

Topic IA. Considerations for iron management in blood donors

Issue: FDA seeks advice from the committee on acceptable procedures for iron management in blood donors

Background

According to a survey of United States (U.S.) blood establishments in 2013, about seven million allogeneic donors donated blood. About a third of these donors were first-time donors. The rest were repeat donors who donated an average of 1.6 donations per year (1). U.S. blood donors must meet the minimum hemoglobin requirements established by FDA in 21 CFR 630.10 (f)(3). Prior to donating again, donors must wait a minimum of 8 weeks (for a single unit of Red Blood Cells) or 16 weeks (for two units of Red Blood Cells) {(21 CFR 630.15 (a) (1)}.

Despite hemoglobin screening and deferral practices to protect the health of blood donors, iron depletion is a well-known consequence of blood donation. Multiple studies have identified female gender (especially premenopausal) and donation frequency as major risk factors for iron deficiency in blood donors (2,3).

Following the donation of a unit of whole blood, a healthy blood donor loses about 200-250 mg of iron. Iron balance in blood donors depends on several factors including volume of blood collected, frequency of donation, dietary and supplement intake, age and sex. For example, a female donor of childbearing age would lose about 225 mg of iron from blood donation. Assuming normal menstrual blood loss and regular dietary intake, the iron deficit after 56 days may be about 113 mg. Therefore, the iron loss from the donation would not be replenished by the time such a donor is again eligible to donate.

There may be no physiologic consequences of iron depletion in the early stages. However, as iron depletion progresses, storage iron is exhausted and iron-deficient erythropoiesis may result. Iron deficiency can cause fatigue, restless leg syndrome, pica

and anemia (4). Also, there is a significant correlation between iron status and impaired cognitive functioning, depression, and anxiety (5). The impact of iron deficiency on the incidence of cardiovascular events is inconclusive (6).

Anemia, which is a late consequence of iron deficiency, is commonly detected in deferred blood donors. A 2013 survey of blood donor deferrals in U.S. blood establishments revealed that of approximately 15 million donors who presented to donate blood, 15% (~ 2 million) were deferred. Half of the deferrals were due to low hemoglobin (7). Iron deficiency is a common reason for low hemoglobin. In a study of donors deferred for low hemoglobin levels, 77% were iron deficient (7). Hemoglobin determination alone is not a good indicator of iron status. The National Heart, Lung, and Blood Institute's (NHLBI) Retrovirus Epidemiology Donor Study-II (REDS-II) Donor Iron Status Evaluation (RISE) study of donor iron status confirmed that blood donors may be iron deficient and yet have acceptable hemoglobin levels at the next donation. This study also revealed that the likelihood of iron deficiency is greater in donors returning for donation in less than 14 weeks (8).

Previous FDA public discussions regarding iron deficiency

The Biologic Products Advisory Committee (BPAC) discussed iron deficiency in blood donors in September 2008 (9). The committee voted unanimously that iron depletion is a concern. They agreed that accurate, convenient, and rapid tests for iron stores were not available. The committee also discussed the risks and benefits of alternative strategies to mitigate iron depletion in donors. There were no consensus recommendations on the implementation of these strategies by the committee.

On July 27, 2010, FDA convened a BPAC meeting to discuss the hemoglobin and hematocrit standards in male and female allogeneic donors and the appropriate interdonation interval. The committee heard presentations of the preliminary results of the REDS II RISE study that examined predictors of iron deficiency and low hemoglobin among blood donors. The committee recommended further analysis of the results of the REDS II RISE study before making a decision on adjusting the interdonation interval (10).

In November 2011, FDA and others sponsored a public workshop to discuss hemoglobin standards and maintaining adequate iron stores in blood donors. At this workshop, participants discussed available data on iron deficiency in blood donors, testing for iron stores and methods to mitigate iron deficiency. Workshop participants concluded that there is a need to consider methods to mitigate iron loss in blood donors e.g. donor education, ferritin testing, adjustment of the interdonation interval or iron supplementation. Participants also noted that pilot studies are necessary to evaluate and prevent iron loss in blood donors, while including compensatory strategies to lessen the impact of any changes on the blood supply (11).

