Acute tubulointerstitial nephritis in Scotland

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Summary

Background and Aims: Acute tubulointerstitial nephritis (ATIN) is a potentially reversible cause of acute kidney injury with the majority of cases drug related. Our aims were to examine the incidence profile of patients with ATIN in Scotland and to assess the impact of corticosteroid treatment.

Design and Methods: All adult patients with biopsy-proven ATIN, diagnosed between 2000 and 2012, presenting to renal units serving 1.9 of Scotland’s 5 million population were included. Patient demographics, presenting, aetiologic and pathologic features, treatment given and outcome were extracted from patient records.

Results: In total, 171 cases representing 4.7% of native renal biopsies were identified. Median serum creatinine (sCr) was 327 μmol/l at biopsy (106 μmol/l at baseline). Eosinophilia, fever or rash was present in 57% with all 3 in only 1.1%. Active urinary sediment was found in 68%. Aetiology appeared drug induced in 73%. Proton pump inhibitors (PPIs) were likely causative in almost as many cases as antibiotics (35% each) and were more frequently implicated than non-steroidal anti-inflammatory drugs (20%). Number of PPI-related cases paralleled the rising prescription of these drugs. Corticosteroids were prescribed in 59% of drug-induced ATIN (median sCr at biopsy: 356 μmol/l vs. 280 μmol/l in those managed conservatively). There was no difference in sCr at 1, 6 and 12 months, with similar proportions of both groups experiencing complete renal recovery (48% vs. 41%) and becoming dialysis dependent (10% in both).

Conclusions: Incidence of biopsy-proven ATIN in Scotland has been rising over the past decade with the majority of cases drug induced. Evidence supporting corticosteroid treatment is lacking.

Introduction

Acute tubulointerstitial nephritis (ATIN) is a recognized and potentially reversible cause of acute kidney injury (AKI). Its pathogenesis is based on cell-mediated immunity against endogenous nephritogenic antigens or exogenous antigens processed by tubular cells.

ATIN is thought to be drug related in the majority of cases1–4 and has been associated with a range of agents. Historically, antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) were the most commonly implicated.4 A recent study from the Spanish Registry of Glomerulonephritis has highlighted the rising incidence of ATIN between 1994
and 2009. The authors speculated that this could be due to an increase in drug-associated ATIN but did not have data on aetiology to support this.

ATIN may also be associated with systemic diseases or untreated infections. In these cases, appropriate treatment is clearer. With drug-induced ATIN, identification and removal of the offending agent has been the mainstay of the treatment. However, given the pathogenic role of cell-mediated immunity, corticosteroid treatment has been commonly employed. Some retrospective analyses have observed no difference in short-term outcomes, with others suggesting that early corticosteroid administration (within 7 days of diagnosis) can improve the recovery of renal function, decreasing the risk of chronic kidney disease. It has been suggested that delayed corticosteroid treatment, once interstitial fibrosis (IF) has taken place, would have a less pronounced or no therapeutic benefit, but there have been no prospective, randomized controlled trials to support the routine use of corticosteroids. Thus, the optimal treatment remains uncertain.

The aims of our study were to describe the incidence, aetiology and outcome of patients presenting with ATIN over the past 13 years to three Scottish health boards together serving 1.9 of Scotland’s 5 million population; to determine any changes during this time and to examine the efficacy of corticosteroid treatment for drug-induced ATIN.

**Methods**

Adult patients with biopsy-proven ATIN presenting between January 2000 and December 2012 were identified by searching the Renal and Pathology databases of three Scottish health boards: National Health Service (NHS) Tayside, NHS Greater Glasgow & Clyde and NHS Forth Valley. Specimens were re-examined by two specialist renal pathologists to confirm the diagnosis of ATIN; cases with another primary renal diagnosis and co-existing interstitial nephritis were excluded.

