Efficacia di un nuovo inibitore pegilato del TNF alfa sulla psroriasi artropatica

A. Dattola

Università degli Studi di Roma "Tor Vergata"

PSORIASI ARTROPATICA (PsA):

- E’ una spondiloartrite sieronegativa
- **Prevalenza:** 0,02-0,25% nella popolazione generale e interessa il 6-48% dei pazienti psoriasici
- **Patogenesi:** sono implicati fattori di tipo ereditario ed anche fattori esacerbanti quali infettivi,traumatici,stress etc.

*Kane D, Stafford L, Bresnihan B, FitzGerald O: A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology (Ox- ford) 2003;42:1460–1468.

PsA

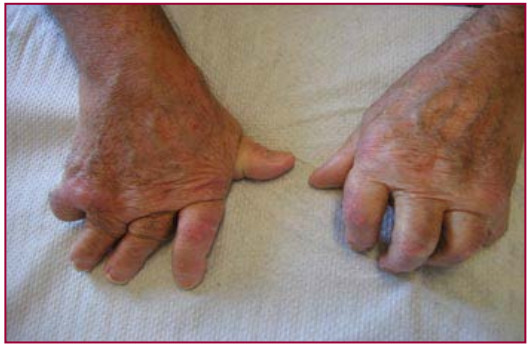
- **Esordio :** tra 35 e i 55 anni, con percentuali sovrapponibili nei due sessi
- **Decorso:** variabile e imprevedibile (cronico-recidivante)
- Infiammazione dei tessuti articolari che si traduce in lesioni di tipo osteolitico ed erosivo delle articolazioni interessate
- **Clinicamente:** dolore, tumefazione e conseguenti deformità, fino alle forme più gravi francamente mutilanti

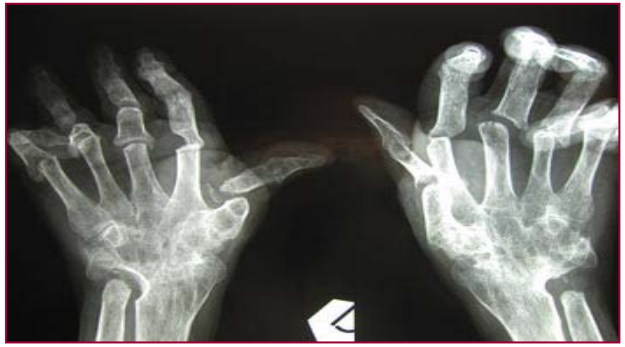
*Kane D, Stafford L, Bresnihan B, FitzGerald O: A prospective, clinical and radiological study of early psoriatic arthritis: an early sy- novitis clinic experience. Rheumatology (Ox- ford) 2003;42:1460–1468.

CLINICA:

In base alle caratteristiche cliniche, si distinguono, secondo la Classificazione di **Moll e Wright** (1973), cinque forme di psoriasi artropatica:

- **Oligoartrite asimmetrica** (dattilite)
- **Poliartrite simmetrica** (o simil-reumatoide)
- **Classica** (a prevalente interessamento delle articolazioni interfalangee distali)
- **Assiale** (o Spondilitica)
- **Mutilante**





Università di Roma Tor Vergata

CASPAR criteria

Established inflammatory articular disease (joint, spine, or entheseal) with three or more of the following

Psoriasis

(a) Skin or scalp disease present today as judged by a qualified health professional

(b) History of psoriasis obtained from patient, or qualified health professional

(c) Family history of psoriasis in a first or second degree relative

Nail changes

Typical nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination

RF negative (except latex method)

Dactylitis

(a) Current Swelling of an entire digit

(b) History of dactylitis recorded by a qualified health professional

Radiological evidence of iuxta articular new bone formation

defined ossification near joint margins (excluding juxta-articular new osteophyte formation) on plain x-rays of hand or foot

