Supplementary Data S2 to S9

Tolerability and Efficacy of s.c. IgG Self-Treatment in ME/CFS Patients with IgG/IgG Subclass Deficiency: A Proof-of-Concept Study

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Table S2: Patient characteristics and treatment response

Pat.	sex/ age [years]	age [years] at disease onset	Bell	infection triggered onset	IgG deficiency	treatment prematurely ceased	responder month 12	response at month 6 or 9
1	m/44	30	50	no	IgG	2 injections		
2	m/33	17	40	EBV	IgG4		yes	
3	f/54	45	25	no	IgG3	month 6		
4	f/39	36	40	respiratory tract infection	IgG/IgG1			yes
5	m/37	28	20	EBV	IgG2			
6	m/60	55	30	no	IgG3			
7	f/32	31	30	respiratory tract infection	IgG3			
8	f/70	42	30	herpes zoster	IgG			yes
9	m/46	43	30	borreliosis	IgG3		yes	
10	f/62	61	40	peri-myocarditis	IgG			
11	f/49	47	20	EBV	IgG3		yes	
12	m/18	15	20	no	IgG4	month 3		
13	f/38	36	20	respiratory tract infection	IgG3		yes	
14	m/29	28	40	bronchitis	IgG4	1 injection		
15	f/54	51	45	respiratory tract infection	IgG3/IgG4	month 3		
16	f/46	36	20	mycoplasma pneumonia	IgG4		yes	
17	m/54	42	30	no	IgG			

[EBV= Epstein–Barr virus; f=female; m=male]

Table S3: Adverse events

adverse event	treatment completed (n=12)	treatment not completed (n=5) (P1, P3, P12, P14, P15)
injection site reaction	grade 1: n=10 grade 2: n=2 (P13, P11)	grade 1: n=3 grade 2: n=2 (P3, P14)
flu-like symptoms	grade 1: n=11 grade 2: n=1 (P4)	grade 1: n=2 grade 2: n=1 (P3)
headache	grade 1: n=2 grade 2: n=3 (P4, P7, P10)	grade 1: n= 3 grade 2: n=1 (P3) grade 3: n=1 (P1)
abdominal pain	grade 2: n=1 (P4)	grade 1: n=3 grade 2: n=1 (P3)
diarrhea	grade 1: n=2	grade 1: n=2
liver toxicity (ALT/GPT increase)	grade 1: n=3	grade 3 n=1 (P15)

Grade refers to the severity of the adverse event, as described in the "Common Terminology Criteria for Adverse Events (CTCAE)" Version 5. (grade 1: mild, grade 2: moderate, grade 3: severe)

S4

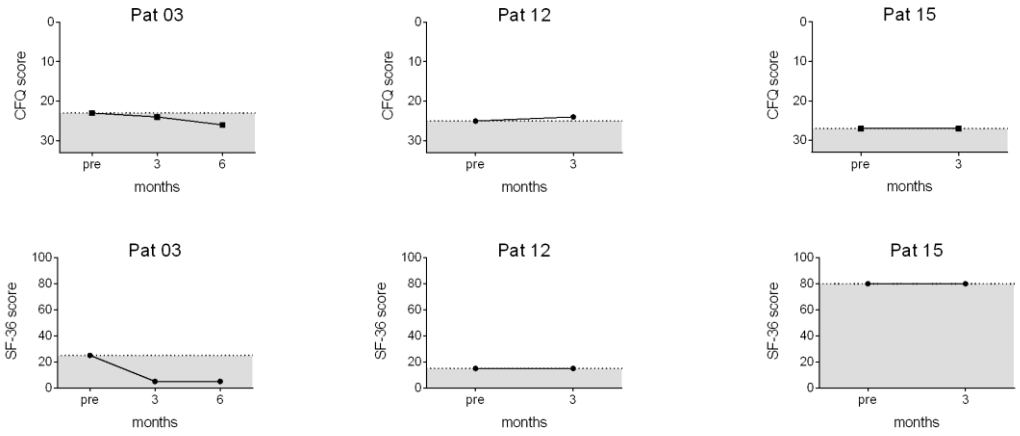

Figure S4: CFQ and the SF-36 data of patients 3 and 6.

