Reactive Macrophage Activation Syndrome: a simple screening strategy and its potential in early treatment initiation

U. Emmeneggera, b, A. Reimersb, U. Freyb, Ch. Fuxc, F. Bibld, D. Semelac, P. Cottagnoudc, A. Cernyd, P. J. Spataeh, Klaus A. Neftelb

a Department of Medicine, Division of Oncology, University Hospital, Geneva, Switzerland
b Division of Internal Medicine, Zieglerspital, Bern, Switzerland
c House Staff Internal Medicine, Inselspital/University Hospital, Bern, Switzerland
d Medicina Interna, Ospedale Civico, Lugano, Switzerland
e ZLB Bioplasma AG, Bern, Switzerland

Summary

Questions under study: starting treatment of reactive macrophage activation syndromes as early as possible (rMAS, haemophagocytic lymphohistiocytosis), e.g., with intravenous immunoglobulins (IVIG), seems to be essential for optimal outcome. However, there is no diagnostic gold standard which reliably indicates need for early treatment. We used a simple screening strategy consisting of serum ferritin measurements and/or morphological assessment of haemophagocytosis and compared the studied patient population with published series.

Methods: Retrospective analysis of clinical and laboratory data of 57 patients experiencing 60 episodes of rMAS.

Results: Screening by serum ferritin measurements and/or morphological assessment of haemophagocytosis of patients presenting with a systemic inflammatory response syndrome (SIRS) indicates that rMAS might be considerably more frequent than stated in the literature. Serum ferritin exceeded >10000 μg/L in 91% rMAS episodes. Although the patient population studied was otherwise similar in most aspects to the published rMAS series, the fact that 40% of patients fulfilled the criteria for Still’s disease (SD) as the disorder underlying rMAS is remarkable and questions the distinct nature of the two diseases. IVIG responders and non-responders did not differ regarding their initial characteristics with exception to the time-point of IVIG administration, confirming the importance of early treatment initiation. Malignancy-associated rMAS however, has a poor prognosis and seems to be refractory to manipulation with IVIG in most instances, even when responding initially.

Conclusions: rMAS has to be considered in patients with a SIRS- or SD-like clinical presentation. Hyperferritinemia ≥10000 μg/l seems to be a good marker for defining patients with or at risk for developing rMAS and should be completed with a morphological assessment of haemophagocytosis. The perception of acute SD and rMAS as two distinct entities has to be questioned at least in a subgroup of patients.

Keywords: reactive macrophage activation syndrome; haemophagocytic lymphohistiocytosis; hyperferritinemia; intravenous immunoglobulin; Still’s disease; systemic inflammatory response syndrome

Introduction

Monocytes and their derivatives play an important role in innate immune defence and at the border to the adaptive immune system. Whereas monocytic disorders are in most cases related to a decrease in function, the reactive macrophage activation syndrome (rMAS) is defined by an inappropriate activation of the macrophage system with consequences such as haemophagocytosis leading to cytopenia, multiple organ dysfunction, fever and rash [1]. Interestingly, these patients present with extremely elevated serum ferritin levels of up to several hundred thousands μg/L, at least in the early phases of their disease [2]. A hereditary form of childhood rMAS termed familial haemophagocytic lymphohistiocytosis (FHL) and other hereditary immunological disorders with an increased lifetime risk of rMAS point to a pivotal pathogenic role of T lymphocytes and nat-
ural killer cells. Impaired cytotoxic capacity of these cells seems to lead to macrophage activation via deregulated feedback loops. But the precise mechanisms remain elusive [3]. Various other disorders can contribute to or trigger the development of a rMAS, especially infections, neoplasia and immunological disorders [1].

Although there are diagnostic guidelines for the FHL and an adapted version for adult rMAS [1], they are far from being satisfactory and a gold standard is missing. For instance, according to literature and our own experience, morphological evidence of haemophagocytosis must not be present during all phases of the disease [4]. Laboratory parameters such as hypertriglyceridaemia are of limited value [5]. Functional tests of natural killer cell or T lymphocyte cytotoxicity are not available on a routine and emergency basis. Therefore, rMAS is often recognised only in advanced, refractory disease state with a genuinely high mortality rate [6].

