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Trial title: Patiromer-facilitated, dose-escalation of mineralocorticoid antagonists for the management of worsening congestion in people with heart failure and hyperkalaemia. A Phase IV, registry-based, randomised, controlled, open-label trial investigating the potential for patiromer-facilitated use of higher doses of mineralocorticoid antagonists in addition to standard care (compared to standard care alone) to improve congestion, well-being, morbidity and mortality.

Short title: RELIEHF: RELieving Increasing oEdema due to Heart Failure

EudraCT number: 2018-003662-14

Summary of results: The RELIEHF trial was set up to find out if giving patiromer allows higher doses of mineralocorticoid antagonists (MRAs) to be used and, if so, whether this improves the control of congestion in both the short- and long-term. The RELIEHF trial opened for recruitment in March 2020 but before the first patient could be enrolled, the COVID pandemic struck, effectively preventing recruitment. Despite gallant efforts by clinical trials unit staff and investigators in the aftermath of the pandemic, recruitment never gained momentum. Moreover, despite administration of substantial doses of MRA, few patients developed a high blood potassium concentration (an important finding). Accordingly, the trial was stopped for futility after only 19 patients had entered the run-in phase of the trial and only 4 patients had been randomised.

Despite early termination, a substantial amount of data has been collected in the screening logs and consented registries and from the open-label run-in on patients recorded in the screening log. Of patients entered on the screening log, 249 were not asked to participate, mainly because the care team felt it inappropriate because the patient was too frail or lacked capacity to consent due to dementia. Of 245 screened patients who were asked to participate, 102 declined, of whom 61 said they were not interested and 28 said they felt too unwell. Only seven indicated concerns over data privacy. Of the 141 patients who agreed to participate in the registry, 102 also agreed to participate in the randomised trial but (mostly due to the effects of the COVID pandemic, we think) only 19 patients (median age 71 years; 7 women) entered the run-in phase. Of the 19 patients who entered the run-in phase, 15 received spironolactone (median dose at end of run-in 75mg/day compared to guideline-recommended dose of 50mg/day) and two received eplerenone (both 50mg/day; the guideline-recommended and maximum licensed dose); one patient had been initiated on eplerenone but dose and name of MRA were not recorded at end of run-in and for a further patient no data on MRA dose or name was recorded at any time.

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In clinical practice, many patients are not given any dose of MRA and the average dose of spironolactone is less than 50 mg/day. Despite using substantially higher doses of MRA, only four patients developed hyperkalaemia and in no case was this severe (maximum value 5.5 mmol/L). Two patients were randomised to usual care and two to patiromer. All patients survived until termination of the trial. Two patients experienced serious adverse events related to worsening kidney function, both of which were considered mild.

In summary, the trial shows that many patients who might be considered eligible for trials of worsening heart failure based on administrative records are considered unsuitable for inclusion in research registries and trials by clinical investigators. Almost 60% of patients who are asked are willing to participate in a 'low-burden' research registry and about 40% to participate in the much more onerous undertaking of a randomised trial. The trial also shows that most patients considered eligible for the randomised trial could tolerate higher doses of MRA than is common in clinical practice without developing hyperkalaemia. Whether there is a substantial requirement for patiromer, or other potassium binding agents, in this population remains to be established.

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