LEVERAGING THE WHO PHARMACOVIGILANCE DATABASE VIGIBASE® : EXAMPLE OF THE SAFETY ANALYSIS OF [^{177}Lu]Lu-DOTATATE

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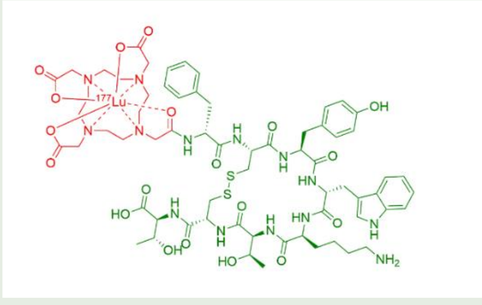
Background & Objectives

[^{177}Lu]Lu-DOTATATE = Therapeutic radiopharmaceutical used in the treatment of metastatic or inoperable, well-differentiated gastroenteropancreatic neuroendocrine tumours expressing somatostatin receptors.
Several clinical trials have been carried out, including the NETTER-1 trial, but they do not fully represent the heterogeneity of patients who may receive this treatment in routine clinical practice.

The objective is **to elucidate a comprehensive safety profile with real-life data of a therapeutic radiopharmaceutical such as [^{177}Lu]Lu-DOTATATE using VigiBase®, the World Health Organisation's pharmacovigilance database.**



Structure of [^{177}Lu]Lu-DOTATATE, from Ladriere T. *et al.*, 2023[1]

Materials and methods

Extraction of individual safety reports (ICSRs) reported and associated with [^{177}Lu]Lu-DOTATATE from VigiBase®.

→ Recording the general characteristics of ICSRs.

→ Creation of a dictionary of adverse drug reactions (ADRs) reported in these reports and associated with [^{177}Lu]Lu-DOTATATE, divided into classes and subclasses.

→ Retrospective disproportionality analysis of ICSRs with the information component (IC, at alpha risk of 0.05: IC_{025}). An $IC_{025} > 0$ is deemed significant.

→ Description of ADR classes: identification of co-reporting between classes and time to onset of ADRs.

Results

- Analysis of 3,984 ICSRs
- Reported mainly by the Americas (65%) and European region (31%) and principally by physicians (45%)
- Top 6 drugs co-reported with [^{177}Lu]Lu-DOTATATE : Octreotide (6%), Amino acids (6%), Ondansetron (6%), Lanreotide (5%), Everolimus (2%) and Capecitabine (2%).
- Disproportionality analysis revealed a significant association (IC_{025} >0) between [^{177}Lu]Lu-DOTATATE and the reporting of hematological disorders, infections, renal failure, hepatic disorders, alopecia, metabolic disorders, and hematologic malignancies (In red in Figure 1).

