Summary of Responses Regarding the Development of CCR5 Antagonists

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Presentation Outline

- FDA Questions
- Summary of Responses
- Conclusions

Respondents

Abbott Laboratories
AIDS Treatment Action Coalition
Boehringer Ingelheim Pharm.
Bristol-Myers Squibb
GlaxoSmithKline
Human Genome Sciences
InPhenoAG
Merck Research Laboratories
Monogram Biosciences
National Institutes of Health
Pfizer
Progenics Pharmaceuticals
Roche Pharmaceuticals
Schering Corporation
Tibotec

Questions

Safety and Tropism Issues

- Potential immunologic adverse effects that require additional monitoring
- Amount and type of information needed at the time of approval

Questions

Long-term Monitoring

- Feasibility concerns for 5-year follow-up
- Mechanisms to ensure adequate data collection
- Adequate control groups

Questions

- CCR5 antagonists in the antiretroviral armamentarium
- Potential role of tropism and resistance testing in clinical practice
- Additional concerns for pediatric drug development

Safety and Tropism Issues

Potential for increased risk of:

- Infection
- Malignancy
- Hepatotoxicity
- Altered viral tropism

Infection

- Important concern based on mechanism of action
- Δ32 mutation not clearly associated with increase in non-HIV infections
- Wide variation in CCR5 expression without known clinical sequelae

Malignancy

- Theoretical concern of decreased immune surveillance
- Possible increased risk of lymphoma in association with one CCR5 antagonist

Hepatotoxicity

- Development of aplaviroc terminated
- Inherent to CCR5 inhibition vs. drug specific
- CCR5 knockout mice with increase in liver injury in an experimental model of T cell mediated hepatitis

Altered Viral Tropism

- May promote shift to X4-tropic virus
- Difficulty in interpretation of tropism results
- Clinical utility still being defined
- Need to correlate with clinical and virologic outcomes

Long-term Monitoring

FDA request for 5-year follow-up:

- Previously requested for treatment-failure patients only
- Now requesting on all patients

Long-term Monitoring

5-year follow-up challenging:

- Increase in loss to follow-up
  - Loss of interest
  - Mobile society
  - Difficulty complying with multiple protocols
- Subsequent exposure to additional therapies
- Treatment-naïve vs. experienced

Long-term Monitoring

Mechanisms to ensure sufficient data collection:

- Prospective enrollment for long-term follow-up
- Focus on settings where patients already receive their medical care
- Improve compliance by minimizing burden of follow-up
- Use experienced sites with demonstrated commitment to continuity of care

Long-term Monitoring

- Use of established observational cohorts
- “Buy-in” by patients and investigators necessary
- Prospective plan for following patients who move
- Evidence of immunosuppression may be more readily detected in other diseases (i.e., arthritis)

Long-term Monitoring

Data to be obtained:

- Viral load
- CD4+ cell count
- AIDS-defining illnesses
- Non-HIV related infections
- Malignancies
- Survival

Laboratory Testing

- Viral tropism testing may be needed in clinical practice to exclude patients with X4-tropic virus
- Resistance testing may be needed in clinical practice but role remains to be defined
- No change in immunologic response that is known to be unique to CCR5 inhibition
- CD38 measurements for T cell activation may be useful

Resistance Testing

Defining a threshold for phenotypic or genotypic resistance prior to approval may be difficult

- Targeting a novel pathway
- Exploratory analyses would need to be confirmed

Tropism Testing

May not be routine in clinical practice:

- Long turn around time
- Expensive
- Not quantitative
- Cannot identify tropism species at low %
- Predictive value of baseline tropism not established

Antiretroviral Armamentarium

- Will be defined by the clinical trials that provide the basis for approval
- Theoretically, may be more beneficial in treatment naïve or post-exposure prophylaxis (higher proportion with CCR5-tropic virus)

Pediatric Issues

Effect of CCR5 inhibition in children unknown

- Effect on developing immune system
- Response to vaccines

Pediatric Issues

Until additional safety data available, pediatric studies should be limited to:

- Highly treatment-experienced
- CCR5-tropic virus
- Limited treatment options

Unacceptable Study Designs

Study designs considered unacceptable to the HIV community

- Use of suboptimal therapy (i.e., prolonged monotherapy)
- Restrictions placed on subsequent treatment
- Termination of therapy upon completion of study

Summary of Responses

- 5-year follow-up will be challenging
- Enrollment in long-term trials should be prospective
- Use sites already providing medical follow-up
- Deferment of pediatric studies except in special situations may be appropriate
- No consensus on the role of tropism and resistance testing in clinical practice
- No specific immunologic parameters to follow