Rifampicin-induced acute renal failure: a series of 60 patients

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Abstract

**Background.** Since 1971, 55 case-reports of rifampicin-induced ARF have been published, but systematic data on this condition are not available, in view of the disparate nature of the observations.

**Methods.** We retrospectively assessed prevalence, clinical and biochemical features, and prognostic factors of 60 consecutive cases (41 males/19 females, age 22–68 years), who were admitted to the Iasi Dialysis Centre from 1987 to 1995 for acute renal failure (ARF) following re-treatment with rifampicin.

**Results.** The clinical appearance consisted mainly of gastrointestinal and ‘flu-like’ symptoms and clinical signs of intravascular haemolysis (the latter in 17% of cases). Frequent laboratory findings were anaemia (96% of cases), leukocytosis (63%), and thrombocytopenia (50%). Severe anaemia was associated with marked haemolysis (25% cases), thrombocytopenia, longer anuria, and slower rate of renal function recovery. Signs of hepatic injury were found in 25% of patients, but it did not seem to affect the outcome of renal function.

Prognostic factors in post-rifampicin ARF proved to be the following: the duration of the anuric phase (correlated with the number of dialysis sessions and with the rate of decrease of azotaemia) and the severity of the immunological abnormalities and inflammatory syndrome (haemolysis, leukocytosis, hypergammaglobulinaemia).

Post-rifampicin ARF accounted for 16.6% of all ARF cases hospitalized in our Centre during the studied period. Its clinical course was favourable; the mortality rate was only 1.6% (1 case), compared to a 20% general mortality rate among all ARF patients. Full recovery of renal function was achieved in 40% and 96% of patients, 30 and 90 days respectively from onset.

**Conclusions.** ARF after treatment with rifampicin is not an uncommon condition, especially when tuberculosis prevalence is high, but renal prognosis is usually favourable. Thrombocytopenia, immune haemolytic anaemia, and intravascular haemolysis are frequent complications which are associated with a more severe renal injury.

**Key words:** acute renal failure (ARF); rifampicin; haemolytic anaemia; thrombocytopenia; hepatic injury

Introduction

Rifampicin is one of the major antituberculosis drugs and a second choice antistaphylococcal agent. The prevalence of tuberculosis is increasing world-wide, particularly in Romania. The antituberculous regimen recommended in our country until 1995 specifically included a twice weekly dose of rifampicin.

Renal toxicity of rifampicin has been reported sporadically. Since the first description by Poole et al. in 1971 [1], 54 case-reports of rifampicin-induced ARF have been published [2–55]. The deterioration in renal function typically appears acutely, after reintroduction of rifampicin [1–8,15,23–26,28,30–32,37–41], determined by an acute tubulointerstitial nephritis and/or acute tubular necrosis [6,9–16]. However, some authors have reported cases occurring during continuous rifampicin therapy [13–14,16–19,21,22,27,36,43]. In addition to the expected interstitial lesions secondary to the immunoallergic mechanism, isolated or superimposed glomerular injury [12] have been described, presenting either with a rapidly progressive picture [20,21], or as a frank nephrotic syndrome [16,22,23].

Apparently, post-rifampicin ARF is characteristically associated with autoimmune haemolysis [4–6,8,15,18,21,25–28,48,52], which is sometimes severe [6,8,27,28], thrombocytopenia [15,27,28,30], disseminated intravascular coagulation [27,28], hepatic injury [31–34], or tubular defects [13–15,19], thus creating a very polymorphic appearance [6,23]. Although, evidence is now accumulating in favour of a clear, distinct entity, a definite clinical, biological picture of post-rifampicin ARF, has not been established, because of disparate observations. Also, important data concerning prevalence and prognosis are generally missing.

We retrospectively studied all post-rifampicin ARF...
cases hospitalized in the Iasi Haemodialysis Centre between 1 January 1988 (opening of the dialysis facilities) and 31 December 1995. Our goals were to analyse the prevalence, clinical and biochemical features, courses, and prognostic factors of post-rifampicin ARF.

