

Patients with S549R Gating Mutation Treated for 1 Year With Ivacaftor An update

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Class III CFTR Mutations

G551D

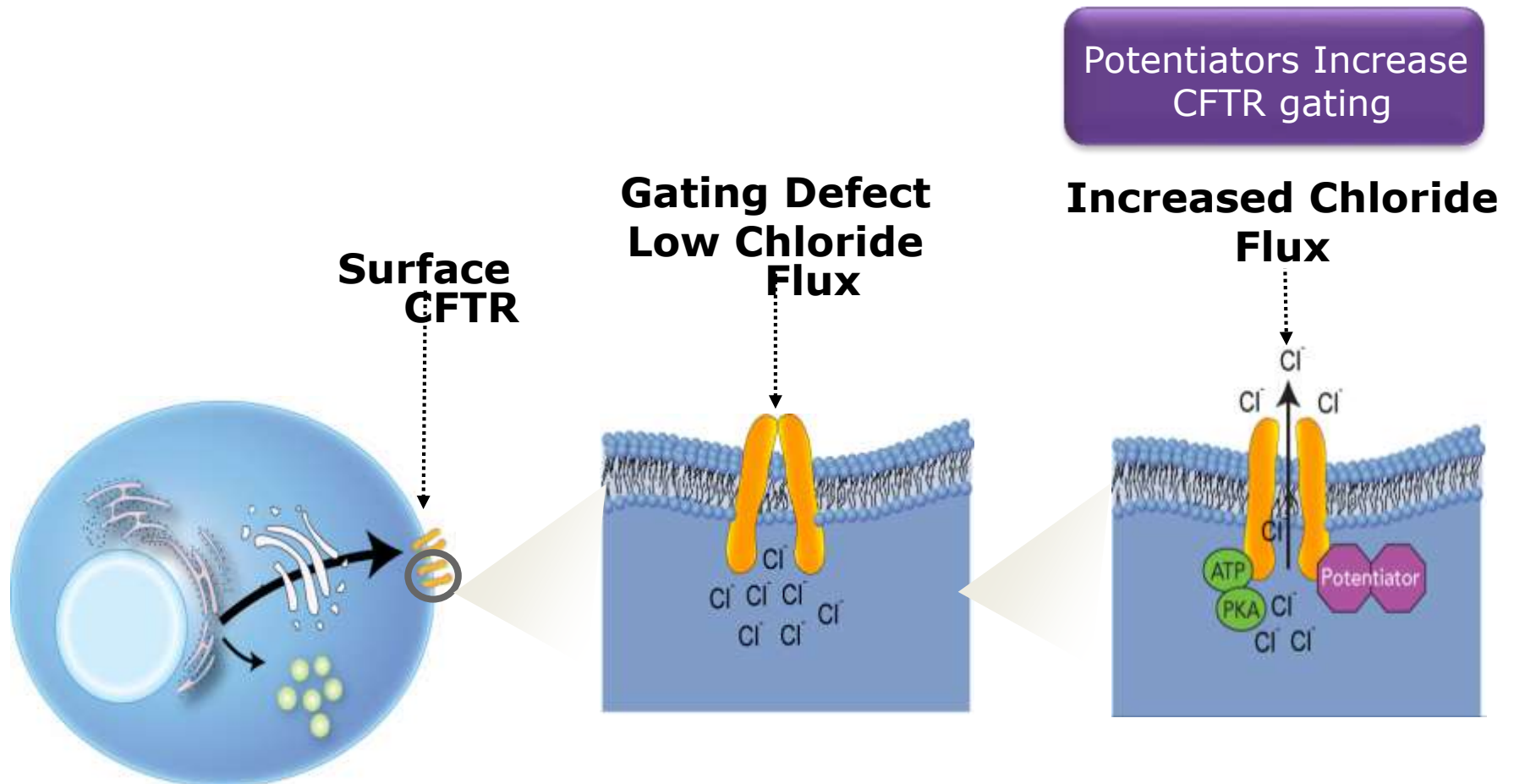
3rd commonest mutation

worldwide frequency – 4-5%

Populations of Celtic descent - 8%

Israel – 0%

Modulators of CFTR Function

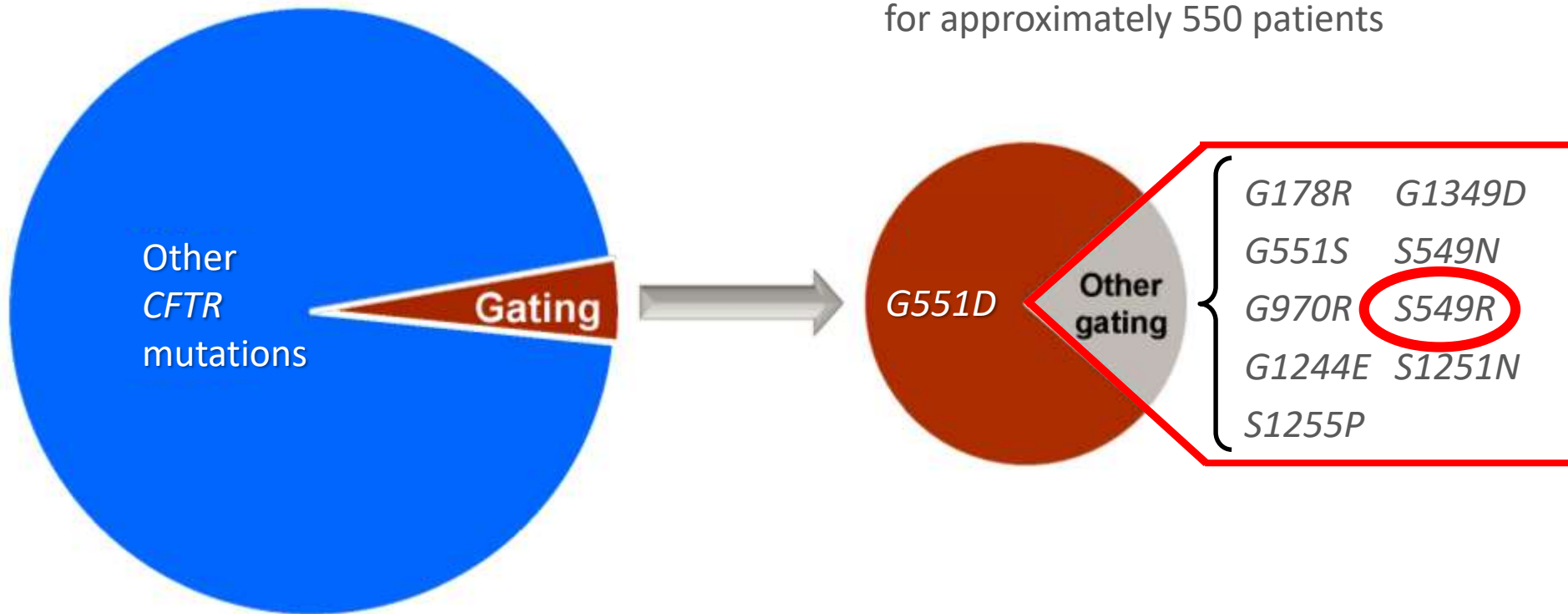


CFTR Gating Mutations

Worldwide, approximately 2,800 CF patients have a gating mutation on at least one allele

G551D is the most common gating mutation, with approximately 2,200 people with one allele

Other gating mutations account for approximately 550 patients



Ivacaftor treatment in patients with **non**-G551D CFTR gating mutations

Mutation, (n)	Absolute Change from Baseline in Percent Predicted FEV ₁ , Mean (min, max)	Absolute Change from Baseline in Sweat Chloride, mmol/L Mean (min, max)	Absolute Change from Baseline in BMI, kg/m ² Mean (min, max)
