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ScienceDirect
Journal of the Chinese Medical Association xx (2011) 1–5
www.jcma-online.com

Original Article

Kinetics and involvement of interleukin-17 in the outcome of peritonitis in nondiabetic patients undergoing peritoneal dialysis☆

Hsin-Hui Wang [a,b,†], Tzong-Yann Lee [c,d,†], Ching-Yuang Lin [e,f,*]

[a] Department of Pediatrics, Division of Nephrology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC
[b] Department of Pediatrics, Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC
[c] Department of Internal Medicine, Division of Nephrology, En Chu Kong Hospital, Taipei, Taiwan, ROC
[d] Department of Integrated Diagnostics & Therapeutics, National Taiwan University Hospital, Taipei, Taiwan, ROC
[e] Clinical Immunological Center and Division of Pediatrics Nephrology, China Medical University Hospital
[f] College of Medicine, China Medical University, Taichung, Taiwan, ROC

Received 24 June 2010; accepted 4 August 2010

Abstract

Background: Peritonitis is the most serious complication of peritoneal dialysis (PD). We previously showed that high levels of interleukin (IL)-12 and IL-18 in PD effluents (PDE) during the early phase of peritonitis correlated with a predominant Type 1 immune response and a favorable outcome in PD-related peritonitis. To further clarify the longitudinal changes of peritoneal immunity during PD-related peritonitis, we examined the kinetic production of IL-17 in PDE during peritonitis. The correlation between the IL-17 expression pattern and peritonitis outcome was analyzed.

Methods: The levels of IL-17 were measured in PDE during various phases of peritonitis in 38 patients undergoing PD. The patients were divided into two groups, according to whether they had a rapid versus a delayed response to antibiotic treatment.

Results: The kinetic expression of IL-17, as measured by enzyme-linked immunosorbent assay, differed between the two groups. In the rapid response group, high level of IL-17 was detected in PDE initially and progressively decreased during treatment. In the delayed response group, IL-17 levels in PDE were persistently low throughout the whole course of treatment. In the early phase of peritonitis, the IL-17 levels in PDE were significantly higher in the rapid response group ($p < 0.05$).

Conclusion: These data suggested that local IL-17 production is part of a protective early immune response to PD-related peritonitis. High levels of IL-17 in PDE during the early phase of peritonitis correlated with a favorable outcome. Manipulation of IL-17 cytokine expression in patients with peritonitis may modulate peritoneal immune response and affect peritonitis outcome.

Keywords: IL-17; Outcome; Peritoneal dialysis; Peritonitis

1. Introduction

Peritoneal dialysis (PD) is an established treatment for end-stage renal disease. Peritonitis is the most serious complication of PD.[1] It is the leading cause of morbidity and mortality in patients undergoing PD[2] and is the major cause of hospitalization, catheter loss, and technique failure.[3] Approximately 20–42% of peritonitis infections are refractory to appropriate antibiotic therapy,[1,4,5] and the mechanisms by which these bacterial infections cause refractory peritonitis are unknown. In addition to differences in the organisms causing the infection,[6] another possibility is a deficient host peritoneal defense response.[7] In a previous study,[8] we found that a progressive increase in CD4/CD8 ratio in PD effluents (PDE) was an indicator of favorable outcome. We also found that a predominant Type 1 T-cell immune response correlated with a favorable outcome during peritonitis.[9,10]

☆ The authors have no conflict of interest to disclose.

* Corresponding author.
E-mail addresses: cylin@mail.cmuh.org.tw, chingyuang@mail.cmu.edu.tw (C.-Y. Lin).
† Hsin-Hui Wang and Tzong-Yann Lee contributed equally to this work.

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doi:10.1016/j.alcohol.2010.11.007

Antibacterial host defense in the peritoneal cavity is regulated by a complex interaction between immunocompetent cells and a network of cytokines and chemokines.[11,12] Examination of intraperitoneal levels of inflammatory mediators has demonstrated that these levels are increased during acute episodes of peritonitis and subsequently return to control levels.[12−14] We found that high levels of interleukin (IL)-12 and IL-18 in PDE during the early phase of peritonitis correlated with a predominant Type 1 immune response and a favorable outcome.[9,10] These studies revealed that local secretion of inflammatory mediators is an important component in the control and outcome of peritoneal infection.[12] Examination of the differences in the expression of cytokines during peritoneal immune responses may provide insights into the roles of the cytokines in the outcomes of peritonitis.

