# ΑΙΜΟΧΡΩΜΑΤΩΣΗ

***Θεραπεία με deferasirox***

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***21-10-2011***

AASLD PRACTICE GUIDELINE

# Diagnosis and Management of Hemochromatosis: 2011 Practice Guideline by the American Association for the Study of Liver Diseases

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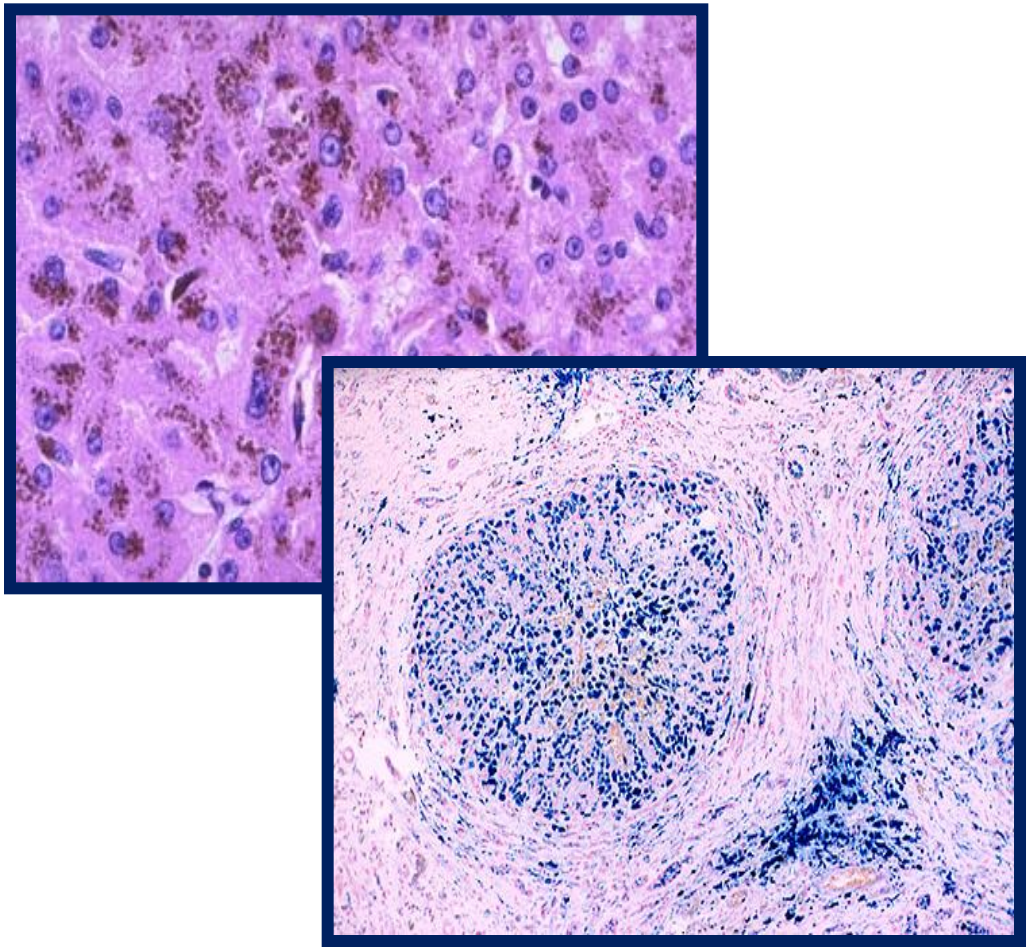
## How I treat hemochromatosis

Paul C. Adams and James C. Barton

# ΑΙΤΙΑ ΑΙΜΟΧΡΩΜΑΤΩΣΗΣ

- Hereditary Hemochromatosis
  - *HFE*-related
    - C282Y/C282Y
    - C282Y/H63D
    - Other *HFE* mutations
  - Non–*HFE*-related
    - Hemojuvelin (*HJV*)
    - Transferrin receptor-2 (*TfR2*)
    - Ferroportin (*SLC40A1*)
    - Hepcidin (*HAMP*)
    - African iron overload
- Secondary Iron Overload
  - Iron-loading anemias
    - Thalassemia major
    - Sideroblastic
    - Chronic hemolytic anemia
    - Aplastic anemia
    - Pyruvate kinase deficiency
    - Pyridoxine-responsive anemia
  - Parenteral iron overload
    - Red blood cell transfusions
    - Iron–dextran injections
    - Long-term hemodialysis
  - Chronic liver disease
    - Porphyria cutanea tarda
    - Hepatitis C
    - Hepatitis B
    - Alcoholic liver disease
    - Nonalcoholic fatty liver disease
    - Following portocaval shunt
  - Dysmetabolic iron overload syndrome
- Miscellaneous
  - Neonatal iron overload
  - Aceruloplasminemia
  - Congenital atransferrinemia



