Innovative therapies call for innovative methods to support regulatory decision making

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Declaration of interests and disclaimer

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- Personally received fees from Atrium, the Danish Pharmaceutical Industry Association for teaching at pharmacoepidemiology courses
- Professorship in pharmacovigilance supported by the Novo Nordisk Foundation
- Member of the WHO International Working Group for Drug Statistics Methodology
- Member of the European Network of Centers in Pharmacoepidemiology and Pharmacovigilance (ENCePP) Working Group 2 on Transparency and Independence
- Views and opinions expressed in this presentation are entirely my own and I am not speaking on behalf of any organisation or institution
Background – some developments shaping the future of evidence generation for regulatory decision making

• The concept of a drug has changed
  • Chemicals -> Biologicals -> Advanced Therapy Medicinal Products (ATMP)

• The concept of post-marketing assessment has changed
  • Spontaneous Reporting System -> Post-authorisation Safety and Effectiveness Studies (PASS and PAES)

• The processes of evidence generation is changing
  • From reactive to proactive approaches
  • From epidemiological studies to surveillance

• Increasing use of ‘real-world’ healthcare data
  • For pharmacoepidemiological studies evaluating safety and effectiveness
  • For proactive surveillance and signal detection
Increasing interest in RWD and use of RWD

Examining the Impact of Real-World Evidence on Medical Product Development: A Workshop Series

Workshop 3: Application

Workshop Briefing Materials

12 October 2016
EMA/PRCO/CAT/CMDh/PRAC/CHMP/261500/2015
Paediatric Committee (PDCO)
Committee for Advanced Therapies (CAT)
Pharmacovigilance Risk Assessment Committee (PRAC)
Committee for Medicinal Products for Human Use (CHMP)
Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh)

Scientific guidance on post-authorisation efficacy studies
Real-world data and evidence in Pubmed

Number of papers

Search for text string “real-world” or “real world” combined with “data”, “safety”, “effectiveness”, “efficacy”, “evidence”, “outcomes”
Challenges with innovative and advanced pharmaceutical products

- Evidence on efficacy based on small, possibly non-randomised clinical trials: Desire to supplement with observational effectiveness studies
- Few patients treated during clinical development, possibly even in the post-authorisation setting
- Rare adverse events of interest, long-term follow-up desirable (chronic effects, permanent changes in the immune system, cancer)
- Larger populations needed: international patient registries (diagnosis or treatment based), and/or multi-database network studies
- Need for timely evidence: flexible data access, rapid analytics
Safety of immune checkpoint inhibitors used in treatment of metastatic melanoma

- Multiple drugs in sequence and/or combination is used
- A number of immune-related adverse effects monitored for
- Patients closely followed during the first two years, thereafter longer intervals
- Therapeutic progress leading to an increasing number of long-term survivors
- Little is known on
  - The frequency of (re)occurrence of immune-related adverse effects, e.g. endocrine disorders, autoimmune diseases
  - Association with different drugs and treatment patterns
  - Risk factors for developing these adverse effects
  - Patient groups with need for intensified clinical monitoring
- Proposal: create a proactive surveillance system
  - Start with an epidemiological cohort study
  - Proceed with sequential surveillance
Record linkage between clinical databases on malignant melanoma and Danish national healthcare registers

**QUALITY/RESEARCH DATABASES:**
- DMD AND DAMMED
  - Demographics
  - Histology
  - Date of diagnosis (primary, metastatic)
  - Date of first visit
  - Disease stage
  - Lab values
  - Performance status
  - Brain metastases
  - Immunosuppressive medications
  - Significant comorbidities
  - Autoimmune diseases
  - Other malignancies
  - Measurable disease
  - Toxicities

**CDM DATABASE**
- Study population
- Clinical events
- Drug exposures
- Measurements
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**DICTIONARIES**
- Clinical events
- Drug exposures
- Clinical data
- Variable definitions
- Analysis parameters