G1244E (5)	8.4 (-0.9, 18.4)	-55.1 (-75.0, -34.0)	0.6 (0.3, 1.3)
G1349D (2)	19.7 (3.0, 36.4)	-80.2 (-81.5, -79.0)	1.1 (1.1, 1.2)
G178R (5)	8.4 (-0.8, 17.6)	-52.5 (-64.5, -35.0)	0.9 (0.3, 1.5)
G551S (1)	3.1 ^a	-68.0 ^a	0.2 ^a
G970R (4)	2.6 (-1.3, 4.6)	-6.2 (-16.0, -2.0)	0.5 (-0.4, 1.8)
S1251N (8)	8.7 (-19.6, 21.4)	-54.4 (-84.0, -7.0)	0.7 (0.1, 1.8)
S1255P (2)	3.1 (-1.4, 7.7)	-77.8 (-82.0, -73.5)	1.6 (1.4, 1.8)
S549N (6)	11.3 (-2.4, 19.8)	-74.2 (-92.5, -53.0)	0.8 (0.0, 1.9)
S549R (4)	5.2 (-3.1, 12.7)	-60.7 (-70.5, -53.5)	0.5 (0.3, 0.8)
Overall	8.1 (-19.6, 36.4) (n=37)	-55.8 (-92.5, -2.0) (n=36)	0.7 (-0.4, 1.9) (n=37)

Clinical & Demographic Characteristics

	B.Y.	B.S.
	Male 25y	Female 23Y
Age at diagnosis	1.5Y	Birth
Genotype	$\Delta F508 \backslash S549R$	$\Delta F508 \backslash S549R$
Culture	Intermittent <i>P. aeruginosa</i> Intermittent <i>S. maltophila</i>	Chronic <i>P. aeruginosa</i> Intermittent <i>S. maltophila</i>
FEV1 %pred pre treatment	84	55

