Ahead of the Curve – Emerging CF Therapies 2009: Managing Patient Expectations Patients' Case Scenarios

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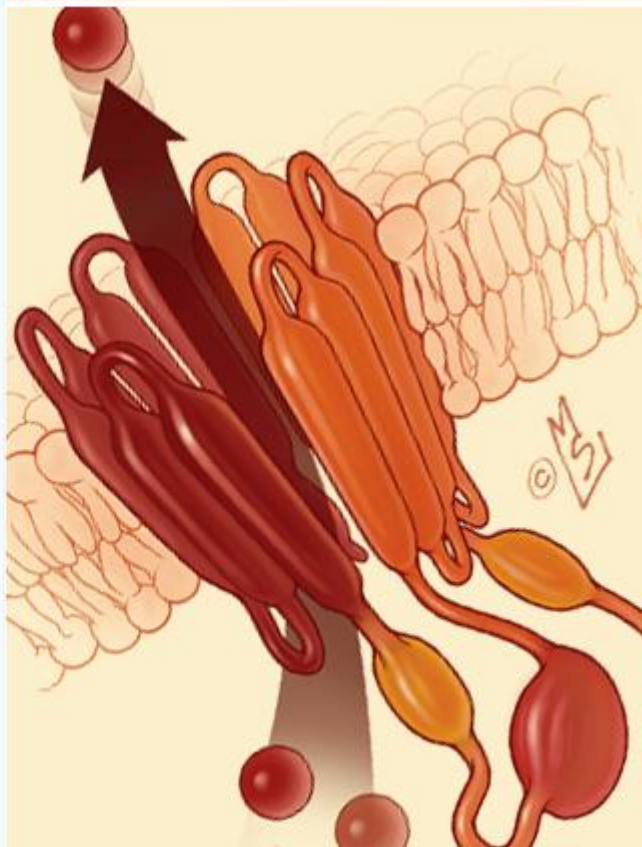

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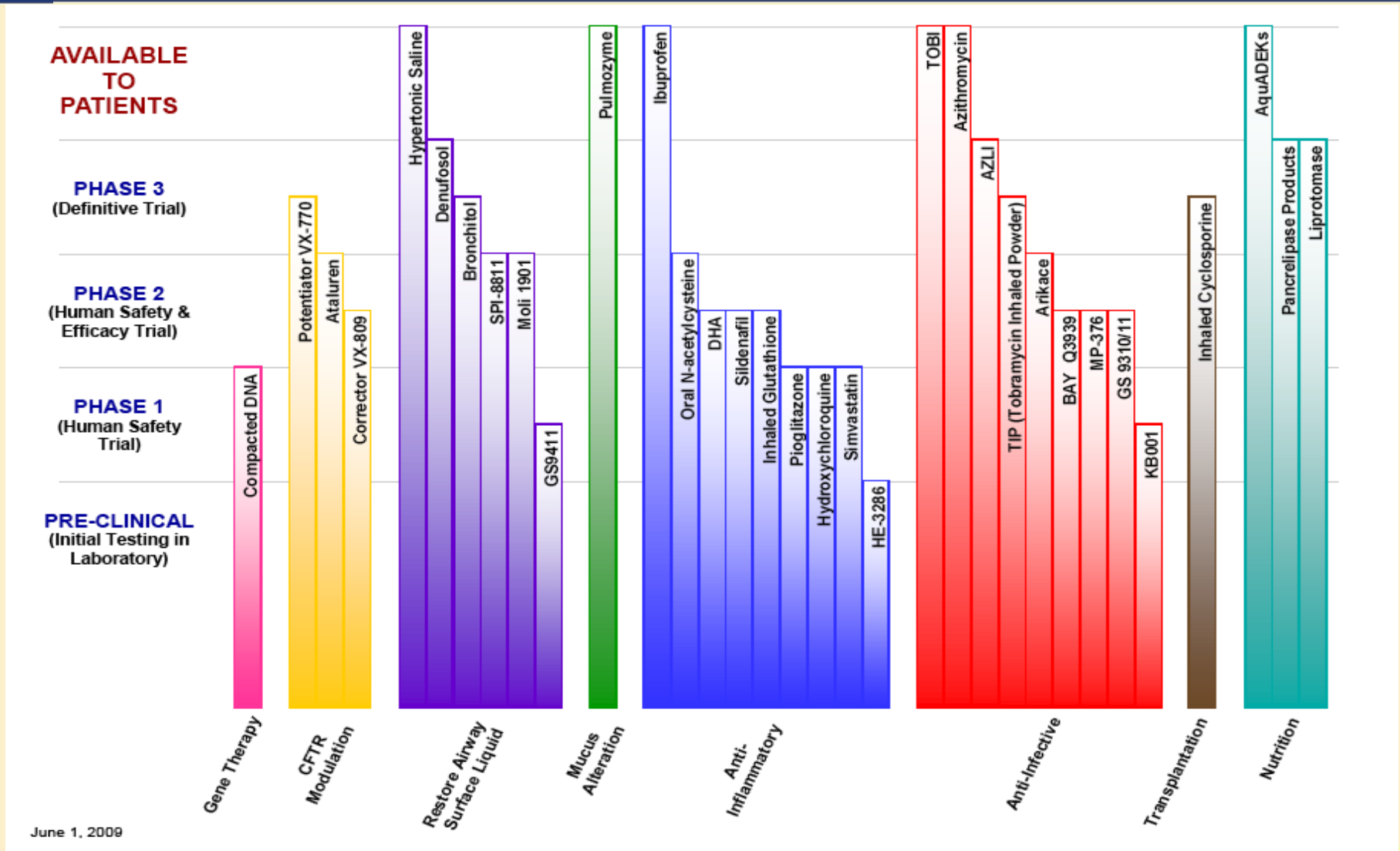
Cystic Fibrosis Foundation Therapeutics Pipeline



Exciting Developments

- New York Times 4/24/2009
  - Dr. Richard Boucher “I do think we will see a cure. …These therapies that hydrate the cystic fibrosis airway surface may be able to stop the progression of the disease in adults. And, very excitingly, in babies you may even be able to prevent it.”

