Ivacaftor in Omani children with cystic fibrosis caused by p.Ser549Arg CFTR mutation

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ARTICLE INFO

Article history:
Received 8 July 2021
Received in revised form 15 September 2021
Accepted 18 October 2021
Available online 29 November 2021

Keywords:
Cystic fibrosis
Ivacaftor
CFTR modulators
Class III mutations
p.Ser549Arg

ABSTRACT

Background: Cystic fibrosis (CF) is a multisystemic chronic disease caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein. These mutations are classified into six classes. Ivacaftor is a CFTR potentiator that partially restores the CFTR function for class III mutations. In Oman, p.Ser549Arg (class III) is the most common mutation (65% of cases). Our study prospectively evaluated the tolerance and clinical efficacy of ivacaftor.

Methods: A prospective observational study was conducted at the Royal Hospital, Oman. All children aged 6–18 years who are followed and carry at least one copy of the p.Ser549Arg mutation were started on Ivacaftor and included in the study. Data collected included weight, height, forced expiratory volume in first second (FEV1), sweat chloride concentration, stool elastase level and liver enzymes at baseline and at 12, 24, 36, and 48 weeks after initiation of treatment. The number of CF pulmonary exacerbations one year before and during treatment were compared.

Results: Twenty one children were started on Ivacaftor (90% homozygous for p.Ser549Arg). The mean age was 10.8 (SD ±3.5) years. When compared to baseline, FEV1 significantly improved by a mean of 10.8 (SD ±13.3) percentage points (pp) and 14.3 (SD ±7.2) pp at 12 and 48 weeks respectively. The sweat chloride level significantly dropped from a mean of 107 (SD ±8.5) mmol/I to 38.5 (SD ±22.3) mmol/I at 12 weeks and remained low. The Body Mass Index (BMI) improved by a mean of 1.37 (SD ±1.3) kg/m2 and 1.9 (SD ±1.35) kg/m2 at 24 and 48 weeks of treatment respectively. The number of admissions the year before and during treatment reduced significantly from a mean of 2.2 (SD ±1.9) to 0.7 (SD ±1) admission per year. Two children developed transaminitis.

Conclusion: Ivacaftor is well tolerated and resulted in a significant improvement in FEV1, BMI and sweat chloride level in children with p.Ser549Arg CFTR mutation.

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1. Background

Cystic fibrosis (CF) is a multisystemic chronic disease that primarily affects the lungs, pancreas, sweat glands, and reproductive organs [1–3]. This autosomal recessive genetic disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The disease is common among Caucasian populations with a prevalence of 1:3000 [1,2,4]. As of January 2021, 442 variants are annotated on the CFTR2 database including 360 CF causing, 48 variants of varying clinical consequence, 23 non-CF causing, and 11 variants of unknown significance [5]. These mutations are traditionally classified based on their effect on CFTR protein production, trafficking, function, or stability into six different classes [6].

Historically, most of the available CF therapies were supportive [7,8]. However, CFTR modulators are new drugs that emerged over the last decade targeting the underlying defects in the CFTR protein [9]. Ivacaftor is a CFTR potentiator that increases the “open probability of CFTR channels at the cell surface” [1] to restore the CFTR function for class III mutations [9].
Class III (gating) mutations are very rare accounting for 1% of patients with CF [10]. Most studies assessing the effect of ivacaftor on class III mutations were performed on patients with G511D mutation [11,12]. In Oman, the class III (p.Ser549Arg) mutation is the most common accounting for 65% of cases [13]. This mutation was included in the KONNECTION study (4 patients) [1]. It was separately studied in a single retrospective cohort study in addition to a case report showing a similar response in comparison with G511D mutation [9,14]. Our study prospectively evaluated the tolerance and clinical efficacy of ivacaftor in Omani children with CF caused by the gating mutation p.Ser549Arg.