# ΘΕΡΑΠΕΙΑ

**Table 9. Treatment of Hemochromatosis**

| |
|---|
| Hereditary hemochromatosis |
| One phlebotomy (removal of 500 mL blood) weekly or biweekly |
| Check hematocrit/hemoglobin prior to each phlebotomy. |
| Allow hematocrit/hemoglobin to fall by no more than 20% of prior level |
| Check serum ferritin level every 10-12 phlebotomies |
| Stop frequent phlebotomy when serum ferritin reaches 50-100 μg/L |
| Continue phlebotomy at intervals to keep serum ferritin between 50 and 100 μg/L |
| Avoid vitamin C supplements |
| Secondary iron overload due to dyserythropoiesis |
| Deferoxamine (Desferal) at a dose of 20-40 mg/kg body weight per day |
| Deferasirox (Exjade) given orally |
| Consider follow-up liver biopsy to ascertain adequacy of iron removal |
| Avoid vitamin C supplements |

**Table 1. Treatments for iron overload caused by hemochromatosis**

| Treatment | Usual route of treatment | Advantages | Principal route/form of iron elimination | Compliance with treatment | Disadvantages | Adverse effects |
|---|---|---|---|---|---|---|
| Phlebotomy | Venipuncture | Much experience; effective on the part of the clinician, widely available, safe, inexpensive; reversal of cirrhosis in some cases; may improve left ventricular diastolic function | Blood as hemoglobin (1 mL of erythrocytes = 1 mg of Fe) | Excellent for iron depletion; good for maintenance | Requires repeated visits to health-care facility; requires normal erythropoiesis; some patients report intolerance | Transient hypovolemia; fatigue; increases iron absorption; iron deficiency if monitoring inadequate or inappropriate |
| Erythrocytapheresis | Venipuncture | Rapid, safe; may be preferred for patients with severe iron overload | Blood as hemoglobin (1 mL of erythrocytes = 1 mg of Fe) | Excellent in selected patients | Limited clinical experience; requires special apparatus and facility, limited availability; expensive | Transient hypovolemia; fatigue; increases iron absorption; citrate reaction; iron deficiency if monitoring inadequate or inappropriate |
| Deferoxamine (DFO) chelation | Subcutaneous infusion | Much clinical experience in iron overload patients without hemochromatosis; widely available; consider its use in patients intolerant of phlebotomy | Urine as chelate; daily iron excretion variable | Fair | Few reports of use in hemo-chromatosis, mostly to achieve iron depletion; inadequate chelation of cardiac iron in some cases; expensive | Infusion site reactions; hearing, vision, growth, skeletal abnormalities; zinc deficiency; *Yersinia* infection |
| Deferasirox (DFX) chelation | Oral | Good chelation of hepatic iron; consider its use in patients with inadequate venous access or intolerant of phlebotomy | Stool as chelate; daily iron excretion variable | Fair | Few reports of use in hemo-chromatosis to achieve iron depletion; no clear benefit for patients with iron-induced cardiomyopathy; expensive | Toxicity often dose dependent; gastrointestinal symptoms; transaminase elevations; elevation of serum creatinine; rash; rare hearing, vision abnormalities; severe (sometimes fatal) liver, kidney, or marrow toxicity |

It is not feasible to estimate net iron loss or gain attributable to diet or medications in individual patients using routine clinical techniques. Some patients with juvenile-onset hemochromatosis, severe iron overload, and iron-induced cardiomyopathy may benefit from combined treatment with phlebotomy and DFO or DFX.

Editorials

GASTROENTEROLOGY 2011;141:1142–1158

# Chelation Therapy for Secondary Iron Overload: Is the Primary Effect Less Iron or Less Liver Fibrosis?

# CLINICAL—LIVER

## Improvement in Liver Pathology of Patients With β-Thalassemia Treated With Deferasirox for at Least 3 Years

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GASTROENTEROLOGY 2011;141:1202–1211

# ΕΙΣΑΓΩΓΗ

- **Το ήπαρ είναι το κύριο όργανο εναπόθεσης σιδήρου σε ασθενείς με υπερφόρτωση σιδήρου λόγω μεταγγίσεων**

- **Λίγες μελέτες έχουν γίνει για την ηπατική ίνωση κατά τη διάρκεια θεραπείας με αποσιδήρωση**
  - *+/- HCV λοίμωξη*

# ΜΕΛΕΤΕΣ 107 & 108

## ΜΕΛΕΤΗ 107

- Διάρκεια 1 έτος
- Τυχαιοποιημένη – ελεγχόμενη μελέτη
- **Deferasirox vs Deferoxamine**
- β-θαλασσαιμία (διάγνωση ≥ 2 έτη)

## ΜΕΛΕΤΗ 108

- Διάρκεια 1 έτος
- Μη συγκριτική μελέτη
- **Deferasirox**
- Ασθενείς πολυμεταγγιζόμενοι (διάφορα νοσήματα)