Clinical Outcomes

1. FEV₁
2. Sweat Chloride
3. Weight
4. Fecal Elastase
5. OGTT
6. OGTT- Insulin secretion

* No change in treatment except for ivacaftor

Conclusions

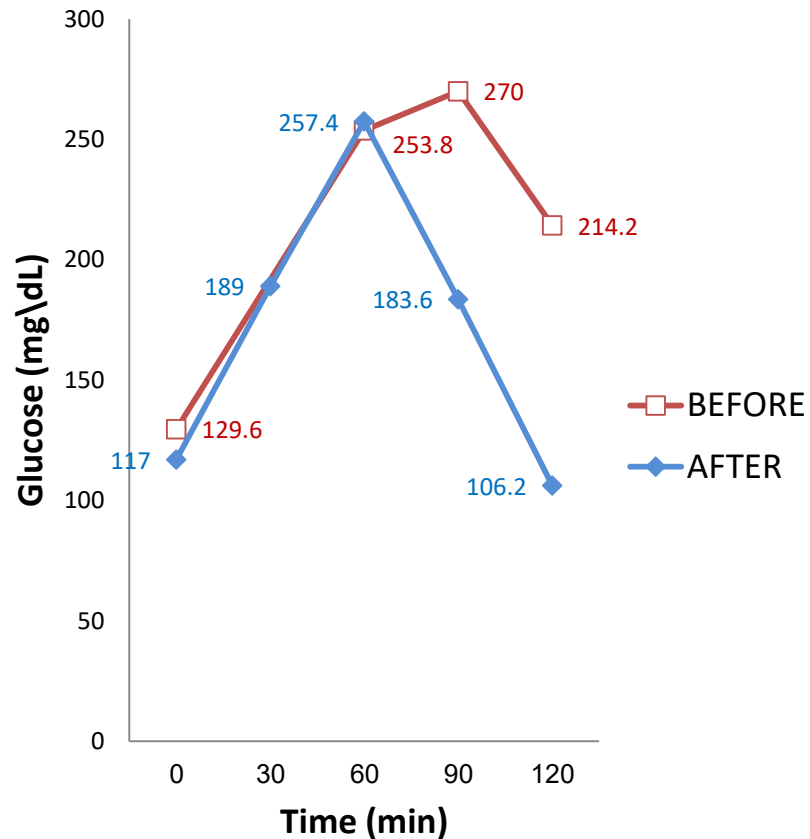
- In these two patients with the S549R gating mutation 16 weeks of treatment with Ivacaftor 150 mg b.i.d. was associated with:

- Improvement of **pulmonary function**
- Decrease in **sweat chloride concentration**
- Improvement in **OGTT**
- Improvement in **Insulin secretion**
- No major **weight** change

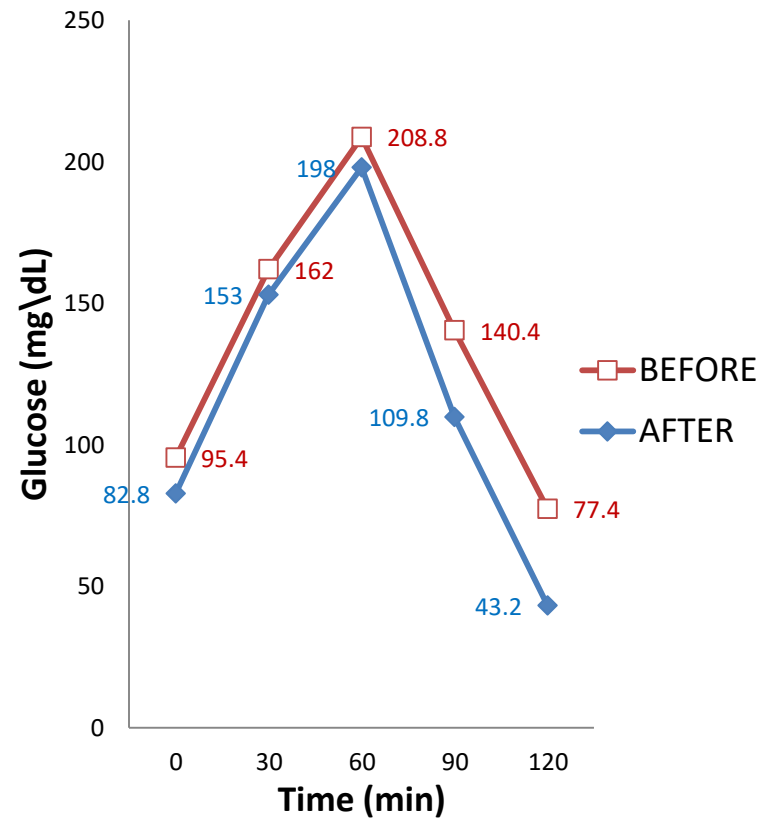
Adverse event - In one patient, transient diarrhea during the first weeks of treatment