2. Methods

A prospective observational study was conducted at the Department of Child Health, Royal Hospital in Muscat which is the major tertiary care center taking care of around 110 pediatric and adult patients with CF. The study was approved by the Ministry of Health research ethical board. Patients consented for data collection. Confidentiality was maintained during data collection, entry, and analysis steps. No external funding was used.

The diagnosis of CF was based on a clinical phenotype consistent with CF or history of CF in a sibling in addition to elevated sweat chloride level (>60 mmol/l) or the identification of two-CF causing mutation using sanger sequencing of the CFTR gene. The sweat chloride was measured using a Macroduct sweat collection system developed by Wescor Inc (Logan, UT, USA).

In early 2016, all children and adolescents aged 6–18 years who are diagnosed with CF and carry at least one copy of the p.Ser549Arg mutation were started on ivacaftor and included in this study regardless of disease severity or baseline pulmonary function. The medication was provided freely by the hospital pharmacy. Data recorded at baseline included age, gender, CFTR mutation, weight, height, forced expiratory volume in first second (FEV1), sweat chloride concentration, stool elastase level, and liver enzymes including aspartate aminotransferase (AST) and alanine aminotransferase (ALT). At 12, 24, 36, and 48 weeks of ivacaftor treatment, weight, height, FEV1, sweat chloride concentration, stool elastase level, and liver enzymes including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured and compared using Wilcoxon test.

3. Results

Twenty-one children were started on KALYDECO® ( ivacaftor) 150 mg administered orally twice per day as recommended by the manufacturing agency. Nineteen patients (90%) were homozygous for p.Ser549Arg and only two were heterozygous. The mean age at the start of treatment was 10.8 (SD ±3.5) years (range 6–18 years). All of them were pancreatic insufficient (stool elastase <100 µg/g) and were not diagnosed with CF-related diabetes either impaired glucose tolerance. Baseline characteristics are shown in Table 1. Six of our patients (28%) had a baseline FEV1 below 40% (range 18–37) percent predicted. At 12 weeks of therapy, 2 patients developed transaminitis defined as ALT and/or AST three times more than the upper limit of normal (ULN) so were shifted to a once per day regimen and were not included in the study analysis beyond 12 weeks. Furthermore, one patient developed acute lymphoblastic leukemia (ALL) at 12 weeks of therapy, and hence, this patient was excluded from the study. However, this child continued to take ivacaftor throughout the chemotherapy protocol. The analysis included all 21 patients at 12 weeks, 19 patients at 24 weeks, and 18 patients at 36 weeks and 48 weeks of treatment as one patient did not show up for appointments.

There was a significant improvement in FEV1 (Fig. 1A) by a mean of 10.8 (SD ±13.5) percentage points (pp) (95% CI 2.9–18.6 pp) at 12 weeks and 14.3 (SD ±7.5) pp at 48 weeks (95% CI 11.5–24.8 pp) when compared to baseline (adjusted p-value 0.005 at 12 weeks and <0.0001 at 48 weeks). When children with a baseline FEV1 < 40% were sub-analyzed, and there was a significant improvement in their FEV1 from a mean baseline of 28.2% (SD± 7.1%) to 42.3% (SD± 10.6%) (Fig. 2). The sweat chloride level (Fig. 1C) dropped significantly from a mean of 107 (SD± 8.49) mmol to 38.5 (SD± 18.4) mmol and 35.9 (SD± 16.5) mmol at 12 and 48 weeks, respectively (adjusted p-value < 0.0001). The BMI (Fig. 1B) improved by a mean of 1.37 (SD± 1.3) kg/m2 (95% CI 0.4–2.1 kg/m2) and 1.9 (SD± 1.35) kg/m2 (95% CI 0.9–2.7 kg/m2) at 24 and 48 weeks of treatment, respectively, which was statistically significant (adjusted p-value 0.0001). All patients remained pancreatic insufficient (stool elastase <100 µg/g) through the study. The mean number of admissions with CF exacerbation the year before and during treatment showed a statistically significant reduction (p-value < 0.0001) from a mean of 2.2 (SD± 1.9) admissions per year to 0.7 (SD± 1) admission per year (95% CI 0.2–1.3).

