Long-term PHARMacovigilance for Adverse effects in Childhood arthritis focusing on Immune modulatory drugs

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EMEA meeting, june 28, 2010

A European collaboration between pediatric rheumatology centers regarding long term outcome and pharmacovigilance for biologics used in Juvenile Idiopathic Arthritis

a PReS/ Printo project

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FDA: ongoing safety review of TNF blockers

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U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

Types of Pediatric Malignancy Reported to FDA

Type of Malignancy	# cases	Type of Malignancy	# cases
Hepatosplenic T-cell lymphoma	10	Renal cell carcinoma	1
Non-Hodgkin's lymphoma	7	Hepatic malignancy	1
Hodgkin's lymphoma	6	Metastatic hepatocellular cancer	1
Leukemia	6	Malignant mastocytosis	1
Malignant melanoma	3	Neuroblastoma	1
Thyroid cancer	3	Colorectal cancer	1
Basal cell carcinoma	1	Yolk sac tumor	1
Lymphoma and AML	1	Myelodysplasia	1
Leiomyosarcoma	1	Bladder cancer	1
Nephroblastoma	1		

11

FDA, June 4th 2008

EMEA statement

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European Medicines Agency

London, 4 August 2009
Doc. Ref: EMEA/493705/2009

EMEA 2010 Priorities for Drug Safety Research

Long term adverse effects of immunomodulators

EMEA statement (2)

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- Concern: adverse events (neurological, infections, malignancies)
- Plausible biological mechanism: failing immune surveillance

- Suitable research methodologies: long-term epidemiological follow-up studies of adverse events; subgroup analysis to study risk factors

EMEA, London, 4 august 2009

FP7 (health, 2010) project: PHARMACHILD

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- **PHARMACHILD aims to detect, assess and understand long term and short term side effects of the use of biologics by studying the pharmacovigilance in a large international cohort of patients with Juvenile Idiopathic Arthritis (children and young adults) in order to support regulatory decisions on marketing authorizations for these products.**

Biologics in children

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- Increasing numbers of indications since 1999
- Increasing numbers of biologics registered for adults (and some for children)
- JIA: most common chronic inflammatory disease treated with biologics
- Existing international network of expert pediatric rheumatology centers

Pharmacovigilance

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- Pharma-industry are obliged to perform post-marketing surveillance
- Rare side effects require large scale registries
- What are the requirements for an international large scale registry to meet this obligation?

FDA workshop for a paediatric rheumatology observational strategy" (May 12, 2009).

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- long term safety of biologics in JIA is lacking.
- Detection of rare events via international collaboration between both sides of the Atlantic.
- Large scale international pharmacovigilance registries are required.
- Support and participation by the pharmaceutical industry is encouraged.

FP7 grant for pharmacovigilance of biologics in JIA

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WP No	Work package Title	Type of Activity	Lead participant No	Lead participant short name
WP1	Data collection, monitoring and statistical analysis	RTD	2	Genoa, Italy
WP2	Analysis of reported adverse events	RTD	5	Manchester, UK
WP3	Biomarker analysis	RTD	4	Münster, Germany
WP4	Synthesis & identification of risk factors	RTD	1	Utrecht, NL
WP5	Consortium Management, assessment of progress and dissemination of results	MGT	1	Utrecht, NL
				TOTAL

RTD = research and technological development; DEM = Demonstration; MGT = Management of the consortium; OTHER = other specific activities

WP1: Large scale epidemiological study

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- Using existing network of expert pediatric rheumatology centers of PReS and PRINTO
- Objective: To built up and enroll children with juvenile idiopathic arthritis (JIA) treated with biologic agents in the PRINTO/PReS web based effectiveness registry. This will include monitoring of data input.
- WEB based
- Meta-analysis of >7000 JIA patients, Statistical analysis
- Reported adverse events will be transferred to WP2

Network of EU registries for biologics in JIA

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Country	Abbreviation	Registry
United Kingdom	BSPAR-BNDR BSRBR	BSPAR Biologics & New Drugs Registry (JIA) and Extended Biologics Study (JIA) British Society of Rheumatology Biologics Register (RA and adults with JIA who received biologics in adulthood)
Germany	RABBIT Etanercept register JuMBO	German long-term observation of biologics in RA Register for children with JIA, receiving etanercept or MTX Register for adults with JIA who received etanercept or MTX in childhood
The Netherlands	ABC-Register	Arthritis and Biologics in Children
Finland	-	Registry of JIA patients treated with anti-TNF
Czech Republic	-	Registry of JIA patients treated with anti-TNF
Spain	-	National Etanercept registry for JIA (Valencia, Spain)
Sweden	-	Registry of JIA patients treated with anti-TNF
Italy	IPERN registry	Registry of JIA patients treated with anti-TNF
France	CEMARA	Platform for reference centers on Juvenile Arthritis
Switzerland	-	Registry of JIA patients treated with anti-TNF

WP2: analysis of adverse events

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- **Objective: To ensure validated robust analysis of the occurrence and risk of observed serious adverse events, and in particular serious infections, malignancy and inflammatory gastrointestinal diseases, in children receiving biologics for JIA.**

WP2, methodology

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- Using MEDDRA
- Expert panels:
  - *Oncology*
  - *Infectious diseases*
  - *IBD*
- Contact individual reporting centers for additional clinical details and possibly biological materials

WP3: analysis of immunesurveillance

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- objective: To analyze immune surveillance mechanisms in a cohort of 80 JIA patients (NL, GE, UK) under treatment with immuno-modulatory drugs and to identify a panel of risk factors for undesirable outcomes such as adverse events in JIA.