Volatility of elevated serum ferritin in anemic hemodialysis patients

David J. Hobbs¹, Allan B. Schwartz¹, Ed Gracely², Toros Kapoian³, Adel R. Rizkala⁴; for the DRIVE Study Group

¹Department of Medicine, Division of Nephrology and Hypertension, Drexel University College of Medicine, Philadelphia, Pennsylvania - USA
²Department of Family, Community, and Preventative Medicine, Drexel University College of Medicine, Philadelphia, Pennsylvania - USA
³Department of Medicine, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, New Jersey - USA
⁴Watson Laboratories Inc., Morristown, New Jersey - USA

ABSTRACT

Background: Value of serum ferritin (SF) as an iron store index in hemodialysis (HD) patients has been questioned, especially at ranges ≥200. The objective of this study was to determine the variability of SF in patients with high SF (500-1,200) and low TSAT (≤25%).

Methods: This was a multicenter observational study. Data were obtained from Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) study voluntary subject screening surveys (n=96), which reported epoetin dose, pre-screening and screening hemoglobin, TSAT and SF. Entry criteria were age ≥18 years, HD ≥90 days, SF 500-1,200, TSAT ≤25%, hemoglobin ≤11 g/dL, epoetin ≥22,500 IU/week or ≥225 IU/kg/week and ≤125 mg i.v. iron/week in the 4 weeks prior to screening. Groups were stratified by intervals of time between laboratory dates: 1-14 days (group 1), 15-28 (group 2) and 29-42 (group 3). Changes from pre-screening to screening were evaluated.

Results: SF changes (ΔSF) in groups 1, 2 and 3 were -63. (range -414 to +415; p=0.013), -191. (range -379 to +427; p=0.001) and -144. (range -541 to +181; p=0.018), respectively. Within group 1, proportions of patients experiencing an absolute ΔSF ≥100, ≥200 and ≥300. were 61.0%, 29.3% and 12.2%, respectively, and 27% exhibited positive changes in SF. Conclusions: SF is a volatile and imprecise indicator of tissue iron stores in anemic HD patients with high SF and low TSAT. This volatility limits clinical utility of SF in this population.

Key words: Anemia, Anemia management, Hemodialysis, Iron overload, Iron therapy, Serum ferritin, Variability

INTRODUCTION

Serum ferritin (SF) is routinely used as a marker of iron status in the management of anemia in hemodialysis patients. The usefulness of this marker has been questioned in the assessment of iron deficiency in patients with nondialysis chronic kidney disease (1) and in hemodialysis patients (2-4). Ferritin is an acute-phase reactant, increasing in response to inflammation (5). Possible mechanisms for increases in ferritin during inflammation are by increased translation of mRNA ferritin subunits via IL-1β and TNF-α (6, 7) and reductions in iron mobilization (8). Multiple non-iron-related factors have also been noted to alter ferritin values in hemodialysis patients, including malnutrition (9), liver dysfunction (10) and multiple cancer types (11-15).

Multiple studies assessing iron status in hemodialysis patients on maintenance epoetin and iron therapy have demonstrated that serum ferritin is reliable when low, but has limited diagnostic properties in patients with values greater than 100-200 μg/L due to diminished sensitivity (16-21). It has also been noted that the coefficient of variation of serum ferritin is estimated to be large (2). These studies, however, included very few patients with SF ≥500. Therefore, given that greater than 50% of hemodialysis patients have a SF ≥500. (22), the applicability of their results to patients with higher ferritin levels is limited at best.

