
Cytokines and acute renal failure

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Introduction

The crucial question in the settings of acute renal failure (ARF) is to elucidate the role of cytokines in the acute and chronic issue of the disease: death or survival with normal kidney function or inevitable evolution to chronic kidney disease (CKD) and terminal renal insufficiency.

Topics for Discussion – Field of controversy

Many years ago the relation between ischemic (mainly septic) ARF in the clinical settings and serum level of pro/anti inflammatory cytokines (IFN γ , TNF α , IL-1 β , IL-6, IL-8, IL-10, ICAM-1, VCAM), is the field of controversy. Intrinsic ARF, as a special form of acute renal insufficiency is also associated with the cytokines production (their blood levels, kidney tissue and urine concentrations). The evolution of obstructive type of ARF may be related with the serum and tissue presence of anti and pro-inflammatory cytokines. ARF after kidney grafting is a differential diagnostic problem between s.c. initial tubulopathy and toxic effects of drugs used in the first few days after kidney transplantation.

Plasma levels of pro and anti-inflammatory cytokines and adequate conservative measures on the one hand, and the mortality ratio in ARF on the other, may be strongly related. Elimination of cytokines from the blood and tissues compartments via extracorporeal procedures may have a beneficial effect on clinical evolution of ARF.

Chronically elevated levels of pro-inflammatory cytokines once the ARF is over, are the signs of inflammation and progression to CKD. The limitations of the cytokines plasma dosing may compromise their clinical benefit.

Sepsis related ischemic ARF

The endotoxins (bacterial corporal lipopolysaccharids, LPS_s) via CD-14, activate and deliver cytokines (TNF α , IL-1 β , IL-6) from polymorphonuclear cells (PMNC_s) in ARF patients, via the process named “cytokines deliberation” with consecutive higher plasma concentration of all measured cytokines when compared to CKD patients (1). The impaired monocyte’s cytokines production in critically ill patients with ARF is presented with a dip fall of the blood levels of TNF α and IL-6 (84% vs 45% respectively) (2). The elevated serum concentrations of sTNF α R I, II are predictive for septic shock induced ARF (3). The IL-6 enhances the renal injury, organs dysfunction and inflammation (producing T-cells activation and elevation of CRP plasma levels) caused by the whole body ischemia-reperfusion in patients with ARF due to

systemic shock or cardiac arrest. The lesions correlate with the plasma level of IL-6: for each 100 pg/ml increase for IL-6, patients are 2.8 times likely to develop organ dysfunction (4). Endotoxemic ARF is caused by direct action of TNF α on TNF α R-1 in the kidney (proximal tubular epithelial cells, PTEC_s). In this case the urinary elimination of TNF α is increased (5). The Fas, FaSL and caspase mediated apoptopsis of PTEC_s by inflammatory cytokines or LPS_s, can be possible mechanism of endotoxic renal dysfunction (6). The cytokines stimulate PMNC_s attraction, aggregations, adhaezion (via ICAM-1 and VCAM), activation and degranulation with lysosims liberation (7). The endothelial lesions, disseminated intravascular coagulation (DIC) via sepsis induced TF, fibrinolysis and prolonged vasoconstriction (because ET-1 production) – lead to tissue hypoxia, inflammation, Tc-mediated injury and ARF (8).

Intrinsic ARF

Many factors are included in the genesis of intrinsic ARF beginning with the obstetric shock and finishing with the acute tubulointerstitial nephritis. The obstetric shock is related to PAI-1 activation, renal DIC and a possible successive partial or total cortical necrosis of the kidney (9). Necrotic vasculitis mainly presented by a glomerulitis or pneumonitis is due to the activation of Th₁ and mediators of tissue injury like leucotriens, TxA₂, PAF, reactive oxygen and nitrogenous metabolites (ROM, RNO), complement, intravascular activation of coagulation and secondary fibrinolysis. Interleukins (especially IL-2, IL-6, IL-8 and IFN γ), via nature killers cells (NK) and macrophages (M Φ) induce vascular (mainly capillary) leak syndrome because elevated plasma concentration of nitrogen oxide (NO). The consequences of capillary wall lesion are extension of interstitial volume, depletion of effective arterial blood volume, arterial hypotension and DIC with effective thrombocytopenia (under 60 000/cmm) and ARF (namely, acute tubular necrosis, ATN) (10). The acute tubulointerstitial nephritis is mediated by elevated plasma levels of interleukins (from IL-1 to IL-7), IFN_s (α , β , γ), platelet derived growth factor –A, B, epithelial growth factor, fibrocyte growth facror-2, TNF α , β and TGF α , β generated by infiltrating and somatic renal cells (11,12).

