depending on the aetiology of ALF. This is emphasized by the low levels in the acetaminophen group and high levels in the group of patients with indeterminate causes at day 1. Whether differences in IL10 and other cytokines show the same pattern as the observed differences in sCD163 are presently being evaluated in the same cohort.

Since the shedding of soluble CD163 involves the loss of macrophage surface molecules, combined measurements of soluble CD163 and surface CD163 (by flow cytometry) would add more information on the regulation of CD163 in ALF, and the ratio between the two parameters possibly better predicts disease outcome (27).

The finding of successively increased levels in healthy, chronic alcoholics, stable alcoholic cirrhosis, and ALF may indicate a wider prognostic capability of sCD163, e.g. for the identification of alcoholic patients with incipient cirrhosis. This, however, was outside the scope of the present investigation.

In conclusion, the levels of soluble CD163 are 10 fold increased in patients with ALF, indicating that activated macrophages contribute significantly to the pathogenesis of ALF. Furthermore very high levels (> 26 mg/l) are correlated with mortality. Further study will be necessary to evaluate its use as a prognostic marker in predicting outcome in the setting of acute liver failure.

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References

1. Liu ZX, Kaplowitz N. Role of innate immunity in acetaminophen-induced hepatotoxicity. *Expert Opin Drug Metab Toxicol* 2006;2:493–503. [PubMed: 16859400]
2. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. *Hepatology* 2000;32:734–9. [PubMed: 11003617]
3. Antoniadou CG, Berry PA, Davies ET, Hussain M, Bernal W, Vergani D, et al. Reduced monocyte HLA-DR expression: a novel biomarker of disease severity and outcome in acetaminophen-induced acute liver failure. *Hepatology* 2006;44:34–43. [PubMed: 16799971]
4. Nagaki M, Iwai H, Naiki T, Ohnishi H, Muto Y, Moriwaki H. High levels of serum interleukin-10 and tumor necrosis factor- α are associated with fatality in fulminant hepatitis. *J Infect Dis* 2000;182:1103–8. [PubMed: 10979906]
5. Moestrup SK, Møller HJ. CD163: a regulated hemoglobin scavenger receptor with a role in the anti-inflammatory response. *Ann Med* 2004;36:347–54. [PubMed: 15478309]
6. Hiraoka A, Horiike N, Akbar SM, Michitaka K, Matsuyama T, Onji M. Expression of CD163 in the liver of patients with viral hepatitis. *Pathol Res Pract* 2005;201:379–84. [PubMed: 16047947]
7. Hiraoka A, Horiike N, Akbar SM, Michitaka K, Matsuyama T, Onji M. Soluble CD163 in patients with liver diseases: very high levels of soluble CD163 in patients with fulminant hepatic failure. *J Gastroenterol* 2005;40:52–6. [PubMed: 15692789]
8. Jalan R. Gc-Globulin to predict outcome in acute liver failure: a panacea ? *Liver transpl* 2005;11:1169–71. [PubMed: 16184541]
9. Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, et al. U.S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002;137:947–54. [PubMed: 12484709]
10. Møller HJ, Hald K, Moestrup SK. Characterization of an enzyme-linked immunosorbent assay for soluble CD163. *Scand J Clin Lab Invest* 2002;62:293–9. [PubMed: 12476928]
11. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;97:439–45. [PubMed: 2490426]
12. Mosser DM. The many faces of macrophage activation. *J Leukoc Biol* 2003;73:209–12. [PubMed: 12554797]

