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Regulatory safety learning driven by the mechanism of action: the case of TNF-α inhibitors

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Background

- Within the European Union, the product information is an important information source to inform patients and health care professionals about the adverse drug reactions (ADRs) that are associated with the use of the drug

- Drugs with the same mechanism of action are expected to have a similar ADR profile and the product information is therefore expected to show substantial overlap in the described ADRs

- Previous studies have evaluated whether safety information has been taken into account as part of the regulatory assessment for drugs within the same class

Aims

- To assess the overlap in mechanism-of-action-related ADRs described in the SmPC of TNF-α inhibitors during the life-cycle of the product

- To assess the time from the identification of new ADRs to the description of the same ADR in the SmPC of another TNF-α inhibitor

- To identify factors associated with the description of ADRs in the SmPC of multiple TNF-α inhibitors

Methods

- All ADRs were extracted from all versions of the SmPCs of the TNF-α inhibitors (excluding biosimilars) through validated text-mining methods
- ADRs were characterized using Medical Dictionary for Regulatory Activities version 22.1 at the high level term level (HLT level)
- Hypersensitivity and administration site reactions were excluded

Version X

4.8 Undesirable effects

Neoplasms, benign, malignant and unspecified	
Uncommon:	Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
Rare:	Lymphoma

incidence of the ADR compared with placebo in pooled data from clinical studies involving 192 patients receiving placebo and 771 patients receiving infliximab (primarily rheumatoid

Version Y

Neoplasms, benign, malignant and unspecified	
Uncommon:	Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
Rare:	Lymphoma
Not known:	leukaemia*

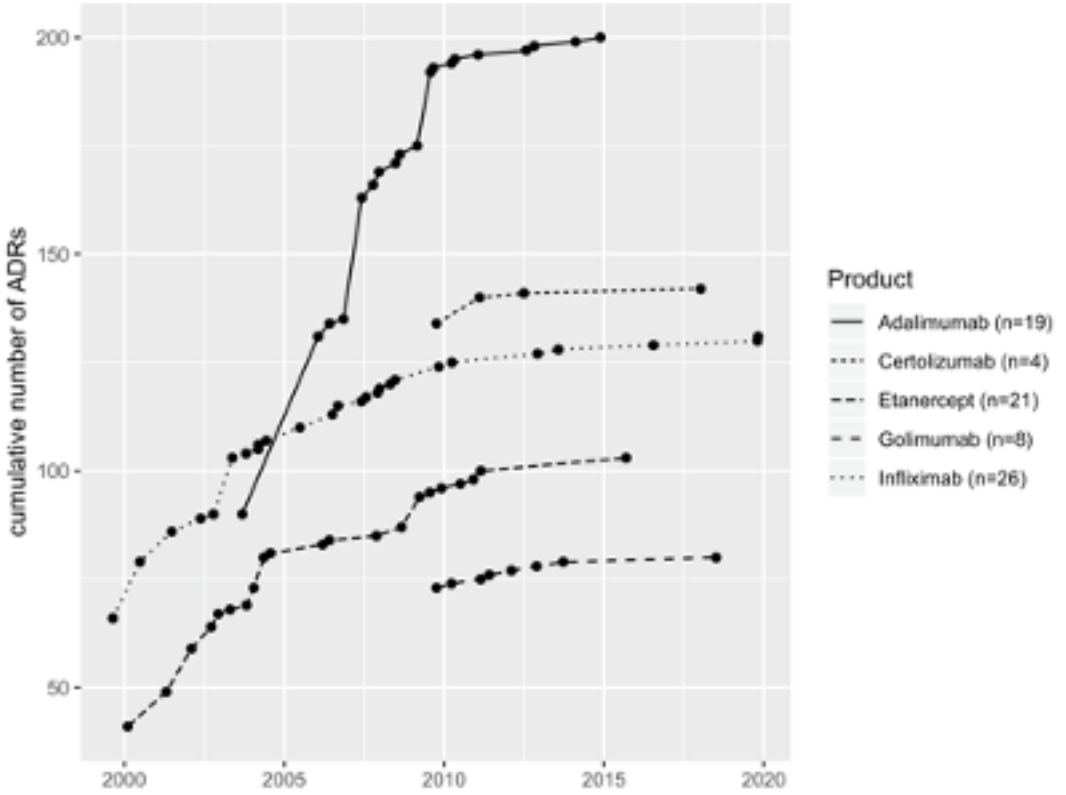
Methods

- The overlap in the ADRs (at the HLT level) described in the SmPCs of the different TNF-α inhibitors was assessed in three ways:
    - Overlap at initial approval
    - Overlap at the end of follow-up (31 December 2019)
    - Lag time in overlap (Kaplan-Meier analysis)

