

INTRAVENOUS IMMUNOGLOBULIN FOR POST-POLIO SYNDROME : A DOUBLE- BLINDED, PLACEBO CONTROLLED, RANDOMIZED TRIAL

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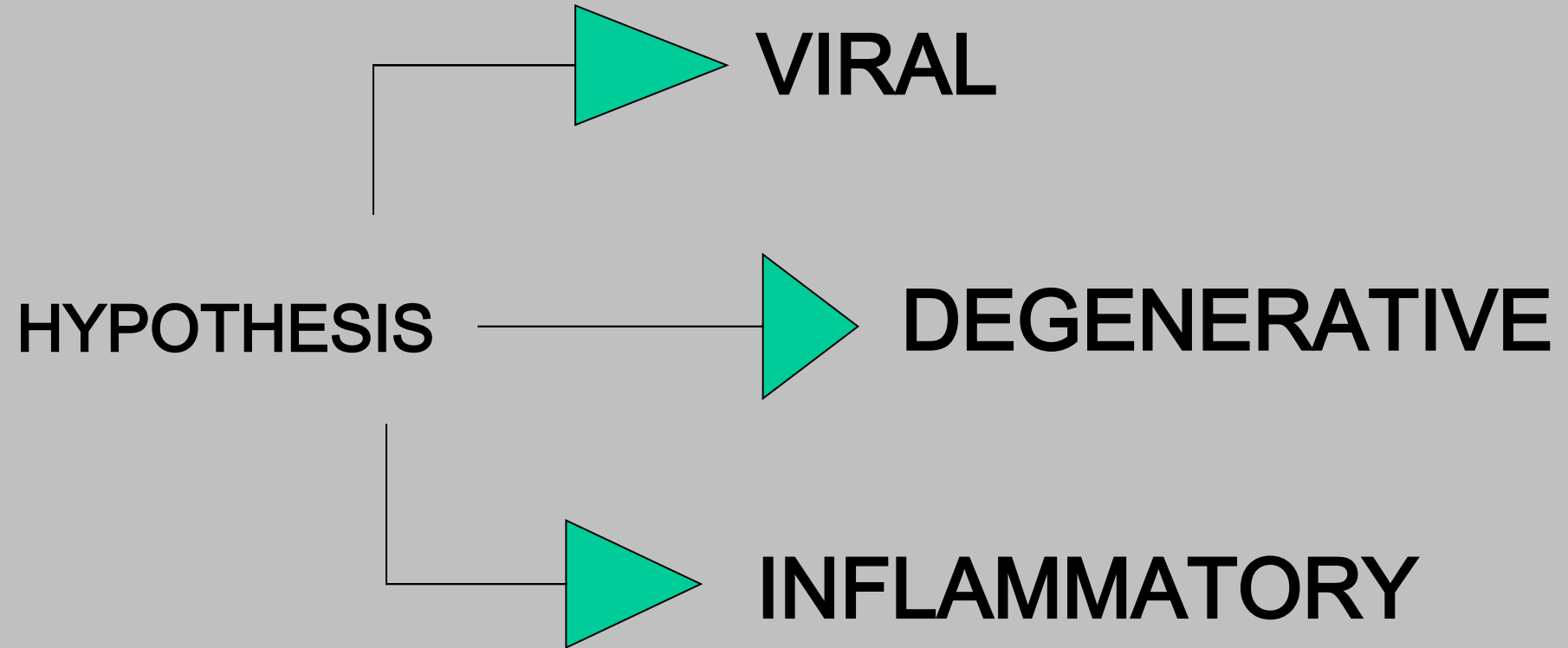


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BACKGROUND: PATHOGENESIS



INFLAMMATORY PROCESS



Journal of Neuroimmunology 150 (2004) 139–144

Journal of
Neuroimmunology

www.elsevier.com/locate/jneuroin

Prior poliomyelitis—IvIg treatment reduces proinflammatory cytokine production

Henrik Gonzalez^{a,b,*}, Mohsen Khademi^c, Magnus Andersson^{a,c}, Fredrik Piehl^c,
Erik Wallström^{a,c}, Kristian Borg^{a,d}, Tomas Olsson^c

- 16 pts
- IVIG 90g
- blood and CSF INF- γ mRNA TNF- α

Intravenous immunoglobulin for post-polio syndrome: a randomised controlled trial



Henrik Gonzalez, Katharina Stibrant Sunnerhagen, Inger Sjöberg, Georgios Kaponides, Tomas Olsson, Kristian Borg

Summary

Background Survivors of poliomyelitis often develop increased or new symptoms decades after the acute infection, *Lancet Neurol* 2006; 5: 493-500

European Journal of Neurology 2007, 14: 60-65

doi: 10.1111/j.1468-1331.2006.01552.x

Post-polio syndrome patients treated with intravenous immunoglobulin: a double-blinded randomized controlled pilot study

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J Rehabil Med 2006; 38: 138-140



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SHORT COMMUNICATION

EFFECT OF INTRAVENOUS IMMUNOGLOBULIN IN PATIENTS WITH POST-POLIO SYNDROME – AN UNCONTROLLED PILOT STUDY

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STUDY DESIGN

Two arms double blinded Randomized Controlled Trial
(treatment vs placebo)

50 pts IVIG/placebo

IVIG 0.4g/kg for 5 days/placebo saline

INCLUSION CRITERIA

1. History of acute poliomyelitis and Post-polio diagnosis according to Halstead's criteria (Orthopedics 1991; 14: 1209-1217), reconfirmed in 2006 by ENFS
 - anamnesis and neurological examination (muscle atrophy, depressed reflexes)
 - electrophysiological examination
2. Exclusion of any other neurological, orthopaedic or medical problems as causes of symptoms
 - electrophysiological examination
 - laboratory analysis
 - (orthopaedic examination)
 - (imaging)