A review of case notes and the electronic laboratory data archive was then undertaken to determine patient demographics and presenting clinical features (including fever, rash and eosinophilia—defined as a count above the laboratory reference range during AKI), histopathological features, in particular the presence of IF/tubular atrophy (TA), as well as physician-defined aetiological factors. Identification of a drug-related aetiology required the prescription of a known causative drug in the absence of systemic diseases associated with ATIN or untreated infections. In cases of multiple potential causative drugs, the likely agent was identified on the basis of temporal relationship to the AKI. We documented the timing and nature of treatment and recorded serum creatinine (sCr) at baseline, time of biopsy, 1 month, 6 months and 12 months. Renal outcome was noted in terms of renal recovery/progression to end-stage renal disease, requiring renal replacement therapy (RRT). Baseline sCr was defined as the lowest value in the 3 months prior to biopsy; for those requiring acute haemodialysis at time of biopsy, pre-dialysis sCr was noted. Complete renal recovery was defined as a return to baseline sCr within 1 year; incomplete recovery was defined as nadir sCr over 12 months > 26 µmol/l above baseline (the minimum criterion for AKI).

Data were also sought from the Information Services Division of NHS Scotland on rates of community prescription of the agents most commonly implicated in drug-induced ATIN during this time. Permission was obtained from the NHS Greater Glasgow and Clyde, NHS Forth Valley and NHS Tayside Caldicott guardians.

**Statistical analysis**

Data were entered in a Microsoft Excel database. Statistical analysis was performed using SPSS for Windows v.19. Continuous variables were expressed as medians and interquartile range when the parameters did not follow a normal distribution. Qualitative variables were compared using the chi-square test and Fisher’s exact test. Quantitative variables were compared using the t-test or Mann-Whitney test for non-skewed variables. A P value < 0.05 was considered significant. Correlation coefficient was calculated using linear regression.

**Results**

We identified 171 separate episodes of ATIN in 169 patients over the 13-year period. This represented 4.7% of the 3604 native renal biopsies performed with an average of 6.9 cases per million population per year. There was a clear trend towards increasing incidence of ATIN (r = 0.936, P = <0.001) and in the total number of renal biopsies performed per year (r = 0.821, P = 0.001) (Figure 1).

**Patient demographics and presenting features**

Patient demographics and presenting features are listed in Table 1. Median sCr at time of biopsy was 327 µmol/l compared with 106 µmol/l at baseline. Baseline sCr was 105 µmol/l (87–128) in those with drug-induced ATIN compared with 112 µmol/l (92–160) in those with other causes (P = 0.13).
Nineteen percent had required acute haemodialysis prior to biopsy. Information on duration of AKI was unclear in 31% but was less than 3 weeks in only 14%.

Typical extra-renal features of eosinophilia, fever and rash were present in 27%, 23% and 8.2%, respectively, and all three were noted in only two patients (1.1%).

An active urinary sediment (red blood cells, white blood cells, red blood cell casts or white blood cell casts) was found in 68%. Thirty-one percent had proteinuria measured or estimated >1 g/day (urine protein:creatinine ratio of >100 mg/mmol).

**Pathology and aetiology**

Biopsy samples typically demonstrated interstitial enlargement with oedema. There was a characteristically focal cellular infiltrate: predominantly lymphocytes and macrophages, with or without eosinophils, with variable accumulation of plasma cells. Granuloma formation (evidence of a delayed hypersensitivity reaction) was seen in both sarcoid and some probable drug reactions. The development of IF (present in 49 cases) seemed to represent a cross-over from an acute to chronic process, though this could occur rather rapidly (present in 4 of the 24 cases whose duration of AKI was confirmed to be <3 weeks). Immunofluorescence and electron microscopy were of no value in determining cause.

Aetiology was thought to be drug related in 124 episodes (73%), secondary to sarcoid/tubulointerstitial nephritis and uveitis syndrome in 17 (9.9%), associated with autoimmune conditions (systemic lupus erythematosus/Sjögren’s syndrome) in 12 cases (7.0%), associated with infection (pyelonephritis/gram-negative bacteraemia) in 14 (8.2%) and unclear in 4 patients (2.3%).

**Treatment and outcome**

Overall, 108 of the 171 episodes of ATIN (63%) were treated with corticosteroids. Seventy-four patients (43%) experienced complete renal recovery, and 75 (44%) had an incomplete recovery; 16 patients (9.4%) were dialysis dependent within 1 year. Of the 32 patients who required acute haemodialysis at time of biopsy, 9 became dialysis dependent (28% vs. 0.5% of those that had not required RRT at presentation, \( P = 0.005 \)), though a similar proportion experienced complete renal recovery (40% vs. 44%).