Subjects and methods

The files of patients with post-rifampicin ARF hospitalized in the Iasi Haemodialysis Centre between 1 January 1988 and 31 December 1995 were retrospectively analysed. All of these patients had ARF occurring after rifampicin retreatment and previously normal serum creatinine and normal size kidneys.

The following data was collected for each patient: demographic data, serum creatinine value before the renal failure event, liver function tests, before and during the ARF (serum protein electrophoresis, ASAT, ALAT, bilirubinaemia, fibrinogenemia, prothrombin time), renal tests (BUN, serum creatinine, Addis–Hamburger test, 24-h urine tests), haematological tests (Hct, WBC-total and differential count, platelet count) and the duration of the oligoanuric phase (days). The biochemical and haematological assays were recorded on admission, and 30 and 90 days from onset. Normal values as described by [58] were used for all haematological and biochemical variables.

The data was analysed using the CSTAT statistic package (Oxford Statistics) on an IBM PC 486. We used the t-test and ANOVA, and for the non-parametric distributions the \( \chi^2 \) test and Fisher’s test; \( P < 0.05 \) was considered significant.

Results

Prevalence, demographic characteristics

In the period between 1988 and 1995 we recorded 60 cases of post-rifampicin ARF (41 males and 19 females, 22–68 years of age, average 45.4±11.1, median 43 years). There were no significant differences between the sexes (M, 44.3±10.3, F, 47.9±12.6 years old), except for a lower Hct in females (30.7±4.8% vs 33.7±8.4% in males, \( P < 0.05 \)). Post-rifampicin ARF accounted for 16.6% of all cases of ARF hospitalized in our haemodialysis centre during this period.

Clinical features

The symptoms and signs at presentation are described in Table 1. ARF occurred immediately after reintroduction of the rifampicin treatment (mean dose until onset of first clinical symptoms, 600±300 mg). The interval from the last rifampicin treatment varied from 21 days to 1 year. Mean dosage/week of the previous rifampicin treatment was 1200 mg. Clinical signs appeared 20±12 h after restarting treatment. In 55 cases rifampicin was indicated as part of antituberculous regimens. In Moldavia, the geographic area served by the Iasi Haemodialysis Centre, 120 132 cases of tuberculosis were treated in the same period (1987–1995), resulting a 0.05% incidence of post-rifampicin ARF in these patients.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Cases (n)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>43</td>
<td>72</td>
</tr>
<tr>
<td>Fever</td>
<td>27</td>
<td>45</td>
</tr>
<tr>
<td>Chills</td>
<td>26</td>
<td>43</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Jaundice</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Lumbar pain</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Hyperchromic urine</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Confusion</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Haematological disorders

Anaemia was observed in 57 patients (96%) with a mean Hct at admission of 32±4.5%. Twenty-three patients had mild anaemia (Hct >35%), 25 patients had a Hct of 30–35%, and 12 patients had more severe anaemia with a Hct <30%. Leukocytosis >10 000/µl was found in 38 patients (60.6%) (mean value 12 395±4312/µl), four patients had eosinophilia (>500/µl) and 30 patients had thrombocytopenia (<150 000/µl). Although reticulocytosis (>100 000/µl) was seen in 35/57 anaemic patients, evidence of severe immune haemolysis (anaemia, reticulocytosis, high serum indirect bilirubin, and normal liver function, haemoglobinuria, positive direct and indirect Coombs’ tests) was found only in 15 cases, 10 of which also had thrombocytopenia (Table 2). The impact of this more intense haemolysis (seen in 25% of our patients) on renal function, was assessed by serum creatinine levels 30 days after injury (Table 4), and by the duration of the anuric phase (15±5.2 days, cf. with 4.6±5.9 days for those with milder or without haemolysis. Generally the haematological manifestations persisted only for 5–9 days after the clinical onset.

