2434

Review of Linezolid (LZD) Use and Onset of Toxicity in 4 Belgian Hospital Centers: a Retrospective Study

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ABSTRACT (edited)

Background: LZD is approved (FDA label and Belgian Summary of Product Characteristics [SmPC]) for the treatment of SSSTI and pneumonia caused by Gram-positive organisms (mainly MRSA and VRE) only. Yet, IDSA recommendations for MRSA infections also position LZD for osteomyelitis and as an alternative for CNS infections and bacteremia (CID 2011; 52: e18–55). LZD use is limited by adverse events, the incidence of which may vary according to the length and conditions of therapy. The aim of this study was to document LZD actual use and onset of adverse events in real life clinical practice.

Methods: Observational, retrospective study in 4 Belgian hospital centers (about 4,000 beds) over 1 year (2016). Analysis of medical files (248 treatments) to collect information on (i) patient's characteristics and treatment modalities, indications, (ii) occurrence, causality and severity of adverse drug reactions (ADR), and (iii) concomitant medications (increasing the risk of developing a serotonin syndrome [SS]).

Results: Only 18 % of prescriptions matched the indications approved in the US and in Belgium, but 47% those mentioned in the IDSA recommendations. 51% of the patients were infected by bacteria resistant to first choice drugs. Decreases in platelet counts (DPC) was observed in 31% of patients (compared to <1% thrombocytopenia in the Belgian SmPC or 25% DPC in 3% of patients in FDA label) and was observed in 18/44 cases for patients with in-Belgian label indications, 41/116 for patients with IDSA indications, and 30/127 for patients with other indications. Treatment > 10 days was the only significant risk factor for DPC (Kaplan Meier; p<0.005 [Mann-Withney]). 8 cases of CNS ADR were reported. Although 40% of patients were prescribed at least 1 drug increasing SS risk, SS was actually observed in only 1 patient.

Conclusion: LZD is mainly used for off-label indications, some of which, however, are in the IDSA recommendations. The high incidence of ADR (41%) as well as the frequent use of co-medication putting patients at risk of SS highlight the importance of follow-up for LZD-treated patients. A prospective study will be started to further identify potential risk factors.

INTRODUCTION & OBJECTIVES

The anti-Gram-positive antibiotic linezolid (LZD) has been introduced on the market in 2000 with limited indications. Due to its excellent bioavailability (favoring patient's discharge) and activity against Gram-positive isolates resistant or less susceptible to first choice drugs (β-lactams, vancomycin, …), it is often used off-label[1]. However it can also lead to severe adverse drug reactions (ADR) such as hematological[2,3] or neurological disorders, or a serotonin syndrome (SS) when associated with serotoninergic drugs.

The objectives of our study were to assess

- the real use of LZD in Belgian hospital centers,
- the nature, time of onset, and frequency of LZD-induced ADRs

RESULTS

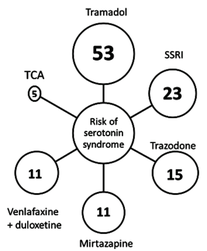
Patients' data and treatment related data:

Patients	230
Treatments	248
Male/Female	143/87
Age (year)	65 (21-95) [a]
Weight (kg)	76 (34-178) [a]
Renal function (GFR in ml/min)	57 (10-96) [a]
Posology	600mg 2x/day
Oral route/IV route	141/89

[a] Median (range)

Number of patients receiving a drug creating a risk of serotonin syndrome (SS)

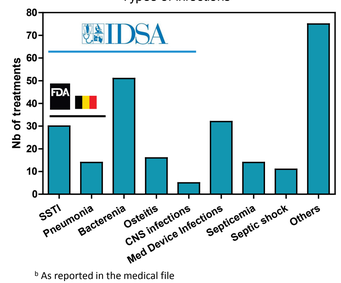
(total: 118 [some patients received > 1 drug])



SSRI: Selective serotonin reuptake inhibitor
TCA: Tricyclic antidepressant

- 92 patients (40% of all patients) received ≥ 1 drug creating a risk of serotonin syndrome
- 1 case was observed (0.4%) (with trazodone [100 mg/day] plus duloxetine [60 mg/day])

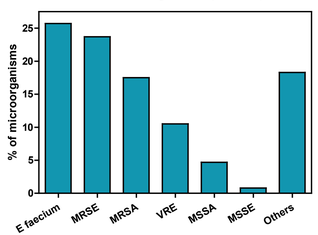
Types of infections [b]



