Evidence, experience and benefits of hemoglobin stability through simplified anemia management

Roberto Minutolo
1. Anemia management
   - Role of ESA responsiveness on negative results of RCTs
   - Modality of ESA prescription and anemia control
   - Role of Mircera in correcting anemia

2. Clinical cases focused on Mircera use in daily practice
Anemia management is getting complex. The evidence that we use to guide anemia therapy is based on observational studies as well as clinical trials. The observational studies have uniformly demonstrated that persons with higher hemoglobin levels enjoy better outcomes, including fewer hospitalizations and longer survival. Randomized controlled trials, on the other hand, paint a different and far more complex picture.
To explain this discrepancy some hypotheses have been proposed

1. The increased risk does not depend on the higher Hb levels *per se* but on the higher doses of ESA required to normalize anemia.
Anemia and anemia correction: surrogate markers or causes of morbidity in chronic kidney disease?

Nosratola D Vaziri

**HYPOTHESIS: DRUG OVERDOSE AS THE CAUSE OF ADVERSE OUTCOMES**

1. Effects on arterial pressure
2. Effects on endothelin, renin and angiotensin, and prostaglandins
3. Effects on the nitric oxide pathway
4. Effects on platelets production and the coagulation system (increased platelet adhesion and aggregation, lower fibrinolysis)
5. Effects on vascular smooth muscle cell proliferation

**All these effects are dose-dependent!**
To explain this discrepancy some hypotheses have been proposed

1. The increased risk does not depend on the higher Hb levels *per se* but on the higher doses of ESA required to normalize anemia

2. Geographical variation of ESA hyporesponsiveness
RCTs on Hb normalization in CKD-ND
United States (red) vs Rest of the World (green)
TREAT trial
Absence of CV benefit in “Hb 13” group...

...was it true everywhere?

<table>
<thead>
<tr>
<th>Region</th>
<th>Darbepoetin alfa</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>416/1259 (33%)</td>
<td>380/1256 (30%)</td>
<td>1.10 (0.96,1.26)</td>
</tr>
<tr>
<td>Latin America</td>
<td>48/229 (21%)</td>
<td>47/209 (22%)</td>
<td>0.99 (0.66,1.48)</td>
</tr>
<tr>
<td>W Europe/AUS</td>
<td>36/172 (21%)</td>
<td>57/198 (29%)</td>
<td>0.66 (0.43,1.01)</td>
</tr>
<tr>
<td>E Europe</td>
<td>109/297 (37%)</td>
<td>98/301 (33%)</td>
<td>1.04 (0.79,1.37)</td>
</tr>
<tr>
<td>Russia</td>
<td>23/55 (42%)</td>
<td>20/62 (32%)</td>
<td>1.26 (0.69,2.31)</td>
</tr>
</tbody>
</table>

Pfeffer-TREAT, NEJM 2009 (Appendix)
To explain this discrepancy some hypotheses have been proposed

1. The increased risk does not depend on the higher Hb levels *per se* but on the higher doses of ESA required to normalize anemia

2. Geographical variation of ESA hyporesponsiveness

3. Pattern of ESA prescription
Administration of the same amount of ESA but at extended interval leads to administration of a greater single dose of drug.

<table>
<thead>
<tr>
<th></th>
<th>CHOIR</th>
<th>TREAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>10,000 IU</td>
<td>0.75 µg/kg</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>Weekly → Bi-weekly</td>
<td>Bi-weekly → Monthly</td>
</tr>
</tbody>
</table>
Erythropoietic threshold

- EPO and rHuEPO levels (mU/ml)
- Days

1. Stable Reticulocyte Release
2. No Hb Cycling

} Maintenance of stable Hb levels
All ESAs are effective if their serum levels are within erythropoietic threshold.
Relationship between dosing frequency and serum levels of erythropoietin

If we progressively increase the interval between doses, the serum level of erythropoietin is not more maintained within the erythropoietic range.
N=16 patients treated with same weekly dose of Epoetin (120 IU/kg s.c.) but at different dosing intervals
Pharmacokinetic simulation changing darbepoetin from weekly to monthly

Weekly Darbepoetin
(0.45 µg/kg)

Monthly Darbepoetin
(1.8 µg/kg)

Darbepoetin levels (ng/ml)