**ANALYTICS**
- Analysis datasets
- Results datasets
- Table output
- Graph output
- Automated reports

**NATIONAL HEALTHCARE REGISTERS**
- Prescription register
- Cancer register
- Patient register
- Laboratory database
- Hospital medication register
- Cause of death register
- Population register

**Person data linked through unique person ID (Danish person number)**

DMD: Danish Melanoma Database
DAMMED: Danish Metastatic Melanoma Database

CDM: Common Data Model (Nordic Common Data Model for Pharmacoepidemiologic Research)
The case of the CAR-T cells
Example: axicabtagene ciloleucel (Yescarta)

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma


BACKGROUND
In a phase 1 trial, axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, showed efficacy in patients with refractory large B-cell lymphoma after the failure of conventional therapy.

METHODS
In this multicenter, phase 2 trial, we enrolled 111 patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma who had refractory disease despite undergoing recommended prior therapy. Patients received a target dose of $2 \times 10^6$ anti-CD19 CAR T cells per kilogram of body weight after receiving a conditioning regimen of low-dose cyclophosphamide and fludarabine. The primary end point was the rate of objective response calculated as the combined rates of complete response and partial response. Secondary end points included overall survival, safety, and biomarker assessments.

RESULTS
Among the 111 patients who were enrolled, axi-cel was successfully manufactured for 110 (99%) and administered to 101 (91%). The objective response rate was 82%, and the complete response rate was 54%. With a median follow-up of 15.4 months, 42% of the patients continued to have a response, with 40% continuing to have a complete response. The overall rate of survival at 18 months was 52%. The most common adverse events of grade 3 or higher during treatment were neutropenia (in 78% of the patients), anemia (in 48%), and thrombocytopenia (in 38%). Grade 3 or higher cytokine release syndrome and neurologic events occurred in 13% and 28% of the patients, respectively. Three of the patients died during treatment. Higher CAR T-cell levels in blood were associated with response.

CONCLUSIONS
In this multicenter study, patients with refractory large B-cell lymphoma who received CAR T-cell therapy with axi-cel had high levels of durable response, with a safety profile that included myelosuppression, the cytokine release syndrome, and neurologic events. (Funded by Kite Pharma and the Leukemia and Lymphoma Society Therapy Acceleration Program; ZUMA-1 ClinicalTrials.gov number, NCT02348216.)
Clinical evidence: non-randomised study of 111 patients
Based on prespecified rate of response of 20% on the basis of historical data

• Pictures subject to copyright
Challenges of CAR-T cell use in clinical practice

Monitoring CAR-T-Cell Therapies Using the Nordic Healthcare Databases

Torbjörn Callréus¹ • Tarec Christoffer El-Galaly² • Mats Jerkeman³ • Peter de Nully Brown⁴ • Morten Andersen¹
‘Real World Data’ – Nordic healthcare registers

- **Patient Register**
  - Inpatient admission and discharge dates
  - Outpatient contact date
  - Hospital, clinic, county
  - Diagnoses, procedure codes

- **Prescribed Drug Register**
  - Drug, dispensing form, strength
  - Package, amount, dose text
  - ATC code, DDDs
  - Patient and prescriber information

- **Hospital Electronic Records**
  - Clinical information
  - Measurements and lab data
  - Inpatient medical treatment
  - Discharge summary

- **Laboratory data**
  - Date, measurement, value, unit

- **Primary Care Electronic Records**
  - Date of contact, diagnoses
  - Clinical and lab data
  - Weight, blood pressure
  - BMI, smoking, alcohol
  - Prescribed medicine

- **Medical Birth Register**
  - Identity of mother and child
  - Social factors, smoking, snuff
  - Maternal, pregnancy, delivery
  - and infant clinical information

- **Quality registers**
  - Specific diagnoses
  - Disease markers
  - Treatment
  - Age at onset of disease
  - Clinical and lab data
  - Disease severity
  - Risk/prognosis assessment
  - BMI, smoking

- **Cancer Register**
  - Date of cancer diagnosis
  - Type of malignancy, histology
  - TNM staging