IL-17 is a potent proinflammatory cytokine. It has been known to be produced by a newly identified subset of activated $CD4^+$ T cell—Th17. Expression of IL-17 has also been detected in some other cell types, including $CD8^+$ T cells, γδ T cells, and NKT cells, in some circumstances.[15,16] Accumulating evidence indicates that IL-17 is involved in the induction and progression of inflammatory diseases. Through IL-17 receptor-mediated signal pathway, IL-17 can stimulate the production of IL-6, IL-8, TNF-α, G-CSF and CXC chemokines, which regulate neutrophil migration and recruitments.[17] IL-17 can also induce the production of antimicrobial peptides against infection.[18] Although initial findings showed that IL-17 could not be classified to the Th1/Th2 paradigm, recent studies showed the important role of IL-17 in the Th1 and Th2 immune responses.[19−22] Using animal model, Witowski et al.[23] reported that IL-17 was capable of selectively recruiting neutrophils into the peritoneal cavity through the release of neutrophil-specific chemokines from the peritoneal mesothelium. However, no report has been published on the *in vivo* production of IL-17 in PDE during peritonitis, and the role of IL-17 in the outcome of PD-related peritonitis is also unknown.

To explore the impact of IL-17 cytokine on the peritoneal immune response during peritonitis, we examined the longitudinal kinetic changes in IL-17 levels in PDE. We undertook a prospective study to evaluate IL-17 levels in PDE produced by patients with PD peritonitis and compared them among patients with different treatment outcomes.

2. Methods

2.1. Patient population

Thirty-eight consenting patients with end-stage renal disease (20 men and 18 women) treated with PD and with a history of peritonitis were included in this study. All patients had a Tenckhoff peritoneal catheter inserted and were treated with the standard double-bag system (Baxter Healthcare Corp., Deerfield, IL, USA). The daily dietary protein intake was 1.2−1.5 g/kg, and the caloric intake was 35−45 kcal/kg, including the absorption from the dialysate, calculated at 3.8 kcal/g of dextrose. Vitamin supplements, including vitamin B complex, were prescribed to each patient. The exclusion criteria included the following: (1) tunnel-tract or exit-site infections, (2) completion of antibiotic therapy for peritonitis within 28 days of study enrollment, (3) the presence of peritonitis attributed to fungal or mycobacterial infection or negative culture, (4) drug sensitivity showing resistance to initial antibiotic therapy, (5) previous immunosuppressive therapy, (6) anemia from a disorder other than chronic renal failure, and (7) insulin-dependent diabetes mellitus. The dialysis and overall clinical management were prescribed by nephrologists. Patients used 1.5-L or 2-L PD bags, with four daily exchanges. The glucose solution concentrations and the exchange times were held constant during the study.

2.2. Peritonitis and response to treatment

Peritonitis was defined as the presence of two of the following criteria: microorganisms on gram staining; subsequent positive culture of PD fluid; cloudy fluid (leukocyte count, >100 cells/mL with >50% polymorphonuclear cells); and/or peritoneal inflammation symptoms. Episodes of peritonitis were treated according to a standard protocol. The initial antibiotic regimen included the intraperitoneal administration of teicoplanin and a third-generation cephalosporin, which was modified on the basis of organism identification and drug sensitivities.

Patients were divided into two groups according to their clinical response. A rapid clinical response was defined as the resolution of symptoms of peritonitis, including disappearance of abdominal pain and clearing of the peritoneal dialysate within 72 hours of initiation of antibiotic therapy, followed by complete recovery within 7−10 days of initiation of treatment. A delayed clinical response refractory to treatment was defined by the persistence of symptoms, positive dialysate cultures, and elevated white blood cell count in the dialysate beyond 72 hours after the initiation of appropriate antibiotic treatment and followed by a fluctuating and protracted course over 10−14 days or longer.

2.3. Collection of PDE

On Day 0, after onset of symptoms and before the initiation of antibiotic treatment, bags of PDE were delivered to the dialysis center of the hospital for routine microbiology laboratory analysis, where 100 mL of PDE fluid was taken aseptically for microbiological culture. The bags were resealed and sent to the research laboratory. During the treatment for peritonitis, overnight dwell bags of PDE were collected and processed as described earlier.