Renal injury

Fifty-seven patients (96%) were anuric at presentation. The duration of the anuric phase was on average, 11.4±7 days. An average of 4.8±4.6 haemodialysis sessions per patient were required. Thirty days after the first day of anuria, the mean BUN level was 0.33±0.14 g/l, with 15 patients in the normal range, and the mean serum creatinine level was 2.38±2.20 mg/dl, with 25 patients in the normal range. Urinalysis abnormalities were found in most patients: 20 cases (33%) with haematuria, 10 cases (16.6%) with haemoglobinuria, and 36 cases (60%) with proteinuria >0.5 g/24 h (1 case in nephrotic range). Previously reported light-chain proteinuria [35,56] was evaluated and found negative in nine patients. Sterile leukocyturia (abnormal leukocyturia at the Addis–Hamburger test, but with sterile urine cultures), considered as a marker of interstitial nephritis, was present in 50 cases (93%). With the exception of one case with transient
Table 2. Occurrence of anaemia, thrombocytopenia, indirect hyperbilirubinaemia, and haemoglobinuria

<table>
<thead>
<tr>
<th>Haematocrit</th>
<th>20–30%</th>
<th>30–35%</th>
<th>35–40%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia (n)</td>
<td>12</td>
<td>25</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>83.3%</td>
<td>56%</td>
<td>26.1%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Raised bilirubin</td>
<td>83.3%</td>
<td>51%</td>
<td>47.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Immune haemolytic anaemia</td>
<td>58.3%</td>
<td>28%</td>
<td>4.3%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Haemoglobinuria</td>
<td>50%</td>
<td>16%</td>
<td>0%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

1Hct >35% vs Hct between 20 and 30% and Hct between 30 and 35%; 2Hct between 20 and 30% vs Hct between 35 and 35 and Hct >35%; 3Hct between 30 and 35% vs Hct t >35%.

glycosuria, hyperchloreaemic acidosis, and maintained diuresis, no other tubular defects were seen in our cohort. Biopsies were performed in only five patients, taking into account the usual favourable course seen by us and described by others [9], and the range of histopathological lesions expected (risk–benefit odds ratio analysis). Four cases had tubulointerstitial nephritis and one tubular necrosis; no glomerular lesions were seen and IF was negative.

Hepatic injury

Hepatic injury was considered in the presence of hepatocytolytic syndrome and either hypergammaglobulinaemia or low prothrombin time and it was found in 15 patients. The mean values of the main hepatic tests are presented in Table 3. There were no significant differences concerning demography, haematology, and renal function (as reflected by azaemia at onset and 30 days from onset and by the number of haemodialysis sessions) between the patients with hepatic injury and the rest of the patients.

Evolution, prognostic factors

No correlation was seen between the severity of renal failure (as assessed by length of the anuric phase, number of HD sessions, initial serum creatinine level, serum creatinine level at 30 and 90 days from injury), and the rifampicin dose that induced ARF, or the total dose of the last rifampicin treatment, or the time from this last treatment.

In order to assess the short-term prognostic factors, we divided the patients into two groups: those who had a normal serum creatinine 30 days after the onset of disease (n=25), and those who did not (n=35). We compared several clinical and biological parameters in these two groups; the differences are presented in Table 4.

There was a direct correlation between the number of HD sessions and the length of the anuric phase (r = 0.47, P = 0.001). Also, patients with higher creatinine levels at 30 days after injury had a longer period of anuria; positive correlation between these two parameters (r = 0.48, P = 0.002). The patients with hypergammaglobulinaemia (n=13) had a significantly longer anuric phase than those without hypergammaglobulinaemia (15.5 ±4.2 days vs 10.4 ±7.7 days respectively; P = 0.05). There was a direct correlation between the level of serum gammaglobulins and the duration of anuria in all patients (r = 0.49, P <0.05; Figure 1).

During the study period there was one death (1.66%) among the 60 patients with post-rifampicin ARF, compared to a 20% mortality rate of all ARF cases hospitalized in the same period (P <0.05). Moreover, this death was attributed to the generalized extension of tuberculosis, with pulmonary miliary lesions and meningitis. There was no need for further renal replacement therapy in any of the patients. Ninety days from onset, serum creatinine and BUN were normal in 57 patients, and abnormal but <2 mg/dl, in two patients.

