The impact of modulators on faecal elastase in children with Cystic Fibrosis

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Introduction

CFTR modulators improve lung function, body mass index, and reduce pulmonary exacerbations. There is some evidence from clinical trials that CFTR modulators may restore some degree of pancreatic function[1,2,3], but this has not been thoroughly investigated in the "real world". A number of children from our centre's cohort, a large tertiary paediatric hospital in Northwest England, have reported a reduction in the symptoms of pancreatic insufficiency (PI) since commencing modulator therapy.

We aimed to investigate the effect of modulator therapy on pancreatic function by repeating faecal elastase (FE) sampling on children reporting improved symptoms.

Methods

FE samples were repeated from children who reported clinical evidence of improved pancreatic function. Clinical evidence included:

- lack of malabsorption symptoms (loose and/or oily stools) when Creon doses were not given with food.
- A change in bowel habit with greater tendency toward constipation (not resulting from change in dietary fibre and/or fluids).

Results

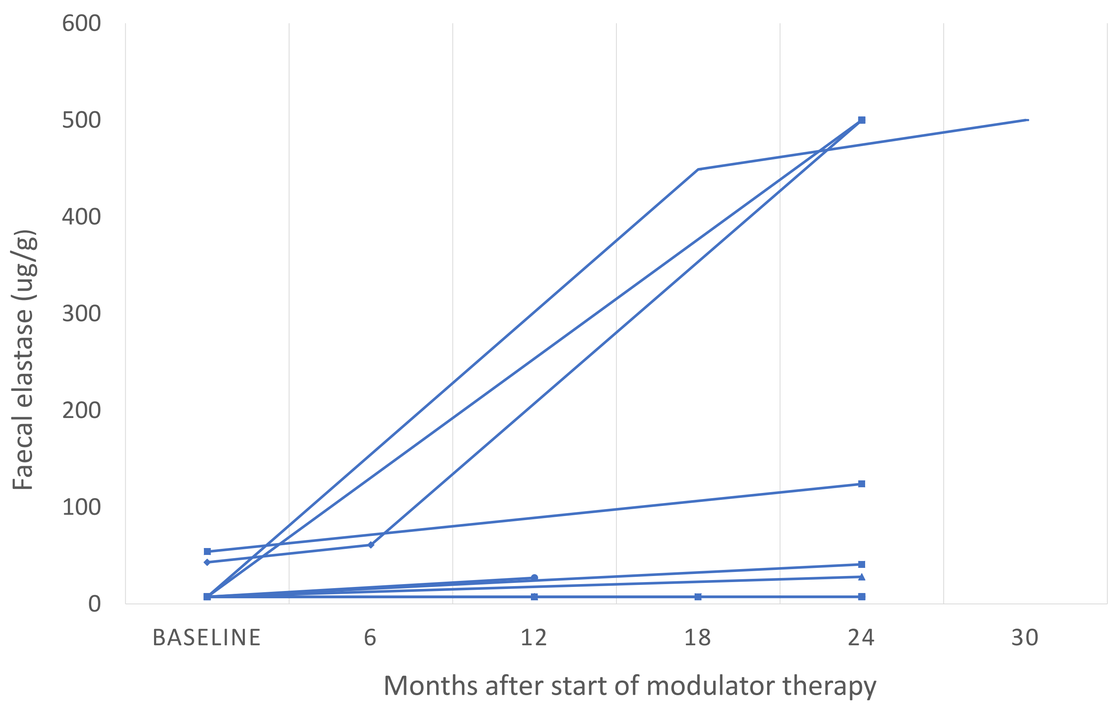
To date 14 children aged 2-14 yrs., with at least one Phe508del mutation, have had a FE repeated. All children were on treatment with ivacaftor (n=1), Orkambi (n=2) or Kaftrio (n=13)

3 children demonstrated an improvement to >200ug/g (defined as pancreatic sufficient (PS)) from a baseline at birth (diagnosis) of <15ug/g.

- Child 1, age 7 yrs., on ivacaftor treatment since age 4 yrs..
- Child 2, age 9 yrs., on Orkambi since age 5 yrs., then Kaftrio since age 8yrs.
- Child 3, age 7 yrs. FE first measured 1.5 years after starting Orkambi age 4 yrs. had increased to 449ug/g. This further improved to >500ug/g 10 months later having changed to Kaftrio age 6yrs.

4 children (3 on Kaftrio, two aged 7 yrs. and one aged 8 yrs., and one on Orkambi aged 3 yrs.) demonstrated an improvement from a baseline of <15ug/g, though still <200ug/g i.e., technically pancreatic insufficient.

7 children (one on Orkambi age 3 yrs., 6 on Kaftrio ages 7-14 years) remained pancreatic insufficient at <15ug/g despite reported improvements to symptoms of malabsorption.



CHANGE IN FAECAL ELASTASE OF 14 PATIENTS AFTER START OF MODULATOR THERAPY

Discussion

Some patients on CFTR modulators demonstrated recovery to pancreatic sufficient levels (PS), others partial recovery but the majority remained pancreatic insufficient (PI). In our patient's cohort to date, improvement in clinical symptoms does not appear to correlate well with biochemical analysis.

The time frame over which improvement occurred was not consistent. One patient who started on Orkambi and moved to Kaftrio showed improvement FE over a 2-year period from a baseline of 43ug/g, to 61ug/g at 6 months from modulator therapy to >500ug/g at 2 years. This reflects the findings in the KIWI and KLIMB studies which showed improvement in FE over the extended study time[1,2], but not the consensus that most FE improvement occurs within the first 6 months of treatment[3]. Munce et al reported 3 cases of pancreatic sufficiency after 2 years of therapy with Ivacaftor[4]. Therefore, those children who remain PI at 6 months may benefit from further FE sampling at 6–12-month intervals to see if there is an increase in FE.

With the use of CFTR modulators consideration should be given to reducing pancreatic enzyme replacement therapy (PERT) dose if children present with a change in bowel habit or symptoms of malabsorption. Reduction of PERT dosing has led to improved symptoms (e.g., abdominal pain when taking Creon)[5].

This makes advice/dosing of PERT challenging as often families are keen to stop PERT even though children are biochemically pancreatic insufficient. Managing symptoms through dose reduction seems to be the most pragmatic approach[5].

Conclusion

The available data on FE changes with CFTR modulators is still not powerful enough to allow for recommendations. It seems reasonable to consider routine FE testing to pick up changes in FE, particularly those presenting with symptom changes. However, in our centre's experience FE data does not appear to correlate well with symptoms. Further evidence is needed to guide management, particularly in those patients who report improved symptoms but have no biochemical evidence of recovery of pancreatic function. Data collection at our centre is ongoing, with further data becoming available. Our data will have a direct impact on clinical practice and could change annual review screening for pancreatic sufficiency in all CF pancreatic insufficient patients.

References

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