AABB recommendations

In 2012, AABB published a bulletin entitled: “Association Bulletin #12-03 - Strategies to Monitor, Limit, or Prevent Iron Deficiency in Blood Donors.” In this bulletin, AABB recommends that blood establishments institute actions to reduce the risk of iron deficiency in blood donors. Recommended actions include ferritin testing, iron replacement or prolonging the interdonation interval (12).

Since the last BPAC meeting and public workshop, there are new studies that further explain the course of iron deficiency in blood donors and the impact of mitigation measures such as ferritin testing and iron supplementation. Other studies have examined the operational feasibility of such mitigation measures.

REDS II Donor Iron Status Evaluation (RISE) Study

Several studies have published findings that enhance our understanding of the course of iron deficiency in blood donors. The REDS-II Donor Iron Status Evaluation (RISE) was presented to the BPAC in 2011 and was published in *Transfusion* in March 2012 (8).

While it was previously understood that frequent blood donors are at risk of iron deficiency, predisposing donor variables were not clearly defined. One of the objectives of RISE was to evaluate the effects of blood donation intensity on iron and hemoglobin (Hb) status and how donor variables such as demographics, reproductive and behavioral

factors modify this relationship. The second aim of the study was to provide data to aid in the development of guidelines for optimal frequency of whole blood donation.

RISE was conducted over a 24-month period from December 2007 through December 2009 as a longitudinal multi-center study. The study enrolled 2,245 red blood cell donors of geographically and demographically diverse populations, who were either first-time (FT), reactivated (no donations in the previous 2 years) or frequent donors of red blood cells (RBCs). Study participants were assigned to one of two cohorts: a FT or reactivated (RA) donor cohort, or a frequent donor cohort (three or more donations for males and two or more donations for female donors in the previous year) and were followed prospectively over two years. Donor variables evaluated included demographics, smoking, dietary intake, iron supplementation, and menstrual and/or pregnancy history. Baseline ferritin, soluble transferrin receptor (sTfR) and Hb were measured. The investigators developed models to predict the two outcomes of interest; absent iron stores (AIS) defined by ferritin < 12 ng/mL and iron-deficient erythropoiesis (IDE) indicated by a log (sTfR/ferritin) value of ≥ 2.07 . Independent risk factors for AIS and IDE were evaluated using multivariable logistic regression models incorporating potential predictor variables.

Median values for Hb, plasma ferritin and sTfR at enrollment were highest in male donors, and lower in frequent donors when compared to FT or RA donors. At the time of enrollment, 15% of donors had AIS and 41.7% had IDE regardless of donation frequency. The prevalence of AIS and IDE in frequent donors was 16.4% and 48.7% in males, and 27.1% and 66.1% in females respectively. The median log (sTfR/ferritin) was higher in the frequent donation cohort for both sexes. Donation intensity was the variable most closely associated with AIS and IDE when comparing frequent donors to FT or RA donors, a finding consistent with previous cross-sectional studies evaluating iron status in blood donors (13, 14). The likelihood of having AIS and/or IDE was increased in donors who were female, younger, and/or menstruating. Lower body weights were also associated with increased likelihood of having AIS and/or IDE. Thirty-nine percent of RISE donors reported taking iron supplementation, which appeared to have a small protective effect for AIS, but not IDE.

The mean number of Hb deferrals per donor was also higher in the frequent donors, 0.79 for frequent females and 0.18 for frequent males, compared to 0.55 and 0.06 in FT/RA females and males, respectively. A previous study found that 10% of all REDS-II donation visits are deferred for low Hb (15). As noted earlier, 77% of low Hb deferrals were associated with iron deficiency. Odds ratios for Hb deferral became nonsignificant at 14 weeks post-donation suggesting that a period of 3-4 months is necessary to replenish iron stores lost through RBC donation. Other predictive factors for Hb deferral were identified as female sex, younger age in women and black race.