Tubular obstruction and ARF

The endotoxins and the same cited pro-inflammatory cytokines provoke direct vasoconstrictive effects in the kidney, enhancement of tubular damage and delay of

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recovery phase. This type of ARF in the clinical practice is known as “nephrohydrostasis” (13).

Acute renal failure after kidney grafting

The persistent urinary excretion of IL-6 and IL-8 means organic sustained ARF. Urinary TNF α and LDH are reduced in severe and increased in mild ARF (14). Severe ARF correlates with increased plasma concentration of TNF α , s TNF α R_s 55,75. If the plasma levels of s TNF α R_s diminish, the renal function improves explicating the better urinary excretion of TNF α R_s (7). Uromodulin decreases in urine in the case of ARF and augments if acute rejection is no longer questionable (15).

Plasma levels of pro and anti-inflammatory cytokines and mortality in ARF

Many plasma cytokines (IFN γ , TNF α , IL-1 β , IL-6, IL-8, IL-10) may predict mortality and correlate with the lethality rate in patients with ARF (2). Proinflammatory cytokines (especially IFN γ , TNF α , IL-1 β , IL-6, IL-8) lead to systemic inflammatory response syndrome (SIRS) and contrary anti-inflammatory response syndrome (CARS) precipitating the lethal issue of ARF (following the results of PICARD study group). The plasma levels of IL-6 (not-survivors: survivors = 235:114, pg/ml), IL-8 (not-survivors : survivors = 36:21, pg/ml) and IL-10 (not-survivors : survivors = 3.1 : 2.4, p/ml) are more increased in patients with ARF not-survivors when compared to survivors (16).

Chronically elevated levels of pro-inflammatory cytokines as a sign of inflammation and progression to CKD

The perpetual production of cytokines (IL-1, IL-6, IL-7, TNF α) is a central event in the pathophysiology of cell mediated damage by resident mesangial, interstitial or infiltrating cells (17). The vascular endothelial dysfunction and accelerated atherosclerosis are related to acute phase proteins (CRP, SAP) and plasma cytokines demonstrating a chronic inflammatory state after ARF (18). Proteinuria transcripts the genes of pro-inflammatory cytokines (mainly TNF α gene) (19). The plasma levels of IL-1, TNF α and IFN γ directly correlate with ICAM-1 and VCAM-1 expression (20). The IFN γ / IL-10 ratio is greater in patients with severe nephrosclerosis due to lupus nephritis (21). The Th₁/Th₂ renal parenchymal predominance support cell-mediated immune response and produce pro-inflammatory cytokines (IFN γ , TNF α , IL-12) as a mediators responsible for progression of renal lesions (22).

Conservative therapeutic anti-cytokines options

Many conservative therapeutic anti-cytokines procedures are trailed in the ARF patients with variable, mainly non-satisfactory results. In the following text will be presented the most acceptable anti-cytokines conservative treatment.

The inhibition of LPS activity is a theoretically very attractive therapeutic modality of septic induced ARF. The use of anti LPS monoclonal (E-5 murine, human anti lipid A region and HA-1A) and polyclonal antibodies (J5) in combination with the anti CD₁₄Ra on the M Φ – is effective

in the experimental setting, but without efficacy in clinical medicine (23).

The inhibition of IL-1 with r hu IL1Ra blocks the basic signal transduction and reduces interstitial cells infiltration (24).

The inhibition of TNF α with murine anti TNF α monoclonal antibodies (afelimomab) in i.v continuous infusion, prevents endothelial lesions and reduce mortality in experimental and clinical cases (25).

The inhibition of IL-6 with IL-6 monoclonal antibodies reduces the renal injury, kidney dysfunction and inflammation caused by ischemia-reperfusion via reduction of immuno-histochemical markers (ICAM-1, P-selectin, nitrotyrosin, ROM and RNM) (4). LPS may induce renal IL-6 mRNA synthesis that may be inhibited by a single dose of ACE inhibitors (like enalaprilate) and in this way, to prevent cytokines-induced renal damage during endotoxemia (31).

