Setting the Stage

JAMIE ELLEN SIEGEL MD

- TREATER
- HTC DIRECTOR
- SPECIAL HEMOSTASIS LABORATORY DIRECTOR
- COMMUNITY ORGANIZATION ADVISOR
- MEDICAL DIRECTOR, DEVELOPMENT
- FACULTY, COURSE IN PHYSICIAN-PATIENT COMMUNICATION
- FAMILY MEMBER WITH A BLEEDING DISORDER

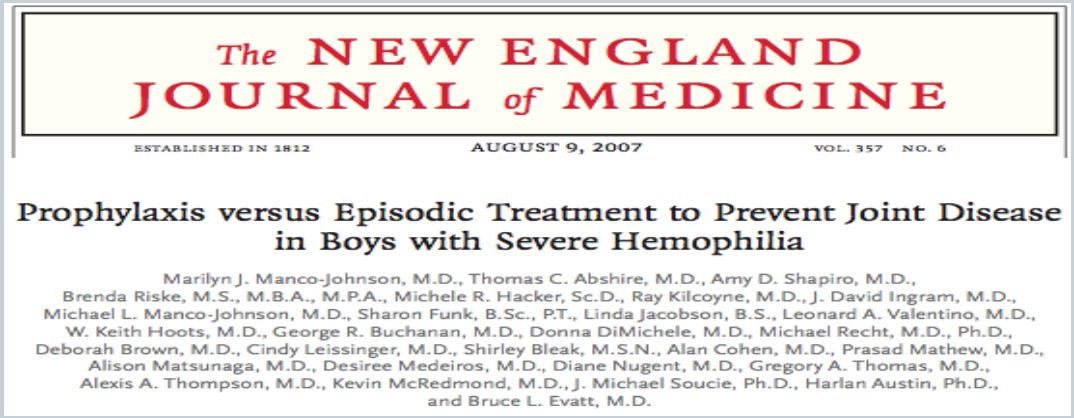
Setting the Stage – When did this all happen?

- HIV 1978 – 1985
- HCV in the blood supply (in the USA) until 1990
- Until 1985 in factor concentrate (26 years old and up)

- By 1982, 73% of persons with hemophilia A at HTCs had received lyophilized concentrates
- By 1982, 54% of persons with hemophilia A were on home therapy

Setting the Stage - Background

- HIV Therapy - ACTG
- Recombinant Factor/Home Care Companies
- Joint Disease Prevention: Joint Outcome Study (JOS)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 9, 2007 VOL. 357 NO. 6

Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia

Marilyn J. Manco-Johnson, M.D., Thomas C. Abshire, M.D., Amy D. Shapiro, M.D., Brenda Riske, M.S., M.B.A., M.P.A., Michele R. Hacker, Sc.D., Ray Kilcoyne, M.D., J. David Ingram, M.D., Michael L. Manco-Johnson, M.D., Sharon Funk, B.Sc., P.T., Linda Jacobson, B.S., Leonard A. Valentino, M.D., W. Keith Hoots, M.D., George R. Buchanan, M.D., Donna DiMichele, M.D., Michael Recht, M.D., Ph.D., Deborah Brown, M.D., Cindy Leissinger, M.D., Shirley Bleak, M.S.N., Alan Cohen, M.D., Prasad Mathew, M.D., Alison Matsunaga, M.D., Desiree Medeiros, M.D., Diane Nugent, M.D., Gregory A. Thomas, M.D., Alexis A. Thompson, M.D., Kevin McRedmond, M.D., J. Michael Soucie, Ph.D., Harlan Austin, Ph.D., and Bruce L. Evatt, M.D.

- Impact on HCV
  - Forgotten disease?

UDC* Data: October 13 2011

Severe: Hemophilia A/B 7634/1,414	**Moderate: Hemophilia A/B 2,697/1,479**	**Mild: Hemophilia A/B 4,055/1,184**
Hepatitis C Positive: 3,207 (**43.9%**)/660 (**48.6%**)	950 (**36.5%**)/420 (**29.8%**)	993 (**25.6%**)/266 (**23.3%**)
History of Hepatitis C Treatment: 642 (**20%**)/150 (**22.7%**)	195 (**20.5%**)/94 (**22.4%**)	261 (**26.3%**)/75 (**28.2%**)
HIV positive: 1,385 (**19%**)/166 (**12.3%**)	248 (**9.6%**)/49 (**3.5%**)	140 (**3.6%**)/23 (**2.0%**)

*UDC - Universal Data Collection, CDC

UDC Data: October 13 2011

VWD Type 1: 5,133	**VWD Type 2: 656**	**VWD Type 3: 339**	**Other: 1,753**
Hepatitis C Positive: 173 (**3.5%**)	72 (**11.5%**)	97 (**29.4%**)	139 (**8.4%**)
Received Treatment for Hepatitis C: 34 (**19.6%**)	16 (**22%**)	17 (**17.5%**)	37 (**26.6%**)
HIV positive: 6 (**0.1%**)	4 (**0.6%**)	6 (**1.8%**)	10 (**0.6%**)

UDC Data – What we don't know

- Of those treated, is there an age group (or more than one age group) that is under-represented?
- Of those who received treatment for HCV, how many are co-infected?
- Of those patients with inhibitors, what is the rate of HCV? Have these patients been less likely to receive treatment because of risk of biopsy?
- Within the "other" category, are there specific bleeding disorder groups that need to be identified?

Setting the Stage - Perspectives

- The Hemophilia Community
  - Multiple levels of interaction
    - High expectations
  - Adult patients vs. Children (what about the teenagers/young adults?)
  - Medical Providers
  - Industry & Home Care Companies
- Health Care Environment
  - RVU* requirements vs. Comprehensive Care
  - Management of public service grants, budgets, research efforts, and our patients
  - Health care cost containment / Medical home

*RVU - relative value unit

Setting the Stage - Perspective

- Need to trust but ……
  - Historic context
  - Iatrogenic infection
- Need for medical background to advocate for self but….
  - Lacking medical training
- Wish for independence, but …….
  - Joint disease, HIV, HCV …….

Setting the Stage – Painful realizations

- For some, factor concentrate was life-saving
- For others, it killed
- For most, it carried both the significant benefit & the complications

- But, this does not include those persons with bleeding disorders who have only been exposed to recombinant or virally inactivated products

Setting the Stage - What is needed now

- Assessment of the current options
- Evaluation of potential obstacles
- Therapeutic advances
- Recognition of the risks in drug development

- Identify if there are issues specific to the bleeding disorders community

UKHCDO guidelines on the management of HCV in patients with hereditary bleeding disorders 2011

J. T. WILDE,* D. MUTIMER,* G. DOLAN,† C. MILLAR,‡ H. G. WATSON,§ T. T. YEE¶ and M. MAKRIS**

- All patients with bleeding disorders who received blood products before 1992 (age 19+) and those who received factor concentrates before 1985 (age 26+)
- It is likely that there are a significant number of patients with mild disorders who have not been identified
- Direct histological examination of liver remains the gold standard
- Occurrence of significant hemorrhage should be no greater than for those with normal coagulation (provided they do not have a factor specific inhibitor/antibody -JS)
- Liver histology is not essential to make treatment decision but is needed to guide long term management

UKHCDO guidelines on the management of HCV in patients with hereditary bleeding disorders 2011

J. T. WILDE,* D. MUTIMER,* G. DOLAN,† C. MILLAR,‡ H. G. WATSON,§ T. T. YEE¶ and M. MAKRIS**

- Pharmacologic treatment is no different for those with or without an underlying bleeding disorder
- Current standard is pegylated interferon and ribavarin combination therapy (unless with liver failure)
- In a meta-analysis overall SVR 61% if HIV negative, 45% for genotype 1 and 79% for non-1 genotypes in those with hemophilia
- HCV RNA in all HIV positive patients
- If on ribavirin, consider adjusting HAART regimens to exclude
  - zidovudine (severe anemia)
  - didanosine and stavudine (lactic acidosis)
  - abacavir (potential inhibitory effect)

UKHCDO guidelines on the management of HCV in patients with hereditary bleeding disorders 2011

J. T. WILDE,* D. MUTIMER,* G. DOLAN,† C. MILLAR,‡ H. G. WATSON,§ T. T. YEE¶ and M. MAKRIS**

- Indications for liver transplantation no different for those with or without a bleeding disorder
- Vaccination for HAV and HBV needed for all
- Extrahepatic manifestations that may be more of an issue for patients with a bleeding disorder – ITP

Role of the Hemophilia Treater

- Identify a good hepatologist
- Guide the hepatologist regarding the underlying bleeding disorder (ie., inhibitor vs. no inhibitor)
- Be sure to screen for HCV in all patients who potentially have been exposed
- Remember the history of how our patients contracted HCV

Treatment Use of Investigational Drugs - FDA

- Investigational products are sometimes used for serious or life-threatening conditions either for a single subject or group of subjects
- There is a mechanism when no satisfactory alternative treatment exists and subjects are generally willing to accept greater risks
- Expansion of access without compromising the protection afforded to human subjects or thoroughness and scientific integrity of product development and marketing approval

Setting the Stage – For Discussion

- Availability of additional information from the UDC database
  - Age, co-infection, presence of specific factor inhibitor & other factors influencing decision regarding treatment and treatment effectiveness
  - In those with an inhibitor, rate of HCV infection and percentage having liver biopsy
  - Within the "other" category, are there specific bleeding disorder groups that need to be identified?
- Determination whether there are differences in response or relative contraindications to therapy in the bleeding disorder population

Setting the Stage – For Discussion

- Expanded access for patients with bleeding disorders
  - Is this still an important need? If so,
  - How to best proceed with clinical trials in this subgroup
    - Include those who are co-infected? Have inhibitors?
    - Identify young men (and possibly women) for outreach
    - Decision regarding subgroups or all inclusive for those with bleeding disorders
- Parallel evaluation of HCV needs as compared to those conditions that have met criteria for expanded access