The primary objective of this study was to evaluate the precision and reproducibility of serum ferritin values in hemodialysis patients with levels of 500-1,200 transferrin saturation (TSAT) ≤25% and adequate epoetin doses after varying time intervals from initial measurement. This was accomplished by analyzing data from subject screening surveys completed during the screening phase of the recently-published Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) study (23).
Methods

Patient selection

The DRIVE study was a multicenter study (37 hemodialysis centers) designed to evaluate the impact of intravenous (i.v.) iron therapy on the hemoglobin of hemodialysis patients with SF ≥500. and low TSAT (≤25%). The entry criteria, design and primary and secondary results have been reported elsewhere (23, 24). Briefly, the primary entry criteria were age ≥18 years, on hemodialysis ≥90 days, receiving a stable dosage of epoetin ≥225 IU/kg per week or ≥22,500 IU/week for at least 2 weeks and having received no more than 125 mg/week i.v. iron during the 4 weeks preceding screening. More importantly, participants’ most recent laboratory values had to include the following: SF 500-1,200, TSAT ≤25% and hemoglobin ≤11. Patients with active infection requiring systemic antibiotic therapy and those who had been hospitalized in the last 2 weeks were excluded.

The DRIVE study was approved by each study center’s institutional review board, and all study participants provided informed consent prior to any study procedures or collection of any health data. Also, the DRIVE study was registered with the National Library of Medicine at http://www.clinicaltrials.gov.

Study procedures

To determine their screening eligibility for the DRIVE study, patients were first pre-screened based on their most recent laboratory results. If a patient’s most recent SF, TSAT and hemoglobin were 500-1,200, ≤25% and ≤11, respectively, the patient was screened through the central laboratory. All oral and i.v. iron therapy was discontinued at or before screening (the date at which the second laboratory results were obtained). All site coordinators were asked to complete a subject screening survey for each patient they screened through the central laboratory. Although they were not obligated to do so. This survey verified compliance to the inclusion and exclusion criteria, including critical pre-screening and screening laboratory values (SF, TSAT and hemoglobin) and dates on which each was obtained.

For the purposes of this report, patients were stratified into 3 groups based on the time elapsed between pre-screening local laboratory values (day 0) and screening laboratory values: group 1 patients obtained screening values 1 to 14 days after pre-screening, 15 to 28 days for group 2, and 29 to 42 days for group 3. Patients with screening values obtained after more than 42 days after pre-screening values were not included in any analyses.

Statistical analyses

To determine if there was significant change between pre-screening and screening SF, TSAT and hemoglobin laboratory studies, we compared all patients with themselves as their own controls, using paired t-test analyses when the values being analyzed were normally distributed, and Wilcoxon signed rank tests when it was not. To see if there was statistical significance among groups in the mean changes in SF, TSAT and hemoglobin and mean epoetin dose we used the Kruskal-Wallis test. Demographic results were reported as means ± standard deviation. Pre-screening and screening SF, TSAT and hemoglobin were reported as medians (range). A p value less than 0.05 was considered statistically significant.

Results

Figure 1 depicts the disposition of subject surveys included in the ferritin volatility analysis. Of the 503 patients who were screened through the central laboratory for the DRIVE study, a total of 102 subject screening surveys were completed by the study coordinators (23). Of these, 6 were duplicate screening attempts of the same patients. Therefore the first screening attempt was considered in the final analysis, reducing the study population to 96. Of those 96 patients, 28 (29.2%) were ultimately randomized into the DRIVE study. This proportion of randomization patients in this study was similar to that seen in the DRIVE study (23), which shows that there was no bias in survey completion based on whether or not patients were randomized into the trial. Furthermore, the variables of age, serum ferritin, TSAT and hemoglobin were consistent with the DRIVE study results (23). For example, the mean hemoglobin of randomized and screen failures in the DRIVE study were 10.3 ± 0.8 and 11.2 ± 1.1 (p<0.001) (23), respectively. Similarly, in this analysis, the mean hemoglobin for randomized and screen failures were 10.3 ± 0.9 and 11.3 ± 1.1 (p<0.001), respectively. Whereas 54.5% of those screened for the DRIVE study were women, only 43.8% of the patients with completed surveys were women (p=0.054).

