CLINICAL DETERMINANTS OF RENAL OUTCOMES IN DRUG-INDUCED ACUTE INTERSTITIAL NEPHRITIS

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Introduction and Aims

- Drug-induced acute interstitial nephritis (DI-AIN) represents an emerging cause of acute kidney injury, especially among polymedicated elderly patients. Moreover, oligosymptomatic presentations may result in delayed diagnosis and impact on renal prognosis.
- Some studies suggest that early treatment with corticosteroids (CS) may be beneficial for renal recovery. However, less is known about the optimal duration of this therapy.
- This study aims to investigate clinical predictors of renal outcomes in patients with DI-AIN treated with CS.

Patients and Methods

- Multicenter, retrospective, observational study in 13 nephrology departments belonging to the Spanish Group for the Study of Glomerular Diseases (GLOSEN).
- Patients with biopsy proven DI-AIN treated with CS between 1996-2016 were included. Other potential causes of AIN such as infections or systemic diseases were carefully ruled out.
- Clinical, biochemical and histologic parameters of prognostic interest were recorded and used to characterize patients with complete renal recovery (CRR), partial recovery (PR) (loss of ≤50% estimated glomerular filtration rate [eGFR]) or no recovery (NR) (loss of >50% eGFR) at six months after the diagnosis.
- Parametric and non-parametric tests were chosen as appropriate for descriptive comparisons of continuous variables, and chi-squared test for categorical variables.
- A multivariate logistic regression model was used to establish the clinical parameters associated with complete renal recovery or persistent renal impairment six months after the diagnosis. The following independent variables were considered: age, gender, rash, fever, oliguria, presence of eosinophilia, hematuria, leukocyturia, proteinuria, serum creatinine at the moment of renal biopsy, tubular atrophy, acute or chronic interstitial infiltrate on biopsy, percentage of glomerular sclerosis and type of drug.
- To prevent overfitting, variables were forced into the multivariate model with a significance of at least $p < 0.01$. All variables in the multivariate model were chosen automatically by conditional progressive inclusion (backwards). Data were presented as mean and standard deviation (± SD) or as median and interquartile ranges or maximum and minimum values. A p-value < 0.05 was considered to be statistically significant.

Results

Clinical and biochemical characteristics of all the patients and according to outcomes (complete, partial or no recovery)

	All patients	Complete renal recovery	Partial renal recovery	Persistent renal impairment	p*
Patients, N (%)	186	72 (39)	75 (40)	39 (21)	
Age, years	67±14	64±15 [a]	73±8	67±14	<0.0001
Sex, male/female	91 / 95	26 / 46	47 / 28	18 / 21	0.005
Rash, N (%)	14 (8)	5 (7)	6 (8)	3 (8)	0.970
Fever, N (%)	34 (18)	14 (19)	10 (13)	10 (26)	0.258
Oliguria, N (%)	41 (22)	15 (21)	13 (17)	13 (33)	0.141
Eosinophilia, N (%)	47 (25)	13 (18)	23 (31)	11 (28)	0.190
Leukocyturia, N (%)	137 (74)	51 (71)	62 (83)	24 (62)	0.041
Hematuria, N (%)	100 (54)	41 (57)	35 (47)	24 (62)	0.251
Baseline serum creatinine**, mg/dl	1.1±0.4	1±0.3 [b]	1.1±0.3	1.2±0.6	0.013
Baseline serum creatinine >1.5 mg/dl, N (%)	18 (10)	3 (5)	7 (10)	8 (24)	0.011
Serum creatinine at renal biopsy, mg/dl	4.4±3	4.9±4.3	3.7±1.7	5±2.2	0.040
Proteinuria, g/ 24 h	0.8±0,9	0.8±0.7	0.7±0.9 [c]	1.2±1.3	0.022
Proteinuria > 1 g/ 24 h, N (%)	34 (18)	13 (26)	9 (14)	12 (39)	0.026
Proteinuria > 3.5 g / 24 h, N (%)	7 (4)	1 (2)	3 (5)	3 (10)	0.242
Dialysis at diagnosis, N (%)	39 (21)	17 (24)	8 (11)	14 (36)	0.006
Tubular atrophy, N (%)	107 (58)	33 (46)	47 (63)	27 (69)	0.030
Acute inflammatory interstitial infiltrate, N (%)	180 (97)	68 (94)	74 (99)	38 (97)	0.323
Chronic inflammatory interstitial infiltrate, N (%)	83 (45)	36 (50)	28 (37)	19 (49)	0.257
Interstitial fibrosis, N (%)	101 (54)	31 (43)	46 (61)	24 (62)	0.050
Plasma cell infiltrate, N (%)	91 (49)	35 (56)	38 (53)	18 (51)	0.913
Granulomatous infiltrate, N (%)	10 (5)	4 (6)	3 (4)	3 (8)	0.676
Glomerular sclerosis***, %	14 [0–23]	10 [0–20]	14 [0–25]	20 [7-30]	0.011[d]
History of NSAIDs intake, N (%)	84 (45)	37 (51)	33 (44)	14 (36)	0.284
History of PPI intake, N (%)	78 (42)	20 (28)	44 (59)	14 (37)	0.001
Intravenous steroid therapy, N (%)	91 (49)	29 (40)	43 (57)	19 (49)	0.119
Initial dose of steroids, mg/day	56±11	56±11	55±10	59±12	0.337
Duration of therapy ***, weeks	9 [7–15]	11 [7–16]	8 [6–13]	10 [7–14]	0.375 [d]

* ANOVA or χ2 inter-groups.
** Data available in 170 patients.
*** Median, interquartile range
a p<0.0001 Complete renal recovery vs. Incomplete renal recovery, Scheffé test
b p=0.013 Complete renal recovery vs. Persistent renal impairment, Scheffé test
c p=0.023 Incomplete renal recovery vs. Persistent renal impairment, Scheffé test
d Kruskal Wallis test

Etiologies of AIN according to renal outcomes

	All patients	Complete renal recovery	Partial renal recovery	Persistent renal impairment	p
Etiology categories, %					
Unknown	55	17	25	13	
Nonsteroidal anti-inflammatory drugs	52	22	22	8	0.335
Antibiotics	38	18	14	6	
Proton pump inhibitors	8	1	3	4	
Others	33	14	11	8	

Multiple logistic regression model for complete renal recovery

Variable	Odds Ratio	I.C. 95% O.R.	p
Sex, male = 1	0.410	0.212; 0.796	0.008
Age, years	0.960	0.938; 0.983	0.001
Interstitial fibrosis in renal biopsy	0.423	0.219; 0.820	0.011

Patients who recovered renal function were characterized by the following clinical profile: young female patient with no interstitial fibrosis

Multiple logistic regression model for persistent renal impairment

Variable	Odds Ratio	I.C. 95% O.R.	p
Proteinuria 24 h, g/24 h	1.431	1.018; 2.010	0.039
Sclerosed glomeruli, %	1.026	1.002; 1.050	0.031

Patients in which renal impairment persisted had a greater degree of proteinuria at diagnosis and higher percentage of glomerulosclerosis

Conclusions

- DI-AIN can lead to irreversible renal damage in a significant number of cases.
- Younger female patients with no interstitial fibrosis may have greater chances for a complete renal function recovery, whereas patients with high-grade proteinuria and higher percentage of glomerulosclerosis may have greater risk for developing irreversible renal impairment and thus, might benefit less from prolonged CS therapy.

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