Diagnosis of postpolio syndrome

1. History of previous established episodes of paralytic polio
2. Partial or fairly complete recovery
3. Period of functional and clinical stability: at least 15 years
4. Sudden or gradual onset of new symptoms and signs of muscle disfunction:
 - muscle weakness or abnormal muscle fatiguability,
 - generalized fatigue
 - new muscle atrophy
 - muscle or joint pain,
 - loss of muscle function
 - cold intolerance

Electrophysiological examination:

ENG and EMG

- Signs of old neurogenic reorganization due to previous poliovirus infection
- Signs of new lower motor neuron lesions

SEPs

- Normal sensory findings: useful to rule out root or nerve trunk pathology

Further investigations:

Imaging studies: mainly spinal MRI in order to rule out entrapment or root compression

Orthopaedic evaluation: to rule out bone or joint involvement

EXCLUSION CRITERIA

- BMI > 30
- Diabetes Mellitus
- Mild or severe heart disease
- Renal Failure
- Hypertension
- History of thromboembolism
- Oral anticoagulant therapy
- Previous IVIG treatment
- IgA deficiency
- Other autoimmune diseases
- Age > 70yrs
- Other causes of contraindication to therapy
- Other causes able to explain the complained symptoms

Baseline characteristics

	treated	placebo
Age of infection mths (mean± SD)	22.7 ±18.5	34.8 ±45.0
Age of onset of PPS yrs	48.4±6.8	47.9±9.9

PHASE I

1. Selection of patients according to inclusion and exclusion criteria
2. Presentation of the project to the patient which also receives informed consent form
3. Electrophysiological examination :
 - 4 limbs ENG
 - EMG
 - stable muscle (no variations over time)
 - healthy muscle (not interested by acute infection)
 - worsened muscle (new muscle weakness after a period of clinical stability of at least 15 years)
 - 4 limbs TMS
 - 4 limbs SEP
4. Laboratory workup:
 - Blood count
 - IgA titration
 - Liver and renal function
 - Serology for HIV and haepatitis

PHASE II

Patient's clinical evaluation:

Muscular Strength

MRC
Dynamic dynamometer

Fatigue

Fatigue severity scale (FSS)

Pain

Visual Analogue Scale (VAS)
101 Point Numerical Rating (101-PNR)

Quality of life

SF-36 (36 item Short-Form)

Muscle function

6 minutes walking test (6 MWT)

PHASE III

TREATMENT

25 PATIENTS

IVIG 0,4 g/Kg/daily for 5 consecutive days

25 CONTROLS

PLACEBO (saline) at the same way

Infusion:

- initial speed: 0,46-0,92 ml/kg/h → 10-20 drops/min
- maximal speed: 1,85 ml/Kg/h → 40 drops/min)

PHASE IV

CLINICAL FOLLOW-UP

- MRC and Dynamometer
- FSS
- VAS and 101-PNR
- SF-36
- 6 MWT

ELECTROPHYSIOLOGICAL FOLLOW-UP

- 4 limbs ENG
- 3 muscle EMG
- 4 limbs SEP
- 4 limbs TMS

2 months

4 months



Estimated period
of participation of the
patient

6 months

The patient can stop the treatment and leave
the study at anytime

RANDOMIZATION

- Double blinded study
- Randomization codes elaborated with statistical software STATA 9.2 (*[HYPERLINK](#)*) by the department of epidemiology and medical statistics, of the University of Verona and delivered to Bussolengo ASL pharmacist
- Every patients gets a code which he/she keeps for the duration of the whole study
- Pharmacy of Bussolengo Hospital prepares the samples: same bags labelled and screened containing IVIG and saline

MAIN RESPONSE VARIABLES

- **PRIMARY END POINT:**
Improvement of physical component of SF-36 in treated patients versus placebo
- **SECONDARY END POINTS:**
 - Increase in muscular strength (MRC, Dynamometer)
 - Reduction of fatigue (FSS)
 - Reduction of pain (VAS, 101-PNR)
 - Improvement in physical ability (6 MWT)

Sample's dimension and statistical power

Assuming:

- An improvement of at least 4 points in the score of physical component of SF-36 (*Gonzalez et al. 2004; Kaponides et al. 2006*)
- Alfa= 0,05
- Power of 80%
- correlation 0,9 (two measures on the same subject)
- Randomization ratio 1:1

...we need 21 subjects in every arm

Which will be raised to **25 PATIENTS** in account of possible dropouts

DATA ANALYSIS

“INTENTION TO TREAT” analysis

Primary and secondary endpoints:

Comparison of differences in the score of the scale used before and after treatment in the two groups by means of

- T-TEST (in case of gaussian distribution)
- MANN-WHITNEY’s TEST (in case of non gaussian distribution)