The authors noted that enrollment criteria excluded donors less than 18 years old. Further studies on the impact of blood donation on iron balance in teenagers are needed. The study concluded that the prevalence of iron deficiency and hemoglobin deferrals would likely be reduced by increasing the interdonation interval or by implementing iron supplementation.

Strategies to Reduce Iron Deficiency Study (STRIDE)

The STRIDE study was designed as a two-year, multicenter, randomized, blinded, and placebo- controlled study to evaluate the most effective operational methods for reducing iron deficiency in blood donors (16). The contextual basis for STRIDE was increased awareness of the high prevalence of iron deficiency in blood donors and that iron status in donors is currently not evaluated. In addition, iron deficiency is not prevented by current donor screening practices. STRIDE had two specific aims: (1) to determine whether regular blood donors would take steps on their own to mitigate donation related iron losses when provided with information about their iron status along with written recommended courses of action and (2) determine if providing iron supplements to donors after each donation without information on iron status would replace donation related iron losses.

The study enrolled 692 frequent donors (men with three or more, and women with two or more, red blood cell equivalent donations within the prior 12 months) who were

randomized into one of five study arms consisting of two educational strategy groups and three interventional groups (see figure 1). Iron deficiency characterized as AIS or IDE was assessed using measurements of ferritin and soluble transferrin receptor (sTfR) as previously defined (8). The educational strategy groups received either a letter containing no information about iron status thanking them and encouraging continued donation (no information letter), or a letter containing their ferritin test result (iron status letter). In the group receiving iron status letters, iron supplements or delayed donation for 6 months was recommended if ferritin was low (< 26 ng/mL). The interventional groups were administered either placebo, 19 mg or 38 mg iron pills (ferrous gluconate) daily for 60 days.