Days

RCT in 490 HD patients, treated at baseline with weekly Darbepoetin

Mean Hb (g/dL) Evaluation

Baseline

Weeks

C.E.R.A. monthly

Darbepoetin / 2 weeks ⇒ Darbepoetin monthly

Nephrol Dial Transplant (2010)
Comparisons of ESA doses and Hb values in the second phase of study (monthly administration of CERA and darbepoetin)

<table>
<thead>
<tr>
<th></th>
<th>C.E.R.A. arm</th>
<th></th>
<th>Darbepoetin arm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 27</td>
<td>Weeks 48-50</td>
<td>Week 27</td>
<td>Weeks 48-50</td>
</tr>
<tr>
<td>Mean dose of drug</td>
<td>260 ± 194</td>
<td>273 ± 264</td>
<td>203 ± 184</td>
<td>303 ± 288</td>
</tr>
<tr>
<td>(µg/mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Hb values (g/dL)</td>
<td>11.6</td>
<td>11.6</td>
<td>11.7</td>
<td>10.5</td>
</tr>
</tbody>
</table>
A new approach to anemia management: avoiding too high/too low EPO levels

- Use the lowest effective dose of drug in each patient
- Respect the pharmacokinetic properties of ESA

Erythropoietic Effect (30-200 mU/ml)

1. Activation of Endothelium
2. Pro-thrombotic effect
3. Proliferation of VSMCs

Increase of BP levels and thrombosis

1. Activation of apoptosis
2. Activation of neocytolisis
3. Up-regulation of Hepcidin

Reduction of ESA efficacy and increase of Hb variability

Each patient
Pilot study (n=40) to investigate whether switching darbepoetin to MIRCERA at doses lower than those recommended is effective in maintaining Hb levels.

Multicenter prospective study (n=157) to confirm effectiveness of switching other ESA to low-dose MIRCERA and to assess clinical predictors of Hb response and MIRCERA dose changes.

Conversion from Epoetin and Darbepoetin to C.E.R.A. in Non-Dialysis CKD Patients: A Multicenter Italian Prospective Study in Nephrology Practice

Roberto Minutolo\textsuperscript{a} Giuseppe Conte\textsuperscript{a} Mario Cozzolino\textsuperscript{b} Pasquale Polito\textsuperscript{c} Carlo Manno\textsuperscript{d} Biagio R. Di Iorio\textsuperscript{e} Domenico Santoro\textsuperscript{f} Marina Di Luca\textsuperscript{g} Felice Nappi\textsuperscript{h} Sandro Feriozzi\textsuperscript{i} Ferdinando C. Sasso\textsuperscript{j} Luca De Nicola\textsuperscript{a}
## Dosing protocol

The 3 starting doses for conversion to once monthly MIRCERA:

<table>
<thead>
<tr>
<th>Previous weekly dose of darbepoetin alfa (µg/week)</th>
<th>Previous weekly dose of epoetin (IU/week)</th>
<th>Monthly dose of MIRCERA (µg/month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>&lt;8,000</td>
<td>120</td>
</tr>
<tr>
<td>40-80</td>
<td>8,000-16,000</td>
<td>200</td>
</tr>
<tr>
<td>&gt;80</td>
<td>&gt;16,000</td>
<td>360</td>
</tr>
</tbody>
</table>

MIRCERA, Summary of Product Characteristics, 2007

The 3 starting doses for conversion to once monthly MIRCERA in this study:

<table>
<thead>
<tr>
<th>Darbepoetin alfa (µg/week)</th>
<th>Epoetin (IU/week)</th>
<th>MIRCERA (µg/month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤20</td>
<td>≤4,000</td>
<td>75</td>
</tr>
<tr>
<td>21-40</td>
<td>4,001-8,000</td>
<td>100</td>
</tr>
<tr>
<td>&gt;40</td>
<td>&gt;8,000</td>
<td>120</td>
</tr>
</tbody>
</table>

Minutolo Blood Purif 2013
### Study design

#### Primary Outcome Measure
- Prevalence of Hb values in the range 11.0-12.5 g/dL

#### Secondary Outcomes Measures
- Clinical predictors of Hb response
- Proportion of visits requiring any dose adjustment
- Clinical predictors of CERA dose change