- **Sociodemographic Registers**
  - Education, income, employment
  - Country of birth
  - Place of residence

- **Family Register**
  - Identity of relatives

- **Population Register**
  - Dates of Immigration, emigration, death

- **Cause of Death Register**
  - Date of death
  - Causes of death
  - Injury, poisoning, intent
Lack of information on in-hospital treatment – how to retrieve more complete data

- Introducing a specific therapeutic code for CAR-T-cell therapy in the patient registers and promoting its consistent use – validation needed
- Record linkage to hospital-based or regional electronic healthcare record systems or clinical databases with more comprehensive information of treatments
- Establishing a treatment-based registry similar to the quality databases that already exist in several Nordic countries in the area of diabetes mellitus, rheumatic diseases and specific cancers
- Finally, wait for the inpatient medication registers (in Denmark, next year?)
- European Bone Marrow Transplant (EBMT) Registry proposed for post-authorisation follow-up of CAR-T cell therapy
Challenges of pharmacoepidemiology studies
Example: A PASS study conducted over several years

Delays caused by
1. Initial approval of data access
2. Statistical programming
3. Data retrieval
4. Data analysis
5. Report writing
6. Repeat 3-5
The classical approach in pharmacoepidemiology – a series of stand-alone studies
Developing health care data analytics supporting clinical and regulatory decision making

- Identify questions and answers relevant for regulatory decisions
- Data of high validity and quality accessible with short delay
- Standardised and state-of-the-art methods (literature, good research practice guidelines and recommendations)
- Data presentation adapted to regulators’ needs
- Rapid analysis framework using a programming-free dashboard approach
- Data visualisation and reporting tools
The classical approach in pharmacoepidemiology – a series of stand-alone studies

1. **DATA**
   - DATA MANAGEMENT AND ANALYSIS
   - Scientific report or paper

2. **DATA**
   - DATA MANAGEMENT AND ANALYSIS
   - Scientific report or paper

3. **DATA**
   - DATA MANAGEMENT AND ANALYSIS
   - Scientific report or paper
Creating analytic infrastructure (modular programs and interfaces) during data analysis
Rapid analysis framework using analytics infrastructure
Programming free approach using dashboards
Comments to the suggested framework

- Protocol and statistical analysis plan with pre-specified design and analysis needed for regulatory decisions
  - Libraries of standardised and validated definitions of exposure and outcome concepts
  - Analytic metadata saved for each project for documentation and reproducibility
- Analytic metadata transferable between frameworks with corresponding data structure facilitating international multi-database network studies
- Future addition
  - Built-in statistical methods for sequential analyses
  - Modules for sensitivity analyses and probabilistic bias analyses
  - Flexible visualisation framework for data exploration
  - Artificial intelligence and machine learning approaches for exploration and data mining
- Analysis programs need testing and validation (double programming, comparison to existing method libraries: Sentinel, OHDSI, other)
Fascination by data

BIG DATA

REAL WORLD DATA

Where are the

• GREAT METHODS
• RAPID ANALYTIC FRAMEWORKS
• COMPREHENSIVE EVIDENCE GENERATING SYSTEMS
Quality of pharmacoepidemiology research

Question

Answer
Quality of pharmacoepidemiology research

Question

Answer
Quality of pharmacoepidemiology research

- Question
- Data
- Answer
- Methods
Quality of pharmacoepidemiology research

Knowledge needed:
- Regulatory
- Pharmacoepidemiological
- Statistical
- Data science
- Programming
- Data management
- Pharmaceutical
- Pharmacological
- Medical

Question

Data

Methods

Answer
Concluding remarks

• Access to ‘big’ data is not sufficient, methods and their implementation necessary

• Open source analytics software should facilitate
  • Transparency: facilitating testing and comparison with other programs
  • Accessibility: not only for pharmaceutical industry and CROs but also for academic and clinical researchers, regulators, not-for-profit organisations
  • Informed decision of regulators based on evidence on real-world use, safety and effectiveness of medicines
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