13. Buechler C, Ritter M, Orso E, Langmann T, Klucken J, Schmitz G. Regulation of scavenger receptor CD163 expression in human monocytes and macrophages by pro- and antiinflammatory stimuli. *J Leukoc Biol* 2000;67:97–103. [PubMed: 10648003]
14. Sulahian TH, Hogger P, Wahner AE, Wardwell K, Goulding NJ, Sorg C, et al. Human monocytes express CD163, which is upregulated by IL-10 and identical to p155. *Cytokine* 2000;12:1312–21. [PubMed: 10975989]
15. Kristiansen M, Graversen JH, Jacobsen C, Sonne O, Hoffman HJ, Law SK, et al. Identification of the haemoglobin scavenger receptor. *Nature* 2001;409:198–201. [PubMed: 11196644]
16. Maniecki MB, Møller HJ, Moestrup SK, Møller BK. CD163 positive subsets of blood dendritic cells: the scavenging macrophage receptors CD163 and CD91 are coexpressed on human dendritic cells and monocytes. *Immunobiology* 2006;211:407–17. [PubMed: 16920480]
17. Droste A, Sorg C, Hogger P. Shedding of CD163, a novel regulatory mechanism for a member of the scavenger receptor cysteine-rich family. *Biochem Biophys Res Commun* 1999;256:110–3. [PubMed: 10066432]
18. Weaver LK, Hintz-Goldstein KA, Pioli PA, Wardwell K, Qureshi N, Vogel SN, et al. Pivotal advance: activation of cell surface Toll-like receptors causes shedding of the hemoglobin scavenger receptor CD163. *J Leukoc Biol* 2006;80:26–35. [PubMed: 16799153]
19. Schaer DJ, Schleiffenbaum B, Kurrer M, Imhof A, Bachli E, Fehr J, et al. Soluble hemoglobin-haptoglobin scavenger receptor CD163 as a lineage-specific marker in the reactive hemophagocytic syndrome. *Eur J Haematol* 2005;74:6–10. [PubMed: 15613100]
20. Møller HJ, Moestrup SK, Weis N, Wejse C, Nielsen H, Pedersen SS, et al. Macrophage serum markers in pneumococcal bacteremia: prediction of survival by soluble CD163. *Crit Care Med* 2006;34:2561–6. [PubMed: 16915112]
21. Møller HJ, Peterslund NA, Graversen JH, Moestrup SK. Identification of the hemoglobin scavenger receptor/CD163 as a natural soluble protein in plasma. *Blood* 2002;99:378–80. [PubMed: 11756196]
22. Møller HJ, de Fost M, Aerts H, Hollak C, Moestrup SK. Plasma level of the macrophage-derived soluble CD163 is increased and positively correlates with severity in Gaucher's disease. *Eur J Haematol* 2004;72:135–9. [PubMed: 14962251]
23. Edwards JP, Zhang X, Frauwirth KA, Mosser DM. Biochemical and functional characterization of three activated macrophage populations. *J Leukoc Biol*. 2006 Aug 11;[Epub ahead of print]
24. Porcheray F, Viaud S, Rimaniol AC, Leone C, Samah B, Dereuddre-Bosquet N, et al. Macrophage activation switching: an asset for the resolution of inflammation. *Clin Exp Immunol* 2005;142:481–9. [PubMed: 16297160]
25. Emmenegger U, Schaer DJ, Larroche C, Neftel KA. Hemophagocytic syndromes in adults: current concepts and challenges ahead. *Swiss Med Wkly* 2005;135:299–314. [PubMed: 16034684]
26. Schaer DJ, Schaer CA, Schoedon G, Imhof A, Kurrer MO. Hemophagocytic macrophages constitute a major compartment of heme oxygenase expression in sepsis. *Eur J Haematol* 2006;77:432–6. [PubMed: 17044836]
27. Davis BH, Zarev PV. Human monocyte CD163 expression inversely correlates with soluble CD163 plasma levels. *Cytometry B Clin Cytom* 2005;63:16–22. [PubMed: 15624200]
28. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29–36. [PubMed: 7063747]

Figure 1.

A. Levels of soluble CD163 in patients with acute liver failure at day 1 and day 3 of enrolment compared to age- and sex-matched healthy controls. B. Levels of soluble CD163 in patients with acute liver failure at day 1 according to aetiology (Acetamin=Acetaminophen, drug hep=drug hepatitis, indeterm=indeterminate) compared to age- and sex-matched healthy controls. The box plots represent median and 25–75 percentiles. Upper and lower lines are the minimum and maximum values.

Figure 2.

Levels of soluble CD163 in patients with acute liver failure in relation to survival (spont surv=patients with spontaneous survival, dead=patients who died without transplantation, transplant=patients who underwent liver transplantation). A. sCD163 measured at day 1, B. sCD163 measured at day 3, C. maximum value of sCD163 at day 1 and 3. The box plots represent median and 25–75 percentiles. Upper and lower lines are the minimum and maximum values.

Figure 3.

Receiver operating characteristics (ROC) for the prediction of fatal outcome in patients with acute liver failure. A. sCD163 measured at day 1, B. sCD163 measured at day 3, C. maximum value of sCD163 at day 1 and 3. AUC=area under curve (95 % CI) (28).

Table 1

Clinical and biochemical characteristics of 100 patients with acute liver failure

Gender (m/f)	26/74	Clinical findings & complications (at enrolment)	
Age (median years)	39	Mech. ventilation (y/n)	60/34
Ethnicity (n)		Ascites (y/n)	11/82
White	67	Periph. oedema (y/n)	26/67
Hispanic	16	Splenomegalia (y/n)	5/84
African American	10	Infection (y/n)	43/51
Other	7	Seizures (y/n)	10/84
ALF aetiology (n)		Gastrointest. bleeding(y/n)	13/81
Acetaminophen	29	Biochemistry (median, 25–75 percentiles) (at enrolment)	
Drug hepatitis	18	INR (ratio)	2.7 (2.0–4.5)
Indeterminate	24	ALT (IU/L)	1534 (574–3617)
Other	29	Bilirubin (mg/dL)	15.0 (5.5–24.5)
Survival (n)		WBC ($10^9/L$)	12.1 (7.9–17.3)
Spontaneous	34	Platelet count ($10^9/L$)	134 (87–195)
Dead	38	Creatinine (mg/dL)	1.4 (0.75–2.8)
Transplantation	28		