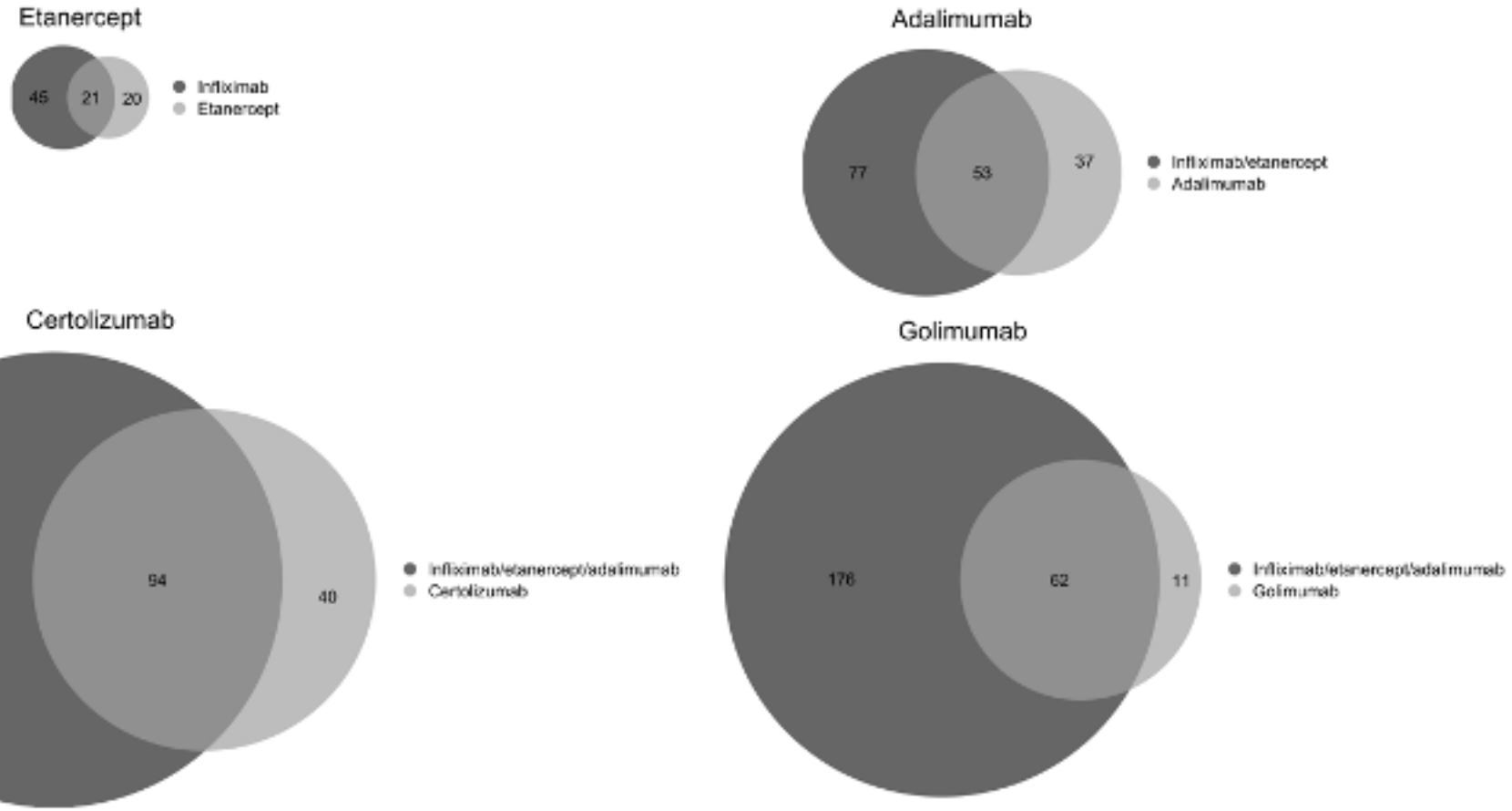
- The following determinants were assessed to study the overlap in the ADRs described in the SmPCs of the different TNF-α inhibitors (Cox regression analysis):
    - Nature of the ADR
    - Seriousness of the ADR
    - Regulatory importance of the ADR
    - First-in-class

Results

- A total of five TNF-α inhibitors (excluding biosimilars) were included
- Substantial variation was observed in the number of ADRs described in the SmPCs



