Occurrence and Risk Factors of Linezolid Toxicity in Clinical Practice: Interim Analysis of a Prospective Multicentric Study

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Background

In a retrospective study in 4 Belgian hospitals [1], we showed that linezolid (LZD) was largely used off-label based on its activity against multiresistant strains and its oral route of administration. Besides, the rate of adverse drug reactions (ADRs) was higher (especially hematological toxicity [anemia/thrombocytopenia]) than described in the summary of product characteristics [1]. Gastro-intestinal disorders and metallic taste were also observed, possibly compromising compliance to the treatment.

The identified risk factors for hematological toxicity in this study [2] were a long treatment duration, renal impairment at the beginning of the treatment and presence of comorbidities (evaluated by the Charlson comorbidity index [3]). LZD trough levels (C_{min}) > 9 mg/L have been associated to a higher risk of hematological toxicity [4]. Therapeutic monitoring may thus help keeping trough values in the recommended range (2-7 mg/L) but is not yet performed in routine in most Belgian centers.

Objectives

To prospectively assess in clinical practice

- The rate of all observed **ADRs**
- The **risk factors** associated with their development
- The relation between the most frequent ADRs and **C_{min}** values

Methods

- Prospective multicentric study in 2 Belgian hospitals (May 2021 – September 2022 [still ongoing study])
- Inclusion of patients treated with LZD (IV or oral)
- Data collection in electronic medical records and via phone calls
- ADRs collection during the treatment (at follow-up visits and through hemogram)
- C_{min} values (every 7 days for inpatients and at follow-up visits for outpatients) [5]
- Statistics: Mann-Whitney U test in SPSS (version 26)

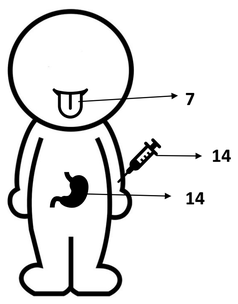
Results

Patients' data

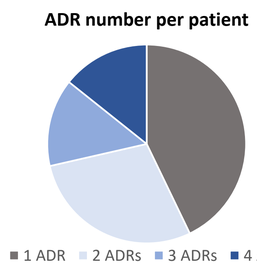
N =38	Median (Min – Max)
♀ ♂	11 / 27
AGE	64.5 years (33-89)
	70.5 ml/min (6-121)
	90 kg (42-154)
Charlson index	2 (0-6)
	600 mg 2x/day

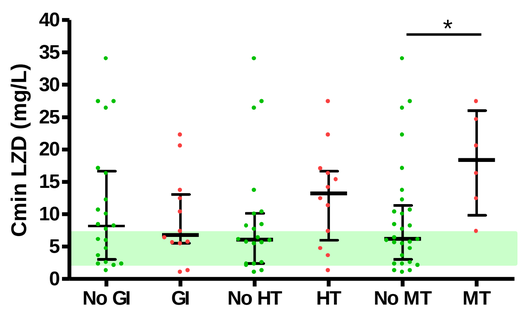
Infections	N	Days
BJI	16	30 (9-121)
2d bacteremia	5	13 (6-23)
SSTI	4	13 (8-17)
Endocarditis	3	17 (15-19)

ADRs data



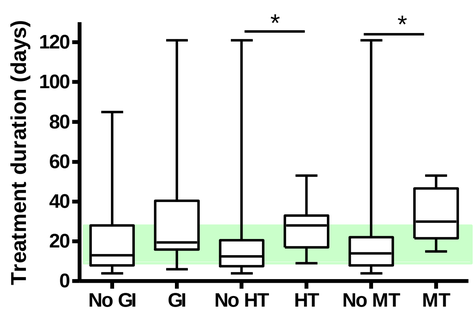
- **43** ADRs in **22** patients
- 2 Anemia – 5 thrombocytopenia – 7 both
- **7** stops because of toxicity (6 hematological disorder and 1 paresthesia)





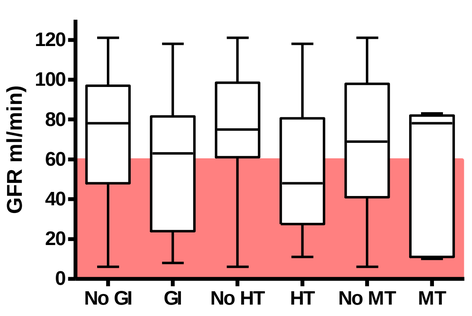
Cmin:

- Recommended range: 2-7 mg/L
- Higher C_{min} in patients with hematological toxicity and metallic taste (statistical difference only for metallic taste)



Treatment duration:

- Recommended duration: 7-14 days with a maximum of 28 days
- Longer treatment duration in patients with ADRs (statistical difference only for metallic taste and hematological disorder)



Renal function:

- Renal failure in patients with GFR < 60 mL/min
- Reduced renal function in patients with hematological toxicity (no statistical difference)

BJI : Bone and joint infection **SSTI**: Skin and soft tissue infection Gastro-intestinal disorder (GI) Metallic taste (MT) Hematological disorder (HT)

Conclusion

Preliminary data → larger sample is required to confirm the trends:

- ADRs more **frequent** in clinical practice than reported in the SmPC
- Hematological toxicity is the major cause of discontinuation
- High **C_{min}** and long **treatment duration** seem to be associated with the development of ADRs
- Detection of at-risk patients possible via therapeutic drug monitoring, follow-up of blood cell counts and renal function

References

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