As per the DRIVE study protocol, all oral and i.v. iron therapy was discontinued at or before the date in which screening labs were obtained (23). Only 56% (n=54) of the subject surveys reported the date of i.v. and oral iron discontinuation. Of that population, 57% (n=31) discontinued iron before the first set of laboratory results were obtained (pre-screening). For groups 1-3, 75% (n=18), 47% (n=8) and
39% (n=5) discontinued iron therapy before pre-screening labs were obtained, respectively. Of the subjects who discontinued i.v. iron between the 2 test dates (between pre-screening and screening), the mean time between pre-screening and the date of iron discontinuation for groups 1-3 was 5.6 days, 16 days and 21 days, respectively. The amount of i.v. iron administered to the subjects was not recorded in the screening forms. Therefore, we were unable to quantify the amount of iron therapy received between test dates, but it is believed to have been low (23). Of the overall sample (N=96), 90, 93 and 94 patients had complete SF, TSAT and hemoglobin data (pre-screening value and screening values with no longer than 42 days elapsed in between), respectively. As shown in Tables I and II, epoetin doses and proportion of women were similar in all 3 groups. Patients in group 3 tended to be younger (50 ± 16 years) than those in group 1 (58 ± 15 years) and group 2 (61 ± 14 years; p=0.054).

Statistically significant declines in median SF and large ranges were noted in all 3 groups (Tab. I, Fig. 2). Serum ferritin dropped significantly in group 1 from 822 to 730. (range -414 to +415.; p=0.013), from 702 to 615 (range -379 to +427.; p=0.001) in group 2, and from 715 to 616 (range -541 to +181.; p=0.018) in group 3 (Tab. I). The comparison of change in SF among groups 1 to 3 was not significant (p=0.137). A substantial proportion of subjects demonstrated relatively large changes in SF between the 2 test times (Fig. 3A). As such, 62% had an absolute change in SF ≥100.

### TABLE I
DEMOGRAPHICS AND CHANGES IN SERUM FERRITIN BY GROUP

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between laboratory dates, days</td>
<td>1 to 14</td>
<td>15 to 28</td>
<td>29 to 42</td>
</tr>
<tr>
<td>Number of patients</td>
<td>41</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>Age, years</td>
<td>58 ± 15</td>
<td>61 ± 14</td>
<td>50 ± 16</td>
</tr>
<tr>
<td>Number of women</td>
<td>13 (31.7%)</td>
<td>15 (48.4%)</td>
<td>10 (55.6%)</td>
</tr>
<tr>
<td>Epoetin dose, IU/week</td>
<td>33,884 ± 18,806</td>
<td>40,450 ± 18,980</td>
<td>38,953 ± 23,674</td>
</tr>
<tr>
<td>Serum ferritin at pre-screening,</td>
<td>822 (494 – 1640)</td>
<td>702 (503 – 1433)</td>
<td>715 (500 – 1707)</td>
</tr>
<tr>
<td>Serum ferritin at screening,</td>
<td>730 (348 – 1485)</td>
<td>615 (183 – 1299)</td>
<td>616 (344 - 1295)</td>
</tr>
<tr>
<td>Change from pre-screening value,</td>
<td>-63 (-414 – 415)</td>
<td>-191 (-379 – 427)</td>
<td>-144 (-541 – 181)</td>
</tr>
<tr>
<td>p Value of change</td>
<td>0.013</td>
<td>0.001</td>
<td>0.018</td>
</tr>
<tr>
<td>Patients with absolute change ≥100</td>
<td>25 (61.0%)</td>
<td>19 (61.3%)</td>
<td>13 (72.2%)</td>
</tr>
<tr>
<td>Patients with absolute change ≥200</td>
<td>12 (29.3%)</td>
<td>17 (54.8%)</td>
<td>6 (33.3%)</td>
</tr>
<tr>
<td>Patients with absolute change ≥300</td>
<td>5 (12.2%)</td>
<td>7 (22.6%)</td>
<td>2 (11.1%)</td>
</tr>
</tbody>
</table>

