Pharmacoepidemiology In Drug and Vaccine Development

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Conflict of Interest Declaration

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Pharmacoepidemiology in Drug and Vaccine Development

Presentation Outline

- Drug and Vaccine Development
  - Role of Pharmacoepidemiology
- Safety and effectiveness assessment
  - Role of Pharmacoepidemiology
Epidemiology is Foundation for Drug and Vaccine Development

“...to understand the Drug or Vaccine, it is necessary to understand the Disease” Harry Guess – Merck Head Epidemiology (1985-2003)

Epidemiology data builds a foundation of understanding the disease and the populations effected by disease

- prevalence, incidence, burden of illness, natural history, risk factors, important co-morbidities and concomitant medications, linking surrogate measures with disease outcomes, validating biomarkers and genetic markers, and understanding prevalence of genotypes and serotypes

# Activities in the Phases of Drug and Vaccine Development

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<tr>
<th>Preclinical Development</th>
<th>I</th>
<th>IIa&amp;b</th>
<th>III</th>
<th>IV/V</th>
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<td><strong>Discovery</strong> - chemical &amp; biological characterization</td>
<td><strong>Ph I studies</strong> healthy volunteers to understand ADME, PK, PD, drug interactions, special groups</td>
<td><strong>Proof of Concept and Dose Ranging</strong> randomized clinical trials - dose(s), efficacy and safety</td>
<td><strong>PhIII pivotal randomized clinical trials</strong> - characterize efficacy and safety</td>
<td><strong>Post-marketing clinical trials</strong> - additional patient subgroups, new indications, combination therapies, endpoint trials</td>
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**Safety & toxicity studies** in animals; formulation development
Pharmacoepidemiology Activities In Phases of Drug and Vaccine Development

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- Descriptive Epidemiology studies to understand disease and population
- Trial planning activities/recruitment issues: selecting RCT design, population, treatment, duration
- Risk management planning; Pharmacoepidemiology studies and analyses to address product safety & understand risks in population with disease
- Linking biomarkers and/or genetic markers to disease outcomes, to understand susceptibility to adverse events or lack of efficacy
Epidemiology in Drug and Vaccine Development

Presentation Outline

Drug and Vaccine Development
  – Role of Epidemiology
    - Understand the disease and population
    - Assist in clinical trial design

Safety and effectiveness assessment
  – Role of Pharmacoepidemiology
Understand Herpes Zoster Burden of Illness

Problem: What is the medical need to vaccinate population against Herpes Zoster and at what ages is vaccine most needed?

Study Design: Analyses of patient level electronic medical record databases in two United States patient care databases capturing physician visits, medication use and hospitalizations due to Herpes Zoster
Herpes Zoster (HZ) Incidence by Age and Sex

- Increasing incidence with age in both men and women
- Average of 3 ambulatory visits per Herpes Zoster patient
- > 70% of HZ cases receive antiviral drugs
- 4% of HZ cases hospitalized
Burden Herpes Zoster in Immunocompromised Patients

Problem: What is the incidence of Herpes Zoster in Solid Tumor (STM) and Hematological Malignancy (HM) populations and how does that compare to general population?

Study Design: Retrospective cohort study (N=13,759) with complete chemotherapy data in Kaiser Permanente Northern California, US enrolled from 2001-2005

- Chart review for all cases and adjudication to validate zoster cases
Compared to individuals of similar age and sex in the general population, rates of HZ were approximately 5-fold higher in patients with HM and 1.8-fold higher in patients with STM.
Planning Type 2 Diabetes Clinical Trials

Purpose: Describe prevalence and incidence data & progression rates for Type II Diabetes Mellitus for clinical trial planning

Data Source: Diabetes Atlas, International Diabetes Federation

Source: Diabetes Atlas, IDF, 2003

Prevalence Estimates of Diabetes

- < 2%
- 2% – 5%
- 5% - 8%
- 8% - 11%
- 11% - 14%
- 14% - 17%
- 17% - 20%
- > 20%
Determine Best Duration of Treatment for Trial using Metformin and Sulfonylurea in T2DM

Data: Electronic Medical Records in UK

Time to A1c > 8% with MF+SU

- Baseline A1c
  - >10%
  - 9-9.9%
  - 8-8.9%
  - 4-7.9%

Trial duration of 2 years duration likely sufficient to show differences in durability

Determine Percent of Patients using Insulin and Sulfonylureas for a Planned Type 2 Diabetes Mellitus Trial

Data: Electronic Medical Records database from UK

In an insulin combo trial, excluding patients on SU would only minimally impact recruitment
Epidemiology in Drug and Vaccine Development

Presentation Outline

- Drug and Vaccine Development
  - Role of Epidemiology
- Safety and effectiveness assessment
  - Role of Pharmacoepidemiology
Development of Pharmacoepidemiology

Safety is the driving force for development of pharmacoepidemiology as a unique discipline.