Oral Glucose Tolerance Test (OGTT)

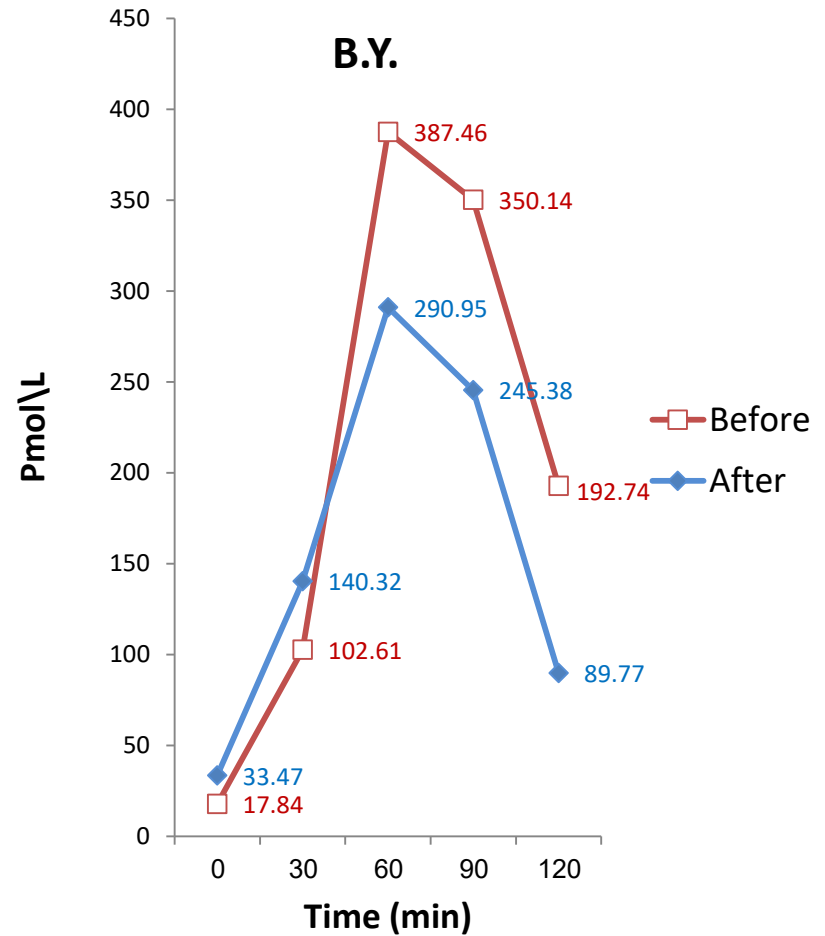
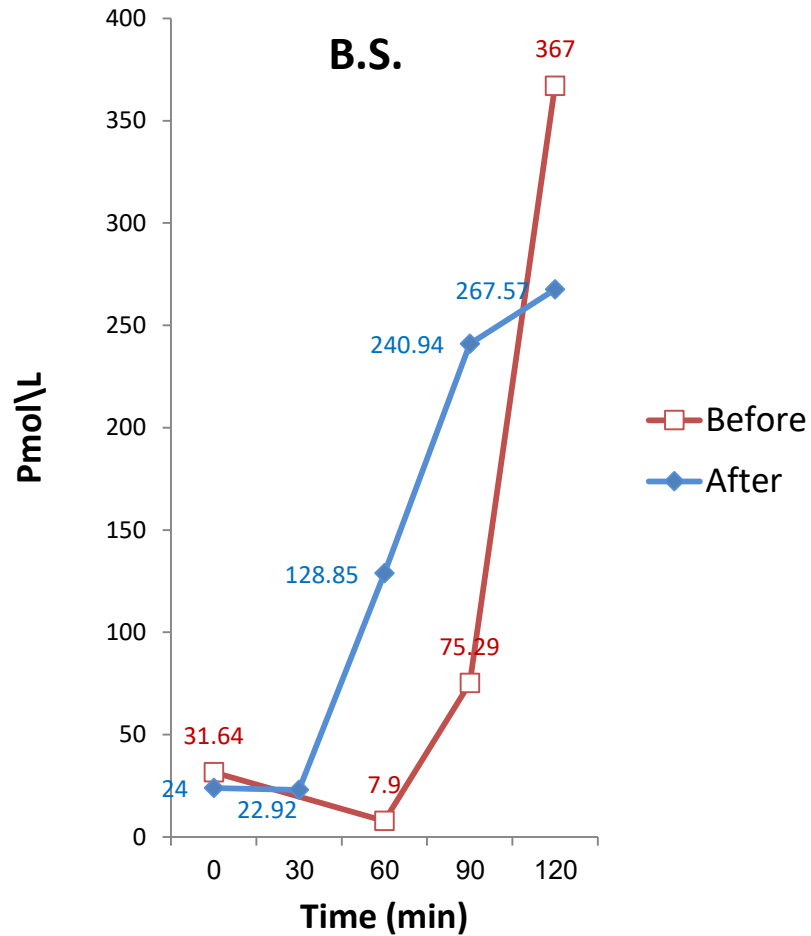
OGTT B.S.