**107 E & 108E**

Συνέχιση και καταγραφή δεδομένων για τα επόμενα 4 έτη

# ΣΚΟΠΟΣ

- **Υποανάλυση των δεδομένων από τις δύο προηγούμενες μεγάλες μελέτες**

- **Αυτή είναι η πρώτη μακροπρόθεσμη ανάλυση εκτίμησης της αποτελεσματικότητας ενός χηλικού παράγοντα σιδήρου στην ηπατική ίνωση σε μια μεγάλη ομάδα ασθενών με υπερφόρτωση σιδήρου που πάσχουν από μεσογειακή αναιμία**

# ΑΣΘΕΝΕΙΣ - ΜΕΘΟΔΟΙ

## ΚΡΙΤΗΡΙΑ ΕΝΤΑΞΗΣ

- Ηλικία ≥ 2 έτη
- ≥ 8 μεταγγίσεις / έτος
- LIC ≥ 2 mg Fe/g dw

**Στην παρούσα υποανάλυση**

- **β-θαλασσαιμία**
- **Deferasirox > 3 έτη**
- **Βιοψία ήπατος > 3 έτη θεραπείας**

## ΚΡΙΤΗΡΙΑ ΑΠΟΚΛΕΙΣΜΟΥ

- ALT > 250 IU/L
- Κρεατινίνη> ΦΤ
- HBV
- HIV
- Ενεργός ηπατίτιδα C

# ΑΣΘΕΝΕΙΣ - ΜΕΘΟΔΟΙ

- **ΔΟΣΟΛΟΓΙΑ**
  - **Deferasirox** : 5-30 mg/Kg/d
  - **Deferoxamine** : 20-50 mg/kg/d x 5 ημέρες/εβδομάδα
- **LIC**
  - Βιοψία ήπατος πριν την έναρξη θεραπείας και στο τέλος της μελέτης
  - Δείγματα με dw< 0.4mg δεν εκτιμήθηκαν για εναπόθεση σιδήρου

# ΚΡΙΤΗΡΙΑ ΑΝΤΑΠΟΚΡΙΣΗΣ ΜΕ ΒΑΣΗ LIC

**Table 1.** Response Criteria Based on LIC From Biopsy

| Baseline LIC (*mg Fe/g dw*) | Success, if LIC at EOS (Group A) | Failure,[a] if LIC at EOS (Group B) |
|---|---|---|
| <7 | 1 to <7 mg Fe/g dw and increase <1 mg Fe/g dw | <1 mg Fe/g dw or ≥7 mg Fe/g dw or increase ≥1 mg Fe/g dw |
| ≥7 to <10 | 1 to <7 mg Fe/g dw | <1 mg Fe/g dw or ≥7 mg Fe/g dw |
| ≥10 | Decreases in LIC ≥3 mg Fe/g dw | Decreases in LIC <3 mg Fe/g dw |

[a]Failure group had lower baseline LIC (10.7 vs 18.3 mg Fe/g dw) and therefore received lower doses of deferasirox, which were often insufficient to achieve an overall reduction in LIC.

# ΑΠΟΤΕΛΕΣΜΑΤΑ

**Table 2.** Demographics and Baseline Characteristics of Patients Who Had Histological Biopsy Data at Baseline and at the End of at Least 3 Years Treatment With Deferasirox by Study Cohort, and Baseline Efficacy Measurements for Patients With Baseline and EOS LIC Assessments by LIC Response Criteria Category

| Characteristic | Study 107 Deferasirox (n = 106) | Study 107 Crossover[a] (n = 94) | Study 108 Deferasirox (n = 19) | All patients (n = 219) |
|---|---|---|---|---|
| Mean age, *y*, (range) | 15.0 (2–36) | 15.0 (3–43) | 22.1 (4–49) | 15.6 (2–49) |
| Male/female | 55/51 | 56/38 | 8/11 | 119/100 |
| Race (Caucasian/Asian/other), n | 100/1/5 | 88/2/4 | 9/4/6 | 197/7/15 |
| History of hepatitis at start of deferasirox treatment, n (%) | | | | |
| No hepatitis B or C | 81 (76.4) | 77 (81.9) | 18 (94.7) | 176 (80.4) |
| Hepatitis B | 10 (9.4) | 7 (7.4) | 0 (0.0) | 17 (7.8) |
| Hepatitis C | 19 (17.9) | 12 (12.8) | 1 (5.3) | 32 (14.6) |
| Hepatitis B and C | 4 (3.8) | 2 (2.1) | 0 (0.0) | 6 (2.7) |
| Hepatitis NOS | 1 (0.9) | 2 (2.1) | 1 (5.3) | 4 (1.8) |
| Any type of hepatitis | 25 (23.6) | 17 (18.1) | 2 (10.5) | 44 (20.1) |
| Baseline liver parameters (mean ± SD) | | | | |
| LIC, *mg Fe/g dw* | 17.8 ± 10.6 | 12.6 ± 8.2 | 19.1 ± 10.3 | 15.7 ± 9.9 |
| TIS | 27.2 ± 11.0 (n = 104) | 22.0 ± 10.4 (n = 92) | 28.6 ± 10.3 (n = 19) | 25.1 ± 11.0 (n = 215) |
| Liver iron ratio,[b] *%* | 66.0 ± 13.9 (n = 104) | 69.3 ± 15.1 (n = 92) | 56.0 ± 14.8 (n = 19) | 66.5 ± 14.8 (n = 215) |
| Median baseline serum ferritin, *ng/mL* (range) | 2148 (367–11,453) | 1716 (273–8529) | 4056 (1402–11,698) | 2069 (273–11,698) |

