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Improvement of Drug-Associated Acute Interstitial Nephritis by Corticosteroids

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ABSTRACT

Objective: To explore the effect of corticosteroids on Acute Interstitial Nephritis (AIN)

Method: A retrospective analysis of 98 patients with AIN mediated by drugs were admitted at the 1st Affiliated Hospital of Chongqing Medical University, China. The patients are divided into 2 groups (treated group and control group) with 49 cases each. According to age, each group are divided into 3 age-groups (18-30, 30-60 and >60 years) denominated A, B and C respectively. After admission, the two groups patients were treated with diuretics, nutrition support therapy, correction of the hydro-electrolytic disorder or maintaining the acid-base balance and other symptomatic treatment. Besides these therapies, patients in treated group received steroids therapy. The main presentation, and blood and urinary analysis on the first day of admission, the first, second, 12th and 24th week were collected.

Results: Improvement in Urea (BUN) and Creatinine (Cr) level as well as other signs and symptoms in the treated group was quicker than that in the control group. Out of the 49 patients in the treated group, only 2 developed ESRF after 24 weeks, while 6 patients in the control group ended with ESRF for the same period of time. The prognosis of old AKI patients (age >60 years old) in both treated and control group were poorer than that of young and mid-aged patients. However, steroid treatment still took effect in the old patients.

Conclusion: Most of the AIN patients treated without steroids may still recover to normal. However, steroids help renal function to recover quickly, and the treatment may benefit to maintain a good short-term and long-term prognosis for AIN patients.

Keyword: Acute Interstitial Nephritis, Corticosteroids, Chronic Kidney Disease (CKD), Corticosteroids, Haemodialysis (HD).

BACKGROUND

Acute interstitial nephritis (AIN) is a form of nephritis that affects the renal interstitium[1], which is an important cause of reversible Acute Kidney Injury[2] (AKI), that accounts 15-20% of End Stage Renal Disease (ESRD). Interstitial Nephritis often occurs as a primary process and its incidence is as high as 20% in Chronic Kidney Disease[3] (CKD). Drug-induced AIN is the commonest aetiology and accounts up to 80% of the causes. Antibiotics[4] are widely used in hospitalized patients and are increasingly recognised as possible agents causing acute interstitial nephritis. Among the antibiotics, the quinolones[5] are recognised as the main culprit. The second main causes after antibiotics are the NSAIDs. Other frequent causes are the Chinese herbals[6] , PPIs, and also infections (bacterial, viral, fungal) and immune disorders (SLE[7] , Sarcoidosis[8] , Sjögren) and tubulo-interstitial nephritis and uveitis syndrome (TINU[9 - 10]). AIN is always defined as a sudden onset and fast decline in renal function, usually presenting with an acute rise in blood urea nitrogen (BUN) and creatinine (Cr) values. The majority of patients affected typically present with nonspecific symptoms such as the classic triad of fever, skin rash, and eosinophilia[11]. In a minority of cases, the affected patients may present with haematuria, proteinuria, and in some very few cases, pyuria. Histopathologically[12], there is a diffuse or patchy infiltration of inflammatory cells into the renal interstitium with an interstitial oedema, However, the glomeruli and the vessels are distinctly normal. Thus, renal biopsy[13] provides the most definitive means of diagnosis. Because of its anti-inflammatory role, inhibition of immune responses, anti-allergy and prevention of fibrosis, corticosteroids is widely used as a treatment for AIN. However, for some authors, there is a controversy about this therapy. Herein, we made a retrospective analysis of the early or long-term effect of corticosteroids on acute Interstitial Nephritis.

METHODS

Patients and Groups

A retrospective analysis of 98 patients with AIN who were admitted from January 2006 to March 2013, at the 1st Affiliated Hospital of Chongqing Medical University, China. According to the therapy with or without corticosteroids, the patients were divided into 2 groups with 49 patients each, named as treated group 1 and control group 2. According to their ages, the patients were furthur divided into three age-groups (age 18-30), (age 30-60) and (age >60), denominated as A, B and C respectively for each group. No patient under the age of 18 years old was considered. Diagnosis of acute kidney injury relied on a combination of a patient's history, clinical signs and symptoms and assessment of the kidney function, renal imaging test or renal biopsy, and the aetiology of AKI include non-steroidal anti-inflammatory drugs, antibiotics (such as clindamycin, aminoglycosides), antiviral drug such as ribavirin, and the Chinese herbals. These patients with other glomerular diseases such as chronic glomerulonephritis, diabetic nephropathy, lupus nephritis, and other types of nephritis were excluded from this study. The table 1 below shows the demographic and clinical features on the day of admission for both groups. There was no difference in ages and gender between the two groups and we can easily notice that there is a high predominance of Urea and Creatinine among the patients (declining renal function) as well as the presence of oedema and hypertension in both groups. Fever, rash, eosinophilia and haematuria were more or less equal in both groups, oliguria/anuria and flank/loin pain were almost similar in both groups.