[b] As reported in the medical file

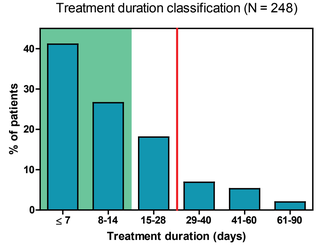
In-label prescriptions:
- 18% according to the FDA [5] and/or Belgian SmPC [3]
- 47% according to IDSA guidelines [4]

Causative microorganisms (N = 257)



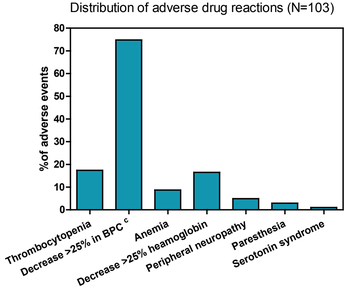
- 51% of patients infected by isolates resistant to first-line drugs (VRE: vancomycin, MRSA and MRSE: β- lactams)
- 10% of patients infected by 2 microorganisms

Treatment duration classification (N = 248)



- 67%: recommended duration according to the Belgian SmPC [3] and FDA label [5] (< 14 days)
- 86%: authorized duration according to Belgian SmPC [3] and FDA label [5] (< 28 days)
- Treatment duration: mean = 10 days (extr. 1-90)

Distribution of adverse drug reactions (N=103)

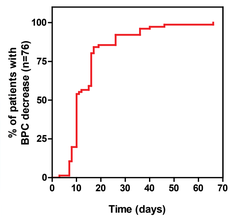


[c] BPC: Blood Platelet Count; >25% decrease is substantial according to the FDA label [5]

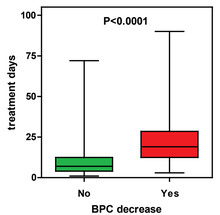
- Incidence of all ADRs = 41% of all treatments (n=248)
  - 35% of patients with at least 1 ADR
  - 10% of patients with 2 or ADRs
- Substantial decrease in blood platelets count (BPC): 31% of all treatments (much more than in the FDA label [5] [2.4 % [0.3-10%]] or the Belgian SmPC [3] [<1% of treatments])

Characteristics of the Blood Platelets Count (BPC) decrease (> 25%)

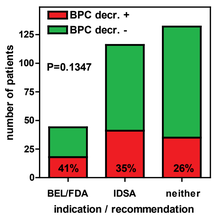
A: time of onset



B: treatment duration



C: indication / recommendation



Decrease of > 25% of BPC observed in 76 patients (out of 248)
- with median time for first detection at day 10 (**A**)
- with a significant (Mann Whitney U test) impact of treatment duration (**B**)
- with a trend for a larger percentage (but not significant [Chi-square test]) for patients for whom LZD was prescribed according to Belgian and/or FDA label (**C**; discounting prescription for VRE)
- without significant correlation with decrease in renal function, weight, age (Mann Whitney U test) or gender (Fisher exact test) (not illustrated)

METHODS

- Analysis of medical files from patients treated with linezolid between January 2016 and December 2016 in 4 Belgian Hospitals (3 University hospitals; 1 general hospital).
- Main collected information:
  - key patient's characteristics (age, sex, weight, renal function)
  - treatment indications (in comparison with approval labels and IDSA guidelines)
  - type and resistance pattern of the reported causative organism(s)
  - adverse drug reaction data (noted against a predefined list based on Belgian [SmPC][3] and FDA [PI][5] labels)
  - Statistical analysis performed with SPSS version 25.

MAIN MESSAGES

- Linezolid was mainly used off-label if considering the FDA and/or Belgian approved indications, but more often in-label according to IDSA guidelines.
- Hematological (thrombocytopenia, anemia) and other ADRs were observed with a much larger frequency than indicated in the Belgian SmPC[3] or the FDA label[5], which should encourage closer follow-up of patients treated with LZD.
- Serotonin syndrome was uncommon (<1%)[3] despite the high proportion of patients (40%) to whom a serotoninergic drug had been co-prescribed.

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5. ZYVOX® FDA label; revised in 2018 – available from https://goo.gl/Pfmd7K.

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