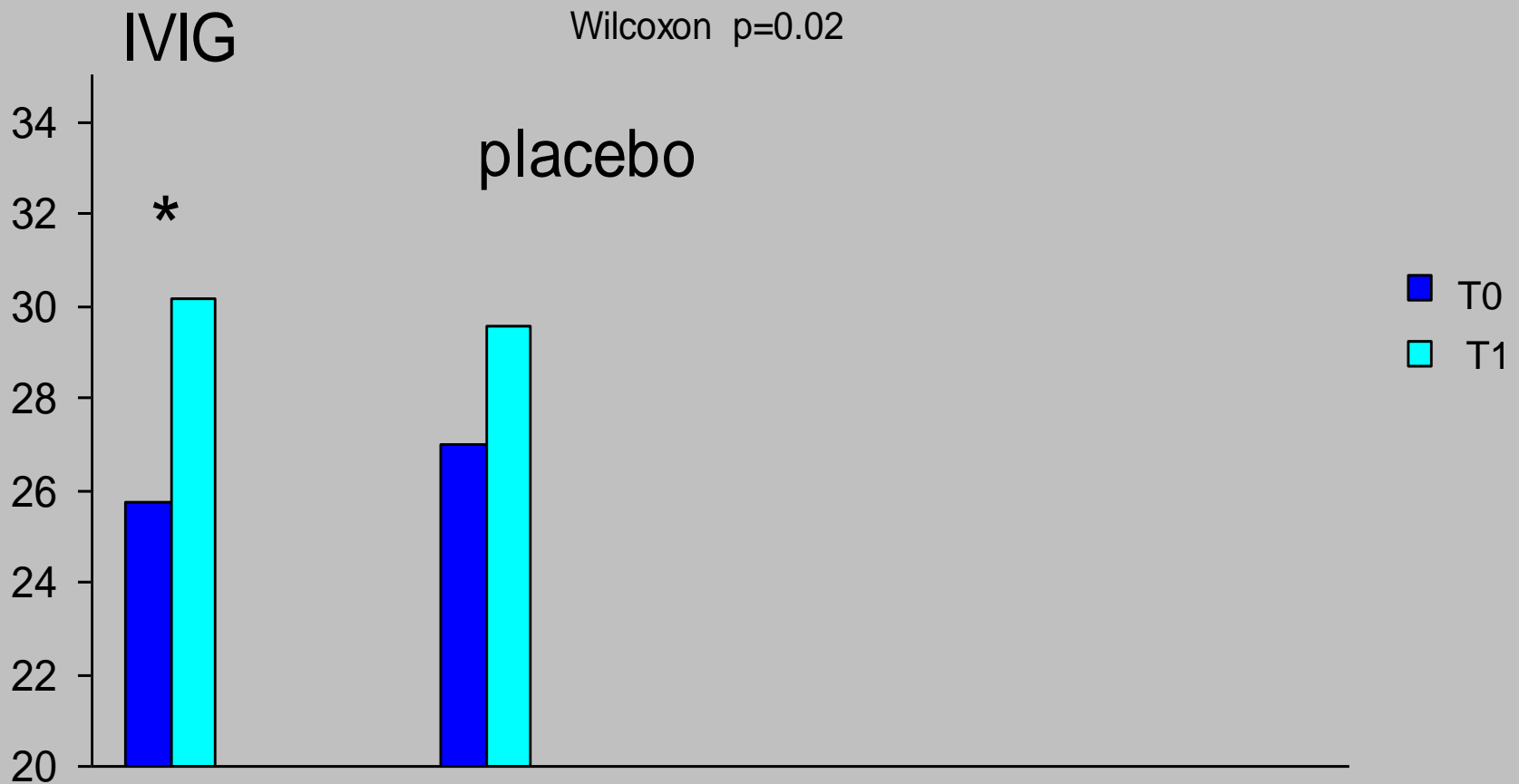
If necessary check out for biases (eg, severity of pathology, age):

- COVARIANCE ANALYSIS
 - Dependent variable: difference between values in variables before and after treatment/placebo
 - Independent variable : group (treatment/placebo); age; disease severity