Table 1: Clinical features of the patients in two groups at the time of admission

Characteristics	Treated group	Control group
Age (years/mean)	**49 (18-66)**	**54 (18-79)**
gender (M/F)	**17/32**	**17/32**
Hypertension	**41(83.7%)**	**39(79.6%)**
Oliguria/Anuria	**4(8.2 %)**	**5(10.2%)**
Loin/Flank pain	**16(32.7%)**	**14(28.6%)**
Oedema	**39(79.6%)**	**30(61.2%)**
Fever	**7(14.3%)**	**4(8.2%)**
Rash	**9(18.4%)**	**5(10.2%)**
Eosinophilia	**5(10.2%)**	**4(8.2%)**
Haematuria	**6(12.2%)**	**3(6.1%)**
Baseline Urea	**12.1+/-5.1 (range 3.90-20.50)**	**13.7+/-2.6 (range 8.10-17.40)**
Baseline Creatinine	**333.7+/-197.5 (range 60-774)**	**392.2+/-195.9 (range 159-837)**

Renal biopsy and pathological findings

Renal biopsy under the guidance of ultrasound was performed in all patients with AIN after the diagnosis was made and the renal pathological features were analysed by the pathologists. A diffuse infiltration of inflammatory cells composed of

lymphocytes, monocytes, eosinophils and plasma cells into the renal interstitium was observed. The severity of diffuse cellular infiltrates and the cellular composition were almost similar in all the patients that were biopsied in our study.

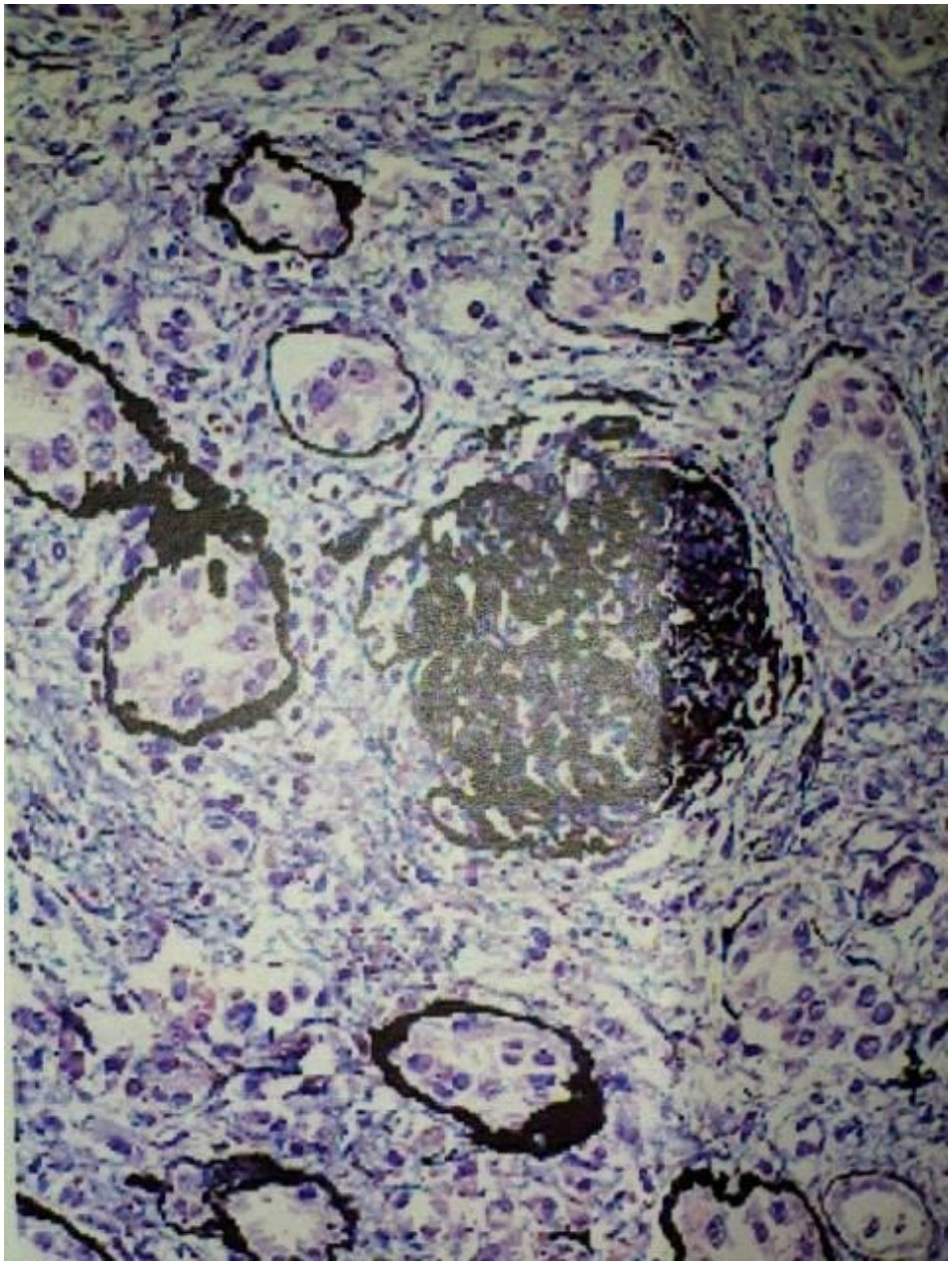

Fig A: renal pathology of AIN patients. Kidney biopsy was performed for all of the patients, and this is an example of acute interstitial nephritis (AIN). The renal cortex shows a diffuse interstitial, predominantly mononuclear, inflammatory infiltrates. Tubules in the centre of the field are separated by inflammation and oedema.

