Swiss Journal for general physicians
Ars Medici

Iron Deficiency Syndrome IDS

Multicenter experience report with computer-assisted benefit evaluation of intravenous iron treatments

Dr. med. Beat Schaub

Special Edition

Iron Deficiency Syndroms IDS

Multicenter experience report with computer-assisted benefit evaluation of intravenous iron treatments

Frequency of iron deficiency symptoms with or without anemia in general practice as well as success rates and tolerability of individually dosed iron infusion therapy in accordance with the marginal utility principle in women with ferritin levels < 75 ng/ml.

BEAT SCHAUB[1)]

Introduction

Women of menstruation age in particular often suffer from symptoms such as fatigue, depressed mood, sleep disorders, headaches, etc., which we first described in 2006 as Iron Deficiency Syndrome (IDS)(1) and confirmed in 2008 in a multicenter experience report (2). In 2003, the University of Lausanne also reported on this condition (3). The first symptoms often occur, as described in the above-mentioned publications, when ferritin values fall below 50 ng/ml (75 ng/ml).

The present study examined the effects of quick, individual loading doses of infused iron - with an initial target ferritin level of 200 ng/ml - on the existing, low-ferritin-induced symptoms of patients with ferritin levels < 75 ng/ml when administered in accordance with a recently developed concept (cost-benefit optimization: as much iron as necessary and as little iron as possible). Symptoms were correlated with age and ferritin groups. Anemia-related factors were also examined.

This publication is a continuation of the work on iron deficiency syndrome published in April 2008 (2). That report relied on historical data for 873 patients (92% female and 8% male). In the current study, the premise remains unchanged and involves 1428 female patients (including girls). For the first time, a comparison can be made between two dosage types (0.2 grams of Venofer versus 0.5 grams of Ferinject) with regard to efficacy, pharmacokinetics and tolerability.

Methodology

Data was collected at 20 iron clinics (19 in Switzerland and 1 in Germany). Treatment cycles were documented as part of a prospective, descriptive drug monitoring study between March 2006 and March 2009 in an online database[2)] with a built-in dose calculation formula (Basler iron formula developed by Dr. Schaub). The cohort of patients examined consisted mainly of menstruation-age women and girls who reported symptoms such as fatigue, difficulty concentrating, depressed mood, sleep disorders and headaches.

To determine the presence of IDS, reports of complaints were collected by means of a questionnaire. Suspected diagnoses based on questionnaire responses were confirmed by ferritin levels below 75 ng/ml. If the above symptoms were accompanied by ferritin levels below 75 ng/ml and other potential causes or contraindications could be ruled out, iron infusions were immediately administered.

The patients received a loading dose of 200 mg of Venofer twice weekly or 500 mg of Ferinject once weekly over an individually calculated time period until reaching the total dosage in accordance with the marginal utility principle.

Patient follow-ups took place 3 weeks after the last loading infusion (T2) as well as after an additional 3 months (T3). Changes in symptoms and laboratory values were recorded. Based on the data collected after 3 months (T3), subsequent therapy (maintenance therapy) was determined. The required annual iron dosage can be calculated via the Health-Banking system, including for effective relapse prevention therapy.

[1)]Co-authors: Dr. med. P. Duner, Dr. med. HR. Fischer, Dr. med. A. Gut, Dr. med. R. Hertli, Dr. med. T. Kaufmann, Dr. med. O. Kehl, Dr. med. M. Kessler, Dr. med. J. Koller, Dr. med. W. Meier, Dr. med. H. Möllinger, Dr. med. H. Rauscher, Dr. med. C. Rindisbacher, Dr. med. R. Rordorf, Dr. med. C. Rothen, Dr. med. K.-D. Schuldt, Dr. med. G. Suter, Dr. med. F. von Orelli, Dr. med. E. Staeger, Dr. med. P. Wagner

[2)] Health Banking (H-Banking) online database for documentation, dosage calculation, therapy control and quality management

Tabelle: **Frequency of symptoms (in %) before therapy, correlatet with age groups**