In conditions suspicious of rMAS serum ferritinaemia is often not determined or not considered as an emergency parameter although its diagnostic and therapeutic value seems to be very promising as recently reported [2]. The present retrospective analysis describes the clinical and laboratory profile of 57 rMAS patients experiencing 60 rMAS episodes defined by serum hyperferritinaemia and/or morphological evidence of haemophagocytosis and compares the results with published series.

Patients and methods

Patients

Adult patients (≥16 years) were recruited between October 1993 and June 2001 based on serum ferritin levels ≥10000 μg/L and/or morphological evidence of haemophagocytosis. The ferritin cut-off was arbitrarily set at 10000 μg/L in order to exclude patients presenting with acute-phase reactions such as common infections. Known iron overload, primary liver disease and absence of an acute febrile illness were exclusion criteria. Eight patients were seen in our institutions, the remaining in 24 primary, secondary or tertiary hospitals in Switzerland. Most of the cases were brought to our attention following educational activities. The majority of subjects were hospitalised in internal medicine units.

Methods

Ferritin measurements were done in our laboratory with the Tina-quant® a Ferritin assay (Boehringer-Mannheim AG, Rotkreuz/Switzerland; with reference ranges of 10–160 and 30–300 μg/L for females and males, respectively). The results from the participating hospitals were compared with our assay and no relevant discrepancies were found. Where ferritin measurements were not available as a routine parameter within 24 hours, fresh samples where sent to our laboratory. Otherwise, sera were stored and transported at ≤–20 °C. Analysis of the bone marrow or tissue specimens was done by the haematologists and/or pathologists of the participating hospitals.

Statistics were calculated by Instat 3.0 software (GraphPad Software Inc., San Diego, California/USA). Laboratory parameters were compared by the Mann-Whitney U or the Kruskal-Wallis test as appropriate. Binomial data was analysed for significance by the Fisher’s exact test. All tests of significance were two-sided with a p-value of <0.05 regarded as significant.

Results

Patients and published series

Of the 61 patients meeting the inclusion criteria, 4 were excluded from further analysis. A 51 year old male diagnosed stage I (oral cavity) T cell Non-Hodgkin lymphoma (NHL) presented with massive haemophagocytosis on a bone marrow specimen drawn as a part of the initial staging with a concomitant serum ferritin value of only 500 μg/L, but without any other clinical evidence of a rMAS. Further evolution was uneventful under chemo- and radiotherapy. Another patient with an advanced diffuse large B cell NHL showed extensive haemophagocytosis in a inguinal lymphnode but without hyperferritinaemia or acute illness. The maximal ferritin value of 46300 μg/L in a female with alcohol dependency was interpreted as resulting from fulminant pancreas and liver necrosis. No cytological or histological data was obtained. A male with end-stage renal failure presented with a serum ferritin of 17700 μg/L with infected gangrene of a toe but without acute signs pointing to rMAS.

In table 1, clinical characteristics of our patients are compared with published series of rMAS. The diagnosis of and screening for rMAS varies in the literature. Kaito et al. [6] suspected rMAS when patients presented with fever unresponsive to antibiotics, general fatigue, pancytopenia of unknown origin and liver dysfunction. Whenever possible morphological evidence of haemophagocytosis was obtained. Reiner and Spivak [7] reviewed reports of bone marrow aspirates of adults (>16 years) with haemophagocytosis and the following exclusion criteria: presence of immune-mediated haemolysis or thrombocytopenia, malignant histiocytosis, evidence of adverse drug reactions or the lack of adequate clinical or laboratory data. Similarly, Risdall et al. [8] and Sailler et al. [9]
analysed patients diagnosed rMAS based on bone marrow specimens. Sailler et al. excluded patients with malignant histiocytosis. Albert et al. [10] refer to the criteria outlined by Risdall. Tiab et al. [11] screened for patients with febrile pancytopenia or characteristics such as high fever, modification of the general condition and/or visceromegaly. The diagnosis of rMAS was retained only after proof of haemophagocytosis in an appropriate clinical context. In the analysis of Wong et al. [12], 40 bone marrow specimens out of >4000 met the criteria of >2% of haemophagocytic histiocytes associated with an otherwise unexplained cytopenia involving at least 2 lines.

