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Long-term treatment with ivabradine over 12 months in patients with chronic heart failure in clinical practice: Effect on symptoms, quality of life and hospitalizations

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ABSTRACT

Background: Ivabradine is indicated to control heart rate in otherwise optimally treated patients with chronic heart failure (CHF) and reduced ejection fraction. However, data on its effectiveness outside clinical trials and longer-term effects are scarce.
Methods: We performed a prospective cohort study involving 249 German resident cardiologists and analyzed the 1-year effectiveness and safety of ivabradine used in CHF outpatients. Data on symptoms, quality of life, and hospitalizations were collected.
Results: In total, 767 CHF patients were enrolled to receive ivabradine twice daily, of whom 684 (90%) were still on ivabradine at study end (mean treatment duration 11.2 months). The cohort was representative of CHF patients seen in clinical practice in terms of age, risk factor profile, and comorbidities. Concomitant beta-blocker therapy was prescribed in 497 patients (65%). After one year, compared to baseline, heart rate in ivabradine-treated patients was 16 bpm lower. This reduction was associated with a significant improvement in NYHA class, and less frequent signs of decompensation (36% to 8%). The proportion of hospitalized patients within 1 year decreased from 23% before treatment, to 5% with ivabradine therapy. These improvements in clinical status were accompanied by a reduction in BNP and an increase in LVEF (+5.1% at 1 year). Quality of life was significantly improved in all measured dimensions. Adverse drug reactions were noted in 26 patients (3%), and were in line with the known safety profile of ivabradine.
Conclusions: Ivabradine was effective and well-tolerated in CHF patients seen in clinical practice throughout 1 year of treatment.

1. Introduction

Chronic heart failure (CHF) is a progressive cardiovascular disorder that considerably impairs quality of life of patients due to debilitating symptoms. In developed countries, the prevalence of CHF is 1–2% of the adult population and increases with age, rising to ≥10% among elderly people [1]. In Germany, heart failure has become the leading cause of hospitalization and in-hospital deaths [2,3]. Due to the aging of the population, the number of heart failure hospitalizations is estimated to increase from 364,000 in 2009 to 449,000 by the year 2025, dramatically impacting the country's healthcare system [4]. Further, worsening of CHF is associated with frequent hospitalizations, whose high costs additionally impact on health expenditures. Optimal medical therapy in CHF with reduced ejection fraction as recommended by heart failure guidelines includes the administration of an angiotensin-converting enzyme inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist [1]. Moreover, elevated heart rate has been shown to be an independent risk factor in CHF [5], and addition of the heart rate reducing agent ivabradine on top of these medications is supported in current European guidelines by a class IIa recommendation (level of evidence: B) for patients with systolic heart failure and heart rate ≥ 70 bpm [1]. Ivabradine acts by inhibiting the I_f current in the sinus node, and lacks other direct hemodynamic effects [6]. In the randomized controlled Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT), ivabradine reduced the combined endpoint of mortality and hospitalization for heart failure by 18%, and hospitalization for heart failure by 26% in comparison with placebo [7]. Ivabradine was also associated with improved clinical status, functional capacity, and quality of life in CHF patients in randomized controlled trials [8,9]. While randomized trials are essential to demonstrate the efficacy and

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safety of drugs by means of a rigorous design, they also need to be complemented by real-life studies to ascertain their effectiveness and safe use in clinical practice. Indeed, profiles of CHF patients seen by practitioners in everyday life often differ from the ones included in randomized clinical trials, which usually constitute carefully selected samples based on restrictive inclusion and exclusion criteria. Only a few studies investigated the effectiveness of ivabradine in CHF patients in real life settings. In a previous study, we found that use of ivabradine was associated with reduced symptom burden in CHF patients and improved quality of life in clinical practice [10]. However, these data were limited by a relatively short evaluation period (4 months of follow-up). We therefore hypothesized that use of ivabradine might be associated with better symptom control and quality of life also in the longer term, paralleled by reduced hospitalization frequency for CHF.

2. Methods

2.1. Study design

The RELIf-CHF (Long-term treatment with ivabradine in ambulatory patients with CHF) study was an observational follow-up study aiming to analyze the long-term effectiveness and tolerability of ivabradine used in compliance with its registered indication in outpatients with CHF. We used a multicenter, prospective design to capture information on the therapeutic effect of ivabradine in routine clinical practice. The study followed the general recommendation of BfArM (German Federal Institute for Drugs and Medical Devices) and Paul-Ehrlich-institute (German Federal Institute for Vaccines and Biomedicines) for non-interventional studies. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the Freiburg Ethics Commission International prior to study start.

2.2. Participating sites and patients

Cardiologist centers throughout Germany recruited ambulatory patients according to ivabradine's registered indication in CHF: patients with New York Heart Association (NYHA) class II to IV and systolic dysfunction; sinus rhythm; resting heart rate ≥75 bpm; combination with standard therapy including beta-blockers or when beta-blocker therapy is contraindicated or not tolerated. Enrolment of patients was based on physician's judgment of the medical usefulness of ivabradine. Dosing of ivabradine followed the recommendations of the product's labeling: starting dose 5 mg twice daily (2.5 mg twice daily for patients ≥75 years); dosage increased to 7.5 mg twice daily or decreased to 2.5 mg twice daily, if clinically indicated. The duration of the observation period was 12 months. The first patient was enrolled in October 2013, and the final documentation of the last patient was in August 2015.