Symptoms	Frequency in iron deficient patients	< 15	15-20	21-30	31-40	41-50	> 50
	n = 1428	n = 56	n = 146	n = 241	n = 361	n = 429	n = 195
Fatigue	88%	88%	84%	88%	91%	89%	91%
Difficulty concentrating	79%	79%	51%	55%	60%	60%	54%
Depressed mood	43%	43%	44%	49%	60%	57%	49%
Neck tension	16%	16%	38%	49%	54%	54%	49%
Headaches	41%	41%	49%	54%	54%	51%	42%
Dizziness	45%	45%	36%	48%	48%	45%	44%
Sleep disorders	36%	36%	38%	36%	41%	49%	53%
Anemia	11%	11%	10%	12%	12%	14%	8%

Treatment is defined as successful if, from the point of view of the patient, symptoms disappear or at least noticeably improve after therapy and ferritin levels fall within the therapeutic target range.
Statistical evaluations were conducted using the predictive analytics software SPSS.

Results

In all, 1428 patients met the inclusion criteria. These were included in the prospective monitoring study and treated with iron infusions (1080 with 0.2 grams of Venofer and 348 with 0.5 grams of Ferinject). The relevant data was documented for all 1428 patients before and after each loading dose. For 938 patients, an additional follow-up took place after another 3 months (789 Venofer patients and 149 Ferinject patients).

This experience report is based on the treatment of women of an average age of 38 years. 56 patients (4%) were younger than 15 years of age, with an average age of 12 years. As shown in *Diagram 1*, the most frequently reported symptoms before the loading dose were fatigue (89%) and difficulty concentrating (58%) followed by depressed mood, neck tension, headaches, dizziness and sleep disorders (44-53%). Only 12% experienced anemia.

Fatigue (88%) and difficulty concentrating (79%) are the most frequently mentioned complaints among children, followed by headaches (41%) and sleep disorders (36%), which are among the symptoms characterizing AD(H)D. *Diagram 1* shows that fatigue and difficulty concentrating (or ADD) in children under 15 years of age may be interpreted as early warning symptoms of iron deficiency (>75%, blue).

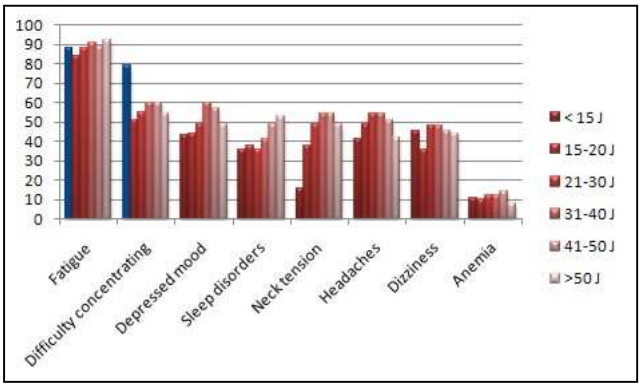

Diagram 1: Frequency of symptoms (in %) before treatment, correlated with age groups

The number of concurrent symptoms increases until the age of 20 and remains quite constant thereafter.Patients under 20 years of age show on average 4 symptoms, those over 20 between 4 and 5 symptoms.

Diagram 2 shows the change in symptoms compiled from questionnaire responses from the patient's point of view after an individual loading dose of infused iron. It should be noted that success rates between 60% and 70% depending on the symptom were achieved (no symptoms or noticeable improvement). Only in the case of neck tension (57%) is the success rate lower.18 to 22% felt minor improvement following treatment.Only between 9% (fatigue) and 20% (neck tension) felt no

change after treatment. In 76% of anemic patients, hemoglobin levels after the loading dose were in the normal range (> 12 g/dl).

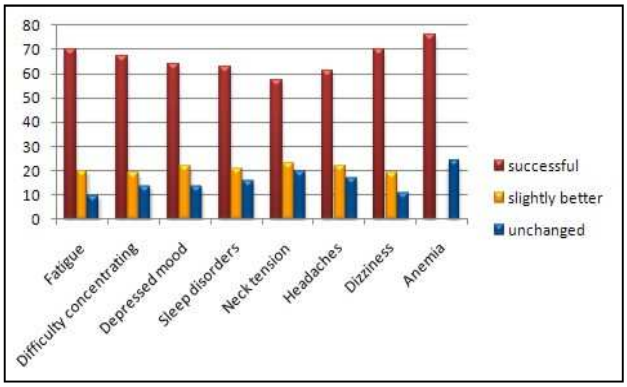

Diagram 2: Success rates (in %) per symptom after intravenous loading dose of iron (success in the case of IDS = no symptoms or noticeable improvement; success for IDA = Hb > 12 g/dl.)