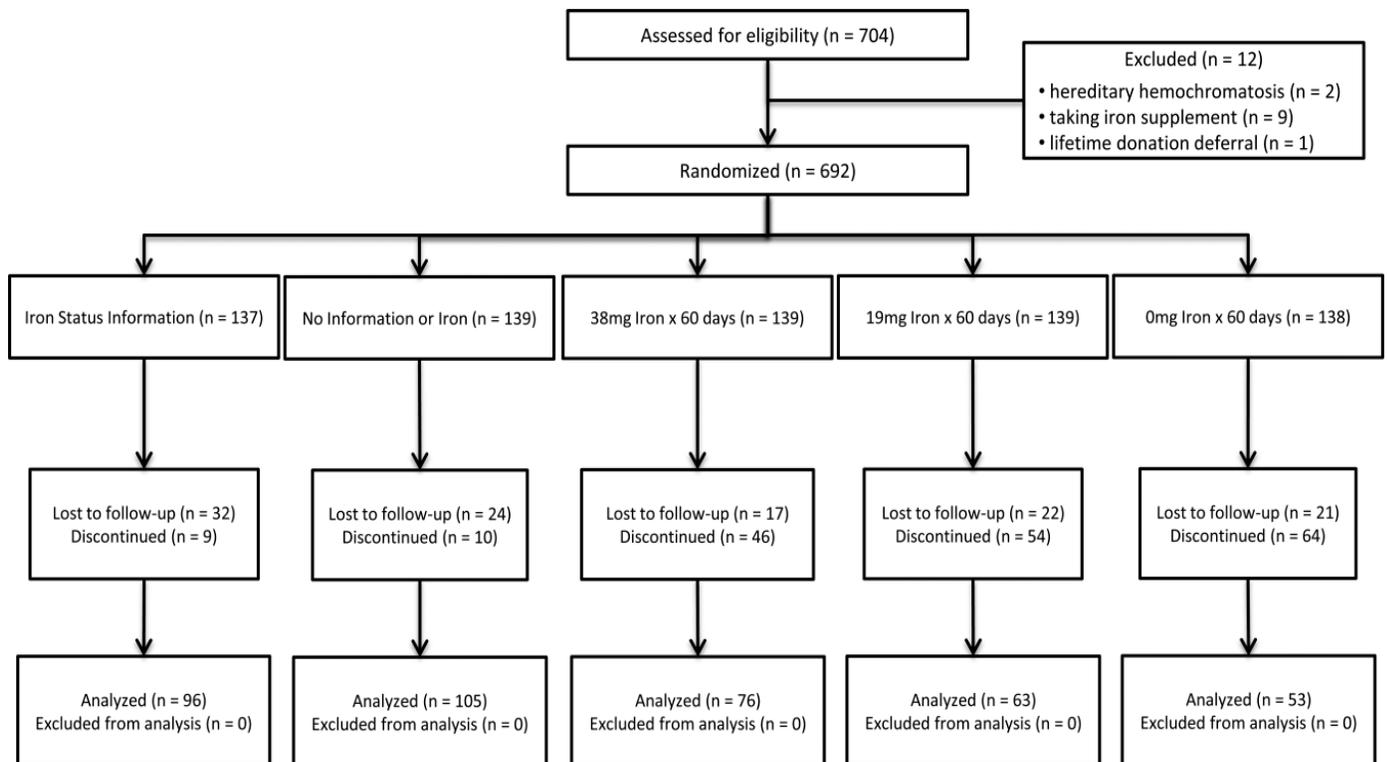


Figure 1: The allocation of participants to the five study arms and the number of each group that were lost to follow-up, disenrolled, and completed the STRIDE study.

Transfusion. 2016;56(6):1588–1597.

STRIDE reported AIS in 17.2% of male and 32% of female frequent donors, while IDE was present in 52.7% of male and 74.6% of female frequent donors at enrollment.

For those subjects that completed the study (57%), the prevalence of iron deficiency (ferritin < 26 ng/mL) decreased by more than 50% in the groups receiving iron status letters, 19 mg of iron daily or 38 mg of iron daily. Iron status at the conclusion of the study assessed by ferritin, log(sTfR/Ferritin) and venous hemoglobin, was significantly better in the three interventional groups than in the control subjects (placebo or no information letter). Mean ferritin increased by 10.3 ng/mL in the iron status letter group, 18.3ng/mL in the group taking 19 mg iron pills and 16.7 ng/mL in the group taking 38 mg iron pills. Correspondingly mean log(sTfR/ferritin) values decreased in the iron pill and iron status letter groups. Mean ferritin levels and mean log(sTfR/ferritin) were unchanged in the placebo pills and no information letter groups , however sTfR showed significant increases, indicating worsening iron status. Figure 2 summarizes the change in laboratory values indicative of iron stores.