Age and epoetin dose are summarized as means ± standard deviation, and pre-screening and screening values as medians (range). Categorical data are summarized using frequencies (percentages).
39% had an absolute change \( \geq 200 \). and 17% had an absolute change \( \geq 300 \). The high ranges of change in SF varied both positively and negatively at values \( >-400 \) to \(+400\). A total of 23% of the study patients (n=21) demonstrated a positive change in SF (Fig. 3A). A total of 39% (n=35) and 17% (n=15) demonstrated an absolute change in SF of \( \geq 200 \). and \( \geq 300 \), respectively (Fig. 3A). Group 1 changes in SF distribution showed a pseudonormal distribution with a left shift, indicating the negative change in SF between pre-screening and screening SF laboratory studies (Fig. 3B). This is a considerable amount of change (range -414 to +415; Tab. I) given the mean time interval between test dates of 8 days for group 1. In group 2, where the mean time interval between pre-screening and screening was 21 days, change in SF distribution was irregularly distributed, with 23% of the patients displaying an absolute change in SF of \( \geq 300 \). (range -379 to +427.) (Tab. I, Fig. 3C). Group 3 change in SF distribution was similar to that of group 1, with 56% of the patients demonstrating a change of \( >-100 \). (Fig. 3D). In group 1, 27% (n=11) exhibited a positive change in SF; group 2, 16% (n=5); group 3, 28% (n=5). In group 1, 61% (n=25), 29% (n=12) and 12% (n=5) had absolute changes in SF \( \geq 100 \), \( \geq 200 \), and \( \geq 300 \), respectively. Groups 2 and 3 had similar patterns (Tab. I).

We investigated the number of patients in whom the change from pre-screening to screening values could directly impact the decision as to whether or not i.v. iron should be administered based on current (25) and past versions (26,

---

**TABLE II**

DEMOGRAPHICS AND CHANGES IN TRANSFERRIN SATURATION AND HEMOGLOBIN BY GROUP

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between laboratory dates, days</td>
<td>1 to 14</td>
<td>15 to 28</td>
<td>29 to 42</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>43</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Age, years</td>
<td>57 ± 15</td>
<td>62 ± 14</td>
<td>52 ± 15</td>
</tr>
<tr>
<td>Number of women (%)</td>
<td>14 (32.6%)</td>
<td>18 (52.8%)</td>
<td>8 (50.0%)</td>
</tr>
<tr>
<td>Epoetin dose, IU/week</td>
<td>35,311 ± 18,822</td>
<td>38,162 ± 18,940</td>
<td>38,789 ± 24,037</td>
</tr>
<tr>
<td>Transferrin saturation at pre-screening, % (range)</td>
<td>18 (10 to 26)</td>
<td>20 (5 to 27)</td>
<td>20 (15 to 52)</td>
</tr>
<tr>
<td>Transferrin saturation at screening, % (range)</td>
<td>21 (13 to 40)</td>
<td>21 (12 to 35)</td>
<td>24 (16 to 64)</td>
</tr>
<tr>
<td>Change from pre-screening value, % (range)</td>
<td>2 (-6 to 28)</td>
<td>3 (-11 to 21)</td>
<td>4 (-35 to 39)</td>
</tr>
<tr>
<td>p Value of change</td>
<td>0.001</td>
<td>0.039</td>
<td>0.328</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>54</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>58 ± 16</td>
<td>60 ± 15</td>
<td>53 ± 14</td>
</tr>
<tr>
<td>Number of women (%)</td>
<td>19 (35.2%)</td>
<td>15 (50.0%)</td>
<td>6 (60.0%)</td>
</tr>
<tr>
<td>Epoetin dose, IU/week</td>
<td>35,617 ± 18,874</td>
<td>39,279 ± 19,032</td>
<td>38,119 ± 26,830</td>
</tr>
<tr>
<td>Hemoglobin at pre-screening,</td>
<td>10.6 (7.5 to 11.5)</td>
<td>10.4 (7.5 to 11.6)</td>
<td>10.2 (7.5 to 11.9)</td>
</tr>
<tr>
<td>Hemoglobin at screening,</td>
<td>11.1 (8.6 to 12.6)</td>
<td>11.3 (8.9 to 12.9)</td>
<td>11.1 (7.9 to 13.2)</td>
</tr>
<tr>
<td>Change from pre-screening value,</td>
<td>0.6 (-1.1 to 1.9)</td>
<td>0.9 (-1.3 to 4.2)</td>
<td>0.3 (-0.6 to 4.3)</td>
</tr>
<tr>
<td>p Value of change</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.138</td>
</tr>
</tbody>
</table>

Age and epoetin dose are summarized as means ± standard deviation, and pre-screening and screening values as medians (range). Categorical data are summarized using frequencies (percentages).
observed in changes in TSAT and hemoglobin.