OGTT B.Y.



OGTT- Insulin secretion



Clinical & Demographic Characteristics

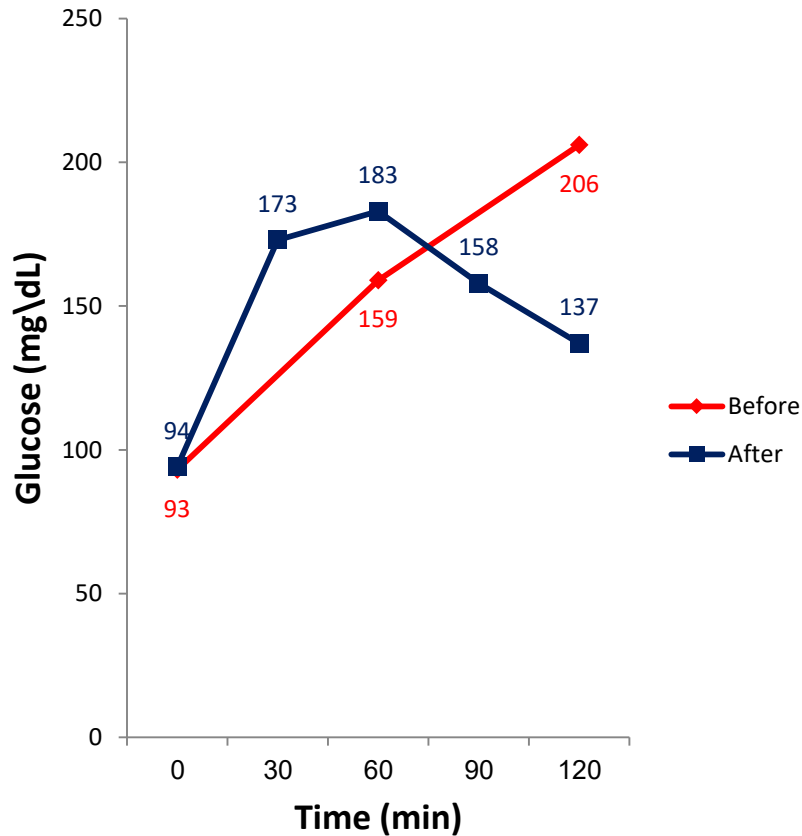
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	T.G.	T.S.
	Male 12y	Female 13.5y
Age at Diagnosis	0.5y	1.5y
Genotype	W1282X\S549R	W1282X\S549R
OGTT Prior to Treatment	NL	CFRD
BMI	16.3	24

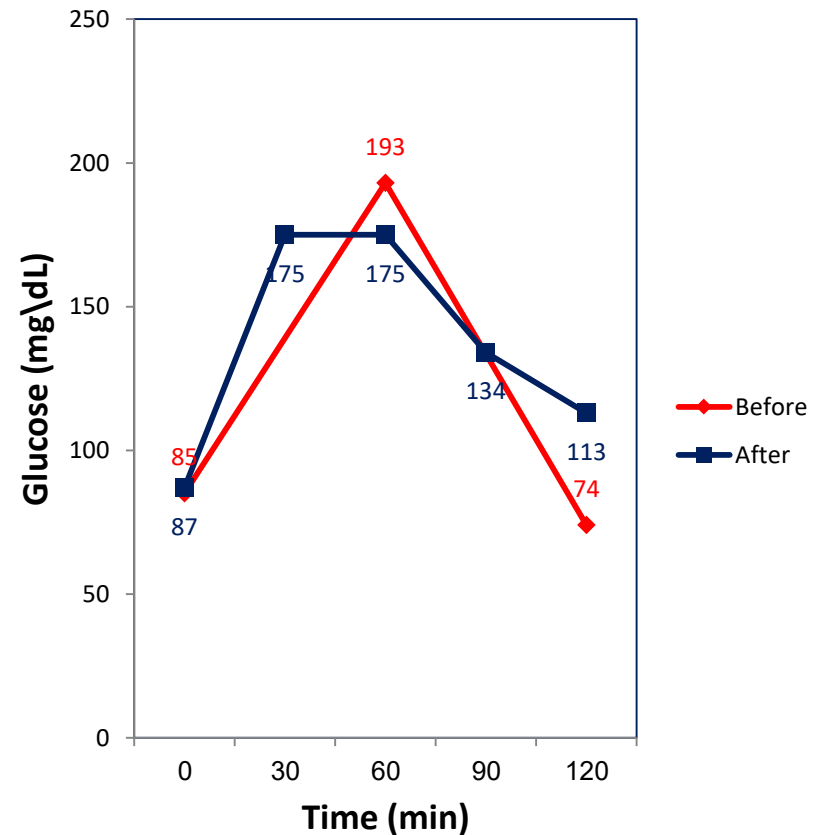
Oral Glucose Tolerance Test (OGTT)