S5

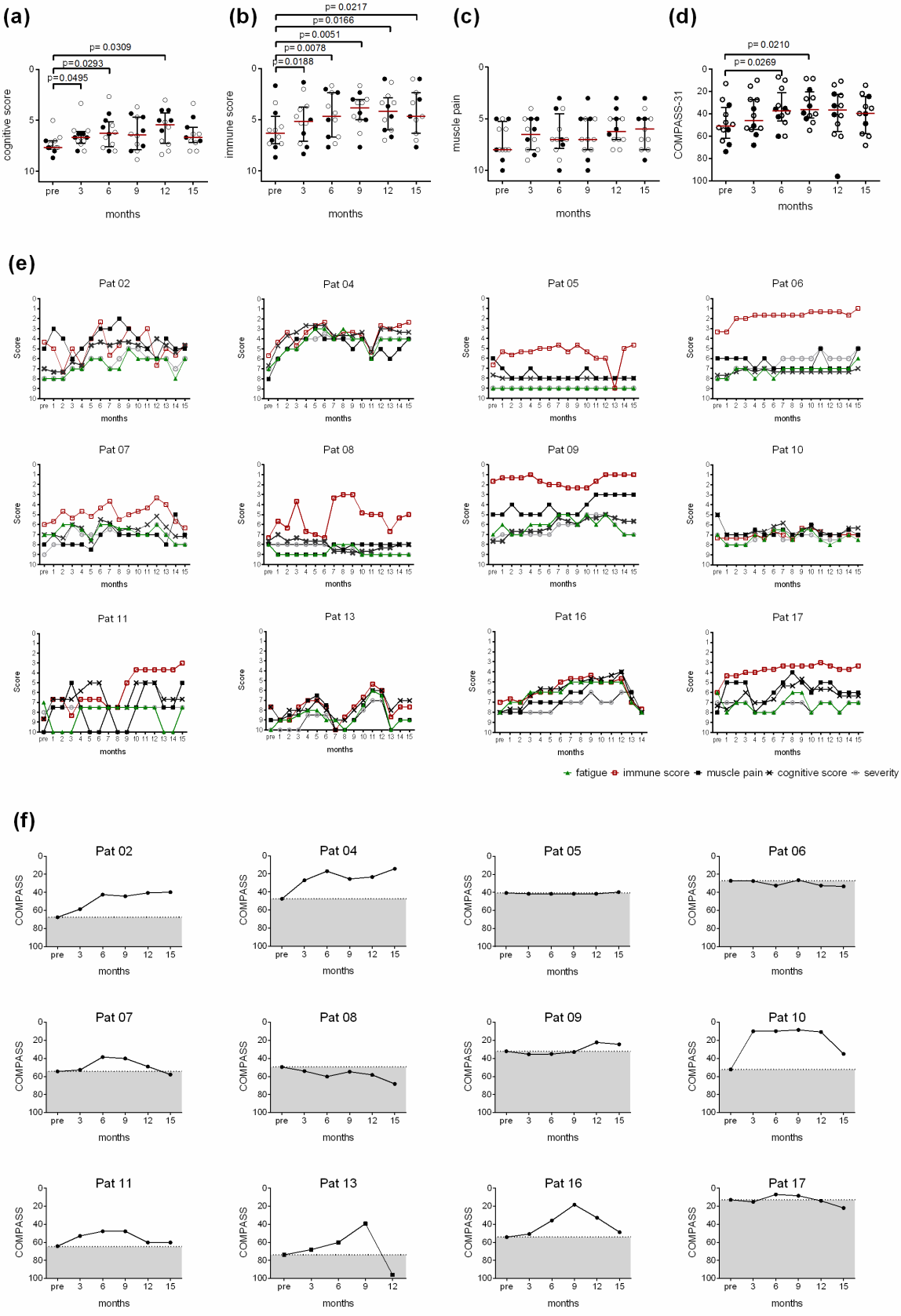
(a)
cognitive score
p= 0.0309
p=0.0293
p=0.0495
months
(b)
immune score
p= 0.0217
p= 0.0166
p= 0.0051
p= 0.0078
p=0.0188
months
(c)
muscle pain
months
(d)
COMPASS-31
p= 0.0210
p= 0.0269
months
(e)
Pat 02
Pat 04
Pat 05
Pat 06
Pat 07
Pat 08
Pat 09
Pat 10
Pat 11
Pat 13
Pat 16
Pat 17
Score
months
fatigue
immune score
muscle pain
cognitive score
severity
(f)
Pat 02
Pat 04
Pat 05
Pat 06
Pat 07
Pat 08
Pat 09
Pat 10
Pat 11
Pat 13
Pat 16
Pat 17
COMPASS
months

Figure S5: Symptoms of patients during s.c. IgG therapy. Median with interquartile range of **(a-c)** CCC symptom scores and **(d)** autonomous dysfunction (COMPASS-31) of the patients before (pre), during (months 3-12) and 3 months after treatment (month 15) are shown (responder indicated as filled circles). An overall significant improvement of symptoms during the IgG treatment at various time points was observed. Two-tailed Wilcoxon matched-pairs signed-rank test was performed for statistical analysis. **(e)** CCC symptom scores and **(f)** COMPASS-31 of the patients before (pre), during (months 3-12) and 3 months after the treatment (month 15) are shown. (COMPASS Score, healthy: 0)