Our data confirm a certain male preponderance mentioned in the literature the biological basis of which is not clear. The mortality rate of 35% corresponds favourably with other series. Regarding underlying disorders, infectious causes seem to be underrepresented in our group of patients. This might be due to the fact that series with high rates of infections have a high percentage of immunodeficient subjects which is not the case in the patients presented here. For instance Risdall et al. [8] describe 13 (out of 19) renal transplant recipients under immunosuppressive treatment. As in other series, lymphoproliferative disorders predominate in the group of malignancy-associated rMAS. An intriguing finding of our series is the rate of patients initially diagnosed with Still’s disease (SD), a rare disorder with an estimated annual incidence of 1 in 100,000 in Caucasians [13].

Table 1

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>infections</td>
<td>14(8)</td>
<td>47</td>
<td>18</td>
<td>87</td>
<td>79</td>
<td>38</td>
<td>43</td>
<td>40</td>
</tr>
<tr>
<td>viral</td>
<td>–</td>
<td>36</td>
<td>12</td>
<td>52</td>
<td>79</td>
<td>12</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>others</td>
<td>14(8)</td>
<td>28</td>
<td>6</td>
<td>43</td>
<td>–</td>
<td>26</td>
<td>22</td>
<td>32</td>
</tr>
<tr>
<td>malignancies</td>
<td>162(16)</td>
<td>38</td>
<td>15</td>
<td>30</td>
<td>–</td>
<td>25</td>
<td>56</td>
<td>45</td>
</tr>
<tr>
<td>non Hodgkin's lymphoma</td>
<td>18(10)</td>
<td>19</td>
<td>6</td>
<td>13</td>
<td>–</td>
<td>15</td>
<td>48</td>
<td>40</td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
<td>4(2)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>hematopathies</td>
<td>2(1)</td>
<td>19</td>
<td>9</td>
<td>9</td>
<td>–</td>
<td>5</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>solid tumors</td>
<td>5(3)</td>
<td>–</td>
<td>–</td>
<td>9</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>immunological diseases</td>
<td>42(24)</td>
<td>4</td>
<td>6</td>
<td>26</td>
<td>5</td>
<td>3</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>Still’s disease</td>
<td>40(23)</td>
<td>–</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SLE</td>
<td>2(1)</td>
<td>4</td>
<td>3</td>
<td>13</td>
<td>5</td>
<td>3</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>others</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>13</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>immune deficiency</td>
<td>5(3)</td>
<td>38</td>
<td>3</td>
<td>17</td>
<td>68</td>
<td>8</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>2(1)</td>
<td>6</td>
<td>–</td>
<td>9</td>
<td>–</td>
<td>–</td>
<td>22</td>
<td>–</td>
</tr>
<tr>
<td>transplantation</td>
<td>4(2)</td>
<td>9</td>
<td>–</td>
<td>4</td>
<td>68</td>
<td>–</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>others</td>
<td>–</td>
<td>21</td>
<td>3</td>
<td>4</td>
<td>–</td>
<td>8</td>
<td>17</td>
<td>–</td>
</tr>
<tr>
<td>unknown</td>
<td>18(10)</td>
<td>15</td>
<td>59</td>
<td>–</td>
<td>16</td>
<td>16</td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>

* age in years unless otherwise indicated
| n: number; d: day(s); m: month(s); na: not available

Diagnostic criteria

46% of our patients met 5 of 5 of the modified criteria for rMAS outlined by Imashuku [1] (see table 2), another 33% 4 of 5. The remaining 21% would not have been diagnosed as rMAS based on Imashuku’s criteria. The published series do not apply Imashuku’s criteria.