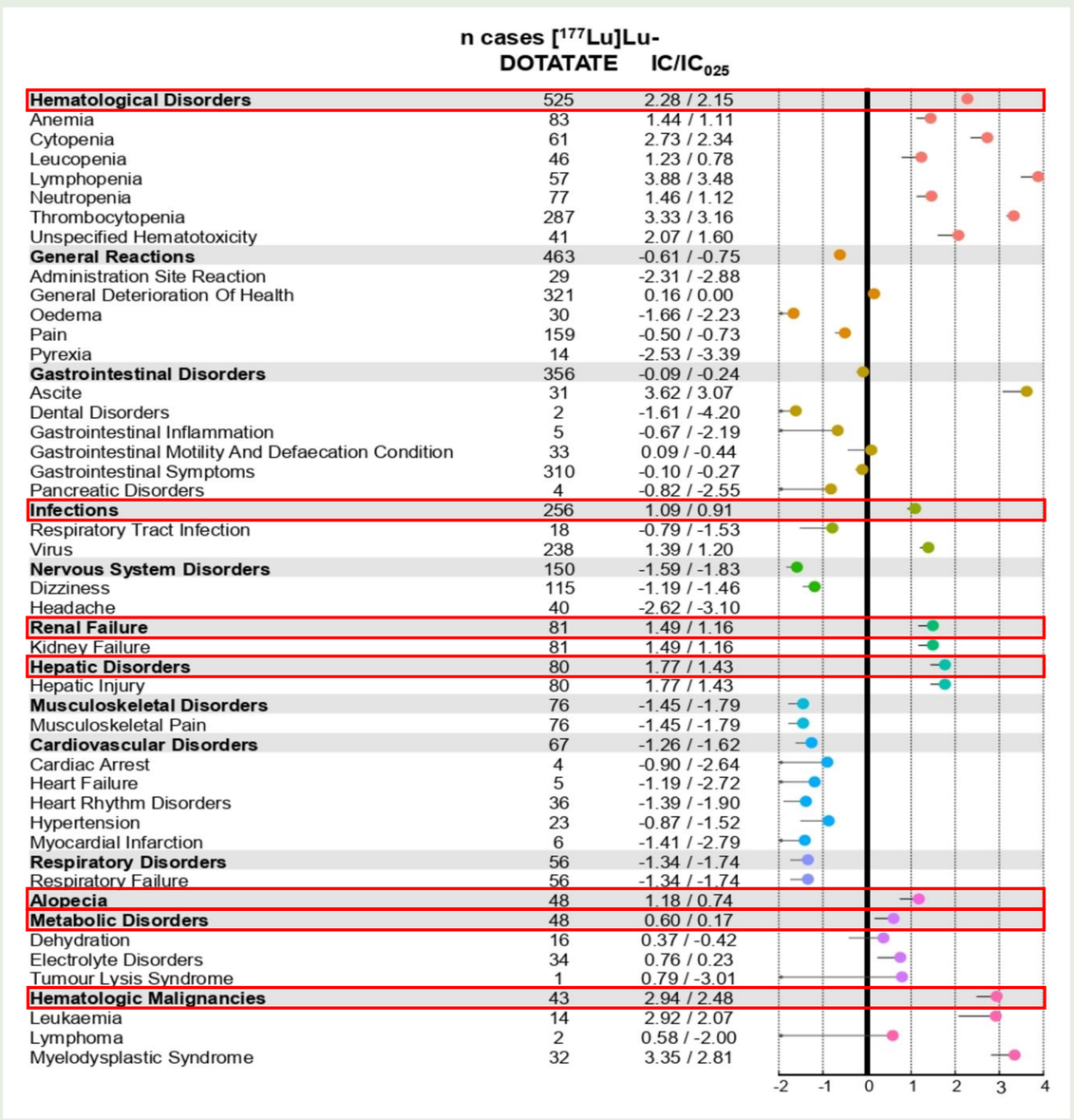


Figure 1: Disproportionality analysis using the information component (IC) and its lower end credibility interval (IC_{025}) for the association between the thirteen classes and thirty-seven subclasses of ADRs and [^{177}Lu]Lu-DOTATATE.