Baseline efficacy measurements for patients with baseline and EOS LIC assessments

| | Group A (LIC response success) (n = 134) | Group B (LIC response failure) (n = 76) | Total (n = 210) |
|---|---|---|---|
| Mean baseline necroinflammatory score (±SD) | 2.2 ± 1.7 | 1.6 ± 1.5 | 2.0 ± 1.6 |
| Mean baseline ALT, *IU/mL* (±SD) | 46.2 ± 41.5 | 30.6 ± 29.0 | 40.5 ± 38.2 |
| Baseline liver parameters (mean ± SD) | | | |
| LIC, *mg Fe/g dw* | 18.3 ± 10.7 | 10.7 ± 5.9 | 15.5 ± 9.9 |
| Total iron score | 27.9 ± 10.9 (n = 131) | 19.5 ± 8.9 (n = 75) | 24.9 ± 11.0 (n = 206) |
| Liver iron ratio, *%* | 65.8 ± 12.7 (n = 131) | 68.0 ± 18.7 (n = 75) | 66.6 ± 15.1 (n = 206) |
| Median baseline serum ferritin, *ng/mL* (range) | 2379 (536–11,453) | 1587 (273–11,698) | 2049 (273–11,698) |

# ΕΠΙΔΡΑΣΗ ΤΟΥ *deferasirox* ΣΤΗΝ ΗΠΑΤΙΚΗ ΙΝΩΣΗ

Μεταβολή -2 έως 0: 149
Στασιμότητα
HCV + : 14
HCV - : 103
Βελτίωση
HCV + : 9
HCV - : 49