2.3. Measurements

Data were collected in a standardized case report form at baseline, at three intermediate time points (planned after 1, 4, and 8 months of treatment), and 12 months after study inclusion. A written informed consent was obtained from each patient before entering the study. The following data were collected for measurement of effectiveness of the treatment at each visit: heart rate at rest, NYHA functional class, presence of symptoms and signs of decompensation (e.g., degree of dyspnea, peripheral edema, ascites, signs of congestion). In addition, we recorded occurrence of episodes of hospitalization due to worsening heart failure within the 12 months before study start, and during study between each visit. If available, brain natriuretic peptide (BNP) values and left ventricular ejection fraction (LVEF) were recorded. Quality of life was evaluated by means of the EQ-5D questionnaire and EQ-VAS (visual analogue scale ranging from 0 [worst imaginable health state] to 100 [best imaginable health state]) at baseline, 4 months, and 12 months. The EQ-5D questionnaire measures 5 dimensions of the patient's life (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), which were rated by the patient according to 3 levels (no problems, some problems, and extreme problems). The distribution of patients in the different levels was calculated for each dimension. A global quality of life score integrating all dimensions was also calculated. At study end, investigators were asked to assess the effectiveness of ivabradine treatment as poor, moderate, good, or very good. Safety of treatment was evaluated by recording adverse events leading to ivabradine's withdrawal during the study (whether or not considered related to the study drug), all adverse drug reactions (considered as possibly related to the study drug), and special situations (such as any drug overdose, lack of efficacy, exposure during pregnancy). All events were coded according to MedDRA 18.0.

2.4. Statistical methods

Due to the design of this open-label study, statistical analyses were kept predominantly descriptive. Mean (standard deviation, SD) or median (quartiles) are presented for continuous variables, and number of patients (percent) for categorical variables. Missing values were handled using the last observation carried forward (LOCF) method. Significance tests were carried out for exploratory purpose only. For heart rate, LVEF, and quality of life scores, changes from baseline to subsequent visits were tested by a Wilcoxon's signed-rank test. A chi-square test was used to analyze the changes in the distribution of patients in the different NYHA, BNP and decompensation classes at the different visits, as well as the frequency of hospitalizations before and after study start and the mean number of hospitalization per patient. p-Values are presented as two-tailed, and significance level was set at alpha <0.05. No correction of alpha level for multiple tests was performed. For NYHA class, signs of decompensation, and occurrence of hospitalizations, data are presented both for the whole cohort and subgroups of patients taking concomitant beta-blocker therapy. Three subgroups were defined according to the dose of beta-blocker: <50%, ≥50% to <100%, and ≥100% of target dose. Statistical analysis was performed using SAS® software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Participants and baseline characteristics

In total, 767 patients were included at 249 study sites. The final examination could be documented in 757 patients (99%). Complete data on all visits were available in 694 patients (90%). The mean study duration per patient was 11.2 months (SD 2.4).

The characteristics of patients at baseline are described in Table 1. Mean age was 65.5 years (SD 11.4), and 43% were female. The median duration of CHF was 2.8 years, ranging between 1.1 and 6.0 years for most patients. CHF was of ischemic origin in 61% of patients, i.e. 58% had established coronary artery disease, and 37% of the total cohort had suffered a myocardial infarction. Dilated cardiomyopathy was reported in 18% of patients. Most patients were in NYHA class II (54%) and III (37%), and 36% presented signs of decompensation at baseline (mostly worsening dyspnea and peripheral edema). Comorbidities/risk factors were present in 81% of patients; the most frequent were hypertension (81%), hyperlipidemia (57%), obesity (39%), diabetes mellitus (32%) and chronic obstructive pulmonary disease (20%). Regarding concomitant medication, 65% of patients were prescribed a beta-blocker (predominantly metoprolol and bisoprolol), 54% an angiotensin-converting enzyme inhibitor, 32% an angiotensin receptor blocker and 21% a mineralocorticoid receptor antagonist. About half of all patients on beta-blocker therapy received between ≥50% and <100% of target dose, and 20% received ≥100% of target dose.

3.2. Ivabradine dosing and tolerability

The mean daily dose of ivabradine was 9.6 mg (SD 2.0) at baseline, and 11.3 mg (SD 2.8) at the final visit. The main reasons for initiating the treatment with ivabradine at the time of study start were (several reasons may apply): the need for further heart rate reduction (603 patients, 80%); decreased exercise capacity (313 patients, 41%); intolerance to beta-blocker (212 patients, 28%); and contra-indication to beta-blocker (138 patients, 18%). At study end, 684 (90%) patients were still on treatment with ivabradine, and 73 (10%) patients had terminated treatment prematurely (data missing in 10 patients). The main reasons for withdrawal from treatment were adverse events (39 patients, 5%), and request of the patient (24 patients, 3%).

3.3. Effect of ivabradine on cardiac parameters

During the course of the study, heart rate decreased from 85 bpm (SD 12) at baseline to 69 bpm (SD 9) at the last visit; thus, mean reduction was 16 bpm (SD 12, $p < 0.0001$). Significant heart rate reductions were noted at all intermediary visits; in detail, heart rate reduction after 1, 4 and 8 months was 11, 15, 16 bpm, respectively. A total of 624 patients (83%) were responders to treatment defined as heart rate < 70 bpm, or reduction ≥10 bpm at last study visit). LVEF was documented at baseline and at least one subsequent visit in 391 patients. Mean LVEF values increased from 44% (SD 13) at baseline, to 47% (SD 12) at 4 months and 49% (SD 12) at the last visit. Corresponding mean change from baseline was +3% at 4 months (SD 6, $p < 0.0001$), and +5% at study end (SD 8, $p < 0.0001$).

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