Due to the retrospective nature of our analysis, timing of the ferritin measurements and the corresponding morphological assessment was not optimal in several cases. In 1 patient, no ferritin value was available at all. In another 5, ferritin never exceeded 10000 μg/L despite evidence of haemophagocytosis and an appropriate clinical setting. But in 4 of these subjects, the interval between maximal serum ferritin and bone marrow analysis was more than one week which might have resulted in declining, ie, only moderately elevated ferritin levels as described previously [2]. In one patient with a high grade T cell NHL, there was no ferritin value available at the most acute disease phase. After the first cycle of chemotherapy, the values stabilised around 5000 μg/L. The individual peak ferritin values range from 343 to 280500 μg/L (median 37250 μg/L).
Fifteen patients did not have any morpho-pathological analysis. Of the remainder, 29 presented with concomitant hyperferritinaemia and morphological evidence of haemophagocytosis. Nine out of a total of 43 bone marrow specimens (in 42 patients) showed no overt haemophagocytosis despite ferritin levels ranging from 10600 to 134900 μg/L. In 6 of these patients, the interval of 0–7 days between available measurements of ferritin and assessment of haemophagocytosis renders the interpretation difficult. Moreover, it is known that the demonstration of haemophagocytosis can require several attempts. Haemophagocytic activity can vary over time and might also spare bone marrow with predominant involvement of other organs of the reticuloendothelial system such as liver and spleen [4]. Interestingly, the 3 patients with hyperferritinaemia and concomitant absence of haemophagocytic activity meet the Yamaguchi criteria for SD [14] (table 3). Of all our patients, 23 had been diagnosed with juvenile or adult-onset SD before or met the criteria during the analysed rMAS episode. Another 11 patients presented with symptoms very similar to SD, but another diagnosis was retained. Hence, around 60% of our patients presented a SD-like pattern.

Clinical and laboratory findings

Of the factors predicting fatal outcome described by Kaito et al. [6], several could be confirmed in our population: presence of coagulation disorders (p = 0.004) and liver dysfunction (p = 0.01), anaemia (haemoglobin [mean ± standard
Reactive Macrophage Activation Syndrome: a simple screening strategy and its potential in early treatment initiation

Discussion

The term reactive macrophage activation syndrome (rMAS) describes a potentially reversible situation of uncontrolled, probably T-lymphocyte/NK-cell driven stimulation of macrophages triggered by various stimuli. The clinical presentation is in many aspects similar to the so-called systemic inflammatory response syndrome (SIRS), which clinically describes the result of an often overwhelming immune reaction elicited by various triggers (mainly of microbial origin) [15]. Moreover, consequences of rMAS such as haemophagocytosis might vary to a great extent over time and regarding organ involvement (exhaustion phenomena) [4]. Therefore, the diagnosis of rMAS is often considered too late or even missed.

We present data of 57 patients experiencing 60 rMAS episodes recruited on the basis of a simple screening strategy: serum ferritin ≥10 000 µg/L and/or morphological evidence of haemophagocytosis. Although both of these criteria have their limitations, these two parameters alone select a patient population in which 79% meet ≥4 of 5 criteria of the currently most widely used diagnostic guidelines for rMAS published by Imashuku [1] (see table 2, note that Imashuku’s definition of hyperferritinaemia [≥3 standard deviations of the normal value for age, generally ≥1000 µg/L] is ten times below our threshold which was arbitrarily set so high as to exclude common infections, for example). To some extent, haemophagocytosis is a physiological phenomenon occurring in the reticuloendothelial system of various organs, which can be enhanced for example after transfusions or following cytostatic treatments [16]. Therefore, morphological evidence of haemophagocytosis per se does not necessarily translate into rMAS as evidenced by two of our initial patients. However, haemophagocytosis should always be considered as of rMAS origin in a clinical setting of SIRS. Serum hyperferritinaemia is found in haemochro-