The New York Times

- The New Yorker 5/4/2009
  - CF patient Chrissy Falletti, Vertex trial participant “After twenty-eight days on the medication, her lung function had increased by eighteen per cent over all. Her lung function began to decline within a week of the trial’s end.”

C Sayre. A Brighter Outlook for Cystic Fibrosis Patients. NY Times April 2009
J Groopman. Open Channels. The New Yorker May 4, 2009: 30

Patient Expectations

- No empirical evidence
  - However – expectations are high at this time
  - Enrollment in the VX 770 study very fast
- May be analogous to expectations in the early 90's with the discovery of the gene in 1989
  - Liposomal delivery of CFTR corrected conductance defect in CFTR null/null mice
  - "There seems to be no reason why this approach should not be transferable to humans.."

Rommens, JM et al. Science 1989;245:1059
Kerem, BS et al. Science 1989; 245:1073
Riordan, JR et al. Science 1989;245:1066
Hyde, SC et al. Nature 1993; 362:250

Challenges of Clinical Research in CF

- Population is limited
  - Cannot address more that a handful of important questions
  - Requires many centers increasing study costs
- Important outcomes like lung function decline and exacerbation rate lead to large sample sizes
- Therapies that correct basic defect will require long follow-up times to assess impact
  - Impact of therapy on survival can’t be directly studied

Historical Perspective

- US Therapeutics Development Network (TDN)
  - Inception in 1998 with 8 centers
  - 50 therapeutic clinical trials
  - More than 3,150 participating subjects from the CF pediatric and adult populations during the last 5 years
  - Network expanded in 2009 to 77 centers
- 30,000 individuals with CF in the U.S.
  - approximately 19,000 are cared for at the 77 Therapeutics Development Centers

Enrollment (Interventional Studies Only)

- For current 77 TDN sites (19,000 patients)
  - Educated estimate = 1160
  - Percentage of total patients = 1160/19000 = 6%
    - 2008 percent of patients enrolled at sites ranged from 16% to 1%
- TDN estimates that during the last half of 2009 and all of 2010
  - Approximately 2,300 patients or 12% of the total patients seen at TDCs

Challenge for Investigators

- Enrollment needs are high in CF given number of studies
  - Study site metrics followed closely
  - Investigators overseeing studies competing for the same patients
  - Increased expectations of subjects that new compounds represent the cure

What do we do as clinicians when results are presented?

- In an ideal world, we weigh evidence from multiple sources
  - Systematic Reviews
    - Cochrane Collaboration
    - CFF Systematic Reviews

Example: Summary of Graded Recommendations

Therapy	Population	Evidence	Benefit	Grade
Inhaled Tobramycin	Mod-Severe Lung disease	Good	Substantial	**A**
	Nl-Mild Lung disease	Fair	Moderate	**B**
Recombinant human DNase	Mod-Severe Lung disease	Good	Substantial	**A**
	Nl-Mild Lung disease	Fair	Moderate	**B**
Hypertonic Saline		Fair	Moderate	**B**
Inhaled Corticosteroids	Ages 6-18 yrs	Fair	Zero	D
Oral anti-inflammatory agents		Fair	Moderate	**B**
Macrolide antiobiotics		Fair	Substantial	**B**
Inhaled β_2 Agonists		Good	Moderate	**B**

Flume, PA et al. *AJRCCM*, 2007;176:957

Strong Evidence in CF Challenging to Obtain

- In a recent systematic review of the treatment of an acute pulmonary exacerbation

  No therapy received a grade of A

  Only 2 questions received a grade of B
  - Continued use of chronic therapies during exacerbation
  - Use of airway clearance during exacerbation

  Remainder received grades of C, D, or I

Off-Label use of Medications

- Lack of pediatric studies may increase off-label use
- Inpatient pediatric wards
  - United Kingdom, Sweden, Germany, Italy, and the Netherlands
  - >50% of the children (421; 67%) received unlicensed or off-label medication during hospital stay
- May be more common in US
- No data in CF

Conroy S. et al. BMJ. 2000;320(7227):79

How Much Evidence is Necessary to Apply New Therapies in CF?

- Gap exists between empirical evidence and patient care
  - Patient expectations must be integrated
  - Study results not necessarily apply to individual patients - "what is best for the patient at hand?"
- Remains a balance for clinicians
  - Must do no harm

Tonelli MR. *Respir Care.* 2001;46(12):1435

Challenges in CF

- Can one use novel agents outside study population?
  - Can one extend use down to infants (a population not in the study)?
  - Could it be used in patients with a different genotype?
  - Can agent be used far beyond study window?
  - If it is employed in non-label populations, how does one monitor its use?
  - Can one apply drugs to different severity categories?

Conclusions

- Advances in CF have been dramatic
- Clinical trials remains key to advancing our knowledge
  - Enrollment will need to be high
  - Expectations will need to be managed
- Integrating the results of trials into clinical care will be challenging
  - A challenge that we are fortunate to have