The long-term effects of the treatments are shown in *Diagram 3*. The number of patients who had no symptoms or who experienced a noticeable improvement in their symptoms remained nearly unchanged for three months.

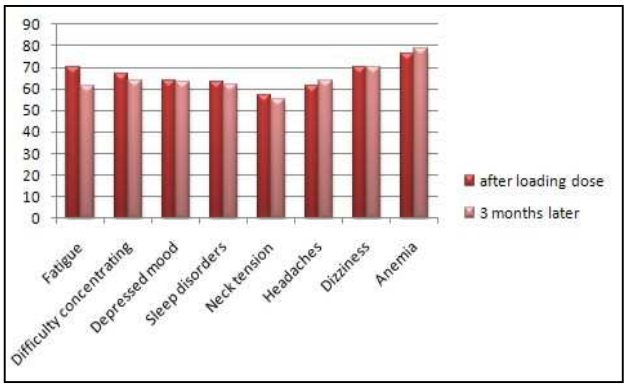

Diagram 3: Success rates (in %) after the loading dose and 3 months later (success = no symptoms or noticeable improvement)

Diagram 4 shows the distribution of success rates across age groups. These range between about 60% and 70% within the individual age groups as well.Most notably, treatment of difficulty concentrating and dizziness symptoms with loading doses of iron was especially successful (>70%, red).

Of the 1428 patients, 87% had initial ferritin levels below 50 ng/ml. Of these, 53% had ferritin levels below 25 ng/ml (*Diagram 5*).*Diagram 6* shows that symptom frequency is barely influenced by ferritin levels, except in anemia cases,where symptoms occur significantly more frequently at ferritin levels below 25 ng/ml (red) than at levels > 25 ng/ml ($p < 0.0001$).

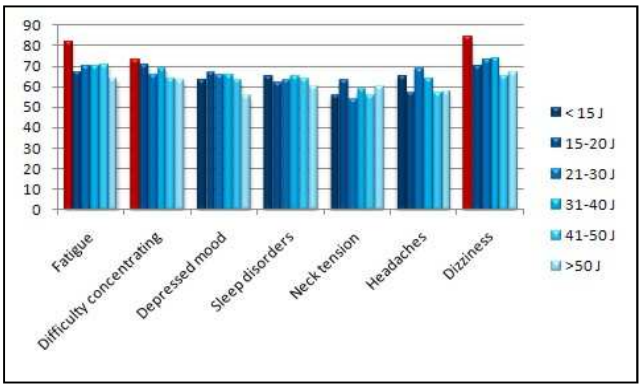

Diagram 4: Success rates (in %) for symptoms, correlated with age groups (success = no symptoms or noticeable improvement)

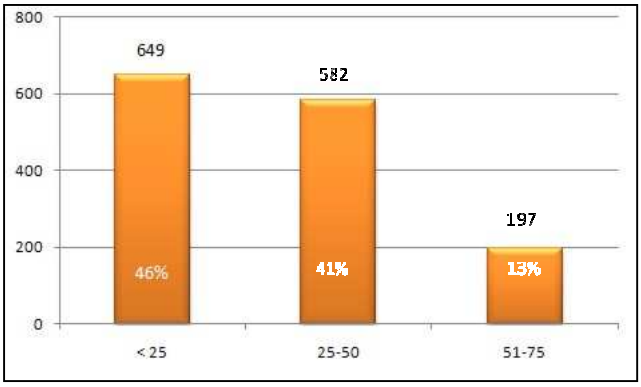

Diagram 5: Ferritin levels before therapy, correlated with the corresponding number of patients

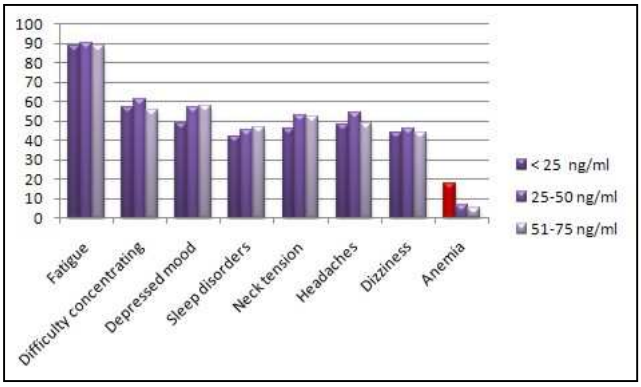

Diagram 6: Frequency of symptoms (in %) before therapy, correlated with ferritin groups (frequency of anemia: 18% at ferritin levels below 25 ng/ml

However, *Diagram 7* does indicate a dependency between treatment success and ferritin levels: success rates in the < 25 and 25-50 ng/ml ferritin groups are comparable and lie roughly between 60% and 75%.