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phases</td>
<td></td>
<td></td>
<td></td>
<td>Titration period</td>
<td></td>
<td>Evaluation period</td>
<td></td>
</tr>
</tbody>
</table>

Switch to MIRCERA
<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.0 ± 12.7</td>
</tr>
<tr>
<td>Female gender, N (%)</td>
<td>80 (51.0)</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>52 (33.1)</td>
</tr>
<tr>
<td>Prior CV events, N (%)</td>
<td>29 (18.5)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>72.3 ± 14.7</td>
</tr>
<tr>
<td>Renal Disease</td>
<td></td>
</tr>
<tr>
<td>Nephroangiosclerosis</td>
<td>55 (35.0)</td>
</tr>
<tr>
<td>Diabetic Nephropathy</td>
<td>36 (22.9)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>17 (10.8)</td>
</tr>
<tr>
<td>Other</td>
<td>49 (31.2)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>26.2 ± 9.4</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.3 ± 0.8</td>
</tr>
<tr>
<td>Darbepoietin at switch, N (%)</td>
<td>124 (79.0)</td>
</tr>
<tr>
<td>Median dose µg/week</td>
<td>20 (15-30)</td>
</tr>
<tr>
<td>Epoietin at switch, N (%)</td>
<td>33 (21.0)</td>
</tr>
<tr>
<td>Median dose IU/week</td>
<td>4,000 (4,000-8,000)</td>
</tr>
</tbody>
</table>
Primary endpoint: maintenance of Hb target (11-12.5 g/dL)

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Hemoglobin levels and MIRCERA dose during 24 weeks of the study

BASAL (median) { EPO pre: 4000 U/wk
Darbo pre: 20 µg/wk

75 µg/mo
75 µg/mo

Hb g/dL (mean±SD)

* 4 is the... ...Magic Number!

Minutolo Blood Purif 2013
Clinical predictors of changes in Hb levels during the study

<table>
<thead>
<tr>
<th></th>
<th>β-Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (5-kg/m²)</td>
<td>-0.029</td>
<td>0.034</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>-0.158</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dosing intervals before switch (days)</td>
<td>0.009</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, diabetes mellitus, history of CVD, GFR, CRP, TSAT, ferritin, use of RAS inhibitors, ESA dose and ESA type. Model summary $R^2 = 0.438$, $P<0.001$.

Administering ESA at too extended intervals induces an effective erythropoiesis only in the first part of the interval. Switch to monthly MIRCERA (effective in the whole period between two doses) induces a more efficient erythropoiesis translating in an Hb increase.
Hb levels during MIRCERA in patients previously treated with ESA at either usual or prolonged intervals (Epoetin ≥7 days, Darbepoetin ≥15 days)

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Prolonged dosing interval before switch (n=75): P=0.003

Usual dosing interval before switch (n=82): P=0.120

Weeks

Mean Hb and 95% CI (g/dL)
MIRCERA dose adjustment occurring during the 24 weeks of the study (931 visits)

Number of dose adjustment per patients: 0.8±1.0.

At the end of the study, MIRCERA dose was:

- **Unchanged in 55% of patients** (84±15 µg/month)
- **Reduced in 28% of patients** (from 94±20 to 55±27 µg/month)
- **Increased in 17% of patients** (from 83±12 to 129±29 µg/month)
Clinical predictors of changes in C.E.R.A. dose during the study

<table>
<thead>
<tr>
<th></th>
<th>C.E.R.A. dose changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-Coefficient</td>
</tr>
<tr>
<td>Body mass index (5-kg/m²)</td>
<td>5.777</td>
</tr>
<tr>
<td>History of CV disease (yes vs no)</td>
<td>14.033</td>
</tr>
<tr>
<td>Dosing intervals before switch (days)</td>
<td>-2.032</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, diabetes mellitus, GFR, basal Hb, CRP, TSAT, ferritin, use of RAS inhibitors, ESA dose and ESA type. Model summary: $R^2 = 0.196$, P=0.004.
Are you still live?
Anaemia management with C.E.R.A. in routine clinical practice: OCEANE (Cohorte Mircera patients non-dialysés), a national, multicenter, longitudinal, observational prospective study, in patients with chronic kidney disease not on dialysis