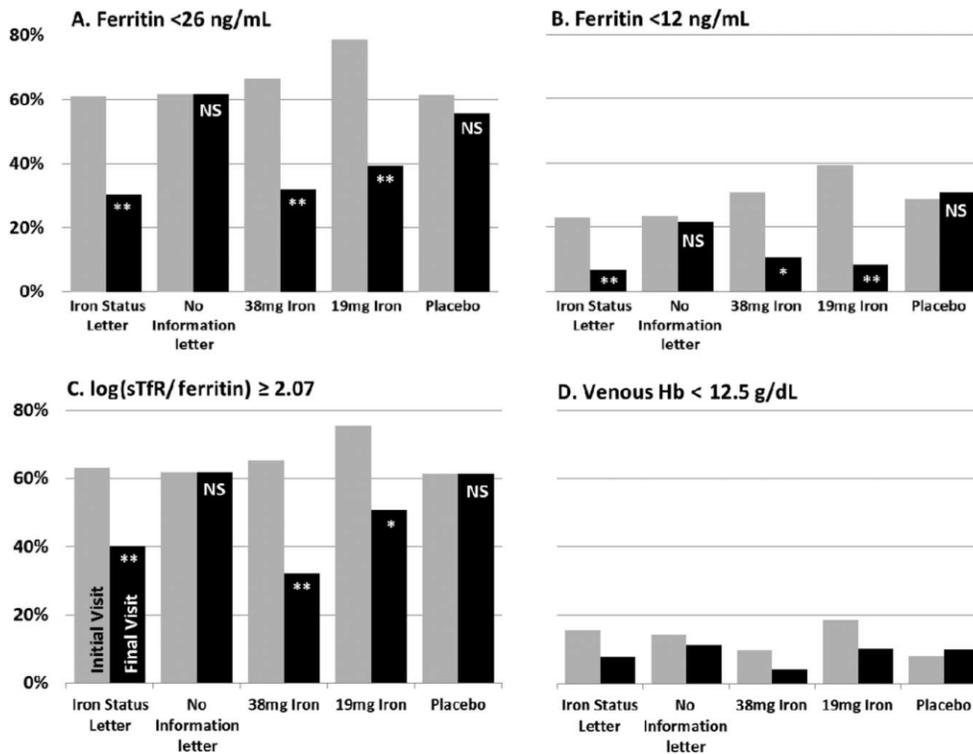


Figure 2: Percentage of subjects who completed the study with laboratory measures of iron status or Hb beyond clinical cutoff values for iron deficiency or anemia. p values for differences between initial and final visits are indicated with **p < 0.0001, *p <

0.01, ^{NS}p > 0.05. For D, no differences were significant at p < 0.05. (□) Initial visit values; (□) Final visit values

Mast et al. Transfusion 2016;56;1588–1597

Evaluation of donors' responses to the iron status letters at the end of the study found that most donors did take action to protect their iron status. Responses from 96 donors who received one more iron status letters and completed the study included the following: 3/16 donors (19%) with normal ferritin levels reported delaying donation, 27/80 (34%) donors with ferritin levels less than 26 ng/mL began taking iron pills, 9/80 (11%) delayed subsequent donations, 13/80 (16%) began taking iron and delayed subsequent donations, 21/80(26%) did not take iron or delay donation and 10/80 (13%) did not respond.

Adverse events reported within 60 days of enrollment were primarily mild gastrointestinal symptoms (5) and were reported only in subjects randomized to the interventional arms (iron pills or placebo) of the study. Gastrointestinal symptoms were reported more frequently in subjects receiving iron than in those receiving placebo. Other less frequently reported adverse events were rash/itching, leg cramps, frequent urination and headache. There were no statistically significant differences in the incidence of adverse events among the three groups taking pills. Donor compliance in the pill group was assessed by counting remaining pills in returned pill bottles.

Though the level of compliance was not reported in the publication of STRIDE results, it was noted that donors randomized to take pills were more likely to withdraw from the study during the first 60 days whereas those receiving letters (control and interventional) were more likely to remain as active participants (17). Reasons for withdrawal included not wanting to take iron, not wanting to receive placebo, and needing to receive iron for diagnosed iron deficiency. The STRIDE investigators summarized the following key findings: (1) 19 mg iron pills are as effective as 38 mg iron pills administered once daily over 60 days for mitigation of iron deficiency in blood

donors, (2) providing information about iron status and offering donors a choice between iron supplementation and delayed donation is also effective for mitigating donor iron deficiency, (3) iron deficiency mitigation strategies improved the hemoglobin status of frequent blood donors, and (4) continued donation in frequent donors without mitigation of iron losses results in progressive worsening of iron deficiency. The authors concluded that providing iron supplements or iron status information (ferritin results) are operationally effective means to mitigate iron deficiency in blood donors.

Hemoglobin and Iron Recovery Study (HEIRS)

The Hemoglobin and Iron Recovery Study (HEIRS) was a randomized, non-blinded clinical trial designed to determine the effect of oral iron supplementation on hemoglobin recovery time and recovery of iron stores in iron-depleted (ferritin \leq 26 ng/mL) and iron-replete donors (ferritin $>$ 26 ng/mL). The objective of the study was to determine the effect of iron supplementation on time to recovery of 80% of hemoglobin removed and recovery of iron stores (ferritin) to baseline (18).