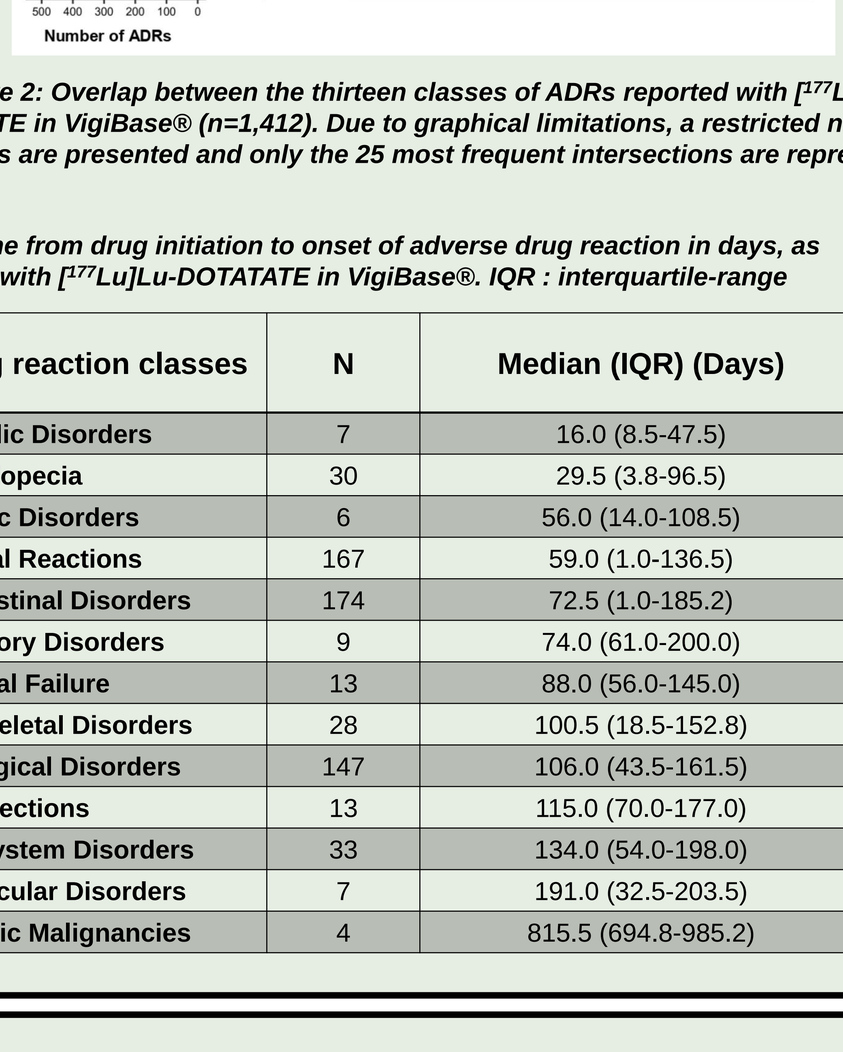


Figure 2: Overlap between the thirteen classes of ADRs reported with [^{177}Lu]Lu-DOTATATE in VigiBase® (n=1,412). Due to graphical limitations, a restricted number of overlaps are presented and only the 25 most frequent intersections are represented.

Table 1: Time from drug initiation to onset of adverse drug reaction in days, as reported with [^{177}Lu]Lu-DOTATATE in VigiBase®. IQR : interquartile-range

Adverse drug reaction classes	N	Median (IQR) (Days)
Metabolic Disorders	7	16.0 (8.5-47.5)
Alopecia	30	29.5 (3.8-96.5)
Hepatic Disorders	6	56.0 (14.0-108.5)
General Reactions	167	59.0 (1.0-136.5)
Gastrointestinal Disorders	174	72.5 (1.0-185.2)
Respiratory Disorders	9	74.0 (61.0-200.0)
Renal Failure	13	88.0 (56.0-145.0)
Musculoskeletal Disorders	28	100.5 (18.5-152.8)
Hematological Disorders	147	106.0 (43.5-161.5)
Infections	13	115.0 (70.0-177.0)
Nervous System Disorders	33	134.0 (54.0-198.0)
Cardiovascular Disorders	7	191.0 (32.5-203.5)
Hematologic Malignancies	4	815.5 (694.8-985.2)

Conclusion

VigiBase® is a database that can be used for disproportionality analysis, overlaps, time to onset of ADRs, rechallenge/dechallenge as well as outcome, with a large amount of data essentially reported in "real life" which may reveal a rare ADR.
VigiBase® = Essential information on the safety profile of [^{177}Lu]Lu-DOTATATE with potential use for other diagnostic and therapeutic radiopharmaceuticals.

Références :1 Ladrière T, Faudemer J, Levigoureux E, *et al.* Safety and Therapeutic Optimization of Lutetium-177 Based Radiopharmaceuticals. *Pharmaceutics*. 2023;15:1240. doi: 10.3390/pharmaceutics15041240

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