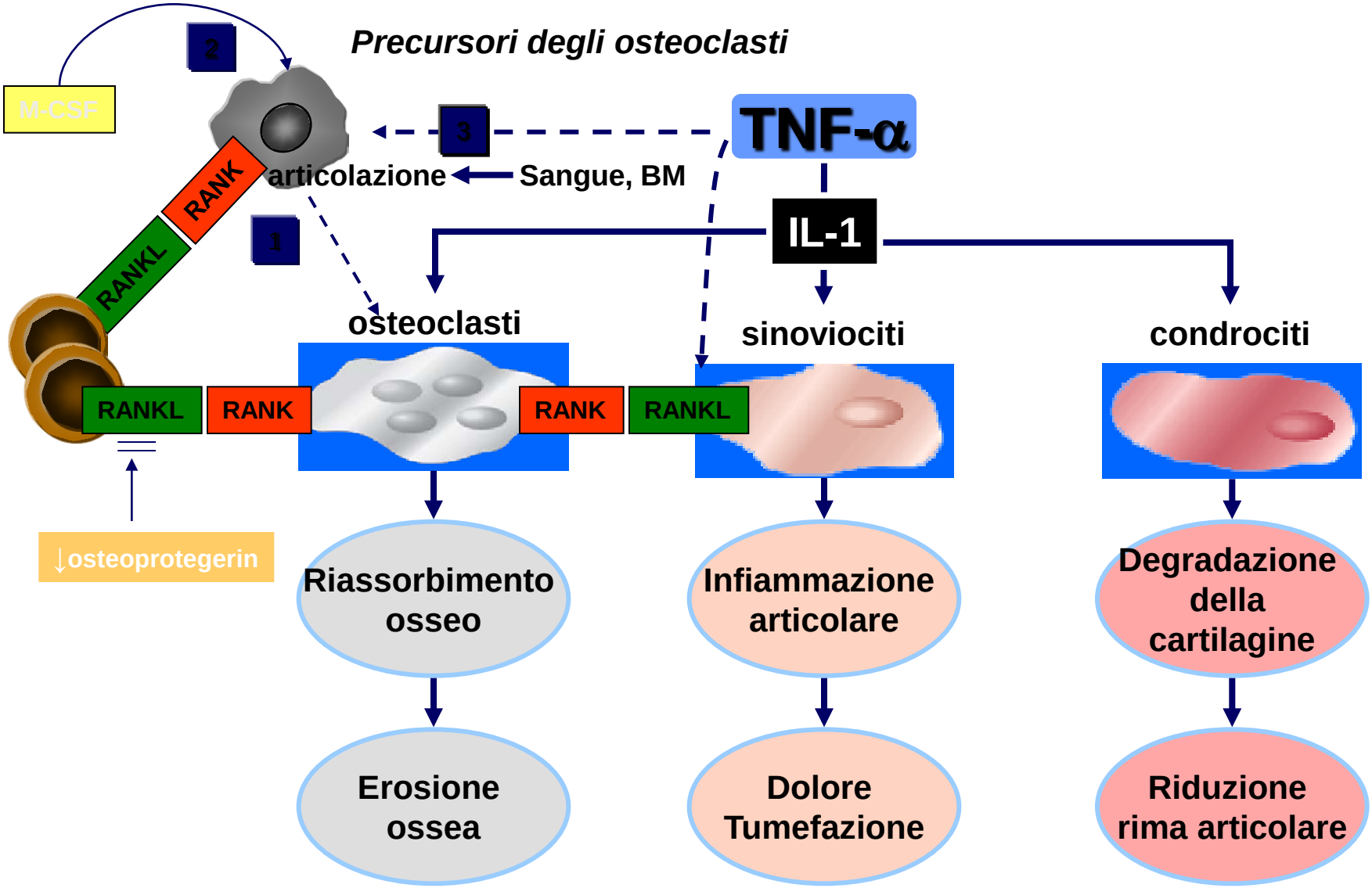
Taylor W, et al; CASPAR Study Group. Arthritis Rheum 2006.

APPROCCIO TERAPEUTICO:

- I DMARDs sono il primo step terapeutico:
  - **Azatioprina**
  - **Sali d'oro**
  - **Methotrexato**
  - **Ciclosporina**
  - **Leuflonide**
  - **Sulfasalazina**
  - **Idrossiclorochina**
- Non esistono tuttavia evidenze cliniche che questi siano in grado di arrestare la progressione del danno articolare
- Gli anti TNFα costituiscono l'unica alternativa terapeutica laddove i DMARDs siano risultati inefficaci
- Sono gli unici farmaci per i quali è stata dimostrata la capacità di inibire la progressione del danno articolare

ACR 2010-[139] - Repair of Bone Erosions in Patients Treated with TNF Antagonists in the Real World. Kaoru Takase, et al.