S6

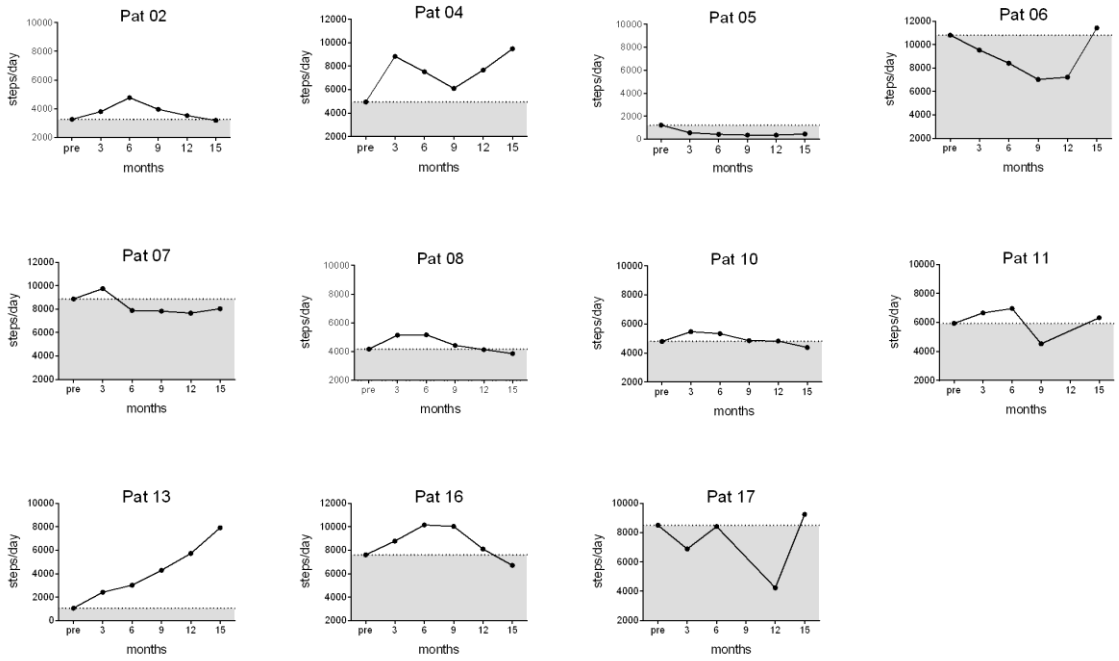

Figure S6: Daily steps assessed by Activity tracking. Steps of patients were counted by Vivofit® activity tracker during s.c. IgG therapy. Mean daily number of steps counted during one week before and thereafter monthly in 11 patients receiving 12 months of treatment.

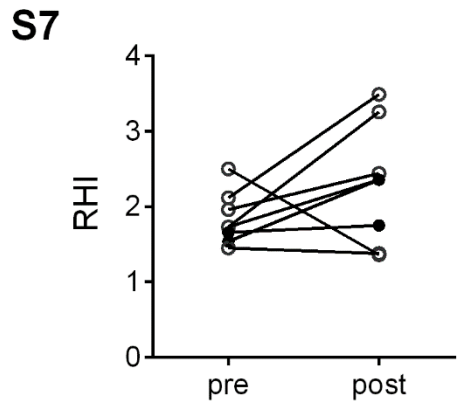

Figure S7: The reactive hyperemia index (RHI) assessed by Endopat. RHI of patients before (pre) and 3 months after the IgG treatment at month 15 (post) is plotted (responder indicated as filled circles).