2.4. Measurements of IL-17 in PDE

Samples of PDE were centrifuged at 400 *g*, at 4°C for 10 min. After centrifugation, the supernatants were collected and stored at −70°C until assayed. The concentrations of IL-17 were measured by using commercial enzyme-linked immunosorbent assay kits (R&D Systems, Mckinley Place,

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MN, USA) according to the manufacturer's instructions. The sensitivity of the IL-17 assays was 15 pg/mL.

2.5. Statistical analysis

All data are presented as mean ± standard deviation. Differences between groups were analyzed by the Mann−Whitney *U* test. Values of p less than 0.05 were considered to represent a statistically significant difference.

3. Results

3.1. Patient characteristics

The baseline characteristics of the two study groups are shown in Table 1. There were 25 patients with rapid clinical responses to treatment and 13 with delayed responses. The two groups were similar in mean age, gender, initial body temperature, initial dialysate leukocyte counts, initial blood leukocyte counts, dialysis duration, peritonitis rate, serum albumin concentration, and adequacy of dialysis before bouts of peritonitis, as indicated by fractional clearance of urea as a function of its distribution volume (Kt/Vurea) and weekly creatinine clearance. In the rapid response group, 56% of the microorganisms causing peritonitis were gram positive, 32% were gram negative, and in 12%, the cultures remained negative. In the delayed response group, the distribution of microorganisms was 53.8% of gram positive, 30.8% of gram negative, and 15.4% of negative cultures, not significantly different from that associated with the rapid response group (Table 2).

Table 1
Baseline characteristics of patients with rapid versus delayed response to peritonitis treatment.

Group	Rapid response ($n = 25$)	Delayed response ($n = 13$)
Men/women, *n*	13/12	7/6
Age, yr		
Mean ± SD	42.35 ± 16.42	40.67 ± 13.25
Range	12−62	15−59
Dialysis duration, yr		
Mean ± SD	3.12 ± 1.21	2.98 ± 1.62
Range	1.1−5.3	0.7−5.9
Peritonitis rates, episode/yr, mean ± SD	0.56 ± 0.20	0.50 ± 0.30
Underlying disease, *n*		
CGN	15	8
PCK	2	1
HUS	1	—
Reflux nephropathy	2	1
Obstructive nephropathy	2	1
Hypoplasic/dysplasic	1	—
Unknown	2	2
Serum albumin, g/dL mean ± SD (range)	3.87 ± 0.36 (3.2−4.4)	3.91 ± 0.23 (3.3−4.5)
Adequacy of dialysis before peritonitis, mean ± SD		
Kt/Vurea (per week)		
Renal	0.23 ± 0.28	0.25 ± 0.26
Total	2.25 ± 0.23	2.21 ± 0.25
wCCr (L/wk/1.73 m^2)		
Renal	9.31 ± 12.53	9.17 ± 11.69
Total	66.78 ± 12.63	65.31 ± 11.98
Initial body temperature, °C mean ± SD	37.6 ± 0.3	37.8 ± 0.2
Initial dialysate leukocyte counts, μL (% neutrophils), mean ± SD	1,063.2 ± 532.1 (84.1 ± 7.3)	1,102.6 ± 498.3 (86.0 ± 5.7)
Initial blood leukocyte counts, μL (% neutrophils), mean ± SD	9,521.4 ± 889.4 (75.4 ± 5.8)	9,428.6 ± 825.9 (77.2 ± 5.7)

Differences between groups are not statistically significant.
CGN = chronic glomerulonephritis; HUS = hemolytic−uremic syndrome; PCK = polycystic kidney disease; SD = standard deviation; wCCr = weekly creatinine clearance.

3.2. Levels of IL-17 in PDE during peritonitis and correlation with treatment outcome

The longitudinal levels of IL-17 in PDE during peritonitis are shown in Fig. 1. In the rapid response group, high levels of IL-17 cytokine were detected in PDE on Day 0, which progressively decreased during treatment. In the delayed response group, IL-17 cytokine levels in PDE were significantly lower than those in the rapid response group on Days 0−3 and remained at a low level throughout the next 6 days. Through Days 0−3, the levels of IL-17 in PDE were significantly higher in the rapid response group as compared with the delayed response group ($p < 0.05$). On Days 4−9, there were no statistically significant differences in the level of IL-17 between the rapid and delayed response groups; however, the level of IL-17 tended to be slightly lower in the rapid response group.