Effetti destruenti del TNF-α



Kastelan D. et al. Med Hypotheses. 2006; Jul 14

Treatments

	Etanercept	Infliximab	Adalimumab	Golimumab	Ustekinumab
Structure	Human fusion protein of IgG1 and p75 receptor	Chimeric MAb	Human MAb	Human Mab	Human Mab
Administration	50 mg ow JRA 0.4 mg/kg SC biweekly	3 –10 mg/kg Q 4-8 weeks intravenous	40 mg q 1 to 2 wks	50 mg sc 1/month	45 mg sc 1-3 months
Half-life	2.9 days	9.5 days	12-14 days	14 days	21 days
Fixes complement	No	Yes	Yes[3]	Yes	No
Lyses TNF-expressing cells	No	Yes	Yes[3]	Yes	No
Binds LTX	Yes	No	No	No	No
MTX therapy	Optional	Required	Recommended	Recommended	Optional

Drugs (2016) 76:675–705
DOI 10.1007/s40265-016-0564-5

REVIEW ARTICLE

Nail Psoriasis: A Review of Treatment Options

Marcel C. Pasch[1]

Therapy

Topical

- Corticosteroids
- Corticosteroids + Vitamin D3 analogs
- Tazarotene
- Calcineurin Inhibitors
- Anthralin
- 5-Fluorouracil
- Allopurinol
- Intralesional Corticosteroids/ Methotrexate
- Colloidal Silicic Acid
- Indigo Naturalis Extract

Systemic

- Methotrexate
- Cyclosporine
- Retinoids
- Apremilast
- Fumaric Acid Esters
- Sulfasalazine
- Leflunomide

Biologics

- **Anti TNF-alpha**

Infliximab
Adalimumab
Etanercept
Golimumab
Certolizumab
Ixekizumab

- **Anti IL-12/23**

Ustekinumab
Apremilast
Tofacitinib

- **Anti IL-17**

Secukinumab

Non-pharmacological

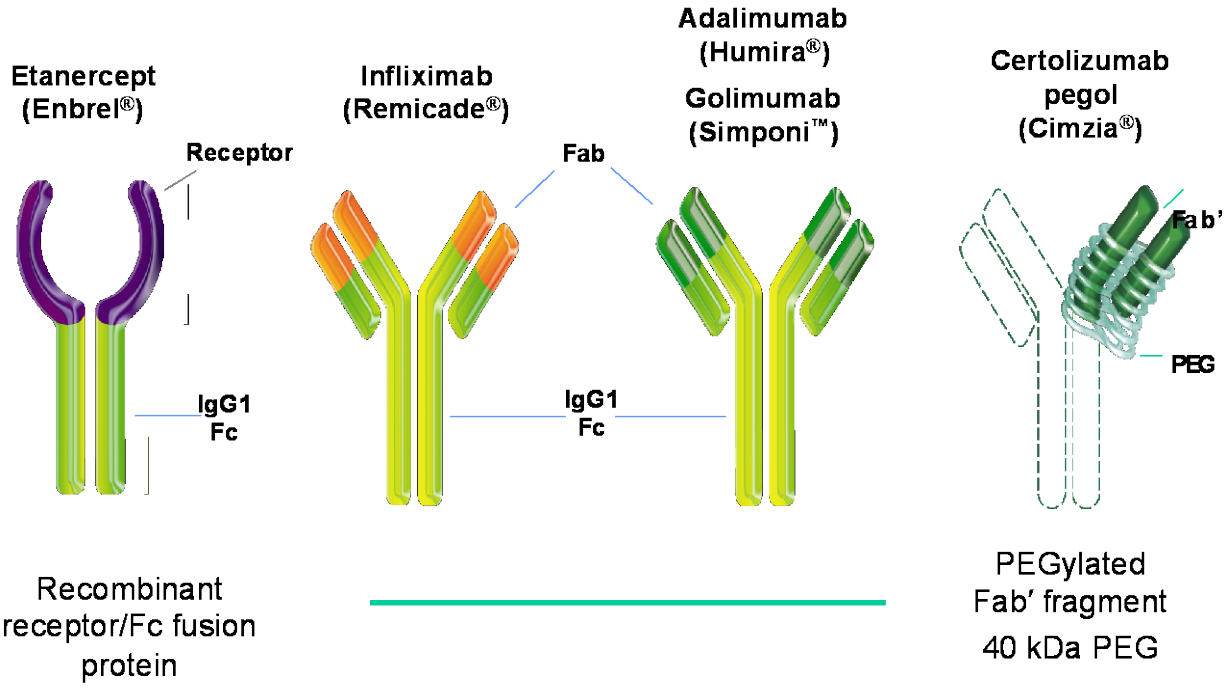
- Laser Therapy
- Phototherapy
- Photodinamic therapy
- Radiotherapy