The study randomized 215 blood donors (no donation in last the four months) to take either 37.5 mg of elemental iron (ferrous gluconate) daily for 24 weeks following whole blood donation or receive no iron. Mean baseline hemoglobin (Hb) levels were comparable between the two groups. After donation of a full whole blood unit, mean (SD) hemoglobin levels declined from 13 (1.1) g/dL to 12 (1.2) g/dL in the iron-depleted group and from 14.2 (1.1) g/dL to 12.9 (1.2) g/dL in the iron-replete group. Participants receiving iron supplementation had a shortened time to 80% hemoglobin recovery in both groups. Mean 80% hemoglobin recovery time in low ferritin participants receiving iron was 32 days with an interquartile range (IQR) of 30-34 days, compared to 158 days (IQR, 126 - $>$ 168) in those not receiving iron. In the higher ferritin group, those receiving iron had a mean 80% hemoglobin recovery time of 31 days (IQR, 29-33) compared to 78 days (IQR, 66-95) without iron supplementation. The median time to recovery of baseline ferritin was also shortened in those receiving iron, to 21 days (IQR, 12-84) and 107 days (IQR, 75-141) in the low and higher ferritin groups respectively.

The median time to baseline ferritin recovery in those subjects not receiving iron exceeded 168 days (IQR, 147- > 168 days, $P < 0.001$) in both groups. The overall median time to iron store recovery was 76 days (IQR, 20- 126) in all participants taking iron. Sixty-seven percent of subjects not receiving iron supplementation did not recover iron stores by 168 days. Only three of the participants receiving iron reported gastrointestinal adverse effects. Participants removed from the study (two) reported constipation and abdominal discomfort. The authors noted that the study dropout rate was higher (9%) in those receiving iron compared to those not receiving iron (1%). Compliance with iron supplementation was 92.5%.

The authors concluded that low-dose iron supplementation, compared with no supplementation, reduced time to 80% hemoglobin recovery of the postdonation decrease in Hb concentration in iron-depleted and iron-replete donors with normal hemoglobin levels. The authors further evaluated the impact of iron supplementation on total body iron (TBI). Iron supplementation increased TBI after blood donation especially in iron depleted donors. Most of the recovery of TBI occurred within the first eight weeks after donation (19).

Feasibility of ferritin-based iron replacement: a blood collection agency-based study

Gorlin and coworkers performed a study to determine the operational feasibility of implementing ferritin testing and iron supplementation in two blood centers (20). They performed ferritin testing on 197 (about 75% were female) frequent fixed site donors who met hemoglobin qualification standards and donated a unit of whole blood. Donors with low ferritin levels (≤ 20 ng/ml for females, ≤ 30 ng/ml for males) were informed of an extended deferral (112 days). They also received ferrous gluconate 325 mg (38 mg elemental iron/tablet) by mail and were advised to take 1 tablet twice a day for one-hundred days. Donors with normal ferritin levels were deferred from donation for fifty-six days and no iron was offered. Following initial ferritin testing on a sample obtained prior to donation, most donors (82% males, 88% females) had low ferritin levels. On follow up visit, donors who initially had lower ferritin levels and had taken iron had

higher ferritin levels and fewer deferrals for lower hemoglobin compared to those who had normal ferritin levels at the initial visit (5% hemoglobin deferrals in low ferritin group compared to 24% in normal ferritin group). Adverse effects were reported in 12% of those who received iron. Constipation was the most common adverse effect reported. More than 90% of those taking iron reported supplement use at least 5 days a week, and over 62% reported daily compliance. The authors concluded that measuring ferritin levels and providing iron supplements was operationally feasible in a blood center and that compliance with iron supplementation was high. They stated, however, that mailing iron supplements to donors can be cumbersome and expensive, and that alternative methods to providing iron should be considered.