Discussion

Rifampicin is an antibacterial agent largely used in the treatment of tuberculosis, a disease with an increasing prevalence. There have been reports of rifampicin toxicity, both in continuous administration [13,14, 16–19,21,22,27,36] and especially in discontinued administration [1–8,15,23–26,28,30–32,37–42], as a result of type II and rarely type III hypersensitivity reactions. The range of rifampicin toxicity was described in 55 isolated case reports published between 1971 and 1995, most of them coming from countries with a high prevalence of tuberculosis.

Our study is the first complete description of a large series of post-rifampicin ARF cases including 60 patients treated in the Iasi Haemodialysis Centre, during a period of 8 years (1988–1995). The results are discussed together with a review of other previous reports.

ARF occurred immediately after rifampicin readministration, even if this acute episode was several months or years (three cases: after 1 year—similar to

Table 3. Mean values for main hepatic biochemical parameters

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGP (IU)</td>
<td>23.3</td>
<td>5.0</td>
</tr>
<tr>
<td>TGO (IU)</td>
<td>23.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Gammaglobulins (g/l)</td>
<td>21.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Quick index (%)</td>
<td>88.9</td>
<td>13.1</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.29</td>
<td>0.9</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>12.9</td>
<td>5.26</td>
</tr>
</tbody>
</table>
Table 4. Comparison of patients with normal creatinine and those with abnormal creatinine values at 30 days after the first day of oligoanuria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Creatinine 30 &lt; 1.2 mg/dl (n = 25)</th>
<th>Creatinine 30 &gt; 1.4 mg/dl (n = 35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>16/9</td>
<td>25/10</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.4 ± 12.5</td>
<td>46.3 ± 10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine-30 (mg/dl)</td>
<td>1.1 ± 0.2</td>
<td>3.2 ± 3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Urea-30 (g/l)</td>
<td>0.5 ± 0.3</td>
<td>0.76 ± 0.3</td>
<td>0.05</td>
</tr>
<tr>
<td>No. days anuria</td>
<td>6.0 ± 0</td>
<td>13.3 ± 7.5</td>
<td>0.001</td>
</tr>
<tr>
<td>No. dialysis sessions</td>
<td>4.0 ± 5.0</td>
<td>5.4 ± 4.3</td>
<td>NS</td>
</tr>
<tr>
<td>Hepatic involvement at onset</td>
<td>5/25 (25%)</td>
<td>10/35 (28.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Gammaglobulins (g/l)</td>
<td>19.8 ± 3.7</td>
<td>23.3 ± 3.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Haematocrit-i (%)</td>
<td>5.2 ± 4.4</td>
<td>33.2 ± 4.8</td>
<td>NS</td>
</tr>
<tr>
<td>Leukocytes-i (per mm$^3$)</td>
<td>10484 ± 3262</td>
<td>13694 ± 5727</td>
<td>0.02</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>10/25 (40%)</td>
<td>28/35 (80%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9/25 (36%)</td>
<td>21/35 (60%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Severe haemolytic anaemia</td>
<td>3/25 (12%)</td>
<td>12/35 (34.3%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*i*, initial values; -30, values at 30 days from onset.

Fig. 1. Correlation between the gammaglobulin level and the length of the anuric period.  

Gamma.

Rifampicin-induced acute renal failure

The most frequent symptoms were gastrointestinal (abdominal pain, nausea, vomiting and diarrhea) [6,7,9,31,42,45] and flu-like (fever, prostration, generalized aches and pains) [5,9,28,45]. In 17% of patients, we also observed clinical signs suggesting significant haemolysis (jaundice, low-back pain, chills, dark brown urine, low BP).

Anaemia was found in many patients, with 25% of them exhibiting features of severe immune haemolysis [4–6,8,15,18,21,24–29,41,44,46,52]. Haemolysis is due either to a generalized type of immune reaction [8], or to the specific reaction of IgM type Ab against RBC Ag I [25,44,46]. In all cases with haemolytic anaemia, as reported previously [27], the indirect Coombs’ test became positive after adding rifampicin, confirming the pathogenic role of the drug.