Anti-TNF treatment in PsA

Recommendation

European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies

TNF inhibitors have demonstrated efficacy in PsA, both for skin and joint involvement, as well as in preventing radiographic damage.



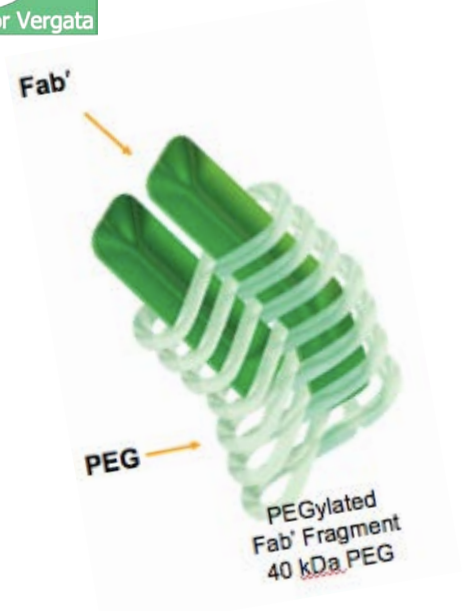
Properties of PEG and PEGylated Molecules

- **Potential Effects of PEGylation:**

  - May improve the pharmacokinetics of therapeutic agents
  - May improve bioavailability
  - May enhance penetration and retention of macromolecules into various diseased tissues
  - May reduce immunogenicity of some proteins (at this time this has not been shown for CZP)

Università di Roma Tor Vergata

Structure of Certolizumab Pegol (CZP)

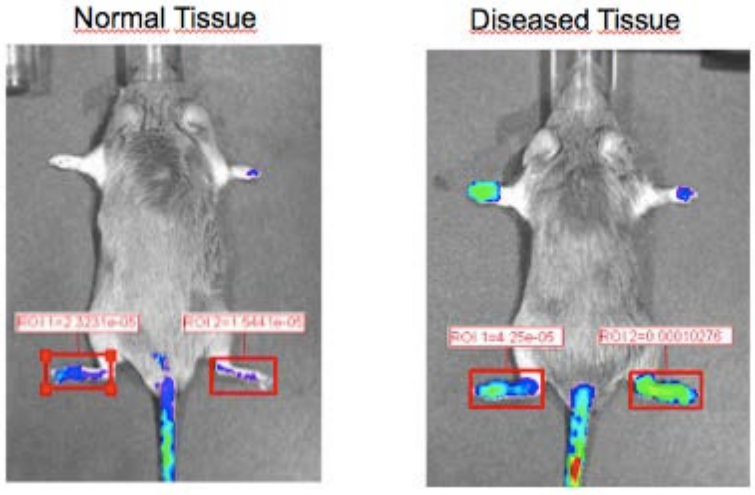


- CZP is the only **PEGylated** anti-TNF-α
- Site-specific PEGylation resulted in:
  - Designed half life of ~14 days
  - Enhanced **penetration of CZP into inflamed tissue** (in animal models)*
- **No Fc region**

