

Supplementary Table 9. Clozapine in Denmark

Danish physicians: leaders in the identification of clozapine-induced myocarditis

They made several first steps worldwide regarding clozapine-induced myocarditis in:

- 1980 with the publication of the 1st case⁸⁵ (versus 1986 for the 2nd case⁸⁶ from the US),
- 1985 with publication of the 1st large sample¹³⁴ of clozapine discontinuations including 1 myocarditis case out of 216 patients (versus 1988 for the 2nd sample¹³⁵ from Sweden),
- 1986 with the 1st case reported to VigiBase (versus 1990 for the 2nd case from Germany),⁶⁷
- 1994 with the publication of the 1st description that this was an “allergic”⁹⁸⁷ or hypersensitivity reaction (versus 1995 for the 2nd description¹³⁶ from Norway), and
- 2012 with publication of a review⁷⁷ showing that clozapine can have pro-inflammatory activity during early titration.

Clozapine-induced myocarditis is rare in the Danish registry

- Rohde et al.⁹⁹ studied 3,262 outpatient starts of clozapine in which 0.03% developed myocarditis in the first 2 months. More importantly, none of the 26 deaths in the first 2 months was explained by myocarditis.

Clozapine-induced myocarditis in Denmark is rare in the VigiBase pharmacovigilance database

- In VigiBase through January 15, 2021,⁶⁷ there were 3,572 clozapine-induced myocarditis cases with 178 deaths. Danish cases accounted for only 12 cases or 0.3% of the total cases and 3 deaths or 0.02% of total deaths.

Long-term clozapine safety in the Danish registry

- Within the long-term data in the Danish registry, van der Zalm et al.¹³⁷ found that clozapine was not associated with increased cardiovascular mortality but with a lower risk of suicide. Moreover, clozapine cessation was associated with a possible increase in suicide deaths.
- The first year of clozapine was more problematic since cumulative use of other antipsychotics for up to 1 year was associated with a lower all-cause mortality and suicide risk than a similar period of clozapine use (all-cause: adjusted hazard ratios=0.73; CI, 0.63–0.85, suicide-adjusted hazard ratios=0.65; CI, 0.46–0.91).¹³⁷

Possible effect on mortality of TRS in the 1st year of clozapine use in Denmark

- Patients with TRS probably have greater risk of mortality than patients with non-TRS.
- Patients with TRS have definitively more pneumonia risk. In Denmark, TRS patients had an annual pneumonia incidence of 1.229% versus 0.758% in antipsychotic-naïve schizophrenia patients.⁷⁴ This means that in Danish clozapine patients, 2/3 of the pneumonia risk is associated with TRS and 1/3 with clozapine.⁷⁴

Definitive effect on mortality of pneumonia in the 1st month of clozapine use in Denmark

- In the Danish registry, Rohde et al.⁹⁹ found, in the first month of clozapine treatment, pneumonia explained 7 of 28 deaths in clozapine patients.

Hypothesis about pneumonia in the first year of clozapine use in Denmark

There are probably two major types of pneumonia during the first month of a clozapine titration:

- those associated with aspiration which may be ↓ by slower personalized titrations, and
- those not associated with aspiration but explained by an infectious agent, typically a bacterium. This may be more associated with the risk associated with TRS while clozapine may have a lesser contribution (possibly ↓ antibodies in some patients).

CI, confidence interval; TRS, treatment-resistant schizophrenia