However, in the case of patients with original ferritin levels between 51 and 75 ng/ml, treatment success is 30% lower on average (anemia).The difference in the success rates for fatigue and neck tension compared to patients with ferritin levels < 50 ng/ml is significant, with $p < 0.05$.

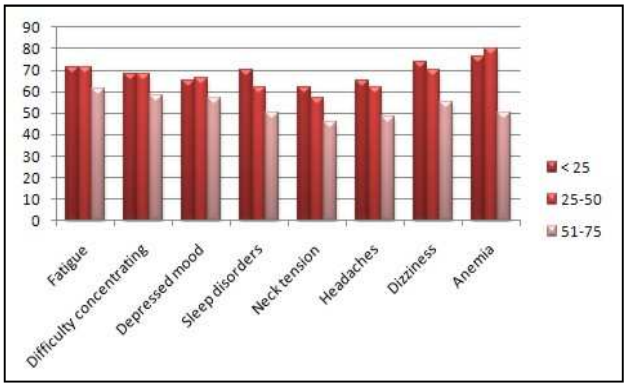

Diagram 7: Success rates (in %) in relation to ferritin levels before treatment

Diagram 8 shows the change in ferritin levels as a result of treatment. Prior to the intravenous loading dose, they averaged 29 ng/ml; 3 weeks after the last infusion,they averaged 223 ng/ml (Venofer patients (0.2 g/infusion): 203 ng/ml, Ferinject patients (0.5 g/infusion): 285 ng/ml).Three months later, ferritin levels averaged 142 ng/ml (Venofer patients: 138 ng/ml, Ferinject patients: 165 ng/ml).

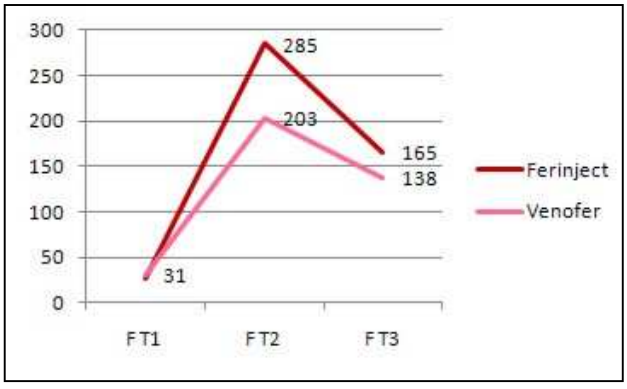

Diagram 8: Ferritin levels before (T1) and 3 weeks after the last infusion (T2) as well as 3 months later (T3)

Diagram 9 shows estimated ferritin peaks between the last infusion and measured levels 3 weeks after.However, the amount of data (own random samples, feedback from clinics and doctors' offices, statements from the manufacturer (7)) is very small, making further studies necessary should additional questions remain, such as from the FDA.

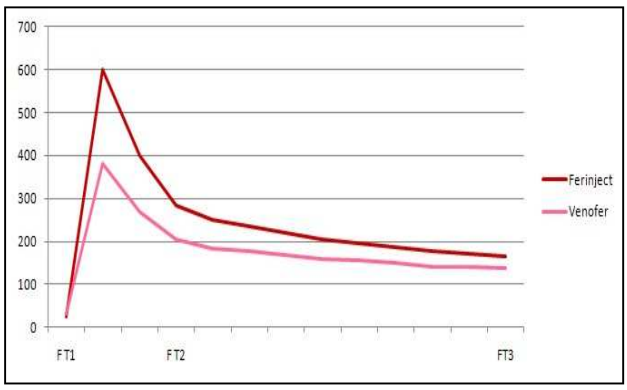

Diagram 9: Estimated average ferritin peaks before ferritin measurement at T2 (3 weeks after the last infusion)

As *Diagram 10* shows, hemoglobin levels during loading rose from 13.1 g/dl to 13.3 g/dl (Venofer patients: 13.4 g/dl, Ferinject patients: 13.3 g/dl).3 months later, hemoglobin levels still averaged 13.3 g/dl (Venofer patients: 13.3 g/dl, Ferinject patients: 13.2 g/dl).