Statistical analysis by means of software STATA 9.2

3 RESULTS PRIMARY ENDPOINTS

SF36- pc

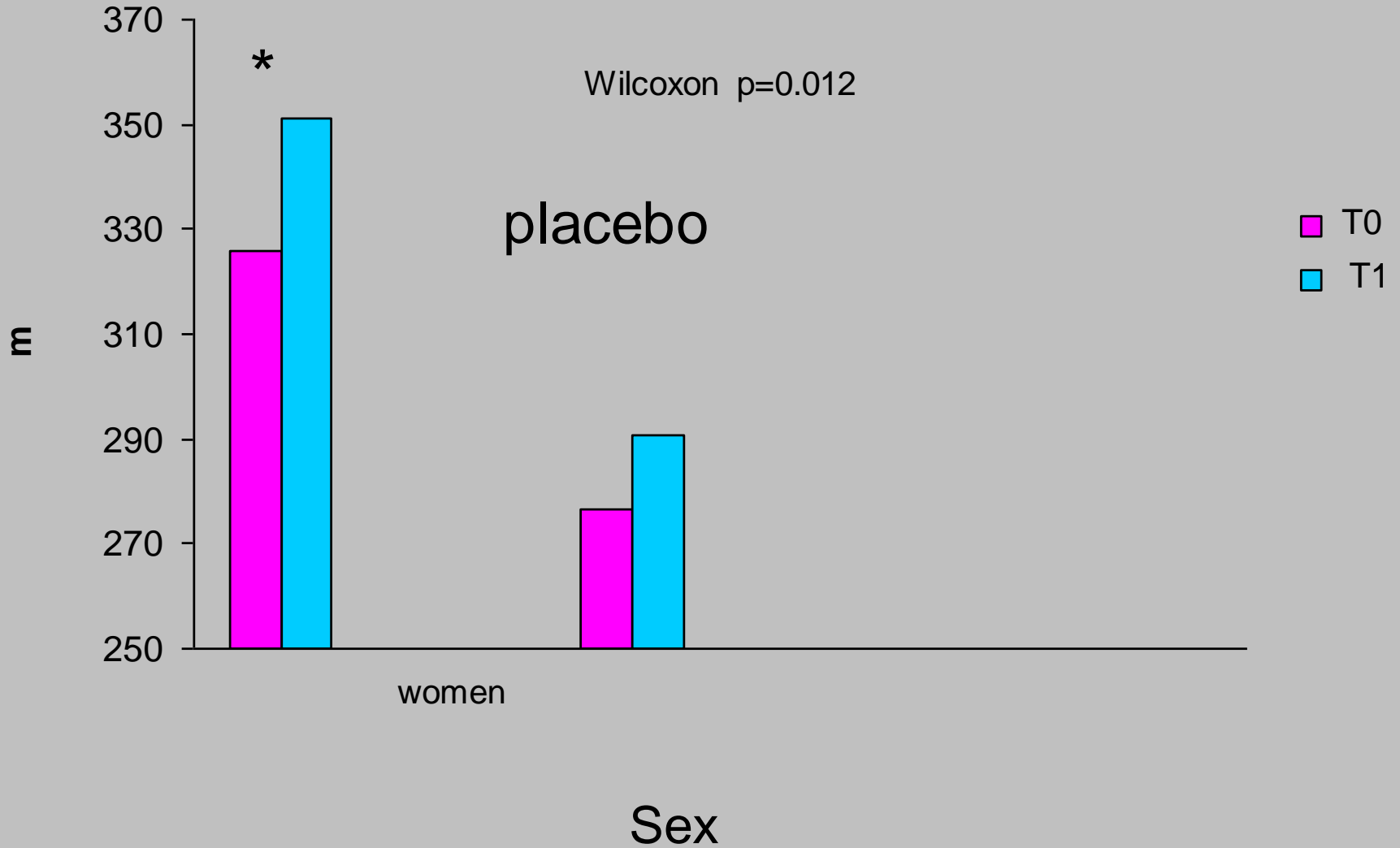


STRATIFIED ANALYSIS

Sex	F	M
Age of infection	<15,5	>15,5
Age of worsening	<50	>50
Time since PPS diagnosis yrs	<7,5	>7,5
FSS T0	<53,5	>53,5
VAS T0	<5,5	>5,5
6 min walking T0	<296,5	>296,5
SF36-pcT0	<24,9	>24,9