Επιδείνωση: 22
Group A : 8
Group B : 12

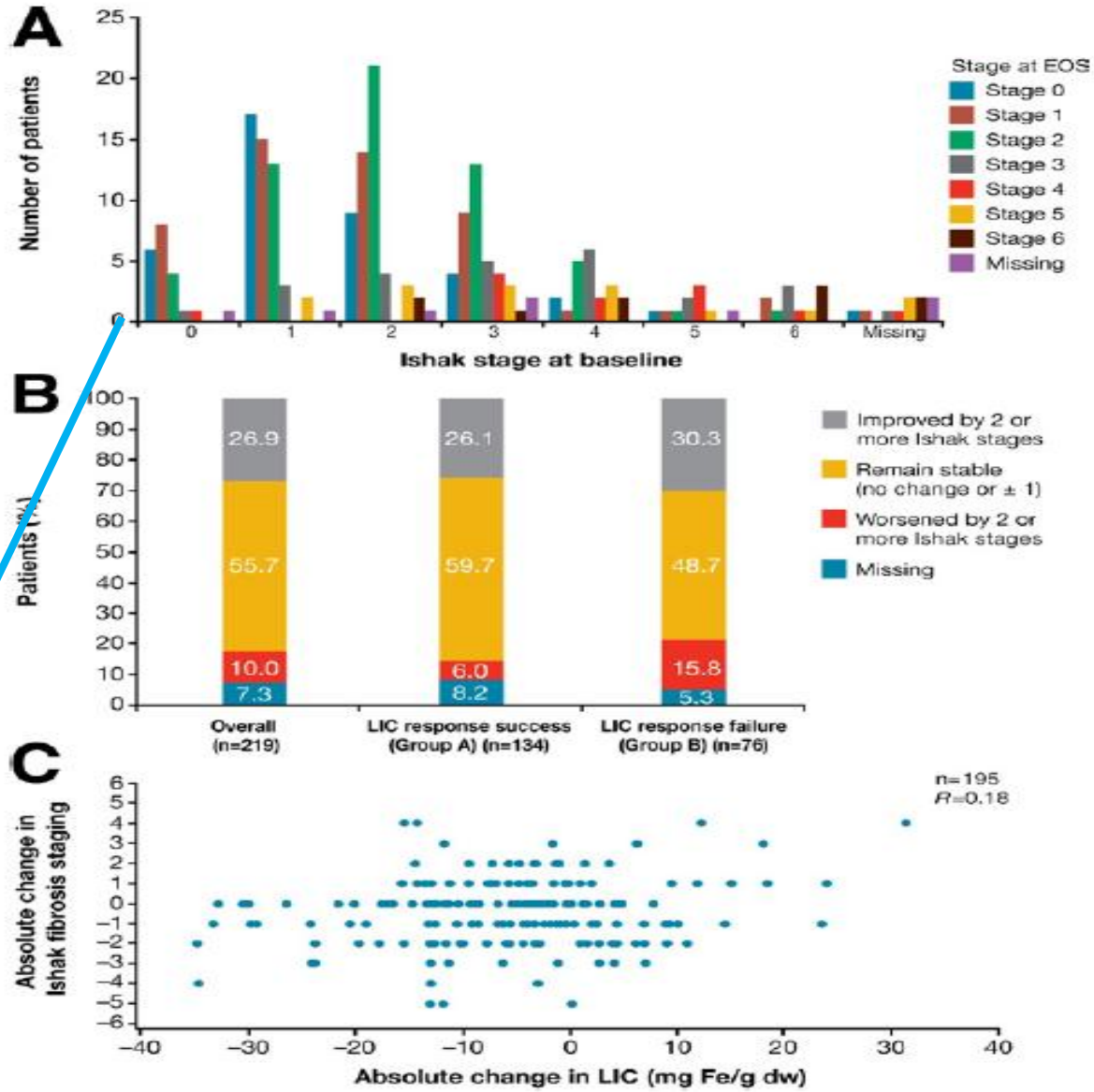



**Figure 1.** (*A*) Distribution of patients based on Ishak stages at baseline and EOS; (*B*) proportion of patients with Ishak stage improvement, stability, or worsening by EOS; and (*C*) scatter plot of absolute changes from treatment initiation for LIC and Ishak fibrosis staging scores. Only patients with LIC and Ishak fibrosis staging at both baseline and EOS are included.