**Drug-induced ATIN**

In the 124 cases thought to be drug-induced ATIN, proton pump inhibitors (PPIs) (35%) were deemed to be causative in almost as many patients as antibiotics (35%) and were more frequently implicated than NSAIDs (20%) (Table 2). Over the 13 years, there was a clear increase in the number of cases likely related to PPIs (Figure 2). As Figure 3 illustrates, there has been no increase in community prescription of antibiotics and NSAIDs in Scotland during this time, though prescription of PPIs has risen steadily.9

Seventy-three of the 124 patients with drug-induced ATIN (59%) were treated with corticosteroids for a median total duration of 3 months. Median sCr at time of biopsy was significantly higher in patients with drug-induced ATIN treated with corticosteroids compared with those managed conservatively (356 μmol/l vs. 280 μmol/l, \( P = 0.03 \)); median age at time of biopsy and baseline sCr...
were, however, similar in both groups (i.e. those treated with steroids had evidence of a more severe AKI). Baseline characteristic of patients with drug-induced ATIN according to whether they were corticosteroid-treated or conservatively managed is listed in Table 3. Comparing the two groups, there was no difference in median sCr at 1 month, 6 months, and 12 months. There was no significant difference in the proportion of the steroid-treated and the conservatively managed groups experiencing complete renal recovery (48% vs. 41%) or becoming dialysis dependent (10% in both groups).

Table 2 Implicated drugs in the 124 cases of likely drug-induced ATIN

<table>
<thead>
<tr>
<th>Implicated Drugs</th>
<th>n  (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>44 (35)</td>
</tr>
<tr>
<td>PPIs</td>
<td>43 (35)</td>
</tr>
<tr>
<td>NSAIDs/COX2 inhibitors/salicylates</td>
<td>25 (20)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Herbal/over the counter medications</td>
<td>2 (1.6)</td>
</tr>
</tbody>
</table>

Figure 2. Number of cases of ATIN attributed by nephrologists to PPI over the duration of the study.

Figure 3. Number of NHS community prescriptions dispensed in Scotland.

Of the patients with drug-induced ATIN who were treated with corticosteroids (n=73), these were administered early (≤7 days after withdrawal of the likely causative agent) in 41%, late (>7 days after) in 48% and timing was unclear in the remaining 11%. Those treated early and late were no different in terms of aetiology, severity of AKI and baseline sCr. There was no significant difference in outcome, with similar sCr in both groups at 1 month, 6 months and 12 months.

Ten percentage of the patients with drug-induced ATIN who were treated with corticosteroids had evidence of severe IF/TA on biopsy (involving at least 50% of the cortex on biopsy). There was no significant difference in aetiology, comparing those with severe IF/TA to those without, though steroids were used more often in those without severe IF/TA (66% vs. 29% in those with severe IF/TA, P=0.001). However, patients with severe IF/TA on biopsy were significantly less likely to experience complete renal recovery (18% vs. 47%, P=0.02) and were more likely to become dialysis dependent (24% vs. 6.5%, P=0.02) within 1 year.

Discussion

Our data have highlighted that the incidence of histologically proven ATIN in Scotland has more than doubled over the past 13 years with the majority of cases thought to be drug induced. Cases presented with AKI but with few symptoms and non-specific features and an increasing number of cases are attributed to PPI prescription. Corticosteroids appeared to have been administered to those with more severe AKI, although overall outcome was similar to those managed conservatively. We did not find compelling evidence for the routine use of corticosteroids in drug-induced ATIN.

Our findings have mirrored recent data from the Spanish Registry of Glomerulonephritis,5 revealing a rising incidence of biopsy-proven ATIN. However, the question remains as to whether this is due to more disease or simply more detection.10 A 1998 report from the UK Medical Research Council Glomerulonephritis Register found that ATIN was drug induced in 58% of cases in patients ≥60 years and 48% in patients aged <60 years.3 However, a 2004 review, including data from three large studies, found drug-related ATIN in a similar proportion to our cohort (72%),2 suggesting the rising incidence of ATIN may well be the result of more drug-associated ATIN. Physicians will naturally have different thresholds for performing a renal biopsy in cases suspected to be drug-related ATIN, when early withdrawal of the offending drug.
may be the only required intervention. Thus, there may be many cases of drug-induced ATIN that recover without biopsy.