Luc Frimat,¹ Christophe Mariat,² Paul Landais,³ Sébastien Koné,⁴ Bénédicte Commenges,⁴ Gabriel Choukroun⁵

*BMJ Open 2013;3:e001888. doi:10.1136/bmjopen-2012-001888*

Multicenter prospective cohort study in 341 ESA-treated patients with CKD-ND (21% transplant patients) switched to MIRCERA and followed for 12 months.
French experience in CKD-ND and transplant patients

ESA-treated Transplant patients (N=70)

![Graph showing hemoglobin levels over time for ESA-treated transplant patients.](image-url)
French experience in CKD-ND and transplant patients

**ESA-treated Transplant patients (N=70)**

MIRCERA doses were lower than recommended and unchanged in 46% of patients

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FRIMAT BMJ Open 2013
Monthly CERA Treatment Maintains Stable Hemoglobin Levels in Routine Clinical Practice of Peritoneal Dialysis Patients

Mª Teresa González¹, Rosa Ramos², Manel Vera³, Francesc Barbosa⁴, Carmen Garcia⁵, Isabel Garcia⁶, Carlota González-Segura¹, Marc Cuxart⁷, Josep Teixido⁸ and Juan José de la Cruz⁹


Multicenter prospective study in 83 PD patients (88% ESA-treated) switched to MIRCERA and followed for 12 months.
Spanish experience in PD

Table 2. Starting CERA doses according to previous ESA treatment.

<table>
<thead>
<tr>
<th>Previous ESA</th>
<th>N (%)</th>
<th>Starting CERA doses median (IQR) (µg/month)</th>
<th>CERA doses according to SPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin &lt;8000 IU/week</td>
<td>50 (60.2)</td>
<td>100 (75–100)</td>
<td>120</td>
</tr>
<tr>
<td>Darbopoetin-α &lt;40 µg/week</td>
<td>18 (21.6)</td>
<td>150 (100–200)</td>
<td>200</td>
</tr>
<tr>
<td>Epoetin 8000–16,000 IU/week</td>
<td>6 (7.2)</td>
<td>200 (137–250)</td>
<td>360</td>
</tr>
<tr>
<td>Darbopoetin-α 40–80 µg/week</td>
<td>9 (10.8)</td>
<td>87.5 (75–112.5)</td>
<td></td>
</tr>
</tbody>
</table>

Note: SPC, summary of product characteristic; IQR, interquartile range.

Table 3. Evolution of the anemia parameters.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, mean (SD) [95% CI], g/dL</td>
<td>11.8 (1.4) [11.6–12.2]</td>
<td>11.8 (1.4) [11.5–12.1]</td>
<td>11.8 (1.5) [11.4–12.1]</td>
</tr>
<tr>
<td>(N = 88) Naïve (N = 10)</td>
<td>11.8 (1.4) [11.6–12.2]</td>
<td>11.8 (1.4) [11.5–12.1]</td>
<td>11.8 (1.5) [11.4–12.1]</td>
</tr>
<tr>
<td>Hb previous ESA, mean (SD) [95% CI], g/dL (N = 73)</td>
<td>11.9 (1.5) [11.6–12.3]</td>
<td>11.9 (1.4) [11.6–12.2]</td>
<td>11.8 (1.5) [11.4–12.1]</td>
</tr>
<tr>
<td>&lt;8000 IE/week or &lt;40 µg/week</td>
<td>12.1 (1.4) [11.7–12.6]</td>
<td>12.2 (1.3) [11.8–12.5]</td>
<td>11.9 (1.4) [11.5–12.3]</td>
</tr>
<tr>
<td>8000–16,000 IE/week or 40–80 µg/week</td>
<td>11.7 (1.4) [11.0–12.3]</td>
<td>11.2 (1.6) [10.4–12.0]</td>
<td>11.2 (1.6) [10.4–12.0]</td>
</tr>
<tr>
<td>&gt;16,000 IE/week or &gt;80 µg/week</td>
<td>11.3 (1.8) [9.4–13.2]</td>
<td>11.8 (0.7) [11.0–12.5]</td>
<td>12.3 (1.4) [10.9–13.8]</td>
</tr>
<tr>
<td>Vitamin B12, mean ± SD, pmol/L (N)</td>
<td>463.2 ± 156.3 (30)</td>
<td>481.2 ± 215.6 (69)</td>
<td>415.4 ± 146.2 (38)</td>
</tr>
<tr>
<td>Fe, mean ± SD, mmol/L (N)</td>
<td>12.4 (5.2) (64)</td>
<td>12.9 (5.5) (60)</td>
<td>12.2 (4.8) (19)</td>
</tr>
<tr>
<td>Ferritin, mean ± SD, ng/mL (N)</td>
<td>231.2 ± 213.8 (70)</td>
<td>238.1 ± 247.0 (66)</td>
<td>223.4 ± 146.8 (64)</td>
</tr>
<tr>
<td>TSI, % ± SD (N)</td>
<td>27.2 ± 12.7 (35)</td>
<td>26.5 ± 9.9 (33)</td>
<td>26.5 ± 9.9 (37)</td>
</tr>
</tbody>
</table>
Monthly Administration of a Continuous Erythropoietin Receptor Activator Provides Efficient Haemoglobin Control in Non-Dialysis Patients during Routine Clinical Practice