# ΕΠΙΔΡΑΣΗ ΤΟΥ *deferasirox* ΣΤΗΝ ΝΕΚΡΟ-ΦΛΕΓΜΟΝΗ

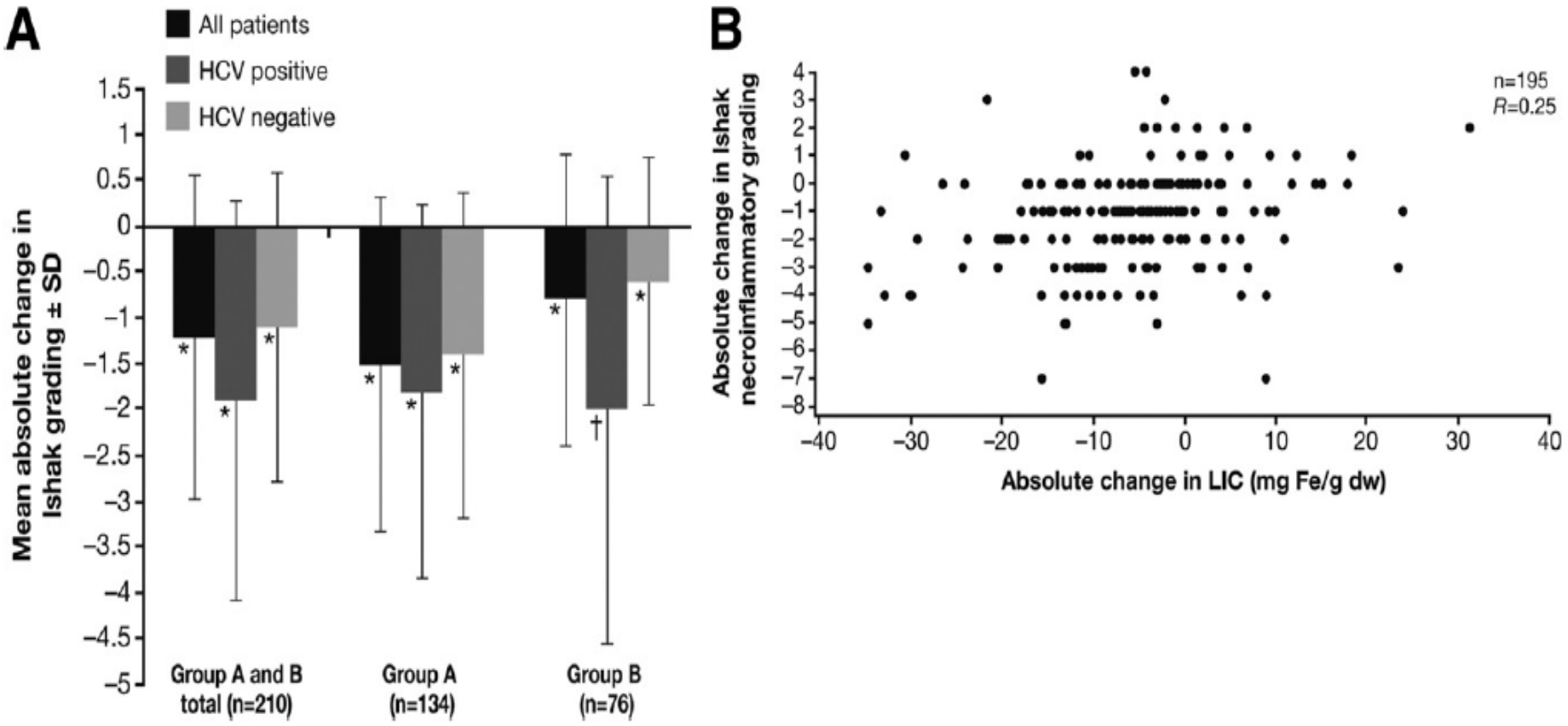



**Figure 2.** (*A*) Mean absolute change in Ishak necroinflammatory grading by EOS; and (*B*) scatter plot of absolute changes from treatment initiation for LIC and Ishak necroinflammatory grading. Only patients with LIC and Ishak necroinflammatory grading at both baseline and EOS are included. *$P < .001$ at EOS compared with baseline. †$P = .002$ at EOS compared with baseline.

# ΕΠΙΔΡΑΣΗ ΤΟΥ *deferasirox* ΣΤΗΝ ALT

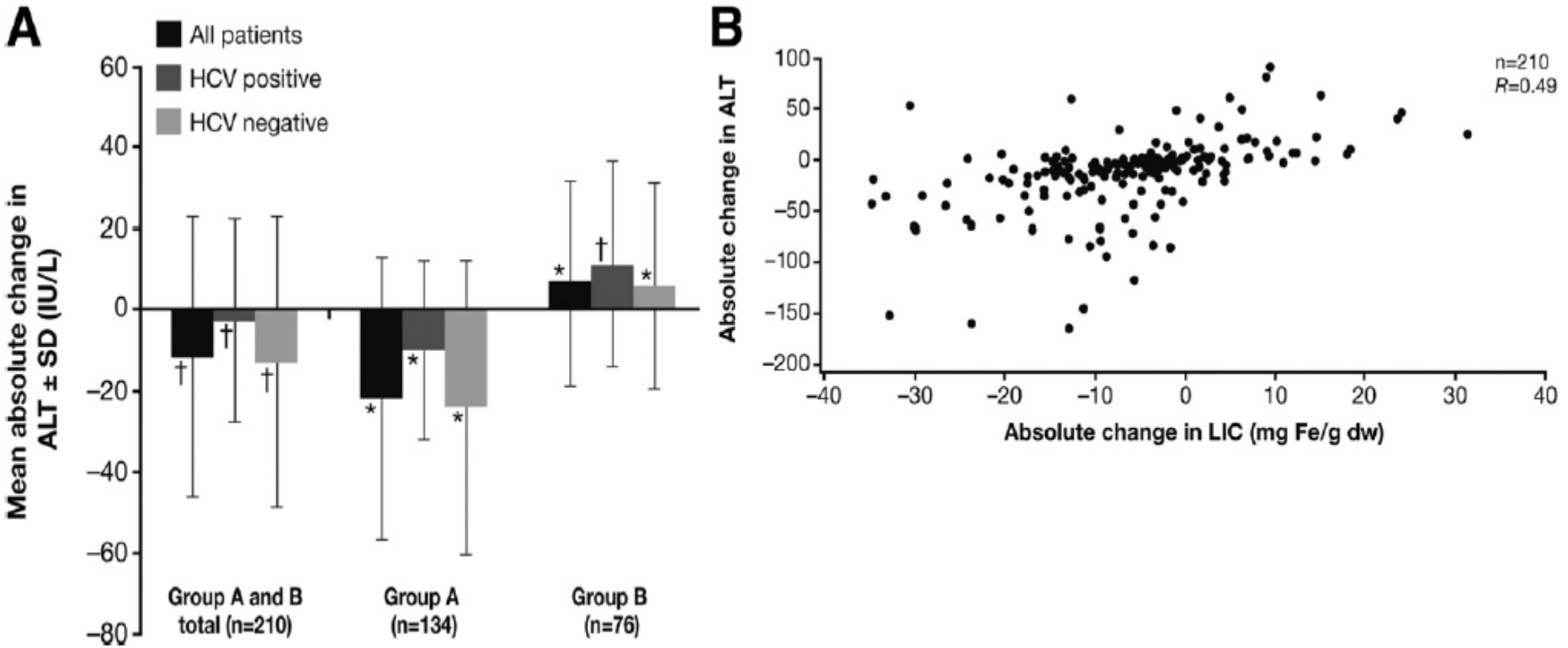
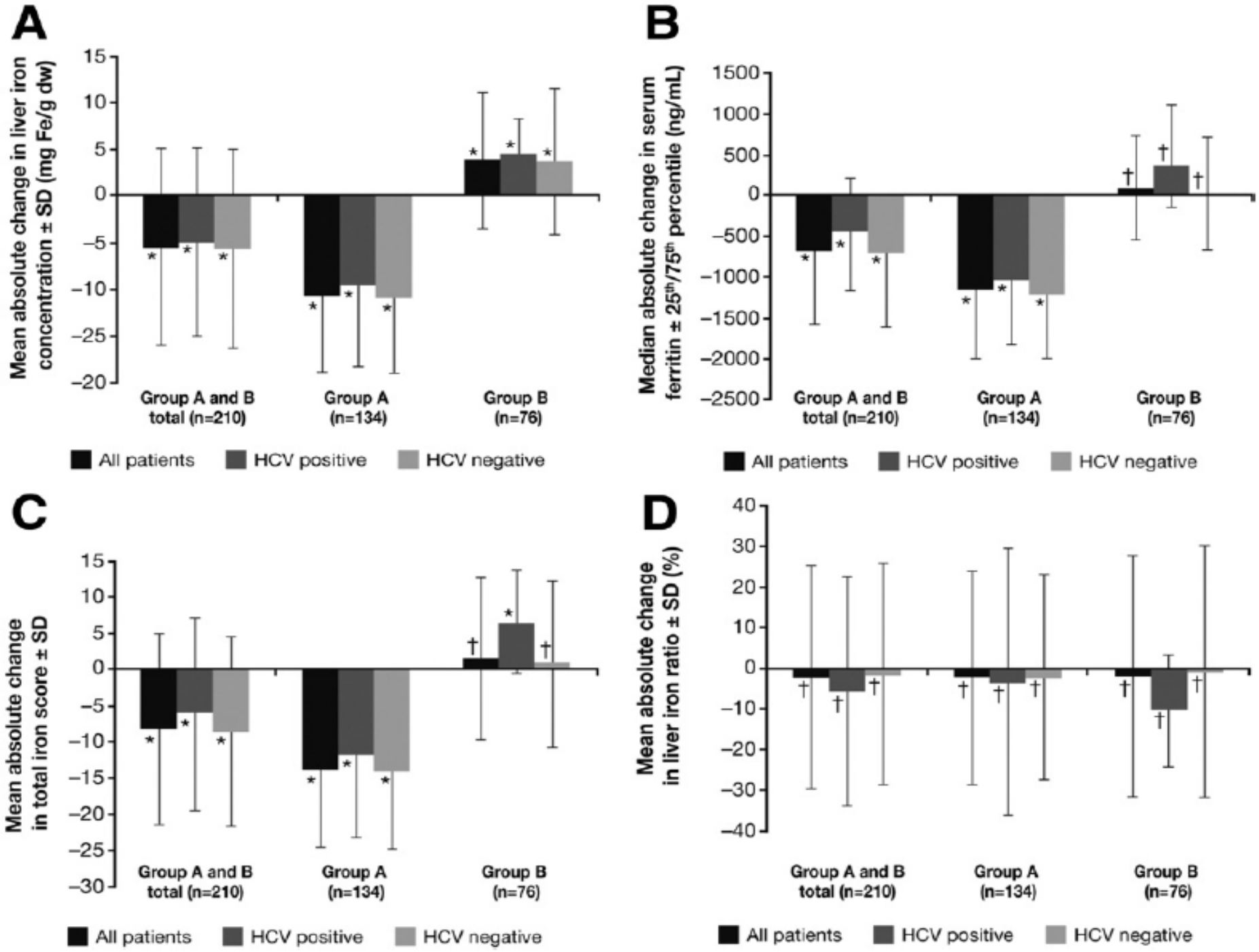