Carmel CF Center

OGTT - T.S.



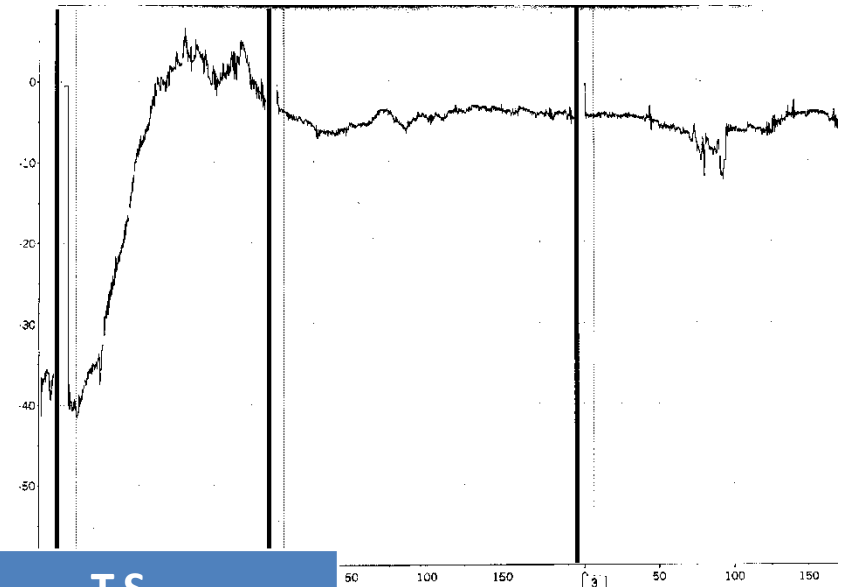
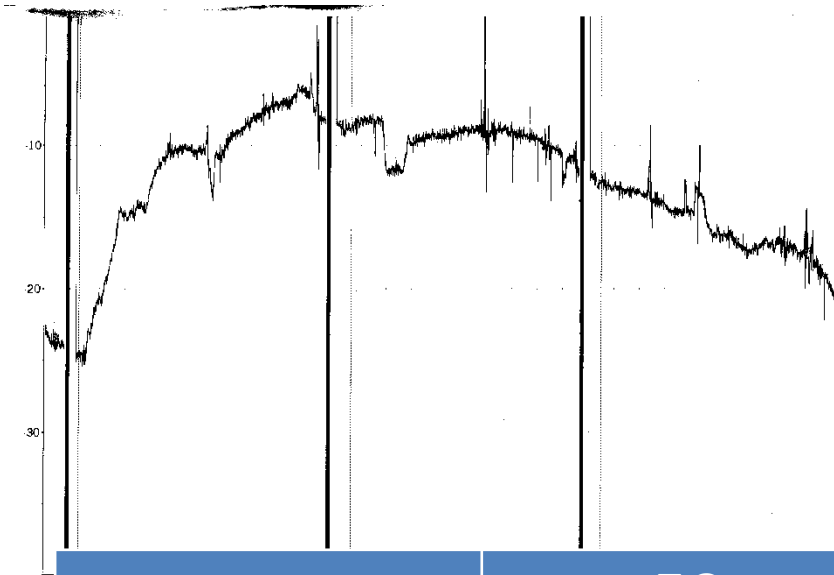
OGTT - T.G.