  May avoid potential Fc-mediated effects such as CDC or ADCC*

  No recycling by FcRn which may lead to longer residency in inflamed tissue

  Non-clinical studies suggest **low or negligible level of placental transfer** of a homologue Fab-fragment of certolizumab pegol



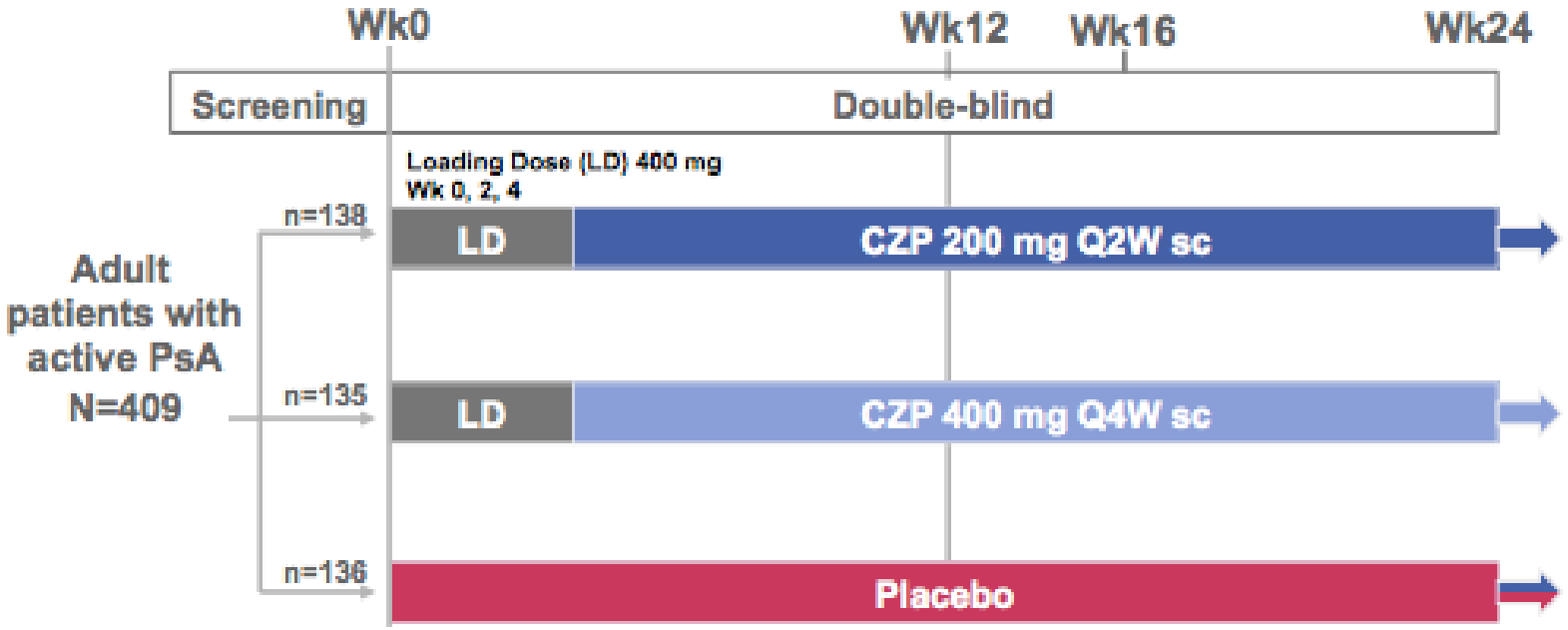
SCT-IMNL-CGR-039_04/2015. Veronese et al. Biodrugs. 2008;22:315-329 Chapman. Adv Drug Deliv Rev. 2002;54:531-545 . Chapman et al. Nature Biotech. 1999;17:780-783 Weir et al. Therapy. 2006;3:535-545 UCB. CIMZIA Summary of Product Characteristics. 2015

CDC=complement-dependent cytotoxicity
ADCC=antibody-dependent cell-mediated cytotoxicity