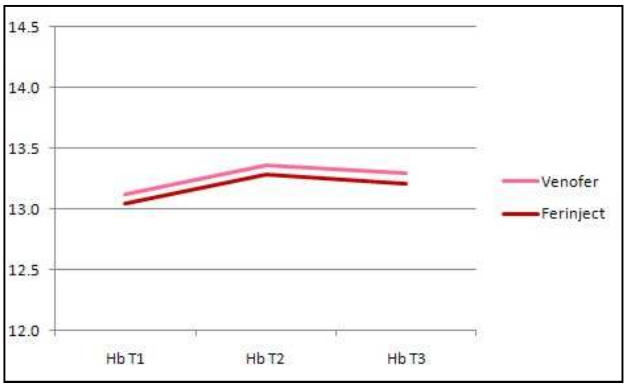

Diagram 10: Progression of hemoglobin levels after loading dose (T2) and three months later (T3)

Adverse effects

Of the 1428 patients treated, 34 (2.4%) suffered minor temporary adverse drug effects (most frequently tiredness, stomach/intestinal problems, skin rashes, joint pain, flu-like symptoms, dizziness). Among Venofer patients (200 mg/infusion), 1.2% suffered these effects, as did 5.7% of Ferinject patients (500 mg infusion).The difference in the frequency of adverse effects between dosage types is significant ($p < 0.001$).Anaphylactic reactions did not occur in either group.

Iron deficiency syndrome (IDS) and iron deficiency anemia (IDA):

There was no anemia present in 88% of patients, although ferritin levels for nearly half of all pati-

Anemia occurs significantly more frequently at ferritin levels below 25 ng/ml than at higher levels ($p < 0.0001$).*Diagram 11* shows the correlation between hemoglobin and ferritin values. It is important to note that in cases where ferritin levels are below 10 ng/ml, hemoglobin is, on average, at the lower end of the normal range, yet still within the previously defined reference range. This indicates that official low normal ferritin levels are generally sufficient to prevent anemia.

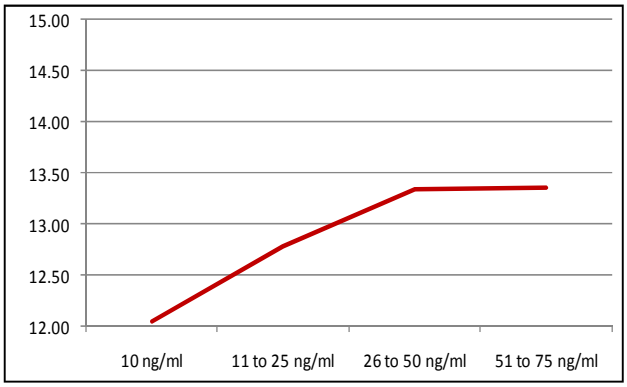

Diagram 11: Correlation between ferritin and average hemoglobin

Discussion

The results of this multicenter monitoring study show that most patients with symptoms such as fatigue, difficulty concentrating, depressed mood or headaches had ferritin levels below 50 ng/ml, i.e., within a range defined by most laboratories as normal and for which no iron treatment has been indicated under these conditions as taught by medical schools.

Overall, the success rate was fairly high. Depending on the particular symptom, 60-70% of patients felt noticeably better or even completely symptom-free, both immediately after a loading dose of iron as well as three months later.Only 15% felt no change after iron administration.This clearly indicates that low iron stores can lead to symptoms even without the presence of anemia.

Based on the great success of treatment with intravenously supplied iron in depressed patients with ferritin levels below 75 ng/ml and in consideration of the meta-analysis published by the FDA in early 2008 (4), which challenges the effectiveness of the top-selling antidepressant psychoactive drug SSRI, physicians should perhaps use a different approach in investigating the causes of endogenous depression.The impact of depleted or low iron stores is clear and should be actively discussed.