Discussion

Many studies have raised the overall concern about the reliability of SF in the assessment of iron storage in hemodialysis patients with SF <500. (2-4, 16-21). Our study furthers this concern in patients with SF 500-1,200, low TSAT (<25%) and adequate epoetin doses. We discovered significant changes in SF with large standard deviations in relatively short time periods. For example, in group 1, where the mean time interval between test times was approximately a week (8 days), the following were reported concerning SF: over a quarter (29%) demonstrated absolute changes ≥200, over a quarter (27%) demonstrated positive changes, extreme range of change varying both positive and negative >400. (Tab. I, Fig.

Fig. 3A-D - Distribution of change in serum ferritin values from pre-screening to screening in A) the overall sample, B) within group 1 (1-14 days after pre-screening), C) within group 2 (15-28 days after pre-screening) and D) within group 3 (29-42 days after screening).

27) of the US National Kidney Foundation (NKF) anemia management recommendations. There were 21 patients (23.3%) who had a pre-screening SF ≥500 and a screening SF <500. Also, there were 19 patients (21.1%) who had a pre-screening SF >800 and a screening SF <800. Lastly, we found 6 patients (6.7%) with pre-screening SF between 500 and 800 and screening SF >800. Median increases in pre-screening TSAT were 2% points (range -6% to +28% points; p=0.001), 3% points (range -11% to +21% points; p=0.039) and 4% points (range -35% to +39% points; p=NS) in groups 1, 2 and 3, respectively (Tab. II). There was no statistically significant difference among groups comparing change in TSAT (p=0.717) or change in hemoglobin (p=0.377). Hemoglobin increased significantly in groups 1 (p<0.001) and 2 (p<0.001), but not in group 3 (p=0.138). Unlike SF, extreme variability was not
These findings reveal the volatile nature of SF in this patient population. Due to extreme volatility, SF cannot be regarded as a reliable or precise marker of iron storage in hemodialysis patients with elevated SF 500-1,200, low TSAT (<25%) and adequate epoetin doses. Although the SF values could be expected to decrease in a patient population receiving high dose epoetin and almost no i.v. iron therapy while below-target hemoglobin levels are corrected, the observed changes in SF are a cause of concern and much greater than anticipated in these time intervals, especially since epoetin doses did not change between pre-screening and screening. What makes our observations even more interesting is that nearly a quarter (23%) of the patients in this study demonstrated a positive change in SF between the 2 test times, which is not accounted for by increased hemoglobin levels and is the opposite of what would be expected in these patients in whom i.v. iron was not given, or at least severely restricted. This is the first demonstration of marked changes in SF largely independent of iron administration among hemodialysis patients with SF 500-1,200 and low TSAT (<25%).

The marked volatility and variability in SF measurements over short time periods has implications for proper monitoring and clinical usefulness of SF in hemodialysis patients with elevated SF and low TSAT, a subpopulation that tends to be difficult to treat. The NKF 2006 renal anemia guidelines recommend quarterly assessment of SF, with more frequent testing in specific settings (25), none of which take into account the spontaneous variability of SF. They further suggest routine administration of i.v. iron is not indicated when SF is >500. (25). Therefore, a single SF measurement of >500 might result in up to 3 months of withholding i.v. iron. If this parameter is to be used in guiding anemia management, reliability over an extended period of time is important. As we observed many patients experiencing significant shifts in SF that can alter the decision of whether to administer i.v. iron over much shorter time periods, we would recommend monthly monitoring of SF in all patients not receiving i.v. iron therapy. This is especially important if it was found to be >500 on routine testing. In addition, as prudently pointed out by the most recent NKF renal anemia practice recommendations (25), we feel that it is important that the decision on whether to give i.v. iron to such patients should not be based solely on the SF value, but should take into account hemoglobin value trends, TSAT values, epoetin responsiveness and the patient’s clinical status.