IVIG

6 min WALKING

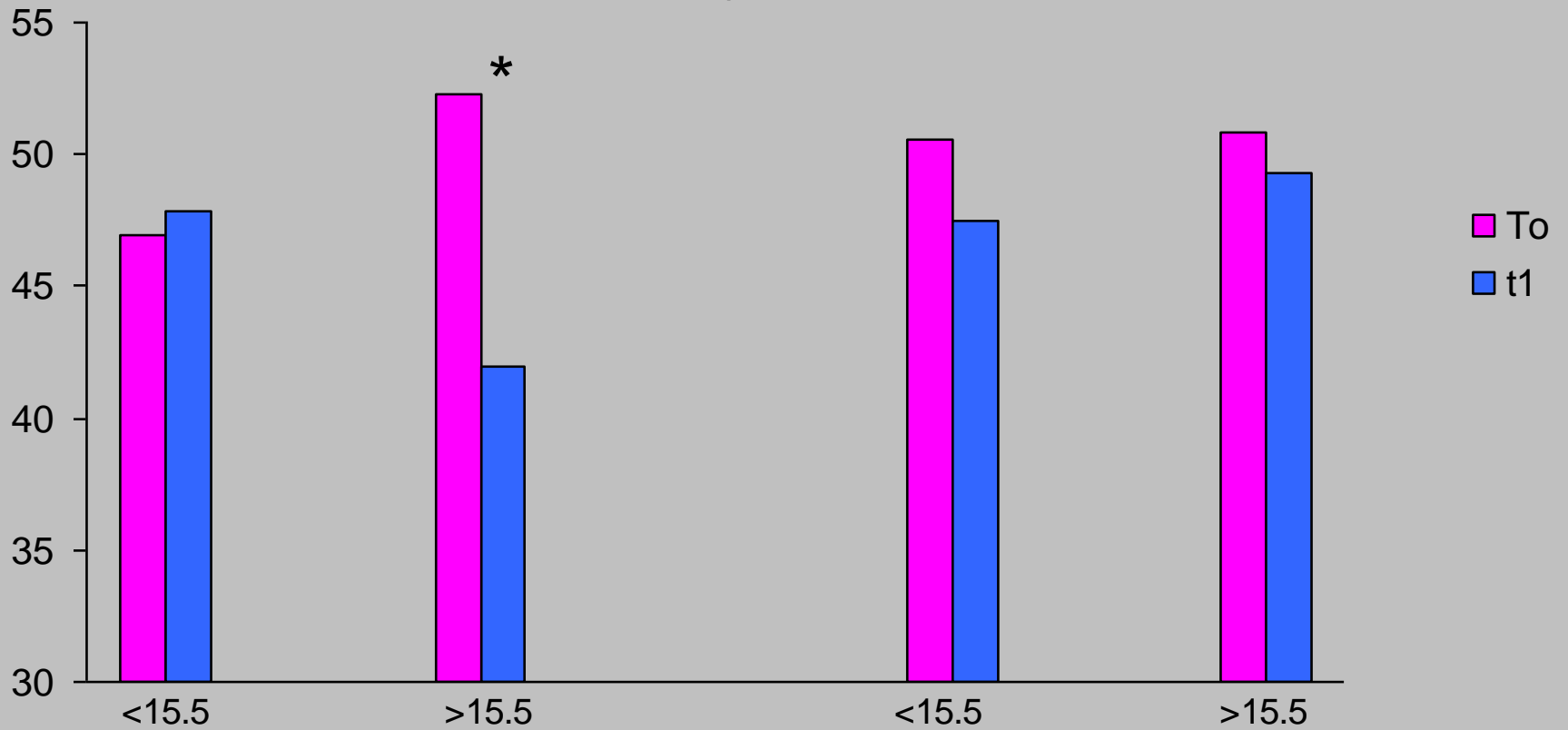


FSS

IVIG

Wilcoxon $p=0.008$

placebo



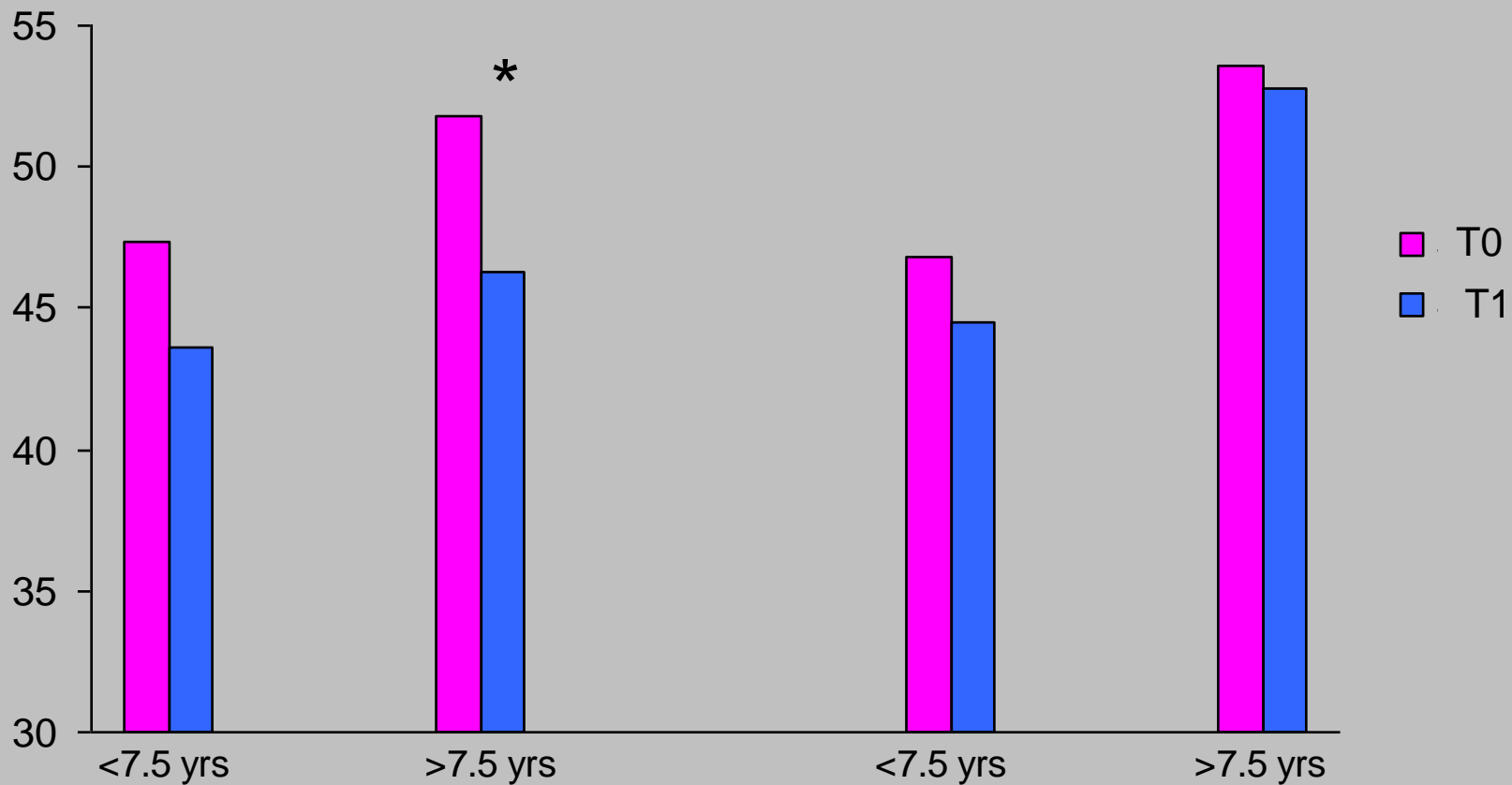
Age of infection

FSS

IVIG

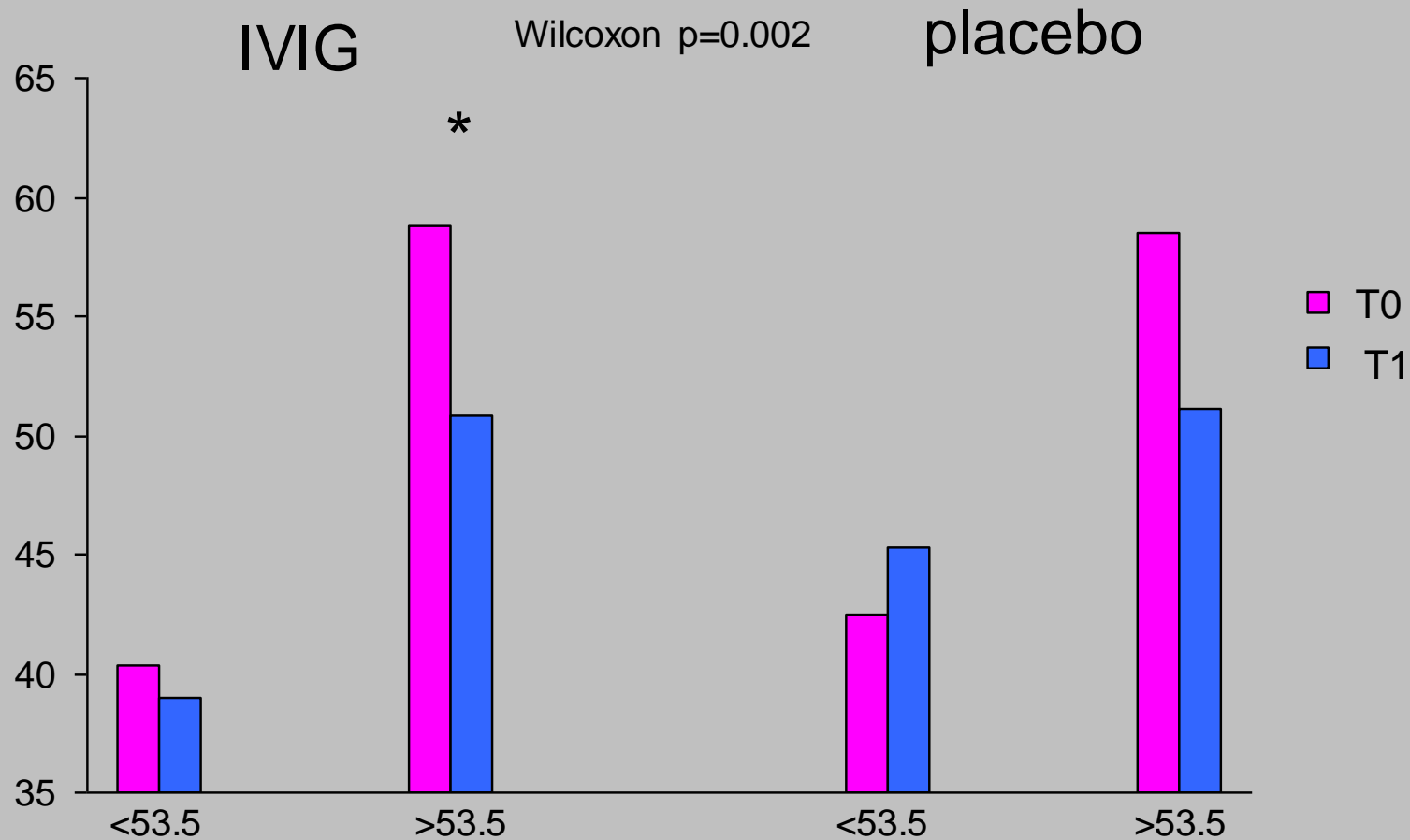
Wilcoxon $p=0.012$

placebo



Time to treatment

FSS



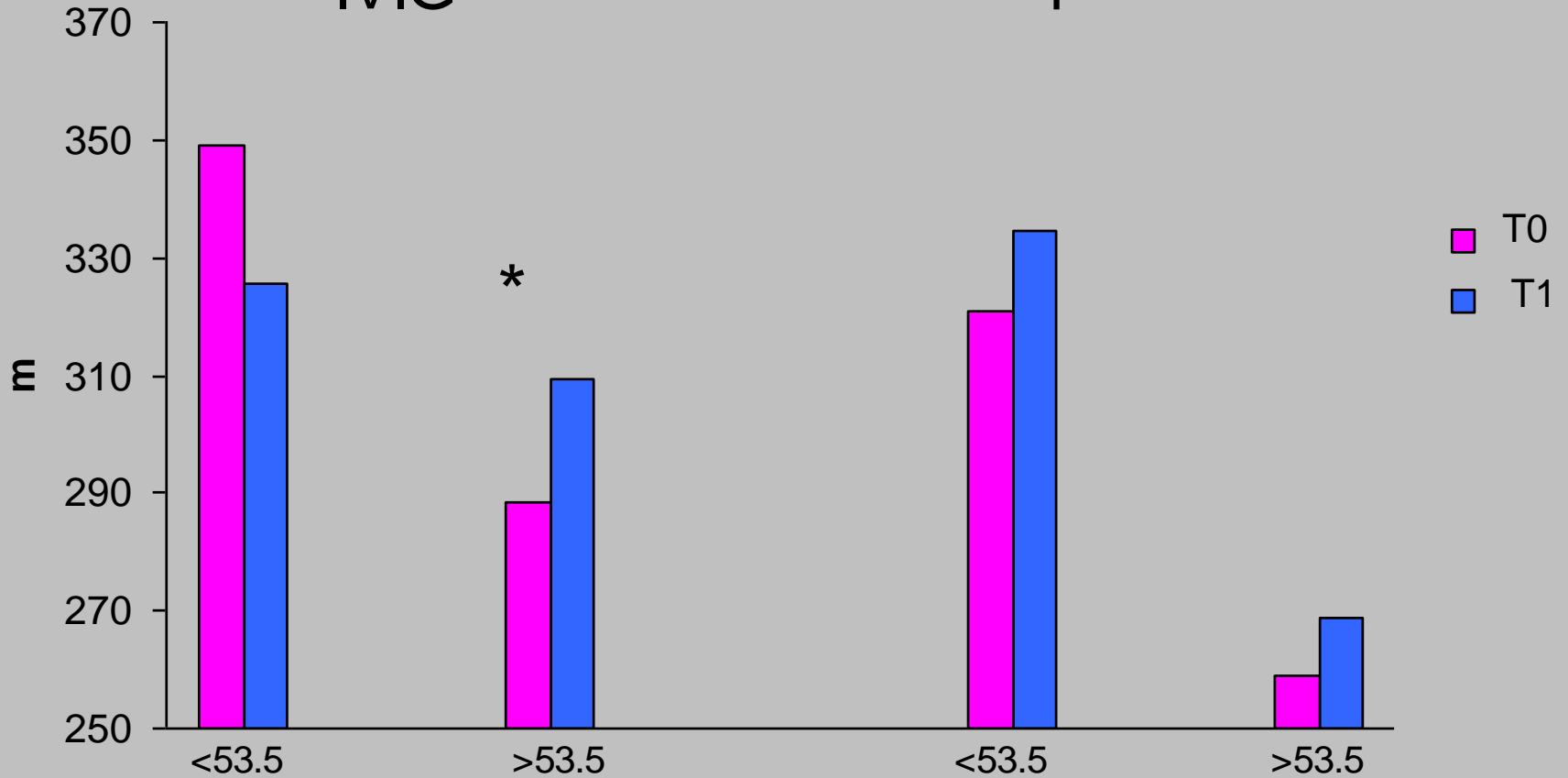