4. Discussion

In this prospective observational study, we re-demonstrated the overall improvement in FEV1, BMI, and sweat chloride level seen in children with class III CFTR mutations who are treated with ivacaftor as shown in earlier studies [1,9,11,12,18–21]. Other reported positive outcomes like the improvement in quality of life, lung mucociliary clearance, lung clearance index (LCI), and Pseudomonas aeruginosa culture positivity were not analyzed in our study [22–24]. The importance of our study is that it is the largest study to examine the effect of this medication on p.Ser549Arg CFTR mutation with a follow-up period extending up to 48 weeks. In addition, it includes a relatively large percentage of children (28.5%) with advanced lung disease evident by low baseline FEV1.

Keeping in mind the difference in methodology, our results are close to the results reported by the KONNECTION group study which followed children ≥6 years of age with non-G511D mutation

Table 1

| Characteristics                          | Subjects, N = 21 |
|------------------------------------------|------------------|
| Female, n (%)                            | 10 (47.62)       |
| Age, years, mean (range)                 | 10.8 (6–18)      |
| Height, cm, mean (range)                 | 127.33 (105–151) |
| Weight, kg, mean (range)                 | 23.87 (13.5–39.1) |
| BMI, kg/m² [2], mean (range)             | 14.34 (11.4–19)  |
| Sweat chloride, mmol/L, mean (range)     | 107.32 (94–119)  |
| FEV1% predicted, mean (range)            | 55 (18–94)       |

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up to 24 weeks of therapy [1]. However, we have seen a higher absolute improvement in FEV1 at 48 weeks compared to the ENVISION group study which included children with a similar age range and G511D mutation followed up to 48 weeks of treatment (14.3 pp compare to 10.7 pp) [11]. We have also seen a higher drop in sweat chloride level at 48 weeks by 71 mmol/l compared to 56 mmol/l in the mentioned study. This difference could be explained by the fact that 90% of children in our study are homozygous for class III CFTR mutation. In addition, pulmonary exacerbations which are associated with the decline in pulmonary function that can be irreversible [25] significantly reduced during the year studied which could have contributed to this improvement in the mean FEV1. In terms of adverse events, ivacaftor was well tolerated by our patients in general. One subject developed ALL during the therapy but continued taking ivacaftor during his/her chemotherapy treatment. Additional two children developed transaminitis so the dose was changed to once daily. No other significant adverse events were noted.

The results of this study need to be interpreted keeping in mind the small sample size and that it lacks a placebo control group which is the main limitation of the method used. In addition, we did not objectively examine the effect on quality of life.

5. Conclusion

In this prospective observational study, Ivacaftor is well tolerated and resulted in a significant improvement in pulmonary function, BMI, sweat chloride level, and admission for exacerbation rates in children with p.Ser549Arg CFTR mutation including those with an advanced lung disease.

Authors roles

Research title: Ivacaftor in Omani children with Cystic Fibrosis caused by p.Ser549Arg CFTR mutation. Dr. Sumaya Al Oraimi:
Investigation, Methodology, Conceptualization, Supervision, Data curation, Writing - original draft, Writing - review and editing. Dr. Hussain Moshin: Formal analysis, Validation, Visualization. Writing - Original Draft, Writing - review and editing. Dr. Zainab Al Musawi: Study institute, Validation, Visualization, view and editing. Dr. Younis Al Balushi: Writing - review and editing. Dr. S. Al Oraimi, H. Mohsin, Z. Al Musawi et al. International Journal of Pediatrics and Adolescent Medicine 9 (2022) 104–107.

Visual abstract

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpam.2021.10.003.

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