matosis, hereditary hyperferritinaemia-cataract syndrome (hyperferritinaemia caused by mutation in the iron-responsive element of L-ferritin which does not reflect macrophage activation) and during common infections and cytolysis especially of macrophage rich organs. However, values ≥10 000 µg/L are exceedingly rare and almost exclusively found in rMAS and Still’s disease (SD) [17]. We have shown that serum ferritinaemia in these situations is subject to fluctuations of several 10 000 µg/L within hours [2]. Although it is not known if morphological haemophagocytosis follows a similar time course, this could explain why delayed bone marrow analysis in some of our patients showed no haemophagocytosis despite previous ferritin levels of >10 000 µg/L. In addition, haemophagocytosis can spare bone marrow and be confined to other organs [4]. This might be the reason for a negative bone marrow analysis in some patients with concomitant hyperferritinaemia >10 000 µg/L. For instance in patients meeting the Yamaguchi criteria of SD with ferritinaemia >10 000 µg/L but no evidence of haemophagocytosis one might consider a liver origin of the hyperferritinaemia given the frequent and often severe liver dysfunction in such patients.

Although the timing of ferritin measurement and bone marrow analysis was not always optimal, our observations allow the following conclusions. Firstly, our screening strategy enables definition of a population of patients with a clinical presentation typical for rMAS as in other published series. Secondly, serum ferritin levels ≥10 000 µg/L in most instances correlate with morphological evidence of haemophagocytosis. However, our data do not allow conclusions regarding the positive or negative predictive value of the chosen ferritin cutoff. Thirdly, a bone marrow analysis is recommended in all patients with hyperferritinaemias, not only for diagnostic accuracy but also given the
high percentage of underlying malignancies (with rMAS being a possible inaugural manifestation) [1]. In forthcoming studies it would be interesting to compare the performance of serum ferritin with other markers of macrophage activation such as neuron-specific enolase [18]. Fourthly, the absence of a systematic screening in the participating hospitals does not permit calculating the incidence of rMAS. But taking into account the experience in our clinic and the findings of eg, François et al. [19] (who found 11 cases with active haemophagocytosis out of 400 intensive care unit admissions), rMAS seem to be several times more frequent than often stated in the literature. Considering the potentially life-threatening nature of rMAS, assessment of ferritin seems to be a cheap and easily measurable marker for early diagnosis.

Our data confirm the particularly poor prognosis of malignancy-associated rMAS and several prognostic factors described by Kaito et al. [6], such as the presence of severe anaemia and thrombocytopenia, coagulation disorders and liver dysfunction. In contrast, age and peak serum ferritin did not influence the outcome in our population. In our opinion, the determination of various cytokines is of limited value regarding clinical management, although the data available from our population precludes a statistical analysis.

Although the screening for massive hyperferritinaemia might have introduced some bias, our findings provoke a re-evaluation of the concepts of Still’s disease (which is in fact defined as a syndrome and the definition of which has its own limitations) and rMAS. SD patients seem to be prone to developing rMAS [20–22]. Intriguingly, recent data show a disturbance of perforin expression in natural killer cells and T-lymphocytes in SD patients with rMAS [23, 24]. Mutations in the gene encoding perforin are responsible for a subgroup of the familial haemophagocytic lymphohistiocytosis, the hereditary form of rMAS [3]. Although neutrophilic leukocytosis (defined as leukocytosis ≥10 G/L with ≥80% neutrophiles) is a major criterion in Yamaguchi's criteria of SD (present in 78% of Yamaguchi's patients), this does not exclude sequential or concomitant macrophage activation. Indeed, 82% of our SD patients presented with neutrophilic leukocytosis at least once during their acute illness. Two explanations emerge. Firstly, a subgroup of patients with purported SD might indeed have rMAS. One might speculate whether this subgroup is similar to the monocyclic (sometimes polycyclic) variant of SD without chronic joint destruction [25]. Alternatively, these patients might succumb to an inappropriate activation of both their neutrophil and macrophage compartment, which is inviting since these cell populations have a common origin. Patients with a predominant neutrophil activation present clinically as SD, patients with a macrophage preponderance as rMAS. It is worth noting that not all rMAS patients can be classified in this SD-like category. A better understanding of the underlying pathophysiological mechanisms is likely to improve the classification of these disorders in the not too distant future.