Thrombocytopenia associated with post-rifampicin ARF [15,27,28,30,57] occurs in 50% of patients. It may be of an autoimmune aetiology [30,57], or less frequently secondary to disseminated intravascular coagulation induced by haemolysis [27,28]. The more severe the anaemia, the more frequent the presence of haemolysis and thrombocytopenia (Table 2), thus certifying the severity of the immune process. Indeed, a correlation between the presence and severity of the haematological signs and the titre of circulating rifampicin antibodies was reported by the well-documented cases of Stradling [44] and Cochram et al. [46], although not confirmed by Mauri et al. [9]. The specific time-course of events, in association with a previous normal renal function and absence of other potential causes for ARF, established rifampicin as the sole aetiology. Therefore, routine examination for antirifampicin antibodies was not considered necessary. Also, post-rifampicin ARF cases without demonstrable circulating antibodies [9,21,34] have been described. When investigated, (five cases), their presence was confirmed, as reported by [8,26,27,32,44]. Finally, after risk/benefit odds analysis, renal biopsy was not considered essential for a positive diagnosis. Biopsy was performed in five cases, revealing only interstitial lesions with normal glomerular appearance.

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Simultaneous signs of hepatic injury (a true hepatorenal failure) were found in 25% of cases, more often than have been previously reported [31–34]. The reason might be pre-existing liver disease despite normal biochemical tests, such as chronic hepatitis possibly induced by the antituberculous drugs themselves. However, hepatic injury, did not affect the outcome, in our patients.

Sterile leukocyturia, found in 83% of patients at presentation, is a marker of interstitial nephritis causing the ARF [27,32,36]. Tubular defects [13–15,19] were extremely rare in our post-rifampicin ARF series (only 1 case with mild abnormalities).

The one case with nephrotic syndrome (as reported in [16,22,23]) and many other cases with significant proteinuria, suggest the presence of glomerular injury, either isolated or superimposed on the interstitial nephritis in patients with post-rifampicin ARF [5,12,16,22,23]. Light-chain proteinuria was not found in the nine patients investigated. Neither the presence nor the severity of proteinuria emerged as negative prognostic factors for this condition (as seen in some primary glomerular diseases), suggesting a pre-eminence of the interstitial lesions [15]. Other possible mechanisms, not seen in our cohort but which may contribute to ARF, are papillary necrosis [36], crescent formation [21], and hypercalcaemia [13].

In addition to the severity of the immune processes (reflected by the level of haemolysis, leukocytosis and serum gammaglobulins), the main prognostic factor is the initial duration of the anuric phase (correlated both with the need for dialysis and with a slower rate of decrease of azotaemia).

The evolution of post-rifampicin ARF is usually benign with only two authors [46,47] describing persistent renal failure, a long time after the acute episode. Although most cases are oligoanuric at presentation, needing 4 or 5 dialysis sessions, urine output returns to normal in about 10–11 days. The mortality is very low and renal function recovery is complete in 40% of patients 30 days from onset and in 96.6%, 90 days from onset.

The high percentage of ARF caused by rifampicin (16.6% in our statistics) is presumably the result of some particular conditions in our country; the high prevalence of tuberculosis, the common twice-weekly regimen of rifampicin administration, and the large number of discontinued treatments in non-compliant patients.

Conclusions

Post-rifampicin ARF is a well-defined entity, with a high prevalence, especially with the increasing incidence of tuberculosis. The most frequent symptoms and signs are oligoanuria, flu-like syndrome, and gastrointestinal signs.

Thrombocytopenia, immune haemolytic anaemia, and intravascular haemolysis are often associated, and their presence complicates the clinical appearance, may worsen the renal injury and therefore the evolution of the disease. The severity of the immune processes and the duration of the anuric phase are the main short-term prognostic factors. The long-term evolution is usually favourable in the large majority of cases.

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