FSS T0

6 min Walking

IVIG

Wilcoxon $p=0.04$

placebo



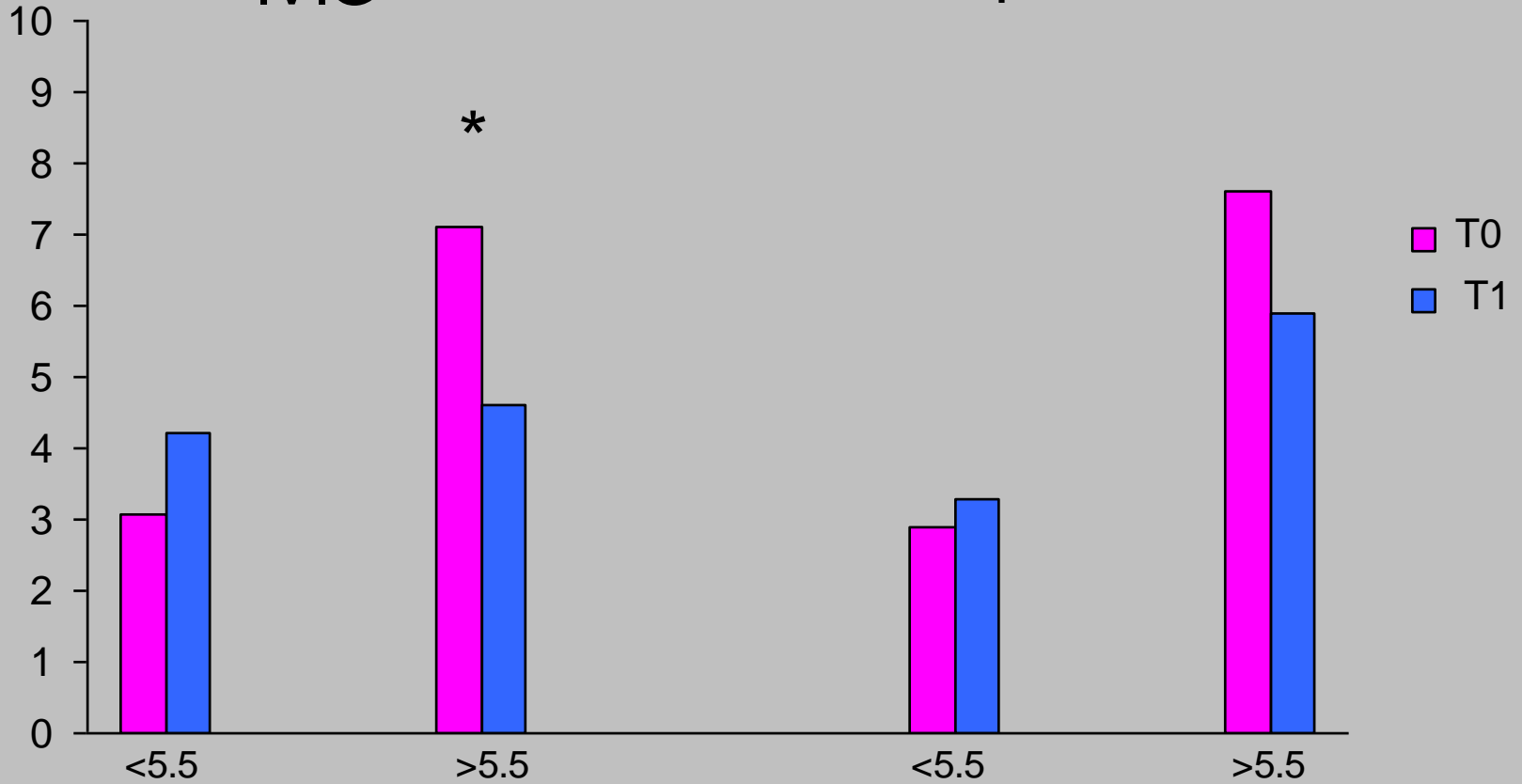
FSS T0

VAS

IVIG

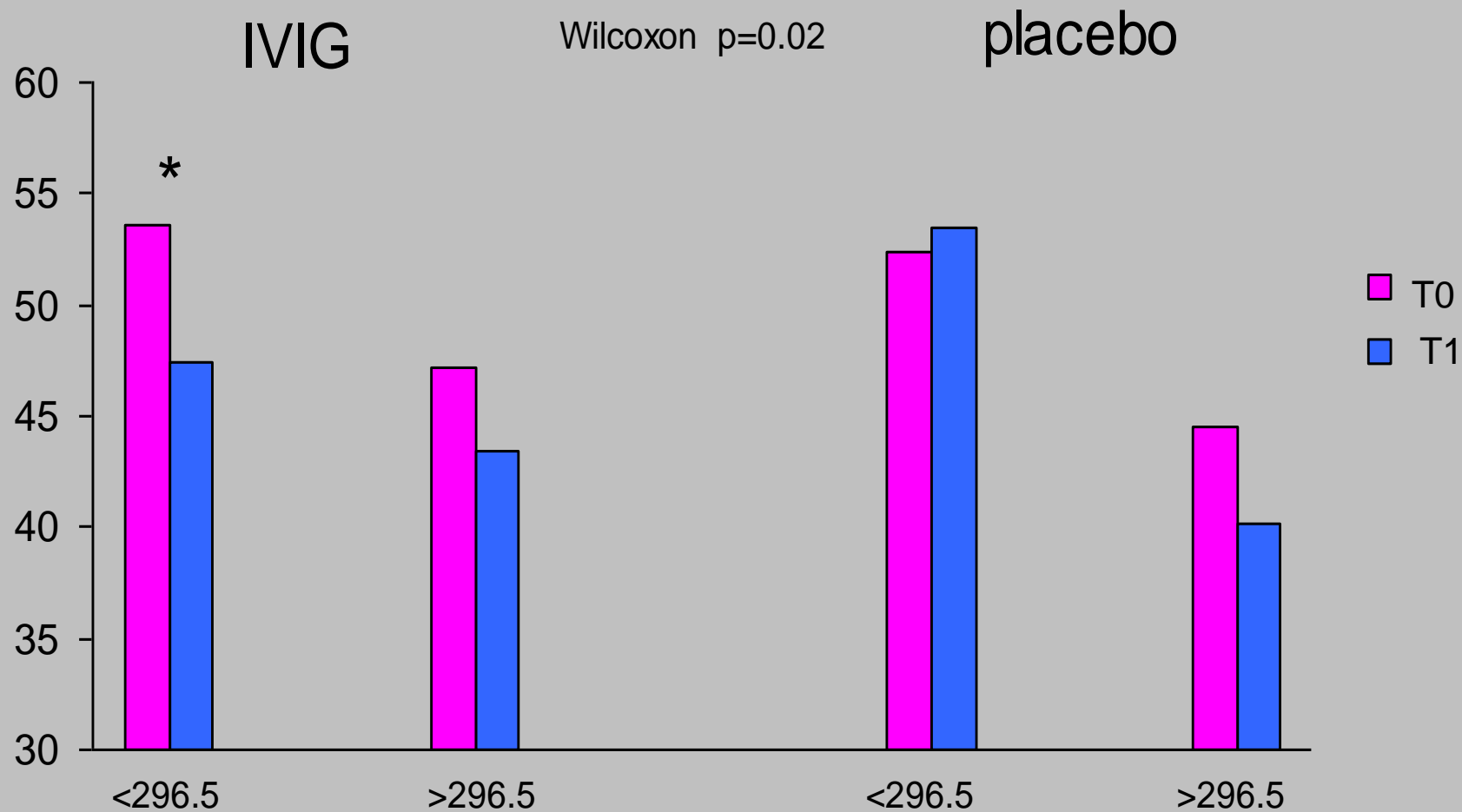
Wilcoxon $p=0.006$

placebo



VAS T0

FSS

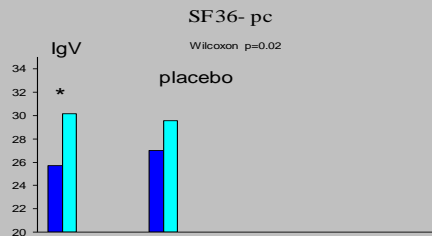


6 min walking

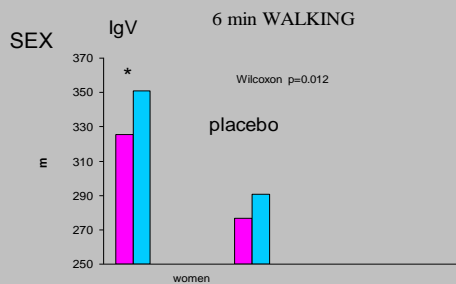