Nasal Potential difference (NPD)

NORMAL

CF



At

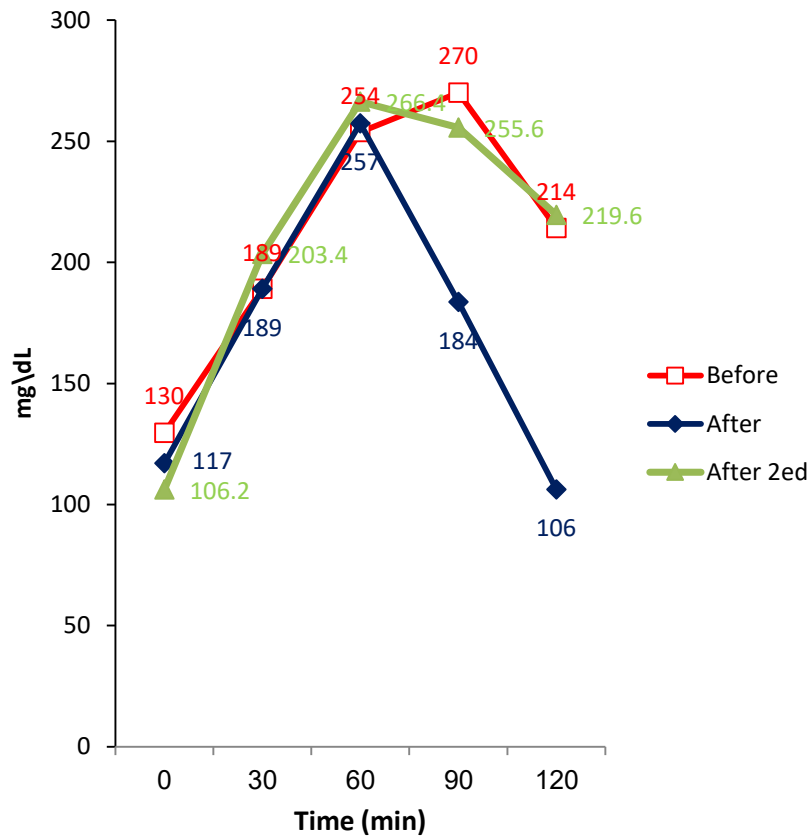
	T.G.	T.S.
Before Treatment	1.33	0.86
After Treatment	0.69	0.37

Isoproteranol

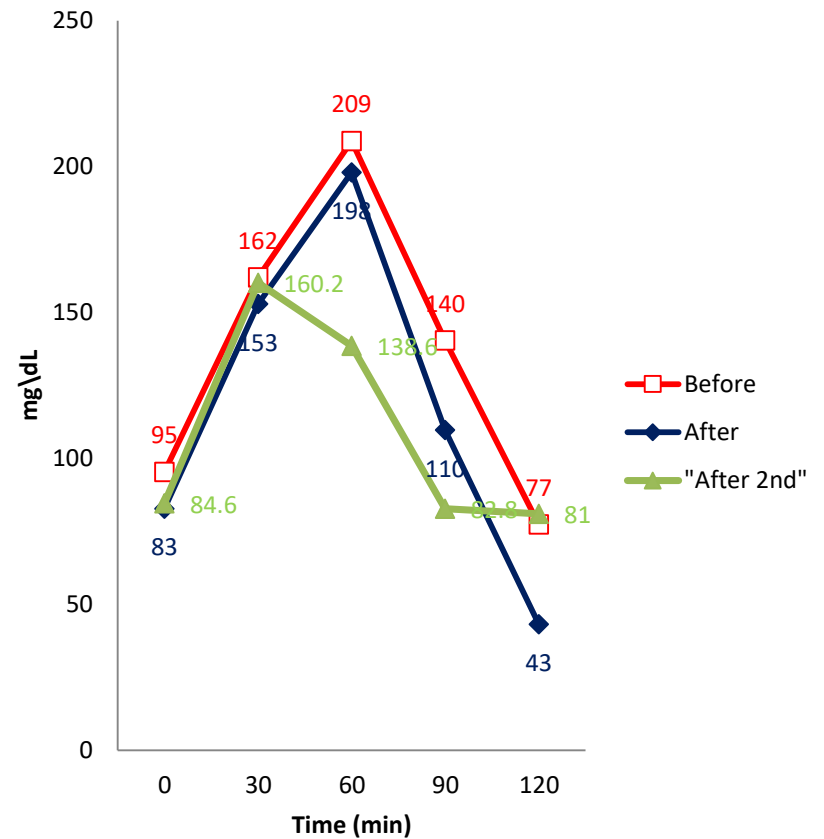
Oral Glucose Tolerance Test (OGTT)

1 Year

B.S.