Over the past decade, published case reports have strongly suggested an association between PPIs and interstitial nephritis. Based on the number of people exposed, it was hypothesized that PPIs could become one of the most common causes of drug-induced ATIN. Trends in national prescribing data that parallel the rising incidence of ATIN appear to support this idea.

Our data do not provide compelling evidence for the routine use of corticosteroids for drug-induced ATIN. A recent multicentre retrospective analysis of the effect of corticosteroids in 61 patients with biopsy-proven drug-induced ATIN found that final sCr in patients who were treated, especially early in the course of disease, were significantly lower than the nine patients in the untreated group. Patients were classed as mild, moderate or severe based on histologic features (the severity of IF/TA has previously been noted as a major prognostic factor). Patients who received corticosteroids early had only a mild degree of IF/TA compared with 30% in the group, which received late steroid therapy. In keeping with our findings, an earlier retrospective analysis of 60 cases of biopsy-proven drug-induced ATIN did not observe any difference in outcome of patients in relation to corticosteroid treatment. The number of cases in each group was comparable and both the groups had similar histology.

Our findings should, however, be interpreted with caution, given the inherent limitations of retrospective cohort studies. The risk of confounding and the lack of control of subject selection mean firm conclusions cannot be drawn. A further limitation of this study is that only 14% of patients had a short duration of AKI raising the question whether patients had chronic rather than acute interstitial nephritis. The numbers of patients are small, however, and so it is difficult to draw conclusions when comparing the presence of IF/TA on the renal biopsy to patients with longer duration of AKI. In addition, we have not captured patients in this cohort with presumed ATIN but without histological evidence. Thresholds of performing renal biopsy may differ depending on the nephrologists within the individual units and the extent of drug history obtained from the patient. Thus, incidence of drug-induced ATIN may, in fact, be higher. The fact that patients treated with corticosteroids had evidence of more severe AKI means an overall outcome similar to patients who did not receive corticosteroids may actually represent a treatment effect. A prospective, randomized controlled trial is required to answer the question definitively.

Nonetheless, it appears that in probable drug-induced ATIN, early withdrawal of the offending agent and the absence of IF/TA on biopsy may be more important determinants of outcome than corticosteroid therapy. This relies on the timely consideration of ATIN in the differential diagnosis of AKI, especially as patients rarely presented with the classic triad of symptoms.

### Conclusion

There appears to be a genuine increase in the incidence of biopsy-proven ATIN in Scotland over the past 13 years. The majority of cases were drug induced and associated with commonly prescribed agents, including PPIs. Clinicians should be aware that the evidence supporting the use of corticosteroid therapy is lacking. Based on our

### Table 3 Baseline data for drug-induced ATIN according to treatment group

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Corticosteroid treated (n=73)</th>
<th>Conservatively managed (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>26 (36)</td>
<td>20 (39)</td>
</tr>
<tr>
<td>Age at biopsy (years)a</td>
<td>67.8 (56.1–75.2)</td>
<td>65.4 (57.8–74.4)</td>
</tr>
<tr>
<td>sCr at biopsy (μmol/l)a</td>
<td>356 (274–590)</td>
<td>280 (216–500)</td>
</tr>
<tr>
<td>Baseline sCr (μmol/l)a</td>
<td>99 (80–128)</td>
<td>109 (95–135)</td>
</tr>
<tr>
<td>Acute RRT (%)</td>
<td>18 (25)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Fever, rash or eosinophilia (%)</td>
<td>33 (45)</td>
<td>26 (51)</td>
</tr>
<tr>
<td>Active urinary sediment (%)</td>
<td>53 (73)</td>
<td>34 (67)</td>
</tr>
<tr>
<td>Proteinuria &gt;1 g/day (%)</td>
<td>22 (30)</td>
<td>14 (27)</td>
</tr>
<tr>
<td>IF/TA on biopsy (%)</td>
<td>7 (10)</td>
<td>17 (33)</td>
</tr>
</tbody>
</table>

sCr, serum creatinine concentration.

aMedian and interquartile range.
data, a prospective, randomized controlled trial of corticosteroid therapy for biopsy-proven ATIN of likely drug-induced aetiology would be justified.

Conflict of interest: None declared.

References