The INTERVAL trial to determine whether intervals between blood donations can be safely and acceptably decreased to optimize blood supply: study protocol for a randomized controlled trial (INTERVAL)

The optimal interdonation interval for whole blood donation varies by country. The REDS RISE study demonstrated that the current 8 week deferral required for donors of a unit of red blood cells in the United States may not be adequate enough to allow recovery of iron stores (8). Several centers in England in collaboration with the National Health Service (NHS) Blood and Transplant have completed enrollment of about 50,000 male and female blood donors in the INTERVAL trial (21). The goal of this study is to determine whether intervals between blood donations can be safely and acceptably decreased. In this study, men were randomized to 8 week or 10 week deferral compared to the standard 12 week deferral, while women were assigned to a 12 week or 14 week deferral compared to the standard 16 week deferral. Outcome measures include the number of blood donations over 2 years, physical well-being of donors, measures of iron status, hemoglobin deferrals, donor attitudes, and cognitive function. Analysis of the INTERVAL study results is ongoing.

International practices related to donor hemoglobin and iron

Iron deficiency in premenopausal females and frequent blood donors has been shown to be a significant problem worldwide. Goldman and colleagues surveyed the international

blood collection community in December 2015, to assess what strategies to mitigate iron deficiency had been implemented (22). The authors surveyed 23 blood collectors including large national and small local centers, and received 20 responses, though some responses were partial. The survey consisted of seven questions related to donor hemoglobin and iron; however responses to the following four questions are relevant to strategies to detect, treat and prevent iron deficiency:

1. What is the maximum number of whole blood donations per year, and the minimum interval between whole blood donations, for male and female donors?
2. Do you provide any educational materials regarding risk of depletion of iron stores?
3. Do you currently have a programme in place for detection of iron deficiency?
4. Do you have a programme in place to provide iron supplements to donors?

Maximum number of annual donations and interdonation intervals

Eight of twenty respondents indicated that maximum donation frequency and interdonation intervals were gender specific, with fewer donations and longer intervals for teenaged and female donors. Overall, the range of minimal interdonation interval was 56-150 days for both male and female donors. The maximum number of annual donations ranged from 3-7 and in some cases was determined by the minimum interdonation interval.

Educational materials

The survey responses showed that a majority of collection agencies do mention a link between frequent donation and iron deficiency in their educational materials although very few recommend supplemental iron. Many of the centers surveyed provide additional guidance for the subset of donors considered to be high risk, including those failing to meet minimum hemoglobin requirements, young donors, females of child-

bearing age and frequent donors. A majority of informational materials emphasize maintaining a well-balanced diet and give recommendations for iron rich foods. When iron supplements are dispensed at one center in Australia, they are accompanied by a brochure detailing the importance of iron, why iron was prescribed and instructions for taking the iron tablets.

Monitoring iron status and iron supplementation

Ten of twenty respondents provided information on their approach to monitoring iron status and providing iron supplementation. The authors note that ferritin is measured for all donors at every donation in Switzerland. Denmark also routinely measures ferritin at the first donation and again every 10th donation or more frequently depending on prior results. Héma-Quebec monitors ferritin only in black female donors at specific blood drives. The authors note that the frequency of donor deferral rates has declined significantly in Switzerland and Denmark. Some respondents including one U.S. center perform ferritin testing on donors failing the hemoglobin test. The approach to iron supplementation varies widely and includes: providing iron to all donors, to all repeat donors, to all female donors of child-bearing age, or to donors failing the hemoglobin screening. Finland and Belgium report providing iron supplementation without performing ferritin testing. Iron formulations, duration of treatment and dose of elemental iron also vary considerably.

Discussion

Studies confirm that iron deficiency occurs in blood donors. Frequent donors and premenopausal females are at highest risk of developing this complication. Recent studies have looked at potential mitigation measures including ferritin testing, and iron supplementation. A large study examining interdonation interval is ongoing but the REDS II RISE and other studies show that it could take 14 weeks or more for iron stores to recover.