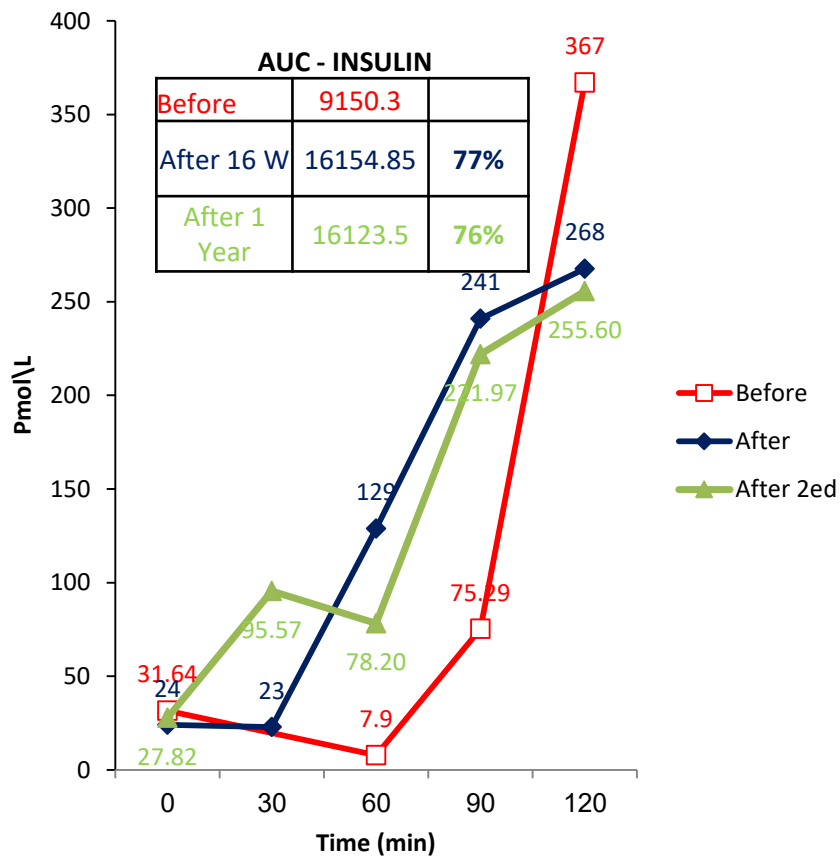
B.Y.



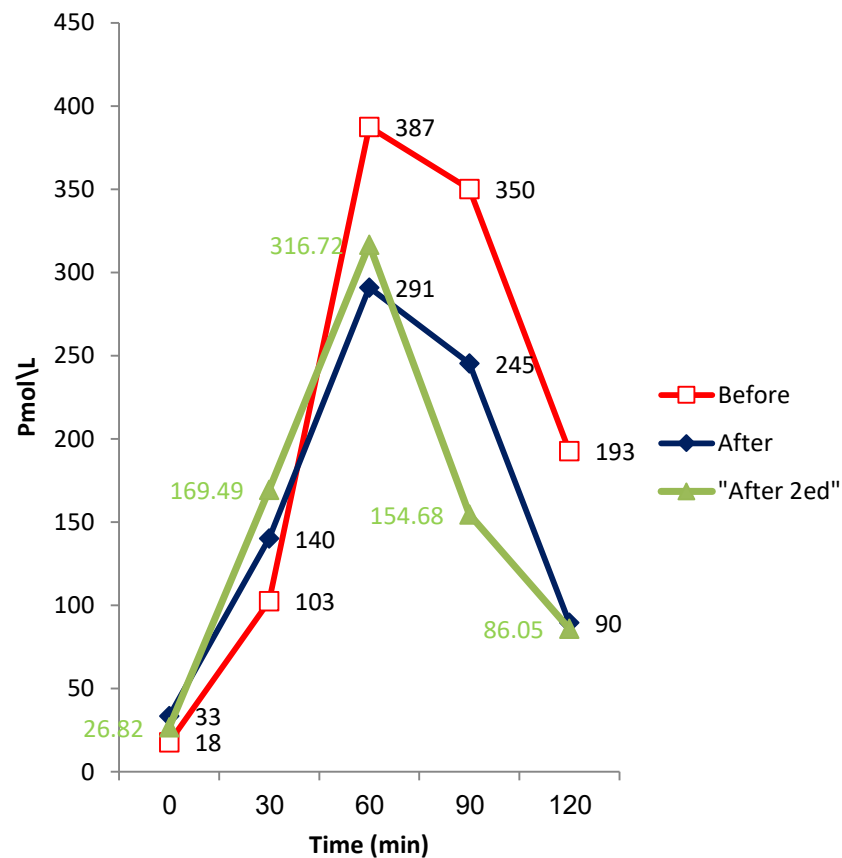
OGTT- Insulin secretion

1 Year

B.S.



B.Y.



Conclusions

- Follow-up after 1 year treatment with Ivacaftor 150 mg b.i.d. in two patients with the S549R gating mutation was associated with:
 - Regression to baseline in **OGTT** in one patient and improvement in the other
 - Maintenance of improvement in **Insulin secretion**
- In other two patients with the S549R gating mutation 10 weeks of treatment with Ivacaftor 150 mg b.i.d. was associated with:
 - Improvement in **OGTT**
 - Some Improvement in **NPD**

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CF Center, Hadassah Medical Center

Multidisciplinary team

