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- Director of Master of Pharmacoepidemiology and Pharmacovigilance
- Professor of Clinical Pharmacology, Department of Biomedical Sciences, Faculty of Medicines and Health Sciences, University of Alcalá, Spain
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Understanding pharmacovigilance for biologicals and the current challenges in Spain

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ROUNDTABLE ON BIOSIMILARS SPAIN
Pharmacovigilance, Traceability, Immunogenicity
Understanding pharmacovigilance for biologicals and the current challenges in Spain

Prof. Francisco J. de Abajo
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Clinical Pharmacology Unit
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Roundtable on Biosimilars Spain
Pharmacovigilance, Traceability, Immunogenicity

Contents

• Pharmacovigilance
  – Concept, operational framework
  – Reactive vs. Proactive pharmacovigilance
  – Risk Management Plan

• What is different with biologicals?
  – Immunogenicity
  – The importance of changing the manufacturing process
    • The case of Eprex (Epoetin alfa)
  – Implications for biosimilars

• Challenges and opportunities in Spain
  – Reporting ADRs from biologicals
    • The Spanish Pharmacovigilance System
    • Particular issues for biologicals: traceability
  – Specific strategies in pharmacovigilance of biologicals
    • Limitations of automated databases
      – Hospital-based treatments
    • Registries of persons exposed: BIOBADASER, BIOBADADERM
      – Signal generation, signal evaluation and effectiveness of minimization measures
Pharmacovigilance

- “A public health activity aimed at the identification, quantification, evaluation and prevention of the risks associated with the use of these medicinal products once they are marketed”

Royal Decree 577/2013

Pharmacovigilance operational framework

- Risk Analysis
  - Risk Identification
  - Risk Quantification (Estimation)
  - Risk Evaluation

  Data

- Risk Management
  - Risk minimization and prevention
  - Risk communication

  Decisions

  Evaluation effectiveness of measures

- Actions
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Stakeholders in Pharmacovigilance

- Competent authorities
  - National Pharmacovigilance Systems
- Pharmaceutical companies
- Healthcare professionals
- Consumers/Patients
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Models in Pharmacovigilance

Classical view: the reactive model

Marketing Authorisation
  ↓
Adverse drug reactions
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Reporting ADRs
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Pharmaceutical companies
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Benefit-Risk Evaluation
  ↓
Competent authorities
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Epidemiological Studies
  ↓
Regulatory decisions

Models in Pharmacovigilance

Modern view: the proactive model

Risk Management Plan

Marketing Authorisation
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Pharmacovigilance planning
  ↓
Risk minimization plan
  ↓
Safety specification
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Risk minimization plan
Risk Management Plan

• Aims
  – To anticipate potential safety issues
  – To carry out epidemiological studies
    • Raise signals as early as possible
    • Characterize the ADR (causality, susceptible populations, risk markers,...)
    • Quantify the risk population impact
  – To implement risk minimization measures
    • Including effective risk communication
  – To check the effectiveness of measures adopted

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Biologics

• Complex molecules
• Immune reactions are more likely with biologicals than with simpler chemical products
  – Lack of efficacy for neutralizing antibodies
  – Hypersensitivity reactions
• Immune reactions can occur with changes in the formulation / manufacturing process
  – PRCA associated with subcutaneous Eprex (Epoetin alfa) in chronic renal failure
  • Introduction of new stabilizer (polysorbate 80) + interaction with rubber uncoated plunger


HSA denotes human serum albumin. Epogen is also marketed as Procrit, and Neorecormon as Recormon.

Bennet et al, NEJM 2004; 351: 1403-1408
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Implications for biosimilars

- Immunogenic reactions of biosimilars may be different as those of the reference product
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Batch number required for biologicals

- ADRs associated to biologicals
  - Can be different to other drugs
    - Infectious diseases
    - Cancer
    - Neurological diseases
  - Difficult to identify and evaluate through case reports
  - There is a need for epidemiological approaches
**ADRs associated to biologicals**

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Automated databases

• Many safety issues nowadays are generated or evaluated using automated databases

• BIFAP is an automated database made up of 8 million people attended by general practitioners in Spain
  – The owner is the Spanish Agency for Medicines and Medical Devices
  – Similar to CPRD (UK), THIN (UK) or ICPC (NL)

• Problem: Most biological treatments are dispensed in hospitals and are not included in BIFAP, nor in many databases used in pharmacoepidemiology

http://www-bifap.org
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Registries of exposed people to biologicals

- BIOBADASER
  - Registry of patients exposed to biologicals used in rheumatic diseases
  - Spanish Society for Rheumatology
  - Funding (Public-private)
    - Spanish Society for Rheumatology
    - Spanish Medicines Agency
    - Pharmaceutical companies
  - 35 hospitals
  - All relevant adverse events are recorded by participating rheumatologists
  - Phase II was closed in 2015 with more than 7,000 patients in the Registry

https://biobadaser.ser.es
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Registries of exposed

- Objectives
  - Raise new signals
  - Quantify incidence of adverse events and confirm signals
  - Evaluate risk minimization measures
    - Infliximab and tuberculosis
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**BIOBADASER: Incidence of tuberculosis in 2000**

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Gómez-Reino et al, Arthritis & Rheumatism 2003; 48:2122-2127

**Conclusions**

- Pharmacovigilance should be as proactive as possible
  - Risk Management Plans
- Biologics have specific features that make pharmacovigilance (and particularly its proactive concept) even more important
- Spanish pharmacovigilance System is well-prepared for the challenge of biologics, but complementary epidemiological approaches would be very convenient, such as Registries of Exposed (the successful experience of Biobadaser / Biobaderm shows a roadmap to follow).
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