Results from the Non-Interventional, Single-Cohort, Multicentre, SUPRA Study

Stefan Heidenreich,1 Frank Leistikow,2 Stefan Zinn,3 Jörg Baumann,4 Andreas Atzeni,5 Vitomir Bajeski,6 Jörn Dietzmann7 and Gert-Peter Dragoun8, on behalf of the SUPRA Study Group

Multicenter prospective study in 335 CKD-ND patients (45% ESA-treated) receiving MIRCERA for 9 months.
German experience in CKD-ND patients

Hemoglobin levels (g/dL)

- All patients
- Pre-treated with ESA
- ESA-naïve

MIRCERA doses (µg/month)

<table>
<thead>
<tr>
<th>Monthly dose at months 1–9 (µg) [mean ± SD]a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
</tr>
<tr>
<td>Month 2</td>
</tr>
<tr>
<td>Month 3</td>
</tr>
<tr>
<td>Month 4</td>
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<td>Month 5</td>
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<tr>
<td>Month 6</td>
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<tr>
<td>Month 7</td>
</tr>
<tr>
<td>Month 8</td>
</tr>
<tr>
<td>Month 9</td>
</tr>
<tr>
<td>Months 1–9, mean ± SD</td>
</tr>
</tbody>
</table>

Heidenreich Clin Drug Investig 2012
CONCLUSIONS

• Studies from different Countries, performed in the real world of clinical practice consistently show a good effectiveness and safety profile of MIRCERA.

• Prolonged half-life of MIRCERA successfully allow monthly administration:

  Maintenance of serum levels in the erythropoietic threshold
  ↓
  Maintenance of stable Hb values
  ↓
  Fewer dose adjustment

• Stability of Hb levels and dosage makes MIRCERA particularly indicated in patients followed on outpatient basis, such as CKD-ND, transplant, PD.
Mircera in the clinical practice: three clinical cases

Roberto Minutolo

Focus on:

- Performing a correct switch from other ESA
- Achieving Hb stability
- Managing Hb overshooting
Clinical history of Marco

- Male, 71 years with familiarity for CV diseases
- Hypertension and dyslipidemia lasting for 20 years
- CKD stage 3A KDOQI, secondary to nephroangiosclerosis diagnosed 5 years ago (slow progressor)
- Severe atherosclerotic vasculopathy (tight stenosis on the left internal carotid artery (95%) and abdominal aortic aneurism)
- April 2009: TIA followed by PTA-stenting of internal carotid artery. He also underwent Coronary angiography showing critical stenosis on both left (IVA: 80% and circumflex 90%) and right (75%) coronary arteries.
- Patient did not receive therapy to prevent contrast nephropathy: creatinine increased from 1.6 mg/dl to 3.0 mg/dl at discharge.
- After one month (May 2009): PTCA right coronary artery (mild hydration and creatinine moved form 2.9 mg/dl to 5.3 mg/dL at discharge)
Cardiologist finally asked for a nephrology consultation: we delayed the second PTCA and suspended furosemide and CEI by adding a CCB with normal sodium intake (β-blockers, statin and anti-aggregant therapy left unmodified)