With the exception of the management of childhood rMAS, termed familial haemophagocytic lymphohistiocytosis [26] and a consensus regarding the importance of controlling any underlying disease, the optimal treatment of rMAS as discussed in the literature, is controversial. In the absence of prospective controlled trials, corticosteroids, cyclosporin A, intravenous immunoglobulins (IVIG) and cytostatic drugs such as etoposide are administered with varied success [27]. Recent case reports show promising results with an anti-TNF-α approach and plasmapheresis [28, 29]. We and others recently described beneficial effects of IVIG administration in rMAS [2, 30]. Meanwhile, we have data on 37 rMAS episodes (in 35 patients). The clinical and laboratory parameters of the responders (23 patients / 25 episodes) and non-responders (12 episodes / 12 patients) were not significantly different with the exception of the higher presence of splenomegaly (most probably explained by the higher rate of lymphoma-associated rMAS) and necessity for dialysis in the non-responders (not related to IVIG administration). These findings confirm our earlier observation that the only predictive factor for response to IVIG is its early administration (within 2 days of ferritin peak) [2]. Although they come to a different conclusion regarding the utility of IVIG, Imashuku et al. also stress the fact that early treatment initiation (in their case etoposide ± CSA for Ebstein-Barr virus-associated rMAS in children and young adults) is mandatory [31 and related correspondence]. Clearly, the efficacy of IVIG may vary according the underlying disease. In malignancy-associated rMAS for example, we have never seen a sustained response. The resistance of malignancy-associated rMAS to IVIG treatment corresponds with the overall poor prognosis of this patient group and might be explained by distinct pathogenetic characteristics. A prospective study about to start will permit better definition of the patient population which is most likely to benefit from early IVIG administration.

In conclusion, serum ferritin measurement is a simple, rapid and inexpensive test ideal for screening patients at risk for rMAS, namely those presenting with SIRS or suspicious of SD. In this clinical setting, ferritin values ≥10000 µg/L might be an indicator for emergency administration of IVIG, a strategy which will be assessed in a prospective, placebo-controlled randomised trial about to start. In cases of hyperferritinaemia, a bone marrow analysis should be performed for assessing the possibility of an underlying neoplastic disorder because these patients seem not to benefit from IVIG.

The authors are grateful for excellent technical help by K. Bruni (Central laboratory, Zieglerspital Bern) for ferritin measurements. We are indebted to the following clinicians for sharing patient data: Inselspital Bern, Inten-
Reactive Marcophage Activation Syndrome: a simple screening strategy and its potential in early treatment initiation

Correspondence:
Professor Klaus A. Nefel
Luisenstrasse 45
CH-3005 Bern
E-Mail: nefpatch@webshuttle.ch

References

What Swiss Medical Weekly has to offer:

- SMW’s impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)
- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

Editorial Board
Prof. Jean-Michel Dayer, Geneva
Prof. Peter Gehr, Berne
Prof. André P. Perruchoud, Basel
Prof. Andreas Schaffner, Zurich
(Editor in chief)
Prof. Werner Straub, Berne
Prof. Ludwig von Segesser, Lausanne

International Advisory Committee
Prof. K. E. Juhani Airaksinen, Turku, Finland
Prof. Anthony Bayes de Luna, Barcelona, Spain
Prof. Hubert E. Blum, Freiburg, Germany
Prof. Walter E. Haefeli, Heidelberg, Germany
Prof. Nino Kuenzli, Los Angeles, USA
Prof. René Lutter, Amsterdam, The Netherlands
Prof. Claude Martin, Marseille, France
Prof. Josef Patsch, Innsbruck, Austria
Prof. Luigi Tavazzi, Pavia, Italy

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

All manuscripts should be sent in electronic form, to:
EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch