
Rare Bleeding Disorders: The Physician's Perspective On Therapeutic Needs

Amy D. Shapiro, M.D.
Medical Director
Indiana Hemophilia & Thrombosis Center
Indianapolis, Indiana

Overview

- Definition and background information
 - Data on some rare deficiencies
- A case in point
- Proposals for moving forward

Definition of Rare Disorder

- Legal definition of a rare disorder in the United States is a disease or condition that affects fewer than 200,000 Americans

Data on FVII Deficiency

- FVII deficiency
 - ~ 1/500,000 population
- Registry data
 - ~ 650* patients identified within registries
 - North American registry for rare bleeding disorders: NARBDR
 - Registry in Europe: Dr. Mariani
- No replacement product licensed for fVII deficiency in United States

* 515 International registry, 135 NARBDR. Unknown if patients duplicated

Data on Rare Deficiencies

- Other deficiencies with potential replacement product
 - FXIII replacement product: Fibrogammin® P
 - Fibrinogen replacement product: Haemocomplettan®
 - Protein C: Ceprotin®
 - FXI: BPL fXI concentrate and Hemoleven® from LFB
 - PAI-1: Amicar® or Cyclokapron®
- Products may not be ideal
- Recombinant replacement product may never be developed
- Other deficiencies so rare to preclude development of a specific replacement product
 - Factor V, X, II, plasminogen, α -2 antiplasmin

Background Information

- Issues in treatment
 - Availability of efficacious product
 - Knowledge of appropriate replacement strategies
- Barriers in development of adequate replacement products
 - Cost of research
 - Cost of clinical trial
 - Limited market
 - Regulatory burden on manufacturer and investigator
- Development of clinical trials
 - Adequate number of patients
 - Not all patients with rare deficiencies are compliant, but still deserve adequate care

Therapy for Rare Diseases: Reimbursement

- Difficult or not able to obtain insurance coverage for therapy
 - Imported for personal use
 - Used off label
- Importation and off-label use not adequate long-term solution
- Given the high price of medications, this issue may become increasingly important as Medicare, Medicaid, hospital budgets etc. are increasingly constrained

Background Information

- Patients with rare deficiencies
 - Limited options for care
 - Standard of care often lower than hemophilia
 - Increased morbidity and mortality

Rolling the Dice with Rare Disorders

- Product licensed in United States but not for this indication
 - Product is available in United States
 - Product is not available in United States
 - Is the manufacturers BLA up to date with the FDA?
- No product licensed in United States for use either on or off label
 - Product licensed outside United States for this indication
 - Product licensed outside United States but not for this indication
- No product in or outside United States for use either on or off label

Rolling the Dice with Rare Disorders: You've Got a Problem

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Ligneous Conjunctivitis

- Rare disease characterized by formation of thick membranes of palpebral surfaces progressing to thick nodular masses that replace normal mucosa
 - May be precipitated by infection or trauma
 - Pseudomembranous lesions may be observed in mucosa of mouth, tongue, nasopharynx, tracheobronchial tree, female genital tract¹
 - May lead to loss of sight, hearing, teeth; sterility, hydrocephalous, dysmenorrhea, chronic sinus or pulmonary disease, death
- Demonstrated to be due to plasminogen deficiency²

1. Schuster V et al. Blood 1997; 90(3): 958-966.

2. Mingers AM et al. Semin Thromb Hemsot 1997; 23(3): 259-269.

Plasminogen Deficiency: A Systemic Disease

■ Plasminogen deficiency manifestations

- Ligneous conjunctivitis¹
- Oral lesions (ligneous gingivitis)²
- Female genitourinary tract³
- Hydrocephalous⁴
- Ear, sinus, tracheobronchial tree abnormalities⁵

1. Schott D et al. N Engl J Med 1998; 339(23): 1679-86.
2. Scully C et al. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001; 91(3): 334-7.
3. Pantanowitz L et al. Int J Gynecol Pathol 2004; 23(3): 292-295.
4. Schuster V et al. Prenat Diagn 1999; 19: 483-487.
5. Chai F & Coates H. Int J Ped Otorhin 2003; 67: 189-194.

Ligneous Conjunctivitis



Schott D et al. N Engl J Med 1998; 339(23): 1679-1686.

Reported Therapeutic Options

■ Topical therapies

- Excision*
- Transplant of amniotic membranes*
- Hyaluronidase
- α -chymotrypsin
- Azothioprine
- Cyclosporin*
- Corticosteroids*
- Heparin*
- Fresh frozen plasma**
- Plasmin
- Plasminogen***

■ Systemic therapies

- Corticosteroids
- Birth control pills**
- Low molecular weight heparin
- Fresh frozen plasma**
- Plasminogen***

* Personal efficacy rating

Ligneous Conjunctivitis



- After treatment with systemic plasminogen concentrate

Schott D et al. N Engl J Med 1998; 339(23): 1679-1686.

A Case in Point

- Patient referred in 2002 with ligneous conjunctivitis
- Literature review revealed Eminase[®] efficacious for local therapy
 - Eminase[®] is fibrinolytic agent containing human plasminogen and streptokinase
 - Licensed in US but no longer marketed or distributed here
 - Available in Europe
- Contacted manufacturer of Eminase[®] who initially seemed willing to supply drug to patient for free
- Contacted FDA to discuss how to proceed
 - Asked to file an IND and reviewed work required to accomplish this from both investigator and manufacturer standpoint

A Case in Point

■ Problems with IND

- Time required of investigator
- Manufacturer must have updated BLA at the FDA (biologics license application)
 - This was not the case with Eminase[®]

■ Everything has a cost

- No funds available to reimburse time
- Manufacturer decides financially not feasible to update data at FDA when potential market for drug does not exist

A Case in Point

- Write a prescription and have patient/physician import personal supply of drug
 - Company did not want to donate drug
 - Cost of drug
 - Fear of legal repercussions in United States
- Send patient to Europe to see another physician and have them prescribe drug
 - Payment for patient travel
 - Payment for drug

A Case in Point

■ In the end

- Plasminogen deficiency is a systemic disease
 - One patient with ligneous conjunctivitis, sinus disease
 - One patient with ligneous cervicitis, infertility, sinus and ear disease, history of ligneous conjunctivitis
 - Two patients with ligneous gingivitis
 - ⊗ One with associated cervicitis, hearing loss, sinus disease
- Optimal treatment is either
 - Medication with demonstrated efficacy that can be used locally in a variety of sites
 - Systemic medication → plasminogen replacement

In Search of Plasminogen

- One report utilized plasminogen concentrate
 - No longer available
- Plasminogen is part of Eminase[®] and is clinical grade
 - Cannot find plasminogen supplier to obtain this one component
- Plasmin presently in clinical trials
 - Manufactured from plasminogen
 - Step at which plasminogen is available not clinical grade
 - Plasmin not efficacious due to inactivation locally in tears by antiplasmins
 - Concern about use of an investigational product for off-investigational use → may derail entire research program
- Make our own plasminogen
 - Cost and financial reimbursement
 - Consistency of product and viral inactivation
 - Legal and regulatory issues

Proposals for Moving Forward

- Form a coalition of agencies with mutual interests
 - NHF
 - ISTH
 - WFH
 - NORD

Proposals for Moving Forward

- Work with FDA and industry to develop mechanisms to allow improved access to therapies
 - Obtain another licensed indication for an already licensed drug
 - NovoSeven for fVII deficiency
 - Obtain a product licensed in another country for use in the United States for which we have no viral inactivated alternative
 - Haemocomplettan®: Fibrinogen replacement
 - Production of a product which does not yet exist
 - Plasminogen or fV concentrate

Proposals for Moving Forward

- Work with FDA and industry to develop mechanisms to allow improved access to therapies
 - Is it possible for FDA and EMEA to harmonize processes?
 - Explore alternative mechanisms of drug importation with FDA

Proposal for Pre-licensure Studies

- Due to rarity of these disorders and lack of universal adequate available therapy, trials such as those performed in hemophilia may not be feasible

Proposal for Pre-licensure Studies

- Pharmaceutical sponsored trial
- Investigator initiated IND process
 - Process may be difficult
 - Can this process be streamlined?
 - Is investigator support available?
- Use of registry data to support license indication
 - Use of registry data should be considered by regulatory agencies
 - Registries encouraged through independent organizations

Proposal for Pre-licensure Studies

- Obtaining orphan drug status based upon therapeutic indication for rare disorder
 - Incentives for obtaining orphan drug status
 - 7 years exclusivity
 - Tax credit of 50% for costs of clinical trials
 - Protocol assistance from FDA
 - Waiver of FDA user fees
 - Access to orphan product research grants for clinical trials
 - Ceridase for Gauchers approved based upon study of 15 patients
 - Peg-ADA approved based upon study of 8 or 9 patients

Proposal for Pre-licensure Studies

- Off label use of currently licensed product
 - Incentive to manufacturer
 - May be eligible SBIR (small business innovative research grant)
 - May be incented by 6 month patent extension if drug investigated in pediatric population even if treatment of rare disorder represents a non profitable group
- Encourage synchronization of European & United States regulatory agencies for rare disorders to prevent repetitive work & increased financial burden on manufacturer

Proposal for Pre-licensure Studies

Minimal Aims for Trials

- Determination of safety
 - Clinically apparent AE's
 - Minimal viral testing if plasma derived products utilized
- Determination of efficacy
- Risk:Benefit ratio
- Some dosing guidelines
- Collection of adequate data to obtain approval through regulatory agencies whenever possible

Proposal for Pre-licensure Studies

- Developed studies for rare disorders should be based upon
 - Declaration of Helsinki
 - ICH Guideline for Good Clinical Practice
- Consistent and verifiable data collection
- Commitment to follow-up

Summary

- Rare disorders have limited therapeutic options
- Patients suffering from rare diseases need access to adequate therapy wherever available
- Clinicians require technical assistance in dealing with manufacturers and regulatory agencies to assure their patients have access to therapies
- Multinational studies may be required to obtain adequate patient numbers

Summary

- Development of multi-organizational clearinghouse or resource center for the purpose of
 - Assisting clinicians
 - Searching for treatment options
 - Protocol development
 - Interfacing with regulatory agencies
 - To find companies that assist with obtaining orphan drug status throughout the world
 - Development and maintenance of listings of
 - Interested private and governmental agencies
 - Manufacturers with potentially effective therapies either licensed or in clinical trials
 - Those companies who may have interest in assuming a product portfolio for a limited indication