**Figure 3.** (*A*) Mean absolute change in ALT by EOS and (*B*) scatter plot of absolute changes from treatment initiation for LIC and ALT. Only patients with LIC and ALT at both baseline and EOS are included. **P* is significant at EOS compared with baseline. †*P* is nonsignificant at EOS compared with baseline.

# ΕΠΙΔΡΑΣΗ ΤΟΥ *deferasirox* ΣΤΟ ΦΟΡΤΙΟ ΣΙΔΗΡΟΥ ΚΑΙ ΤΗΝ ΤΙΜΗ ΦΕΡΡΙΤΙΝΗΣ


A
Mean absolute change in liver iron concentration ± SD (mg Fe/g dw)
15
10
5
0
−5
−10
−25
−20
Group A and B total (n=210)
Group A (n=134)
Group B (n=76)
All patients
HCV positive
HCV negative
B
Median absolute change in serum ferritin ± 25th/75th percentile (ng/mL)
1500
1000
500
0
−500
−1000
−1500
−2000
−2500
Group A and B total (n=210)
Group A (n=134)
Group B (n=76)
All patients
HCV positive
HCV negative
C
Mean absolute change in total iron score ± SD
15
10
5
0
−5
−10
−15
−20
−25
−30
Group A and B total (n=210)
Group A (n=134)
Group B (n=76)
All patients
HCV positive
HCV negative
D
Mean absolute change in liver iron ratio ± SD (%)
40
30
20
10
0
−10
−20
−30
−40
Group A and B total (n=210)
Group A (n=134)
Group B (n=76)
All patients
HCV positive
HCV negative