Overlap at initial approval



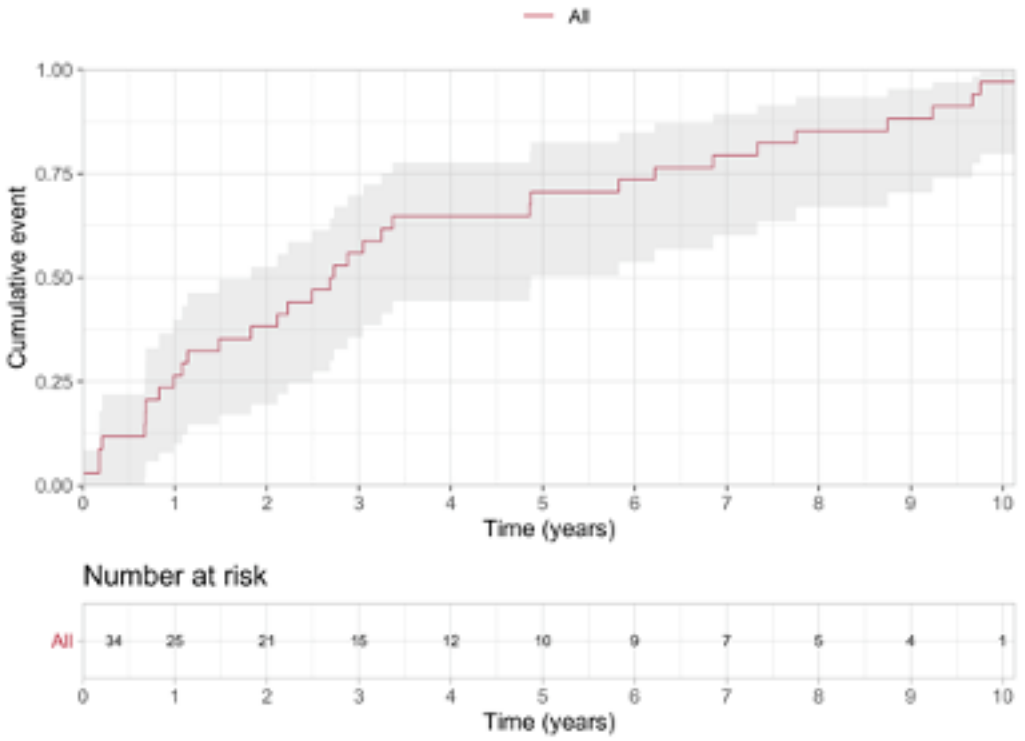
Overlap end of follow-up

- At the end of follow-up (31 December 2019), a total of 318 different ADRs (at the HLT level) were described in the SmPCs of the TNF-α inhibitors
    - 25 (8%) were classified as hypersensitivity reactions and/or administration site reactions and were excluded

- Of the 293 ADRs included ADRs:
    - 133 (45%) were described in the SmPC of one TNF-α inhibitor
    - 58 (20%) in the SmPC of two TNF-α inhibitors
    - 40 (14%) in the SmPC of three TNF-α inhibitors
    - 23 (8%) in the SmPC of four TNF-α inhibitors
    - 39 (13%) in the SmPC of all five TNF-α inhibitors

Lag time in overlap

The median lag time between first description of an ADR in an SmPC to uptake of this ADR in another SmPC was approximately 3 years and ranged from 0 to 15 years



ADR characteristics associated with overlap in ADRs

	# of ADRs in second SmPC (%)	Hazard ratio (95% CI)
Nature of the ADR		
Infections and infestations (n = 20)	9 (45)	2.1 (1.0–4.5)
Other (n = 115)	25 (22)	Reference
Seriousness		
Non-serious ADR (n = 61)	6 (10)	Reference
Serious ADR (n = 74)	28 (38)	4.5 (1.8–10.8)
Regulatory importance		
ADR not classified as important risk (n = 67)	7 (10)	Reference
ADR classified as important risk (n = 68)	27 (40)	4.6 (2.0–10.5)
First in class		
ADR first described in non-first-in-class drug (n = 97)	17 (18)	Reference
ADR first described in first-in-class drug (n = 38)	17 (45)	2.8 (1.4–5.6)

Discussion

- The ADRs described in the SmPC of the TNF-α inhibitors differ substantially in number and type
- To facilitate the assessment of class effects, specific attention should be given to the assessment of the underlying mechanism by constructing adverse outcome pathways
- Within the EU regulatory system procedures are in place to evaluate specific post-marketing safety issues for the group of drugs with the same mechanism of action as a whole
- At the time of approval and as part of extension of indication procedures (potential) class effects should be considered

Thank You

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Clinical Pharmacology & Therapeutics 2020 Dec 5. Online ahead of print

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