A rapid clinical response indicates resolution of symptoms of peritonitis and clearing of the PDE within 72 hours of initiation of antibiotic therapy; we further divided the peritonitis clinical course into early phase (Days 0−3) and late phase (Days 4−9). During the early phase of peritonitis (Days

Table 2
Organisms isolated during peritonitis episodes in rapid and delayed response groups.

Microorganisms	Rapid response ($n = 25$)	Delayed response ($n = 13$)
Gram-positive organisms		
Staphylococcus epidermidis	6	3
Other coagulase-negative *Staphylococcus* spp.	3	2
Staphylococcus aureus	2	1
Streptococcus spp.	2	—
Enterococcus spp.	1	1
Total	14 (56.0%)	7 (53.8%)
Gram-negative organisms		
Pseudomonas aeruginosa	1	1
Escherichia coli	3	2
Proteus spp.	2	—
Klebsiella spp.	2	1
Total	8 (32.0%)	4 (30.8%)
Culture negative	3 (12.0%)	2 (15.4%)

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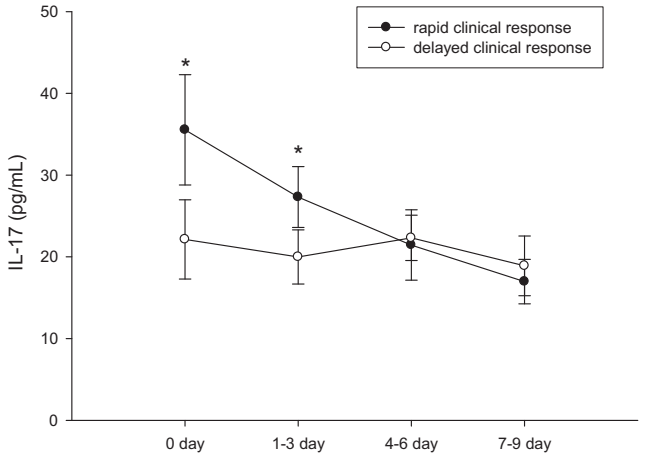

Fig. 1. Levels of interleukin (IL)-17 in peritoneal dialysis effluents during peritonitis. Serial changes in IL-17 levels in PDE during peritonitis. Data are mean ± standard deviation values. *$p < 0.01$ for rapid versus delayed clinical response.

0−3), the levels of IL-17 in PDE were significantly higher in the rapid response group as compared with those of the delayed response group ($p < 0.05$) (Fig. 2). On Days 4−9, there were no statistically significant differences in the levels of IL-17 between the rapid and delayed response groups (Fig. 2). These results indicated that patients in the rapid response group had high levels of IL-17 in PDE during the early phase of peritonitis, and this cytokine provided significant protection in the early peritoneal immune response.

4. Discussion

In the present study, we report that the dialysis effluent of PD patients with clinical peritonitis contains significant levels of IL-17. Our data indicate that local IL-17 production is part of a protective early immune response to PD-related peritonitis. IL-17 is a potent proinflammatory cytokine; its differential response in relation to treatment outcome has not been previously reported with respect to peritoneal immunity. This study provides evidence that locally produced IL-17 may play an important role in regulating the peritoneal host defense against PD-related peritonitis.

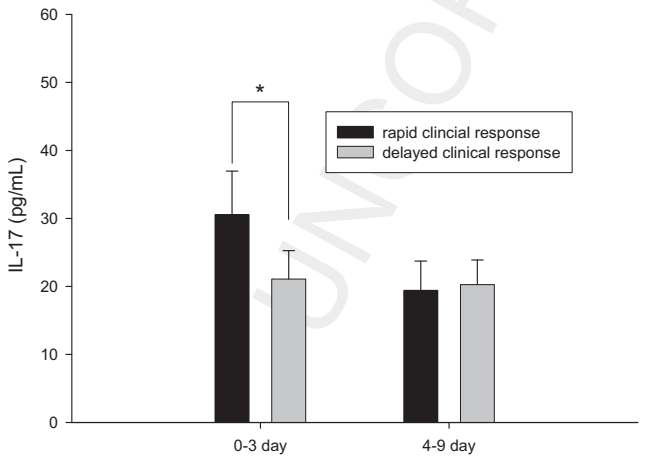

Fig. 2. Levels of interleukin (IL)-17 in peritoneal dialysis effluents (PDE) during the early and late phases of peritonitis. During the early phase of peritonitis (Days 0−3), the levels of IL-17 in PDE were significantly higher in the rapid response group. During the late phase of peritonitis (Days 4−9), there were no statistically significant differences in the level of IL-17 between the rapid and delayed response groups. Data are mean ± standard deviation values. *$p < 0.01$ for rapid versus delayed clinical response.

Increasing evidence suggests that IL-17 may significantly affect neutrophil maturation and promote their generation, migration, and accumulation.[17,24] IL-17 plays an important role in neutrophil homeostasis and recruitment; however, its role in peritoneal inflammatory response is not clear. A previous study demonstrated that IL-17 possesses a significant potential to recruit neutrophils into the peritoneum.[23] Our results showed that, in the rapid response group, the production of IL-17 in PDE was high initially and progressively decreased during treatment. In contrast, the level of IL-17 remained low during the whole course in the delayed response group. Although the expression of IL-17 coincided with neutrophil appearance in PDE in the rapid response group, it was not correlated in the delayed response group. These findings suggested that IL-17 may affect the peritonitis outcome through an immune response other than innate (neutrophil recruitment) immunity.

Recent studies showed the importance of IL-17 in the induction of Th1 and Th2 immune response.[19] IL-17/IFN-γ double-positive T cells are found in both human and mouse inflammed tissues.[20−22,25] Under IL-12 stimulation, these populations can be stimulated to Th1-like cells. A recent study also showed that IL-17 can promote Type 1 T-cell immunity against pulmonary intracellular bacterial infection.[18] In our previous study,[9] a Type 1 T-cell response was found to be critical for favorable outcome after peritonitis treatment. We found that IL-12 and IL-18 together exert a synergistic effect on IFN-γ production by Th1 cells. The presence of IFN-γ during the early stages of infection is critical for the development of a strong Type 1 T-cell response to infection. In the present study, patients in the rapid response group had high levels of IL-17 in PDE during the early phase of peritonitis. These results indicate that IL-17 cytokine, similar to IL-12 and IL-18, provided significant protection in the early peritoneal immune response. Further study will focus on how the IL-17 cytokine modulates the peritoneal Th1/Th2 immune response and on its interaction with IFN-γ during peritoneal infection.

IL-17 is the hallmark of Th17 cells. Th17 has been thought to be a distinct effecter of T-cell subsets in the recent years.[26] Besides IL-17, Th17 cells can express a heterogeneous cytokine profile, including IL-17A, IL-17F, IL-22, IL-26, CCL 20, and IFN-γ.[27] Previous studies showed the involvement of IL-17/Th17 in host defense against bacterial infection.[28−30] Some other studies suggest some relationship between the Th17 and the Th1 differentiation program.[21,22,25] In this study, we found significant levels of IL-17 in the PDE of PD patients with peritonitis. The expression pattern of IL-17 correlated with treatment outcome, and the local IL-17 production showed a protective early immune response. However, it remains unclear which cells are the major sources of IL-17 cytokine production in peritoneal immunity. Further studies to delineate

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the peritoneal Th17 cells and the relationship between the peritoneal Th17 and Th1 subsets will provide new insights into how peritoneal inflammation and outcome are modulated.

Peritonitis is a local inflammatory disorder. All of the resident peritoneal cavity cells as well as the leukocytes that are recruited and infiltrate, coordinate the immune response associated with peritoneal infection.[11,12] IL-17 serves as a potential link between the innate and adaptive immune responses during bacterial peritoneal infection. During the initial stages of bacterial peritoneal infection, IL-17 can recruit innate immune cells and stimulate proinflammatory cytokine production. Subsequently, IL-17 can shape the nature of the adaptive immune response by T cells. The results from this study demonstrated that during the early phases of peritonitis, high levels of IL-17 correlated with good treatment response. However, the role of IL-17 during the later phases of peritonitis remained unclear. Combined with our current results, additional studies delineating the role of IL-17 at different phases of peritonitis will enhance our understanding of the innate and adaptive immune mechanism during peritoneal inflammation.

In conclusion, the present study found that local IL-17 production was part of a protective early immune response to PD-related peritonitis. The expression pattern of IL-17 in PDE may determine the outcome of peritonitis in PD patients. Our results could have implications for designing therapeutic interventions aimed at the manipulation of early cytokine cascades in patients with peritonitis. These findings enhance our understanding of the peritoneal immune response and facilitate the development of new strategies for peritonitis treatment.

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