RAPID-PsA objectives and design

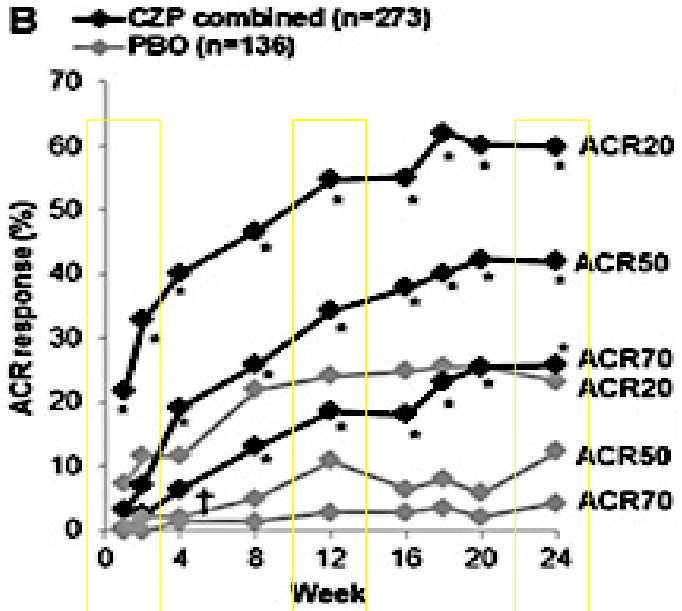
- To demonstrate efficacy of CZP on the **signs and symptoms of active PsA** and on the **inhibition of progression of structural damage** in adults with active PsA

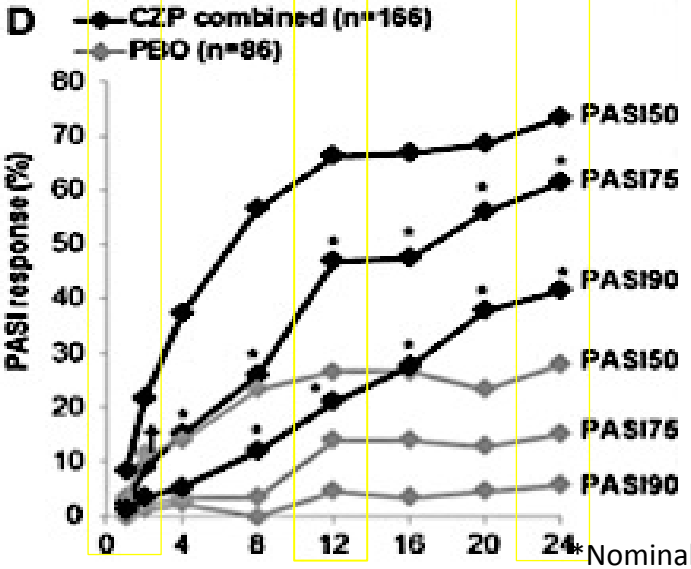
- To assess the effects on **safety and tolerability** and to demonstrate the effects of CZP on: Health outcomes, Psoriatic skin disease in the subgroup of affected patients (>3% BSA) at baseline, Dactylitis, Enthesitis



Adapted from PJ Mease et al, Ann Rheum Dis. Epub. 2013; SCT-IMNL-CGR-039_04/2015

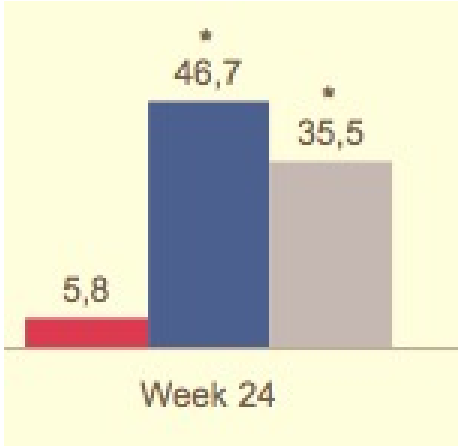
RAPID-PsA ACR and PASI Response





- ✓ At week 12, **58.0% and 51.9%** in the **CZP** 200 mg Q2W and CZP 400 mg Q4W groups vs 24.3% in the plcebo group achieved an **ACR20** response
- ✓ A clinically significant difference in ACR20 response between both CZP treatment groups and placebo was observed as early as **week 1**

