Current FDA Considerations on Pathogen Reduction

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Merits of the Current Approach of Donor Screening and Testing

Advantages

- No toxicity issues for recipients of products
- Detection is specific for particular agents
- New methods can be developed for novel and emerging pathogens

Disadvantages

- For certain pathogens detection is not 100% successful
  - Bacteria
  - Protozoa
  - Viral (window period)
- Development of detection methods for novel and emerging pathogens would be delayed due to lack of knowledge about the pathogen
- Additional tests for emerging pathogens increase cost

Merits of Pathogen Reduction Technology as an Alternative to Donor Screening and Testing

Advantages

- Shown effective against many organisms including some emerging pathogens
- May prevent GVHD and other wbc related adverse events

Disadvantages

- May not be effective against all organisms
- May not be 100% effective even against sensitive pathogens
- Current technologies are not applicable to all types of transfusion products
- May have toxicity due to residual compounds
- May damage the transfusion product
- May lead to alloimmunization by neoantigens
- May cause unexpected adverse events

Recommendation of the HHS Advisory Committee on Blood Safety and Availability (ACBSA) Regarding Pathogen Reduction

- At a meeting in January 2008 the ACBSA recommended that the Department should:

  “Adopt as a high priority the urgent development of safe and effective pathogen reduction technologies for all blood transfusion products and implementation as they become available”

- FDA fully supports the ACBSA recommendation through its evaluation of Pathogen Reduction Technologies

配布につき、FDAの了解済み。

Benefits of Pathogen Reduced Products Should Outweigh the Risks

Benefit =

Reduction of Current risks:

- HTLV 1/ 2,993,000
- HIV 1/ 2,135,000
- HCV 1/ 1,930,000
- WNV 1/ 350,000
- HBV 1/ 277,000
- Sepsis 1/ 86,000[1]

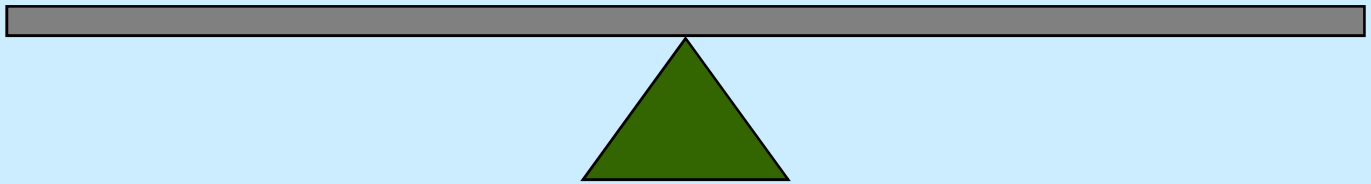
Reduction of future risks:

- Emerging pathogens 1/?????

Tolerable Risk

Toxicity, adverse events should be much less than the expected benefits

<< 1/86,000



1) Eder, A. F. et al. Transfusion 2009, 49:1554-1563

Determination of the Risks Associated with Pathogen Reduced Components

- Pre-clinical evaluation
- Clinical trials in healthy volunteers
- Pivotal evaluation of efficacy and safety through clinical trials in transfused patients
  - Prospective, randomized, blinded clinical trials of PR treated vs. conventional transfusion products
    - Platelets
    - Red cells
    - Plasma

Phase III Clinical Trials of Pathogen Reduced Red Cell Products

Cerus S303 and Vitex pen 110

- Patients developed antibodies to treated red cells
- Both sponsors voluntarily halted their trials

Benjamin, R.J., ISBT Science Series (2006) 1, 222-226

Clinical Endpoints that Reflect Efficacy and Safety of a Platelet Transfusion Product

- Efficacy
  - Transfusion response (corrected count increment, (CCI)
  - Transfusion frequency
  - Bleeding Frequency (Grades 2-4)
- Safety
  - Adverse events
  - Alloimmunization

Clinical Trials of PR Platelets in Thrombocytopenic Patients

- Prospective studies
  - Sprint and Eurosprite trials (Cerus)
  - Hovon 86 (Dutch Blood Service)
  - Mirasol trial (Caridian)

- Surveillance studies on routine use of PR platelets
  - France and Belgium

Pathogen Reduced Platelets Have Lower Corrected Count Increments (CCI)