- Jul-2009: PTCA left coronary and we asked for arteriography of renal arteries showing stenosis of left (90%) and right renal artery (70%)
- With adequate therapy for preventing CM nephropathy creatinine only slightly increased (from 4.1 mg/dl to 4.7 mg/dl)
- August 2009: episode of flushing pulmonary edema
- Sept-2009: stenting - PTA left renal artery (creatinine from 4.0 to 3.5 mg/dl)
- Oct-2009: stenting - PTA right renal artery (creatinine from 3.0 to 3.3 mg/dl)
- Dec-2009: diagnosis of anemia treated with darbepoetin 30 µg/week without iron supplementation (TSAT 25% and Ferritin 178 ng/ml)
Changes of Hb and GFR

- **Hb (g/dL)**
  - Dec-09: 9
  - Jan-10: 10
  - Feb-10: 11
  - Apr-10: 12
  - Aug-10: 13
  - Nov-10: 14
  - Feb-11: 15

- **GFR (mL/min/1.73m^2)**
  - Aranesp 30 µg/week
  - ↓ Aranesp 30 µg/4 wks
  - ↓ Aranesp 30 µg/2 wks
  - ↑ Aranesp 20 µg/week
  - Switch to Mircera to Improve Hb stability
  - ↓ Aranesp 20 µg/10 days

Diagram shows the fluctuations in Hb levels and the changes in Aranesp dosage from Dec-09 to Feb-11.
Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin

**Up excursion**

84% due to ESA increase

**Down excursion**

77% due to ESA hold/reduction
Real-life experience for switching other ESAs to Mircera: which dose?

- At which Mircera dose do you switch a patient receiving Darbepoietin 20 µg/week?
  - 120 µg/month
  - × 75 µg/month  (20 x 4 =80)
  - 30 µg/month
Hb and iron status under Mircera therapy

Switch to CERA 75 µg

↓CERA 50

CERA 50

↓CERA 30

GFR

<table>
<thead>
<tr>
<th></th>
<th>25</th>
<th>27</th>
<th>28</th>
<th>29</th>
<th>31</th>
<th>33</th>
<th>33</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb-11</td>
<td></td>
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Clinical history of Maria

• Female, 62 years with prior CHD (history of MI 4 years before)
• Hypertension lasting for 25 years
• Diabetes diagnosed 3 years ago in treatment with insulin
• At referral in our clinic: CKD stage 4 KDOQI (GFR 22 mL/min/1.73m²), likely secondary to glomerulonephritis (in the past years she reported 3-4 episodes of macrohematuria with peripheral edema)
• Presence of ankle edema, BP 156/99 mmHg, Uprot 2.5 g/day, PTH 334 pg/mL, phosphate 5.6 mg/dL and Hb 9.4 g/dL without iron deficiency.
• Start therapy with CEI and furosemide (in substitution of CCB), phosphate binder (sevelamer), paricalcitol 1 µg/day (one month later) in addition to insulin, aspirin and statin.
• For anemia: β-epoetin 2000 IU 3 times per week.
Changes of Hb in the first 4 months of epoetin

- Phosphate from 5.6 to 4.8 mg/dL
- PTH from 334 to 111
- B.W. from 80.4 to 74.6 kg
- BP from 156/99 to 145/90 mmHg
- Uprot from 2.5 to 1.1 g/day
- TSAT from 29% to 15%
- Ferritin from 144 to 51 ng/mL
Changes of Hb in the following 5 months

- **TSAT**: 15%, 21%, 27%
- **Ferritin**: 51, 61, 132

- **Iron sulphate**: 105 mg bid for 6 months
- **Switch to Mircera to facilitate therapy** (9 pills + 4 injections)
Real-life experience for switching other ESAs to Mircera: which dose?

- At which Mircera dose do you switch a patient receiving Darbepoietin 20 µg/week?
  - 120 µg/month
  - 75 µg/month (20 x 4 = 80)
  - 30 µg/month

- At which Mircera dose do you switch a patient receiving β-epoetin 6000 IU/week?
  - 120 µg/month [1:200 = 30 x 4 = 120] or [6000 / 50 = 120]
  - 75 µg/month
  - 30 µg/month
Changes of Hb during 8 months of Mircera

- Switch to Mircera 120 µg/month
- Mircera 120 µg/month
- Preparation of AVF (late referral)
- Oral Iron
Clinical history of Pietro
(our first patient treated with MIRCERA)

• Male, 57 y.o.
• CKD stage 3B KDOQI (GFR 42 mL/min/1.73m²), secondary to biopsy-proven IgAN diagnosed 10 years before.
• Hypertension and dyslipidemia lasting for 5 years
• January 2008: diagnosis of iron deficient anemia treated with oral iron (iron sulphate 105 mg x 2)
• March 2008: for the persistence of low Hb started β-epoetin 2000 IU/3 times per week and continued oral iron.
Anemia correction during epoetin

Because of reaching Hb 13.0 g/dL ($\Delta$Hb 1.6 g/dL/month) β-epoetin was progressively reduced

β-epoetin
- 2000 IU T.I.W.
- 1000 IU T.I.W.
- 1000 IU B.I.W.

Mircera available in Italy
Switch to CERA 120 µg/mo (according to SPC)
Anemia correction during Mircera

- **CERA 100**
- **CERA 50**
- **CERA 75**
- **CERA 120**
- **Oral Iron**
- **CERA withdrawal**
- **Patient moved to another city**

Hb (g/dL) over months from Jan-09 to Dec-10.
Hb levels after ESA withdrawal because of Hb overshooting


Hb decline = 0.3-0.4 g/dL/wk
## C.E.R.A. dosing algorithm to maintain Hb target in patients with Hb overshooting (>12.5 g/dL)

<table>
<thead>
<tr>
<th>Hb actual visit (g/dL)</th>
<th>Hb previous visit (Hb/dL)</th>
<th>Dose adjustment</th>
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<tbody>
<tr>
<td>12.6-13</td>
<td>&lt;11</td>
<td>Decrease by 50%</td>
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<td>11-12.5</td>
<td>Decrease by 25%</td>
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<tr>
<td></td>
<td>12.6-13</td>
<td>Decrease by 25%</td>
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<td>&gt;13</td>
<td>Not administer</td>
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<tr>
<td>&gt;13</td>
<td>Any value</td>
<td>Not administer</td>
</tr>
</tbody>
</table>

Minutolo Blood Purification 2013
Incidence and management of Hb overshooting during MIRCERA

Hb Overshooting (Hb >12.5 g/dL)
N=57 (36%)

After 4 weeks from Hb overshooting:
- Hb values from 13.2±0.6 to 12.2±0.6 g/dL
- ΔHb -1.0±0.6 g/dL/month
- CERA from 83±19 to 44±34 µg/month
- Hb target (11-12.5): 70%

Dose reduction (65%)
- CERA from 91±17 to 65±15 µg/mo
- ΔHb -0.8±0.5 g/dL/month
- Hb from 13.0±0.5 to 12.2±0.5 g/dL
- Hb target (11-12.5): 81%

Mircera withdrawal (35%)
- CERA from 67±12 µg/mo to 0
- ΔHb -1.3±0.7 g/dL/month
- Hb from 13.6±0.7 to 12.3±0.9 g/dL
- Hb target (11-12.5): 50%
Conclusions: MIRCERA in clinical practice is useful for:

**Nephrologist**
- Good effectiveness with monthly administration associated to good safety profile.
- Easy to manage (*switch*: multiply by 4 the weekly Darbe dose; *naïve*: 1.2 µg/kg/month)
- Fewer dose change due to Hb stability
- No dose penalty when the drug is administered I.V. (*same half-life with s.c. and iv route*)

**Nurse**
- Reduced workload and less storage problems (*due to the lower number of injections*)
- Lower need of Hb testing (*dosing interval corresponds to the length of erythropoietic cycle*)

**Patient**
- Less punctures (*simplify adherence to therapy especially in comorbid patients*)
- More physiologic stimulation of erythropoiesis with lower risk of Hb fluctuation (*due to the persistence of serum levels within erythropoietic threshold*)
- Easy to transport (*30 days at air temperature*)
Questionnaire on satisfaction with MIRCERA in comparison with previous ESA administered to patients (n=97) and nephrologists (n=97)

- Patients: 54% CERA better, 46% Equal, 0% CERA worse
- Nephrologists: 54% CERA better, 46% Equal, 0% CERA worse

Heidenreich Clin Drug Investig 2012
Thank you for your attention