Our monitoring study further shows that low ferritin levels can cause problems as early as in childhood, frequently increasing until age 20, after which they remain more or less constant. This observation essentially forces doctors to treat symptoms obviously caused by low ferritin levels early, or at least before they become fully developed. In children, the most frequently occurring iron deficiency symptoms, such as fatigue, difficulty concentrating, sleep disorders and headaches, point to AD(H)D. It is thus reasonable to assume that attention deficit may often be the result of iron deficiency.

In the case of initial ferritin levels between 50 and 75 ng/ml, therapy success is between 10% and 30% lower than in the case of ferritin levels below 50 ng/ml. This observation suggests that ferritin levels above 50 ng/ml may approach the physiological "optimal range" and/or that, in the case of patients with higher ferritin levels (50-75 ng/ml), symptoms typically associated with iron deficiency are caused by other factors as well.

Only 12% of the 1428 iron deficiency patients were identified as being anemic. This proves that the diagnosis of manifest iron deficiency is in no way dependent on anemia.

The results of the study confirm that low normal ferritin levels as taught in medical academia (10 ng/ml) are typically sufficient for preventing anemia.However, ailments typically begin to occur at ferritin levels below 75 ng/ml.Because many people feel healthy even with low ferritin levels, a low normal level is difficult to define.Defining it at 50 ng/ml, for example, could give people with lower values the impression of being ill.

Due to significantly higher adverse effect rates at higher-than-individual doses (0.5 and 1.0 grams of iron), in our view, the use of high individual doses should be reconsidered.Treatment of IDS patients with individual infusions of 0.2 grams of iron (twice weekly) until the total calculated dose is reached has shown maximum efficacy and tolerability.Therefore, for the time being it is probably advisable to reserve higher individual doses for anemic iron-deficient patients, for whom Ferinject was developed and clinically tested.Such restraint is recommend at least while no comparative scientific studies are available and the FDA rejects the approval of the medication in the US for reasons including dosage concerns (5).

Conclusions

1. Our study proves and confirms earlier observations that IDS exists and that successful treatment through targeted iron administration is possible.

2. In depressed patients with ferritin levels below 75 ng/ml, due to the high success rate of iron infusions, a suspected diagnosis of depression as a result of iron deficiency should be given special attention.Iron administration as a primary treatment approach should be considered, particularly in light of the US meta-analysis published in 2008, which calls into question the effectiveness of SSRI.

3. Ferritin level measurement is advisable for all children under 15 years of age with AD(H)D symptoms.If iron stores are low, iron administration is recommended as a primary treatment approach.

4. In light of the fact that iron administration can prevent or cure not only anemia but a number of other symptoms as well and that such healing is associated with a significant increase in ferritin levels in the blood as a result of iron replenishment, we recommend iron substitution treatment even if low ferritin levels lie within the previously official normal range.

5. Low normal ferritin levels are difficult to define due to individuality.Rather, the individual optimal ferritin range for iron-deficient patients at which no symptoms occur should be determined.

6. Ferinject was developed for patients with IDA for the purpose of administering high individual doses.Due to the lack of scientific evidence of the efficacy of the medication in IDS patients and increased adverse effects after high individual (0.5 gram) doses, for the time being we recommend individual 0.2 gram doses of iron for IDS patients.

7. Iron dosage calculation formulas per Ganzoni (6), developed in 1968 for patients with iron deficiency anemia, cannot be used for IDS patients.The Basler iron formula developed for IDS patients and in multicenter use since 2005 has proven to be suitable and is the primary standard.

Literature

1. The iron deficiency syndrome IDS (Iron Deficiency Syndrome), Ars Medici (Jan. 2006)
2. The iron deficiency syndrome IDS (Iron Deficiency Syndrome), Ars Medici and Österreichische Ärztezeitung (April 2008)
3. Primary care: Iron supplementation for unexplained fatigue in non-anemic women: double blind randomized placebo controlled trial, F. Verdon, Lausanne, BMJ 2003;326:1124 (24 May)
4. Antidepressants ineffective in practice (Federal Drug Administration FDA), Public Library of Science (Feb. 2008)
5. Non Approvable Letter FDA (03/12/2008)
6. Ganzoni formula from 1968: Hb(target) – Hb (actual) x weight x 0.24 + 500 mg iron.
Promotional brochure for Ferinject (November 2008)

November 2009

Dr. med. Beat Stephan Schaub
Specialist for Internal Medicine
Bottmingerstrasse 50
CH-4127 Binningen / Basel
Email: bschaub@magnet.ch