Treatment

Withdrawal of the offending drugs was started as soon as diagnosis was built or on admission. Moreover, all patients in both groups were treated with diuretics, nutrition support therapy, correction of the hydro- electrolytic disorders or maintaining the acid-base balance and other symptomatic treatment. Besides these 49 patients with AIN that receive supportive therapy, the remaining 49 patients with AIN from the treated group received steroids therapy. The steroids therapeutic regimen was intravenous methylprednisolone (80mg) once daily for one week, followed by oral prednisone (0.5 mg/kg/day), tailing off in 4–8 weeks.

Data Collection
The data of clinical presentations, blood and urinary tests, as well as Urea and Creatinine, and the size of kidney by Ultrasound examination were collected. All the patients were followed up for a period of 24 weeks.

Statistical Analysis.
Measurement data of normal distribution were expressed as mean ± SD. Data of abnormal distribution were expressed with median. For statistical analysis, chi-square test was used for gender. T-test was used to compare the two groups and rank-sum test was used for analysis of different sub age-groups. The graphs were performed with Excel. Statistics were calculated using SAS 9.13 for Windows. $P < 0.05$ was regarded as the significant difference.

RESULTS

Improvement of clinical symptoms in AIN patients treated with corticosteroids
Mostly, the clinical symptoms of AIN patients such as rash, flank/loin pain are being relieved quickly in 1-5 days when treated with steroids. Urinary volume increased quickly in the first week in those patients presenting with oliguria or anuria, then the oedema and hypertension alleviate gradually while it took in average more than 1-2 weeks more in the control group.

Improvement of renal function in AKI patients treated with corticosteroids
All the patients have a renal dysfunction and the mortality rate in both groups was nil after 6 months. Those ending with ESRF was 4.1% (n=2) on the treated group and 12.2% of the patients progressed to ESRF in the control group that were treated without steroids. The baseline Cr in the control group is a little higher than that of the treated group (392±195.5; range 159-837 vs 333.69±197.46; range 60-774), and the urea values in control group are higher as well (13.7±2.6; range 8.1-17.40 vs 12.1±5.1; range 3.90-20.50).

However, the final values of Urea and Creatinine were drastically decreased as shown in (Fig 1 & 2) in the treated group (5.7±1.8 and 96.2±18.3; respectively) compared to that in the control group (7.7±1.1 and 141.9±34.4; respectively). Furthermore, in the treated group, 95.9% of renal function recovered completely while 87.7% in the control group recovered fully after 24 weeks. Moreover, only 4.1% of patients in treated group transformed to end stage renal failure compared to 12.2% in the control group and eventually ended into haemodialysis.

Table 2: Characteristics of treated group and control group

	Treated group (n=49)	Control group (n=49)	p-value
Baseline Urea	**12.1±5.1(3.90-20.50)**	**13.7±2.6(8.10-17.40)**	**< 0.0001**
Baseline Creatinine	**333.7±197.5(60-774)**	**392.2±195.9(159-837)**	**< 0.0001**
Duration of steroids (weeks)	**8 (1-24)**	**0**	**NS**
Final Urea	**5.7±1.8(2.90-11.70)**	**7.7±1.1(5.9-11.1)**	**< 0.0001**
Final Creatinine	**96.2±18.3(67-132)**	**141.9±34.4(92-220)**	**< 0.0001**
Complete Renal Recovery	**47 (95.9%)**	**43 (87.7%)**	**NS**
Ending into ESRF	**2 (4.1%)**	**6 (12.2%)**	**< 0.0001**

The speed of improvement in kidney function by corticosteroids for AKI patient
As shown in Fig 1 & 2, the slopes (decreasing curve) for both serum Urea and Creatinine in the treated group were significantly steeper than that in the control group, especially at the early stage as early as the first 2 weeks, which indicated that steroids therapy may help to improve the renal function in AIN patients earlier and quicker than that in the control group.

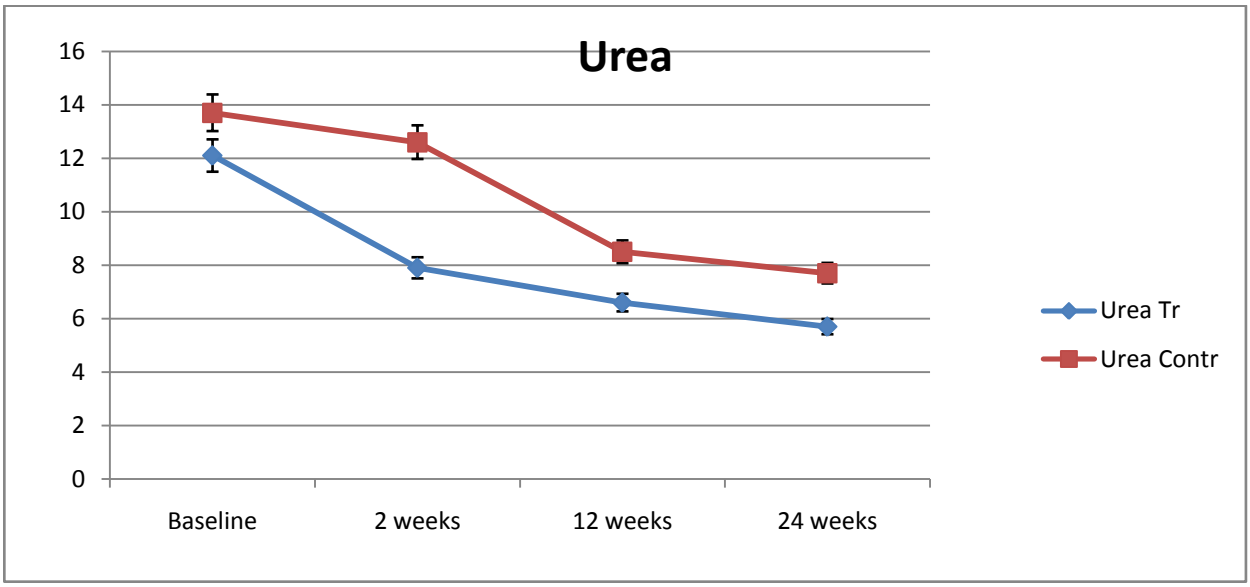

Fig 1 : Urea Mean Values (Treated & Control)

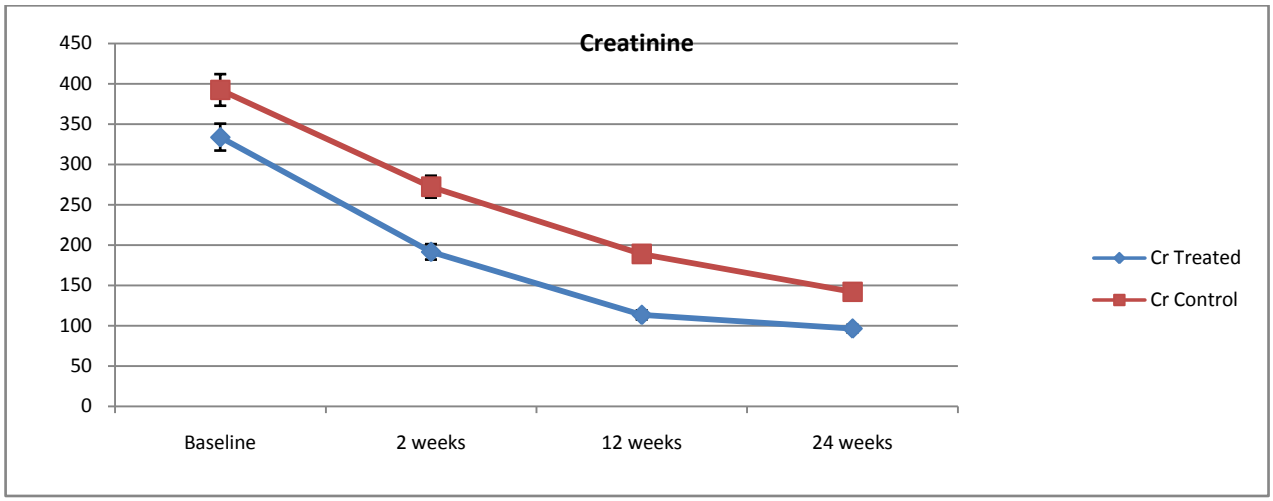

Fig 2 : Creatinine Mean Values (Treated & Control)

Effect of age on renal function recovery of AKI patients treated with corticosteroids

To further explore the effect of age on renal function recovery, we divided the patients into 3 sub-groups according to ages. As shown in Table 3, we noticed that the improvement of renal function in age-groups A (18-30) and B (30-60) are much better than C (>60) in both groups, no matter when treated with or without steroids**.**

Table 3: The change of serum urea and creatinine in different age-groups

Treated gp 1	**Age-group A(18-30)**	**Age-group B(30-60)**	**Age-group C(> 60)**	**p-value**
Baseline Urea	11.1±4.8(5.5-19.3)	12.1±5.2(3.90-20.50)	14.3±5.2(6.9-19.9)	< 0.0001
Baseline Creatinine	388.1±188.6(110-678)	330.5±205.2(84-774)	235±147.5(60-459)	< 0.0001

Final Urea	6±0.85(4.20-7.20)	5.3±1.7(2.90-11.70)	7.7±2.47(5.20-10.8)	< 0.0001
Final Creatinine	98.5±15.7(67-122)	93.9±17.9(68-123)	106.6±24.4(71-132)	< 0.0001
Control gp 2				
Baseline Urea	12.8±3.3(8.1-17.4)	14.9±1.6(11.9-17.2)	11.6±2.2(8.7-14.6)	< 0.0001
Baseline Creatinine	500.4±181.9(250-732)	544.9±225.9(159-837)	501.5±119.8(297-655)	< 0.0001
Final Urea	7.7±.7(6.7-8.8)	7.3±0.5(6.5-8.3)	8.5±1.8(5.9-11.1)	< 0.0001
Final Creatinine	135.6±23.3(97-175)	141.2±37.3(92-220)	149.6±36.3(98-201)	< 0.0001

Furthermore, it also seems that the renal function in age-group B improved better than that in age-group A when being treated with steroids. However, considering the baseline serum Urea and Creatinine, no significant difference may be found between these two subgroups.

Our data showed that as for old patients above 60 years of age, the prognosis of AIN patients became poorer. However, we found that the renal function recover much better in steroids-treated patients compared to that of the patients in control group, indicating that the therapy with steroids in time for AKI patients may improve the prognosis, even for old patients (Fig 3 & 4).

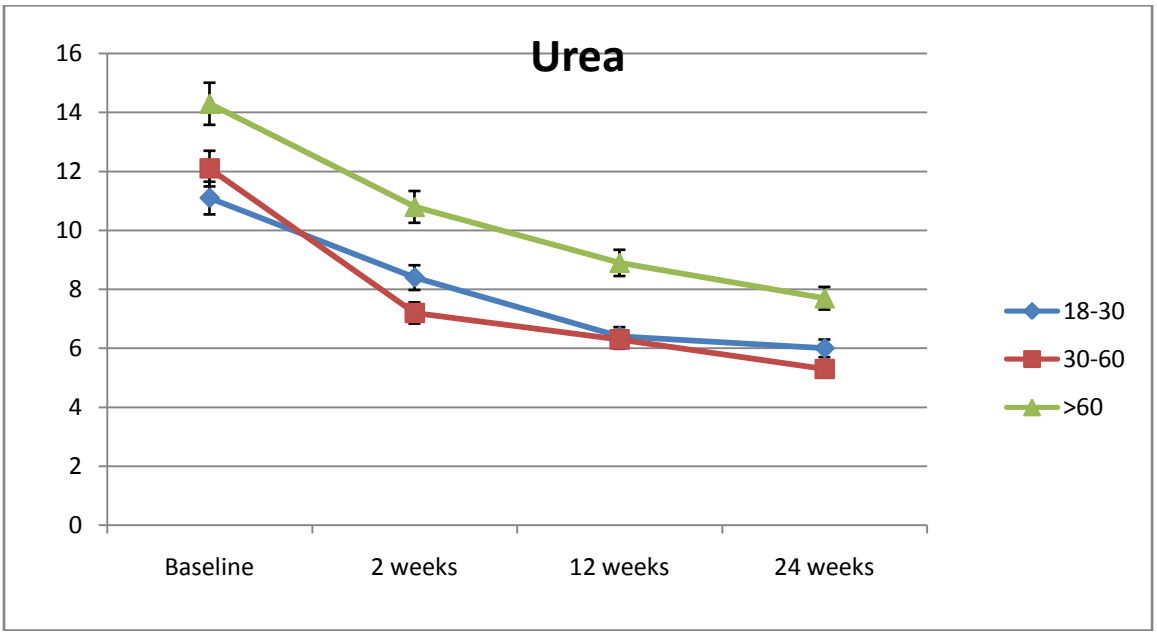

Figure 3: The change of Urea in different age-groups treated with steroids

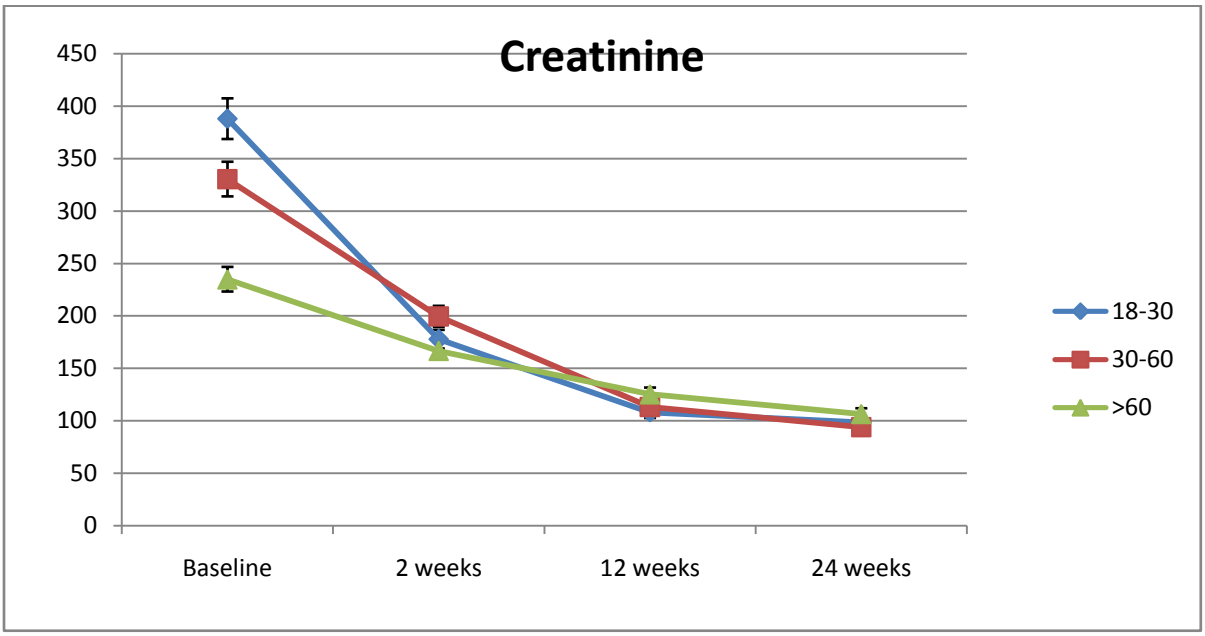

Figure 4: The change of Creatinine in the different age-groups treated with Steroids

Urea and Creatinine improve quite slowly when not being treated with steroids (Fig 5 & 6) compared to the rapidity in the treated treated-group. It takes a much longer time for baseline Urea (13.7±2.6; range 8.1-17.4) to return to normal level (7.7±1.1;range 5.9-11.1) as well as for creatinine with a baseline level (392.2±195.9;range 159-837) and final level (141.9±34.4; range 92-220).

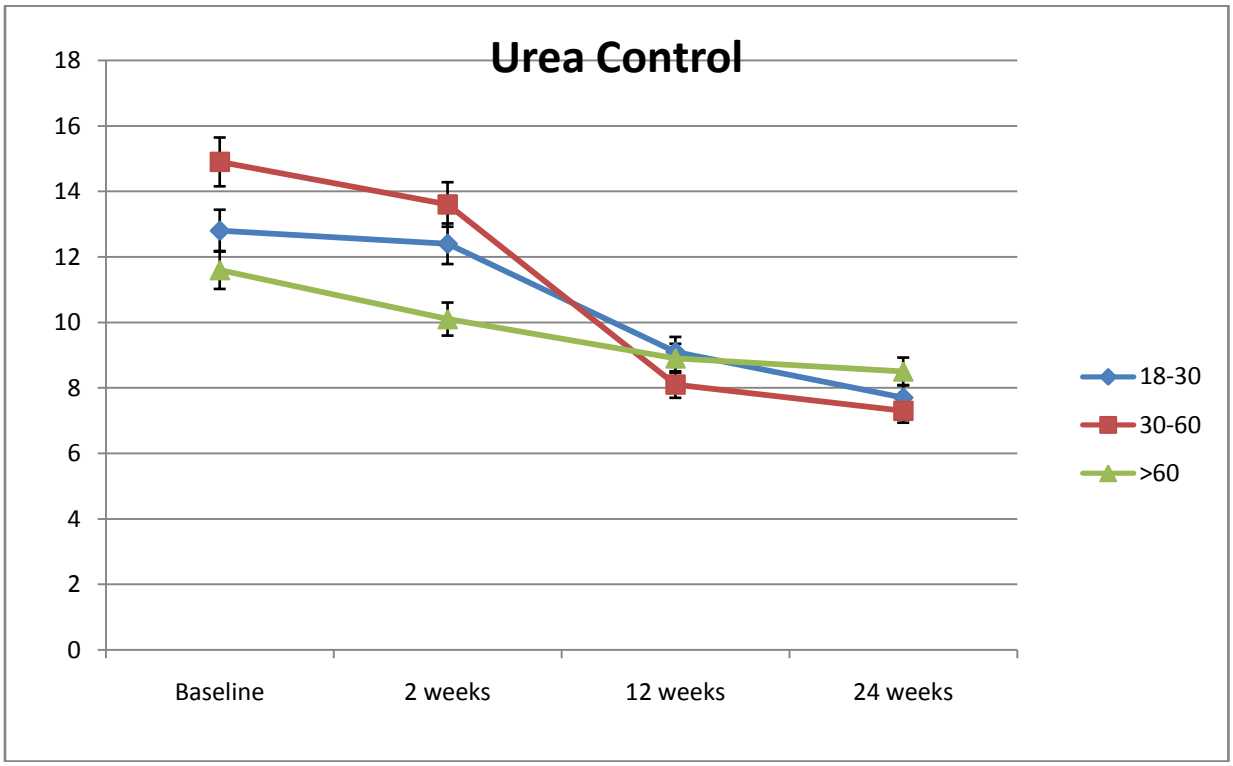

Figure 5: The change of Urea in different age-groups treated with steroids.

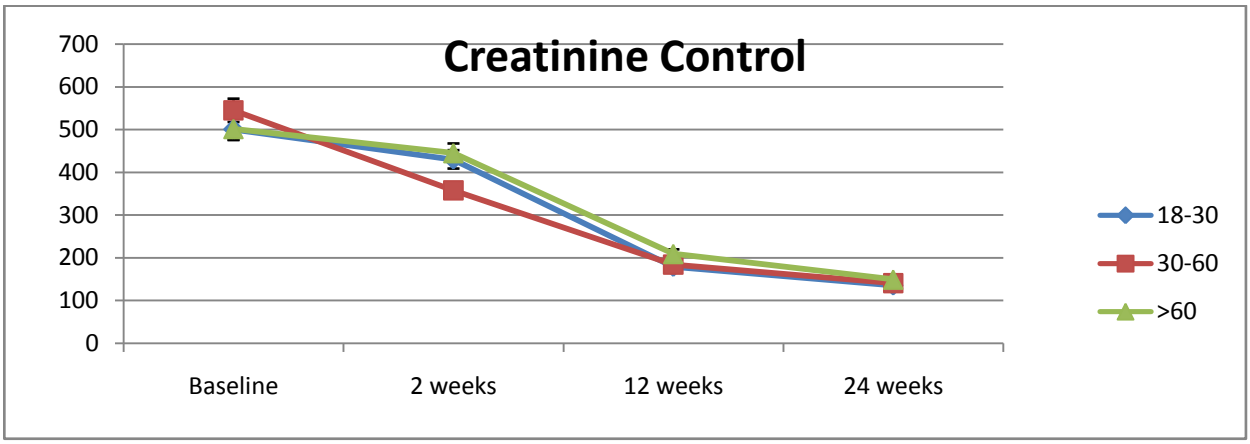

Figure 6: The change of Creatinine in different age-groups treated without Steroids

DISCUSSION

AIN is a renal tubulointerstitial nephritis with abundant inflammation and cell filtration, which always cause an acute attack of renal function. Most AKI patients recover quickly and only a small number of patients may subsequently develop into chronic kidney disease because of chronic interstitial inflammation and fibrosis. In our study, the data of 98 AIN patients were retrospectively collected. All of these patients with AKI induced by medications includes non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antiviral drugs (ex. ribavirin), or Chinese herbals, and the renal pathology showed filtration of considerable inflammatory cells into the renal interstitium.

As we all know, Corticosteroids have a very important role in the anti-inflammatory process and in the prevention of interstitial fibrosis[17]. However, the role of steroids on AIN is still controversial according to some authors. Herein, our study provided an analysis of a large series of biopsy-proven AIN gathered so far (98 patients) and follow-up sufficiently long to ascertain the final outcome of every patient, and demonstrated that corticosteroids remained an important treatment for AIN. Our data showed that the patients who receive treatment with steroids not only had a more quicker relief of clinical manifestations such as rash, loin/flank pain, oliguria/anuria or oedema and hypertension, but also had a significantly lower final Urea and Creatinine levels than those who were treated without steroids in 24th week, and the proportion of patients that entered into chronic dialysis was significantly less than those in the control group, suggested that therapy of steroids may improve the short-term and long-term prognosis of AIN patients. Furthermore, we found that the early initiation of steroid treatment may accelerate the recovery of the AIN patients. This effect was taken especially as early as within two weeks after steroid treatment has started. Some documents confirmed that the introduction of Prednisone earlier can achieve a better control[18] and prevent relapses. But Clarkson et *al*[19] performed a retrospective study in a relatively large series of 60 patients with biopsy-proven AIN to define the influence of steroids on this disease. Of them, 25 patients (60%) received steroid treatment, whereas the remaining 17(40%) received only supportive care. No difference in serum creatinine levels was observed between the two groups after 1, 6, and 12 months following AIN. However, in Clarkson's study a considerable delay for the introduction of steroids therapy (median time 3 weeks) after renal biopsy may be an important reason. Our study showed that 95.9% AKI patients almost fully recover their renal function after the introduction of corticosteroid at the very beginning, suggesting that steroid treatment should be started immediately or soon after the diagnosis is made in order to avoid the risk of incomplete renal function recovery.

Additionally, we further observed the effect of AKI patients' age on renal function recovery. Our research indicated that for old AKI patients (above 60 years old), renal function recover much more slowly that young (18-40) and middle-aged (40-60) patients, However, even for old patients, therapy with steroids in time for AKI patients still improved their prognosis.

No significant side effects attributable to steroids were observed, probably due to the short duration of treatment (1-12 weeks). We think that this latter point has not been sufficiently emphasized because most of the patients with AIN started to improve after the withdrawal of the offending agent or treatment of the causative aetiologies.

In conclusion, our data strongly suggests a very beneficial influence of steroids on the outcome of AIN, regardless of age.

REFERENCES

[1] Eric G.Neilson: Division of Nephrology and Hypertension, Departments of Medicine and Cell Biology, Vanderbilt University Medical Center, D-3100 Medical center North, Nashville, Tennessee 37232, USA. The Journal of Clinical Investigation December 1999 | Volume 104 | Number 12.
[2] Christos Chatzikyrkou, Iyas Hamwi, Christian Clajus, Jan Becker, Carsten Hafer, Jan T Kielstein: BMC Nephrology 2010, 11:19. http://www.biomedcentral.com/1471-2369/11/19.
[3] Manuel Praga, Department of Nephrology, Hospital Universitario 12 de Octubre, Hospital 12 de Octubre, Avda de Co´rdoba s/n, 28041 Madrid, Spain: Kidney International (2010) 77, 956–961
[4] CHARLES M. KODNER and ARCHANA KUDRIMOTI, Diagnosis and Management of Acute Interstitial Nephritis ; www.aafp.org/afp, AMERICAN FAMILY PHYSICIAN JUNE 15, 2003 / VOLUME 67, NUMBER 12.
[5] Chi-Chih Hung, Mei-Chuan Kuo, Jer-Ming Chang,Hung-Chun Chen : Fluoroquinolone induced acute interstitial nephritis. Nephrol. Dial. Transplant. (January 2006) 21 (1): 237-238.doi: 10.1093/ndt/gfi178
[6] Yang, C-S et al, Amer J Kidney Diseases, 'Rapidly progressing fibrosis interstitial nephritis associated with Chinese herbal drugs ', 2000, 35(2), 313-318.
[7] Tron F, Ganeval D, Droz D. Immunologically-mediated acute renal failure of nonglomerular origin in the course of systemic lupus erythematosus [SLE]. Report of two cases. *Am J Med.*1979 Sep;67(3):529–532.
[8] Josep M Cruzado, Rafael Poveda, Joan Mañá, Luis Carreras, Marta Carrera, Josep M. Grinyó, Jeroni Alsina : Interstitial nephritis in sarcoidosis : Simultaneous multiorgan involvement *American Journal of Kidney Diseases*, Volume 26, Issue 6, Pages 947-951.
[9] Andrew Tze-Ming NG, George John MANGOS, Yuk-Luen CHAN : Tubulointerstitial Nephritis and Uveitis : a rare cause of renal Failure : Hong Kong Journal of Nephrology, Volume 4, Issue 2, October 2002, Pages 105-107
[10] Kim T. Sinnamon, Aisling E. Courtney, Camille Harron, Declan M. O'Rourke and Robert N. Mullan : Tubulointerstitial nephritis and uveitis (TINU) syndrome : epidemiology, diagnosis and management : NDT Plus (2008) 2: 112–116
[11] Rossert J : Drug-Induced AIN. Kid Int 2001,60:804-17
[12] MichelleA. Josephson, May Y. Chiu, E.Steve Woodle, J.Richard Thistlethwaite, Mark Haas : Drug-induced acute interstitial nephritis in renal allografts : Histopathologic features and clinical course in six patients ; Volume 34, Issue 3, September 1999, Pages 540–548.
[13] Perazella MA, Markowitz GS : Drug Induced Acute Interstitial nephritis. Nat Rev Nephrol 2010,6 : 461-70.
[14] Clarkson M, Giblin L, O'Connell F, O'Kelly P, Walshe J, Conlon P, O'Meara Y, Dormon A, Campbell E, Donohoe J (2004). "Acute interstitial nephritis: clinical features and response to corticosteroid therapy". Nephrol Dial Transplant 19 (11): 2778–83
[15] A M Davison, C H Jones : Acute Interstitial Nephritis in the elderly: Nephrol Dial Transplant (1998) 13 [Suppl 7]: 12-16
[16] Pasternack, A., Tallqvist, G. and Kuhlbäck, B. (1970), OCCURRENCE OF INTERSTITIAL NEPHRITIS IN ACUTE RENAL FAILURE. Acta Medica Scandinavica, 187: 27–31. doi: 10.1111/j.0954-6820.1970.tb02902.x
[17] Schwarz A, Krause PH, Kunzendorf U, Keller F, Distler A: The outcome of acute interstitial nephritis: risk factors for the transition from acute to chronic interstitial nephritis. Clin Nephrol 2000, 54(3):179-190.
[18] Gonzalez E, Gutierrez E, Galeano C, Chevia C, de Sequera P, Bernis C, Parra EG, Delgado R, Sanz M, Ortiz M, Goicoechea M, Quereda C, Olea T, Bouarich H, Hernandez Y, Segovia B, Praga M, Grupo Madrileno De Nefritis Intersticiales: Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. Kidney Int 2008, 73(8):940-946.
[19] Clarkson MR, Giblin L, O'Connell FP et al. Acute interstitial nephritis: clinical features and response to corticosteroid therapy. Nephrol Dial Transplant 2004; 19: 2778–2783.