Clinical Trial	Patients in study	% of plasma stored platelets CCI at 1 hr	P value
SPRINT [1, a]	**645**	**-31%**	**< 0.001**
HOVON [1, b]	**184**	**-31%**	**<0.0001**
MIRASOL [2, c]	**118**	**-31%**	**<0.0001**

1 = UVA/psoralen 2 = UVB/riboflavin

a = McCullough, J et al Blood. 2004 Sep 1;104(5):1534-41.
b = Kerkhoffs JL et al. Br J Haematol. 2010 Jul;150(2):209-17
c = Goodrich et al. Transfusion, May 2010

Hemostatic Efficacy for UV A/psoralen (Intercept) Treated Platelets

SPRINT study	Control platelets	Pathogen reduced platelets	p
Proportion of pts with Grade 2 bleeding	58.5%	57.5%	NS for inferiority
Days of Grade 2 bleeding	2.5	3.2	0.023
% patients with Grade 2-4 bleeding	34	43	0.02

HOVON study	Control platelets	Pathogen reduced platelets	p
% of patients with Grade 1-3 bleeding	19	32	0.034

Hemostatic Efficacy for UVB/riboflavin (Mirasol) Treated Platelets

MIRASOL study	Control platelets	Pathogen reduced platelets	p
% of patients with Grade 2-4 bleeding	15	30	NS

Adverse Events Reported in the SPRINT Study

- 898 adverse event types were reported by blinded observers
- 11 adverse event types were different with statistical significance….all went against the treatment arm
- 4 of the 11 were clinically significant Grade 3 and 4 events:
  - Hypocalcemia, Syncope, Pneumonitis, Acute Respiratory Distress Syndrome (ARDS)

Snyder E et al. Transfusion. 2005 Dec;45(12):1864-75

ARDS Rates in the Treatment vs. Control Arms of the SPRINT Study

Snyder E et al. Transfusion. 2005 Dec;45(12):1864-75

<u>Prospective</u> and blinded evaluations during the clinical trial

	Intersol (PR) platelets	Control platelets	p value
Patients (N)	318	327	
ARDS	**5**	**0**	**0.03**

<u>Retrospective</u> review of medical charts by a blinded expert panel

	Intersol (PR) platelets	Control Platelets	p value
Patients (N)	78	70	
Total Acute Lung Injury (ALI)	19 (6.0%)	16 (4.9 %)	0.60
ARDS	**12 (3.8%)**	**5 (1.5%)**	**0.09**
ALI, non-ARDS	7 (2.2%)	11 (3.4%)	0.48

Can adverse event signals captured in a prospective, randomized, controlled and blinded study be evaluated through a passive adverse reporting study?

- France and Belgium have been using pathogen reduced platelets for several years
- Adverse events on transfused patients are reported through a passive hemovigilance reporting system
- Frequency of reporting of adverse events is much lower than what was reported in SPRINT trial
- There is no active control group to identify events specifically related to PR platelets

配布につき、FDAの了解済み。

Comparison of Adverse Event Reporting in the SPRINT Trial vs. European Hemovigilance Studies

	SPRINT Phase 3 US study		Osselar et al. Transfusion 2008 Cerus plts 2005-2007 Hemovigilance		Osselar et al. Vox Sang 2008 Cerus plts 2003-2005 Hemovigilance	
	Per transfusion	Per patient	Per transfusion	Per patient	Per transfusion	Per patient
N	2678	318	5106	651	7437	1400
% stem cell transplant patients		78		7.2		8.6
% of pts with any reaction		99.7	1.1	6.4	0.9	3.2
% of plt related reactions	3.0	26.0	0.8	4.9	0.7	2.8
% of plt with serious reactions		27.0	0.1	0.15	0	0

Summary and Conclusion

- Pathogen Reduction of labile blood products could improve blood product safety, especially for platelets, but should not add greater risks
  - Clinical trials with Pathogen Reduced red cells have demonstrated antibody generation
  - Clinical trials with Pathogen Reduced platelets have demonstrated decreased efficacy and associated adverse events including acute lung injury in the SPRINT trial.
  - These reports raise concern that the benefits of current pathogen reduction technologies may not outweigh the risks
- Further clinical trials of current technologies are needed to resolve FDA's concerns over decreased efficacy and increased adverse events seen with Pathogen Reduced platelets