There are other therapeutic conservative modalities used more or less successfully in patients with ARF like thyroid hormones (26), growth factors (EGF, HGF, IGF-1) (27), soluble P-selectin GP ligand –1 (28) and R hu PAF Ra (29). The blockade of sepsis induced tissue factor (TF) with site inactivated F VIIa (s.c.TF-F VIIa-complex) is a mode to attenuate kidney injury in septic shock (32). With Zn-bis DL-OH aspartat may be stimulated the production of heat shock proteins (mainly HSP-70) and the regeneration of necrotic tubular cells (33). The BMP-7 reduces the harmful effects of pro-inflammatory cytokines (IL-1 β , IL-6, IL-8, TNF α , MCP-1) on kidney proximal tubular cells after inflammation related to ischemic injury and stimulates a tubular cells proliferation (42). The monomethyl arginin (L-NMMA) as a NO synthase (NOS) – blocker (34), vasodilative atrial natriuretic peptides (ANP_s) (35), anti-endothelin – 1 monoclonal antibodies and receptor antagonists (Anti ET-1 Mo abs; ET-1 Ras) (36,37), anti ICAM-1 monoclonal antibodies (38) and Arg-Gly-Asp (RGD) peptides (39) - are also trailed in clinical studies.

Active therapeutic anti-cytokines options

The aim of active therapeutic procedures is to eliminate or diminish the production of pro-inflammatory cytokines related to different haemodialysis membranes or to promote the elimination of active reactants from the blood, via extracorporeal devices (membranes, adsorbents).

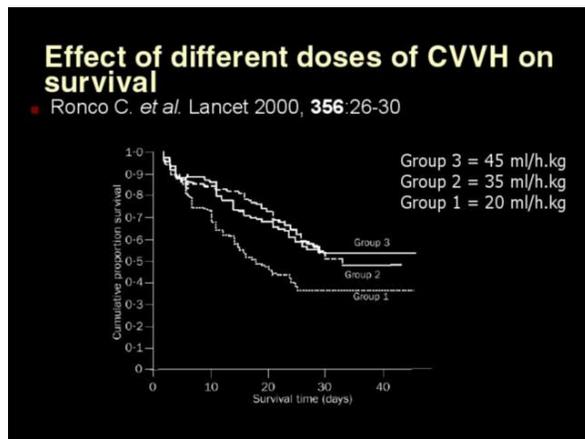
Today it is largely accepted that the cuprophan membrane enhances activation of various pathways of tubular cells injury during the haemodialysis procedure like ROM, RNM, cytokines, eicosanoides, complement production and PMNC_s activation, as compared to synthetic membranes (40).

The hydrophobic biocompatible high flux dialyzers membranes (PAN, PS, PA, PMMA, PAES) do not activate the M Φ , PMNC_s and do not deliberate cytokines and other active chemical reactants (41).

Elimination of active reactants via extracorporeal devices (membranes, adsorbents) today is accepted as an attractive therapeutic modality. Classical haemodialysis (HD) not influence the plasma levels of many cytokines (IL-1 β , IL-2R, IL-6, TNF α), but reduces the blood levels of hemokine IL-8 for 50% (43). CVVH \pm HD improve hemodynamics in septic shock related ARF with or without modifying plasma concentration of cytokines (IL1 β , TNF α) except IL-6, although the clearances for two basic pro-inflammatory cytokines is about the same (Clearance for TNF α = 21 ml/min; clearance for IL-6 = 25 ml/min) (44).

High permeability hemofiltration (HPHF) using polyflux hemofilters with nominal cut-off point of 60 kD and intermittent hemoperfusion – hemofiltration (HP-HF), eliminate TNF α (Clearance = 15-28 ml/min), IL-6 (Clearance = 23-42 ml/min) and IL-1 Ra (Clearance = 25-54 ml/min) in septic patients with ARF (45). Plasmaferesis eliminates endotoxins (LPS_s), cytokines (IL-1 β , IL-6, TNF α) soluble cytokines-binding proteins, C₃ and Ca⁺⁺ (30).

The molecular adsorbens recycling system (MARS) eliminates albumin-binding toxins, water soluble toxins, NO, IFN γ , TNF α , IL-6 and IL-8 in sever liver failure and Multi Organs Dysfunction Syndrome (MODS) with marked decrease of sequential organ failure assessment (Sequential Organ Failure Assessment, SOFA score reduction from 9.7 to 7.0). MARS may increase the serum levels of IL-6 by unknown mechanism (47).



Limitations of cytokines plasma dosage

The soluble receptors have almost all pro-inflammatory cytokines (IL-1, IL-2, IL-6, TNF α , IFN γ); that's the active interleukins fraction is difficult to know. The cytokines retention may be due to reduced renal clearance a blood accumulation. The tissue (namely effective) cytokine concentration differs from the plasma levels for the same cytokine and the conclusion about his efficiency following the blood cytokines presence is inconclusive. Finally, the cytokines network is interrelated and may compensate for each other.

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