As these patients under study were required to be receiving ≥22,500 IU/week of epoetin, this population consumes a disproportionate share of the cost of anemia management. Furthermore, they are at greater potential health risk (28). Improved anemia management of this group could have dramatic cost-saving (29) and health benefits, while suboptimal management might lead to increased costs. The volatility of elevated serum ferritin observed in this study undermines the validity of using ferritin to guide iron treatment in this population.

The DRIVE study found the response rate to i.v. iron was virtually identical when SF was 500-800, compared with 801-1,200. (23). The lack of utility of SF in predicting the response to i.v. iron, is consistent with studies of patients with SF <500. (16-18, 20, 21). Taken together, these studies suggest a low SF (<200) is highly predictive of i.v. iron responsiveness, and a higher SF has little or no discriminative value. This may be in part due to the substantial volatility of SF we note in our study, as well as the large coefficient of variation for SF reported by others (2).

Given the marked volatility and variability of SF, use of other iron status markers to help guide iron treatment decisions would seem ideal. Iron status markers of current interest include reticulocyte hemoglobin content (CHr) and percentage of hypochromic red cells (%HRC). Some studies (16, 20) concluded that a low CHr was a satisfactory predictor of responsiveness to i.v. iron in hemodialysis patients. However, these studies lacked appropriate controls and examined only dialysis patients with SF <500. Results from the DRIVE study indicate that in patients with SF of 500-1,200, and TSAT ≤25%, a CHr greater ≥31.2 pg was more predictive of a response to i.v. iron, although values <31.2 pg did not preclude a clinically significant response to i.v. iron (24). While the DRIVE study did not examine %HRC as a predictor of response to i.v. iron, 3 other studies (2, 21, 30) reported %HRC to be a feasible indicator of patient’s response to i.v. iron.

Our study has limitations. First, due to the nonobligatory nature of this survey study, only about 20% of the 503 patients who were screened through the central lab had complete subject screening surveys. Although our screening laboratory values and randomization percentages parallel those of the DRIVE study (23), it is plausible that if we had received more screening forms our results might have been different. However, it was not possible to include any patients for whom no survey form was completed since the relevant pre-screening laboratory values were not captured on any other study document. Second, although many sites’ pre-screening values were obtained from the central laboratory, many others obtained their pre-screening values from different laboratories. Although interlaboratory fluctuations of serum ferritin values have never been investigated, they can potentially be another source of variability. Lastly, we were unable to obtain extensive patient demographic information.
and medical information, because such records were obtained only from patients randomized into the DRIVE study (23). However, such information would not have explained the extreme variability of ferritin values reported herein.

**CONCLUSIONS**

Serum ferritin is a volatile and imprecise indicator of tissue iron stores in hemodialysis patients with levels 500-1,200, TSAT ≤25% and adequate epoetin doses. This limits the clinical utility of serum ferritin in this patient population. Additional indices of iron stores and utilization are needed in combination with more frequent SF testing in anemia management of hemodialysis patients with SF 500-1,200, and TSAT ≤25%.

Financial support: This study was sponsored, in part, by Watson Laboratories Inc. A.B.S. has received clinical research grants from and/or is a member of the speakers’ bureau of Watson Laboratories Inc., Keryx, Ortho Biotech, Sanofi-Aventis, Genzyme and Astellas. T.K. has received clinical research support from Watson and Novaflux Technologies and is a consultant to Baxter Healthcare, Pfizer and Amgen. A.R.R. is an employee of Watson Laboratories Inc.

Conflict of interest statement: D.J.H. and E.G. have no conflicts of interest.

This research was presented as a scientific poster at the American Society of Nephrology annual meeting, November 2006, in San Diego, California.

**Address for correspondence:**
Allan B. Schwartz, MD
Drexel University College of Medicine
Department of Medicine
Division of Nephrology and Hypertension
Mail Stop 427
245 N. 15th Street
Philadelphia, PA 19102-1192, USA
allan.schwartz@drexelmed.edu

**REFERENCES**


Received: December 19, 2007
Revised: June 18, 2008
Accepted: July 14, 2008

© Società Italiana di Nefrologia