Ferritin testing

Ferritin is a good indicator of iron stores and has been used alone or together with iron supplementation to manage iron deficiency in blood donors. Studies show that it is operationally feasible to implement ferritin testing in blood centers (20). However the analyzers that perform this test or Point-of-care devices are not readily available in blood collection settings. Therefore it would be difficult to use a ferritin test to qualify a donor at the time he/she presents for donation. Ferritin testing and its impact on future donations have been examined in several blood donation settings. O'Meara and coworkers revealed that performing ferritin testing on Swiss blood donors and donor counseling by a physician providing results and options for encouraging iron recovery decreased the incidence of future predonation anemia and donation ineligibility (23). A study of Canadian donors informed of their low ferritin results revealed that notification reduced donor return rates and donation frequency. Qualitative interviews of the donors revealed that while most donors took some kind of action following notification of a low ferritin result, donors were not well informed about iron needs (24).

Iron supplementation

Iron supplementation in blood donors with or without ferritin testing has been shown to improve hemoglobin recovery, reduce deferrals due to low hemoglobin and minimize the incidence of iron deficiency (16, 18, 20). In addition, iron supplementation can reduce the incidence of consequences associated with iron deficiency including anemia, fatigue (25), and decreased cognitive function (26). Varying doses of iron over different periods have been studied in blood donors and found to be effective.

Challenges with iron supplementation in blood donors

1. Determination of administration options: This could include distribution of iron tablets by the blood center, issuance of coupons to purchase iron tablets or educational information about iron supplementation. Blood centers would need to determine which option is most effective operationally.
2. Adverse effects of iron preparation: Studies in blood donors have shown a

higher risk of adverse effects associated with iron supplementation when compared to placebo (27). These include stomach cramps, constipation, darkened stools, diarrhea, vomiting and taste disturbances. Donors may be intolerant to certain preparations of iron. Experience with iron supplementation has shown that switching iron preparations e.g. ferrous gluconate instead of ferrous sulfate might decrease the occurrence of adverse effects related to iron.

3. Compliance with iron supplementation. While most studies have reported high compliance rates, the definitions of compliance differ (e.g. ingestion of all tablets versus ingestion of 90% or ingestion everyday versus every other day). Differences in compliance could be due to factors such as adverse effects of iron preparations, participation in a study (including compensation), the variability in methods used to provide personalized iron education (e.g. donor counseled by blood center or personal physician), type of iron supplement used, and availability of iron supplements.

Risks

The risks associated with iron supplementation should be considered. These include adverse effects of iron, possible masking and delay of diagnosis of underlying illness such as colon cancer, failure to identify donors with hemochromatosis, iron-drug interactions, iron-food interactions, and exacerbation of diseases such as gastric ulcers (28).

FDA would like the Committee to review the available data and discuss the benefits and risks of monitoring iron stores in blood donors and the use of iron supplements.

Questions for the Committee

1. Please comment on the need for routine monitoring of iron stores in:
 - a. Frequent blood donors (male and female)
 - b. Premenopausal female donors
 - c. All blood donors
2. Does the available scientific evidence confirm that iron supplementation in blood donors improves hemoglobin recovery and mitigates iron deficiency?
3. Please comment on the feasibility of iron supplementation in consideration of:
 - a. Potential adverse effects
 - b. Adherence
 - c. Appropriate follow-up
4. Please comment on whether available scientific data support the following methods for iron supplementation in blood donors:
 - a. Educational material provided to the donor
 - b. Iron supplements provided to the donor by the blood center
 - i. If yes, what minimum effective dose would the committee recommend?
 - ii. Should iron supplements be offered to all blood donors or to select high risk donors?
5. Please comment on whether there are adequate data at this time in support of a strategy of increasing the minimum inter-donation intervals for men and women, absent monitoring of iron stores.

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