“Pharmacoepidemiology is the study of the use of and the effects of drugs and vaccines in large numbers of people.”*  

– The realization that rare adverse effects of drugs or vaccines could be better understood through the application of epidemiological research methods gave rise to pharmacoepidemiology

Pharmacoepidemiology in Safety Assessment and Evaluation Pre-Approval

- Understand the types of adverse events occurring in the randomized clinical trials for registration.
- Conduct systematic reviews of literature and studies to understand population to be treated:
  - Types of co-morbidities
  - Use of other medications
  - Risk factors for adverse events
  - Background rates of potential and identified adverse events that might be expected
Risk Management Planning

- Evaluation and management of identified adverse events from the randomized clinical trials
  - Risk Management Plans
  - Risk Evaluation and Mitigation Strategies

- Evaluate potential adverse events based on knowledge of the disease and the drug

- Respond to regulatory agency questions about:
  - Potential and identified adverse events
  - Epidemiology of the disease

- Prepare for meetings with regulatory agencies with epidemiology data on the disease and background rates of adverse events in the disease population
Examples of Questions

- Impact of in-hospital insulin use on hypoglycemia, length of stay, in-hospital mortality and in-hospital ischemia events in insulin users versus non-users
- Incidence and prevalence of hemorrhagic and necrotic pancreatitis in T2DM and non-T2DM patients
- Prevalence of renal insufficiency among patients with osteoporosis
- Incidence and prevalence of scleroderma in women with osteoporosis
- Incidence of cancer by cancer type in patients with HIV versus general population
Pharmacoepidemiology in Safety Assessment and Evaluation Post-Approval

- Further understand product safety in larger populations - conduct post-approval safety and drug utilization analyses and studies
  - Patterns of drug utilization - who is using product and how product is used in real world use
  - Understand safety in subgroups and special populations
  - Understand risk factors for adverse events
  - Safety relative to other drugs for the same indication
  - Determine new or very rare adverse events
  - Understand risk as compared to benefit
  - Develop reliable methods and study designs to increase reliability of observational studies
**Problem:** Fever (≥102°F) reported in clinical trials after MMRV at a higher rate than MMR+V in 12-23 Month Olds

**Regulatory Commitment to study MMRV post-authorization**

- **Primary Objective - Febrile seizures (FS)**
  - Incidence 5-12 days after first dose of MMRV
  - Other protocol time windows include 0-4 and 0-30 days
- **Secondary Objective - General safety**
Study Design & Population

- Observational cohort study - conducted and data analyzed at Kaiser Permanente Southern California (KPSC)
- Target of 25,000 children for primary objective
  - 1st dose of ProQuad® between 12-60 months of age
  - MMR & varicella disease/vaccination negative children
- Matched Comparison Group: MMR+V
- Children with health care contact in outpatient, ER, or hospital setting - all ICD-9 diagnosis codes
- All study results reviewed & interpreted by external, independent Safety Review Committee (SRC)
- All cases of Febrile Seizure reviewed to determine if Confirmed case by independent, blinded external physician group
Importance of Chart Review and Adjudication in Database Study

Coding practice changes at KPSC from 2004-2007 resulted in documented increase in seizure code use over study period

- Adjudication likely removed most of this bias, improving validity of results

Adjudication Committee (3 KPSC Physicians)

- Reviewed medical records data using Brighton Collaboration definition for FS
- The adjudication process identified “confirmed FS”
Kaplan-Meier Curves - MMRV and MMR+V

Unconfirmed Febrile Seizures

Days after Vaccination

Cumulative Incidence

\[ p = 0.0221 \]
Kaplan-Meier Curves - MMRV and MMR+V Confirmed Febrile Seizures

Cumulative Incidence vs Days after Vaccination

- MMR+V
- MMRV

\[ p = 0.6617 \]
Summary

Assure that Pharmacoepidemiology is well integrated into drug and vaccine development

- Understand the disease, and population for design of clinical trial program (prevalence/incidence, population, natural history, risk factors, biomarkers, genetic markers)

- Understand safety and manage risks
  - Pre-approval - risk management planning, risk mitigation strategies, understand underlying risk of population that will use the product after product approval
  - Post-approval – further understand risks and benefits of product by conducting well designed safety and/or effectiveness studies
“...to understand the Drug, it is necessary to understand the Disease” Harry Guess

"It is more important to know what sort of person has a disease than to know what sort of disease a person has"

Hippocrates