HCV TREATMENT IN PATIENTS WITH INHERITED BLEEDING DISORDERS

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Background

- Forum for Collaborative HIV Research held meeting on “HCV DRUG ACCESS FOR PEOPLE WITH BLEEDING DISORDERS” on 10/17/2011
- Factor concentrates used prior to 1987 led to extremely high prevalence (80-100%) of HCV in patients with inherited bleeding disorders
  - Many coinfected with HIV (1978-1985)
  - Population is aging and many have liver-related morbidities

DISCUSSION TOPICS

- HCV TREATMENT TRIALS
  - Current Literature- LIMITED
  - Are HCV responses in Patients with Inherited Bleeding Disorders Different?-PROBABLY
  - Factors Limiting Access
- STUDY DESIGN CONSIDERATIONS
- SAFETY ISSUES

TREATMENT OF HCV
Patients with Inherited Bleeding Disorders

Author	Reference	N	Treatment	Other	SVR
Zhang	Haemophilia 2010	22 (all HIV+)	PEGIFN		41%
Alavian	Liver International 2010	367 (Naïve/Experienced)	PEGIFN + Riba	29% Non-1,4	61% 43% Among Prior Non-responders
Mancuso	J Thromb Haemost 2009	34 (all HIV+)	PEGIFN + Riba (WB)	63% Non Genotype 1	44%
Denholm	Haemophilia	13 (all HIV +)	PEGIFN + Riba (WB)		8%
Rahmani	Haemophilia 2009	103	IFN + Riba	70% Non Genotype 1	56.3%
Katsarou	Acta Haematol 2008	50	PEGIFN + RIBA		40% 58% HIV- 10.5% HIV+
Maor	Haemophilia 2008	43	PEGIFN or IFN + Riba		46% (PEG group) 37% Geno 1
Mancuso	Haematolog 2006	64 (all HIV neg)	PEGIFN + Riba (WB)	66% Genotype 1	63%
Santagostino	Transfusion, 2004	34	IFN + Riba (WB)		41%
Hanabusa	CID, 2002	30	IFN alfa 2a (9 MU)	56%	40% HIV- 33% HIV+
Fried	Hepatology2002	113	IFN alfa + riba (1000)	32%	29%
Schulman	Haemophilia, 2002	61	IFN alfa 2b + riba		41% 22% geno 1
Burton	Eur J Gastro Hepatol	58	IFN		14%

<800 Patients in Multiple Regimens and with Treatment Naïve/Experienced & HIV

How Are Patients with Inherited Bleeding Disorders Different?

- Genotype Change
- Quasispecies Complexity and Polymorphic Expression at Resistance Sites
- Immunologic Responsiveness

SAFETY ISSUES

- Liver Biopsy- Safe but Expensive
- Inhibitors- Significance unknown

CLINICAL TRIALS
Design Options for Consideration

- TREATMENT TRIALS- HOW
  - Permit patients to enter planned trials
    - Pros
      - Special trials not needed
    - Cons
      - High cost of entry biopsy or ability to use poorly validated non-invasive markers
      - Unclear whether differences in population affect outcome
      - Limited ability to gather safety data due to low enrollment in any one trial
  - Inherited Bleeding Disorder Only Large Multicenter Trials (300-500 patients)
    - Pros
      - Opportunity to focus on special population
      - Comparison with non-hemophilic arm would definitively address questions of comparability
    - Cons
      - Limited qualified sites
      - Costly for relatively small and heterogenous population
        - » Treatment naïve vs. Experienced; HIV+ vs HIV-
  - Targeted Small Trials (1-3 center/20-50 patients)
    - Pros
      - Safety
      - Intense sampling, dynamic modeling

Barriers to Trial Enrollment

- Lbx- Not a barrier per FDA and EMEA
- Heterogeneity of Population
- Distrust and fear of side effects
- Inclusion/Exclusion criteria like PTT

Opportunities

- Enrollment in current/planned trials
- Targeted trials
- ?Orphan drug status
- National registry

CONCLUSION

- Treatment of HCV in patients with inherited bleeding disorders has not been adequately studied
- Limited evidence raises the possibility that unique biological factors could influence outcomes
- Study designs should attempt to answer key questions in the most efficient manner
  - A mix of small and enrollment in larger studies might permit evaluation of key issues
  - Opportunities exist for extension of label