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CONCLUSIONS

Patients treated with IVIg had significant improvement of SF36-pc

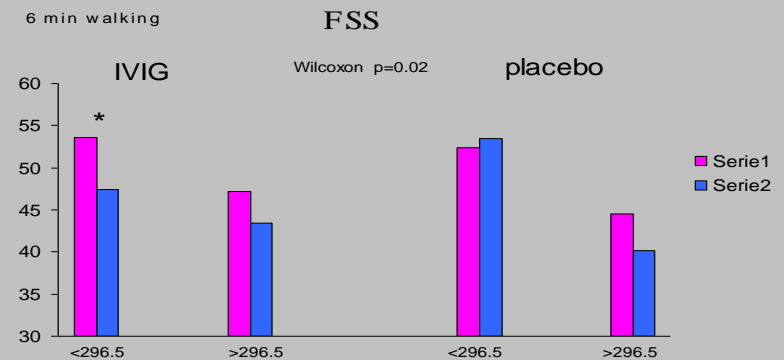
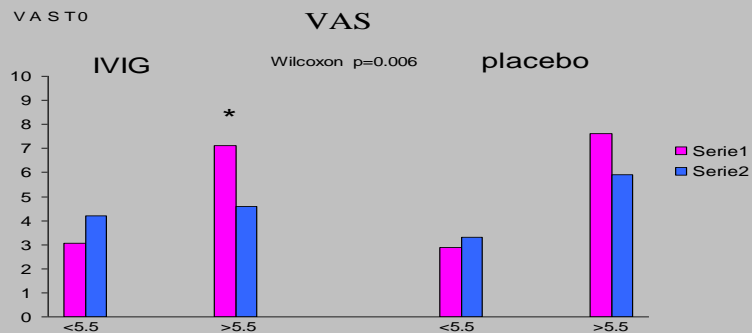
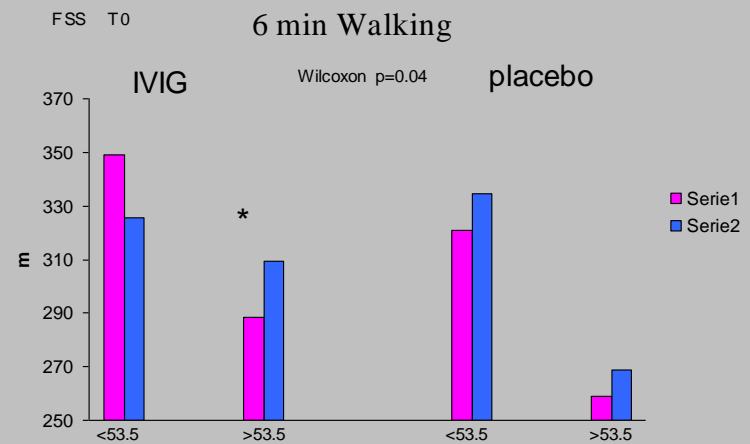
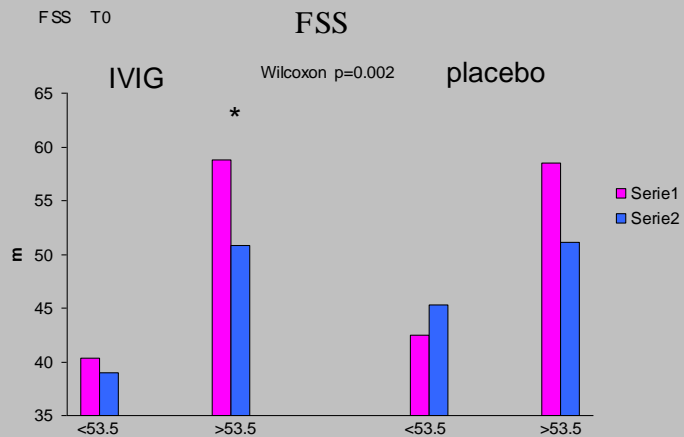


•Women vs men: significant improvement of 6 min walking test



CONCLUSION

- most severe clinical conditions receive the greatest benefit from the treatment



LIMITATIONS and QUESTIONS

- OPTIMAL THERAPY CYCLE
- TREATMENT INTERVALS
- LONG-TERM EFFECTS
- OPTIMAL DOSE
- RESPONDERS AND NONRESPONDERS