# ΠΕΡΙΛΗΨΗ ΑΠΟΤΕΛΕΣΜΑΤΩΝ

**Table 3.** Summary of Changes in Liver and Iron Parameters From Baseline Until EOS

| Summary of results | Group A (n = 134) | Group B (n = 76) | Total (n = 210) |
|---|---|---|---|
| Absolute change from baseline | | | |
| Mean necroinflammatory score (±SD) | −1.5 ± 1.8 | −0.8 ± 1.6 | −1.2 ± 1.8 |
| Mean serum ALT, *IU/mL* (±SD) | −21.5 ± 35.0 | 6.8 ± 25.2 | −11.3 ± 34.6 |
| Mean LIC, mg *Fe/g dw* (±SD) | −10.7 ± 8.2 | 3.9 ± 7.4 | −5.5 ± 10.6 |
| Mean total iron score (±SD) | −13.7 ± 10.9 | 1.5 ± 11.2 | −8.2 ± 13.2 |
| Mean liver iron ratio, % (±SD) | −2.4 ± 26.1 | −1.9 ± 29.6 | −2.2 ± 27.4 |
| Median serum ferritin, *ng/mL* (range) | −1149 (−10,164 to 1681) | 72 (−2735 to 4929) | −675 (−10,164 to 4929) |

SD, standard deviation.

# ΣΥΖΗΤΗΣΗ

- **Θεραπεία με *deferasirox* για ≥ 3 έτη είχε ως αποτέλεσμα <u>υποστροφή/ βελτίωση ή σταθεροποίηση</u> της ηπατικής ίνωσης στο 83% των ασθενών με θαλασσαιμία και υπερφόρτωση με σίδηρο.**

- **Αυτό το θεραπευτικό αποτέλεσμα ήταν <u>ανεξάρτητο</u> από μείωση της συγκέντρωσης σιδήρου στο ήπαρ (LIC) ή από ιστορικό έκθεσης στον ιό HCV.**

# ΣΥΖΗΤΗΣΗ

- Σε σύγκριση με μελέτες για άλλους χηλικούς παράγοντες τα αποτελέσματα που παρουσιάζονται είναι πιο ενθαρρυντικά για το *deferasirox*
  - Σε ασθενείς με β-θαλασσαιμία και θεραπεία με deferiprone για >3 έτη δεν παρατηρείται σημαντική αλλαγή στην ηπατική ίνωση, ενώ σε άλλες μελέτες αναφέρεται επιδείνωση
  - Σε ασθενείς με β-θαλασσαιμία και θεραπεία με deferoxamine από 2-9 έτη φαίνεται σταθεροποίηση της ίνωσης

# A Phase 1/2, Dose-Escalation Trial of Deferasirox for the Treatment of Iron Overload in *HFE*-Related Hereditary Hemochromatosis

Pradyumna Phatak,[1] Pierre Brissot,[2] Mark Wurster,[3] Paul C Adams,[4] Herbert L. Bonkovsky,[5] John Gross,[6] Peter Malfertheiner,[7] Gordon D. McLaren,[8] Claus Niederau,[9] Alberto Piperno,[10] Lawrie W. Powell,[11] Mark W. Russo,[12] Ulrich Stoelzel,[13] Wolfgang Stremmel,[14] Louis Griffel,[15] Nicola Lynch,[15] Yiyun Zhang,[15] and Antonello Pietrangelo[16]

(HEPATOLOGY 2010;52:1671-1679)

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

**Safety and Efficacy of Deferasirox (ICL670) in Patients With Iron Overload Resulting From Hereditary Hemochromatosis**

This study has been completed.

First Received on November 1, 2006. Last Updated on May 24, 2011 History of Changes

| | |
|---|---|
| **Sponsor:** | Novartis Pharmaceuticals |
| **Information provided by:** | Novartis |
| **ClinicalTrials.gov Identifier:** | NCT00395629 |

| Phase |
|---|
| Phase I<br>Phase II |

REVIEW

Blood Reviews 25 (2011) 17–31

# Controversies surrounding iron chelation therapy for MDS

Heather A. Leitch *

*Division of Hematology, St. Paul's Hospital, University of British Columbia, Vancouver, BC, Canada*

# Supportive care and chelation therapy in MDS: are we saving lives or just lowering iron?

*Heather A. Leitch[1] and Linda M. Vickars[1]*

blood

2009 114: 5251-5255
Prepublished online August 26, 2009;
doi:10.1182/blood-2009-07-234062

**Objectives of iron chelation therapy in myelodysplastic syndromes: more than meets the eye?**

Vinod Pullarkat