S8

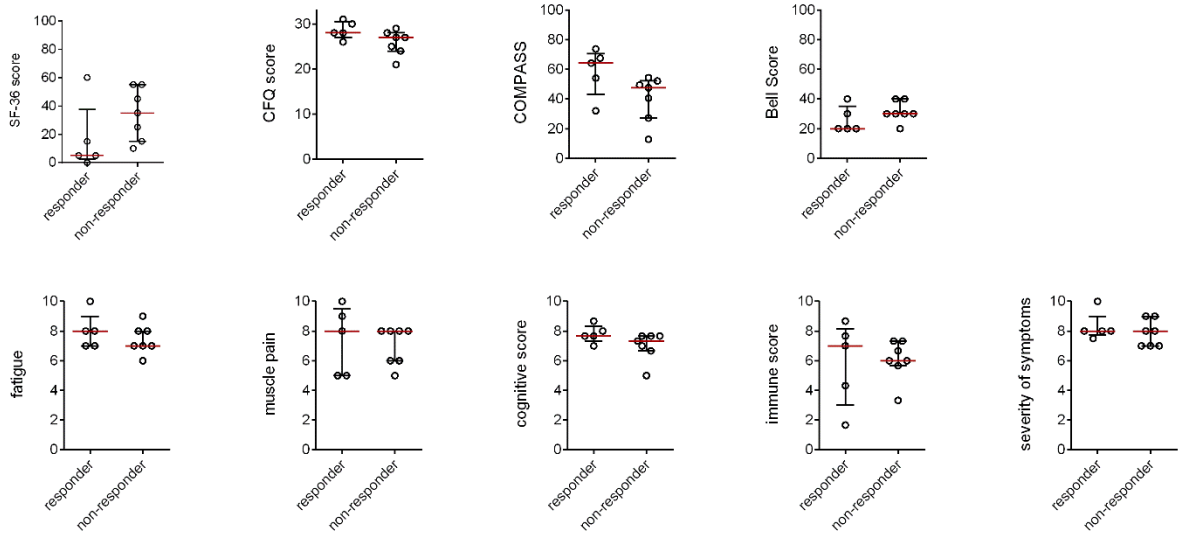

Figure S8: Comparative analysis of pretreatment symptoms of responder vs. non- responder. Median with interquartile ranges of SF-36, CFQ, COMPASS, Bell and CCC symptom scores of 5 responder and 7 non-responder patients, receiving 12 months of treatment, are shown.

Table S9: Laboratory values pretreatment (median with interquartile range [IQR])

parameter	responder at month 12 (n=5)	non-responder (n=7)	reference range
leukocytes [/nl]	7.96 (4.86/8.59), n=5	6.31 (5.86/8.66), n=7	3.90-10.50
lymphocytes [/nl]	1.86 (1.635/2.565), n=5	2.07 (1.705/2.425), n=7	1.50-3.00
erythrocytes [/pl]	4.5 (4.45/5.45), n=5	4.9 (4.5/5.2), n=7	4.3-5.8
Hb [g/dl]	14 (12.8/16.35), n=5	14.8 (13.7/15.1), n=7	13.5-17.0
MCV [fl]	86 (80.5/87), n=5	85 (83/87), n=7	80.0-99.0
MCHC [g/dl]	35.8 (34.15/36.15), n=5	35 (34/35.7), n=7	31.5-36.0
LDH [U/l]	298 (242.5/314), n=5	225 (212/266), n=7	135-250
CK [U/l]	121 (52.5/192.5), n=5	89 (63.75/113.5), n=6	< 190
CRP [mg/dl]	0.7 (0.4/2.05), n=5	0.8 (0.3/3.6), n=7	< 5
IgG [g/l]	8.96 (7.825/9.925), n=5	6.55 (5.68/9.97), n=7	7.00-16.00
IgG1 [g/l]	3.923 (3.768/4.907), n=4	3.28 (3.043/6.315), n=7	2.800-8.000
IgG2 [g/l]	4.122 (2.514/4.644), n=5	2.510 (1.832/3.353), n=7	1.120-5.700
IgG3 [g/l]	0.282 (0.166/0.8255), n=5	0.376 (0.127/0.558), n=7	0.240-1.250
IgG4 [g/l]	0.12 (0.03/0.5195), n=5	0.138 (0.1/0.273), n=7	0.052-1.250
soluble IL-2 receptor [U/ml]	328 (259/367), n=5	475.5 (316.8/650.3), n=6	< 710
IL-8	126.6 (75.2/205.1), n=5	84.4 (70.75/145.1), n=6	< 150
ANA	negative	negative	n.a.
β2 AdR AAB [Units/ml]	4.83 (3.705/8.79), n=5	5.395 (2.638/7.84), n=6	n.a.
M3 AchR AAB [Units/ml]	3.49 (2.795/7.955), n=5	3.02 (2.188/4.115), n=6	n.a.

sCD26	866.5 (811.1/1058), n=5	722.6 (621.3/1061), n=7	n.a.

[ANA= Antinuclear antibodies; CK= creatine kinase; β2 AdR AAB= autoantibody against β2 adrenergic receptor; CRP= C-reactive protein; Hb= hemoglobin;Ig=immunoglobulin; IL=interleukin; LDH= lactate dehydrogenase; MCHC= mean corpuscular haemoglobin concentration; MCV= mean corpuscular volume; M3 AchR AAB= autoantibody against Muscarinic acetylcholine receptor M3; sCD26= soluble Dipeptidyl peptidase-4; n.a. not available]