PASI90 Response at Weeks 24

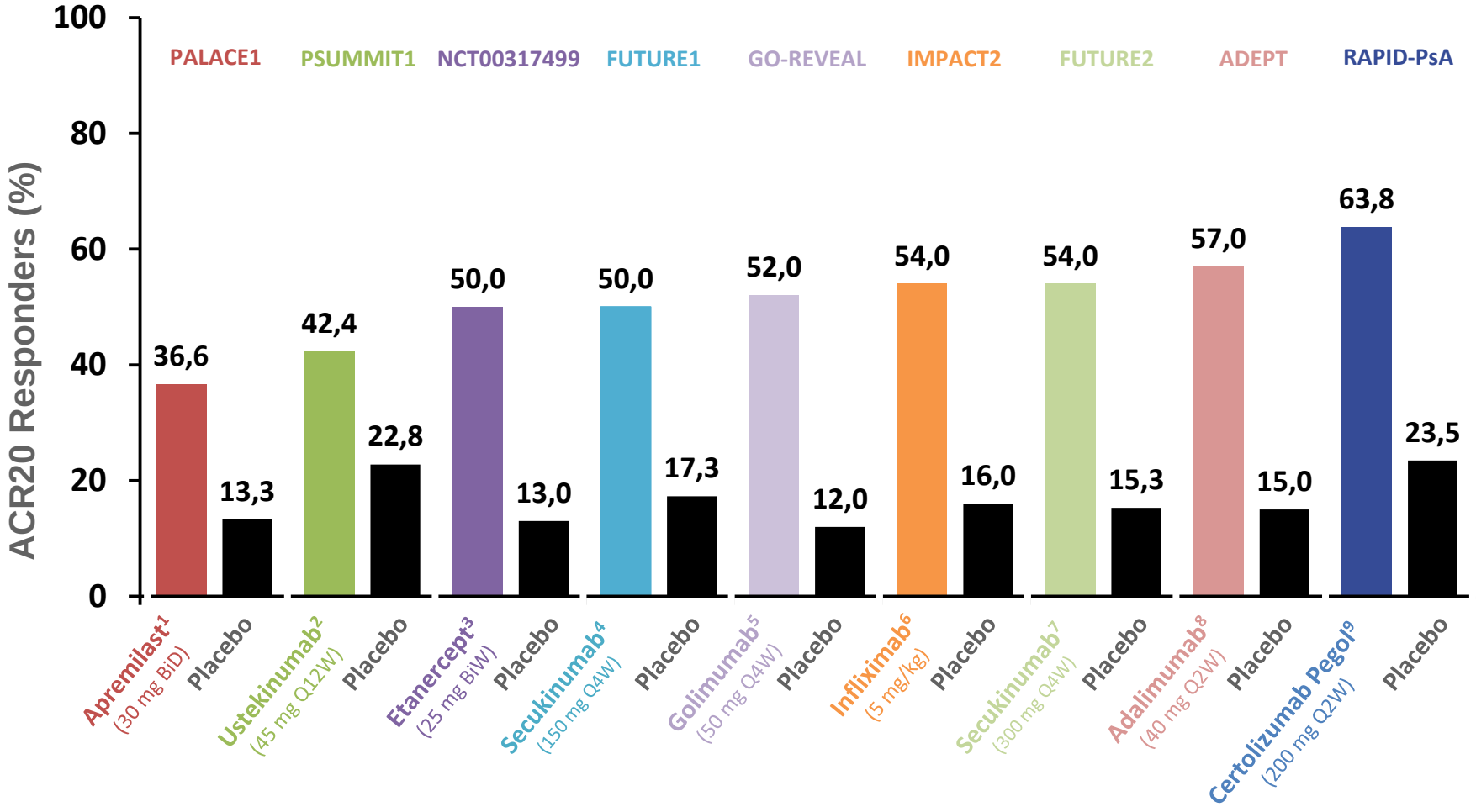


*Nominal p value <0.001;

J Mease et al, Ann Rheum Dis. Epub. 2013; SCT-IMNL-CGR-039_04/2015

Not a H2H comparison; direct comparisons cannot be made

Efficacy of Licenced Biologic Treatments in PsA

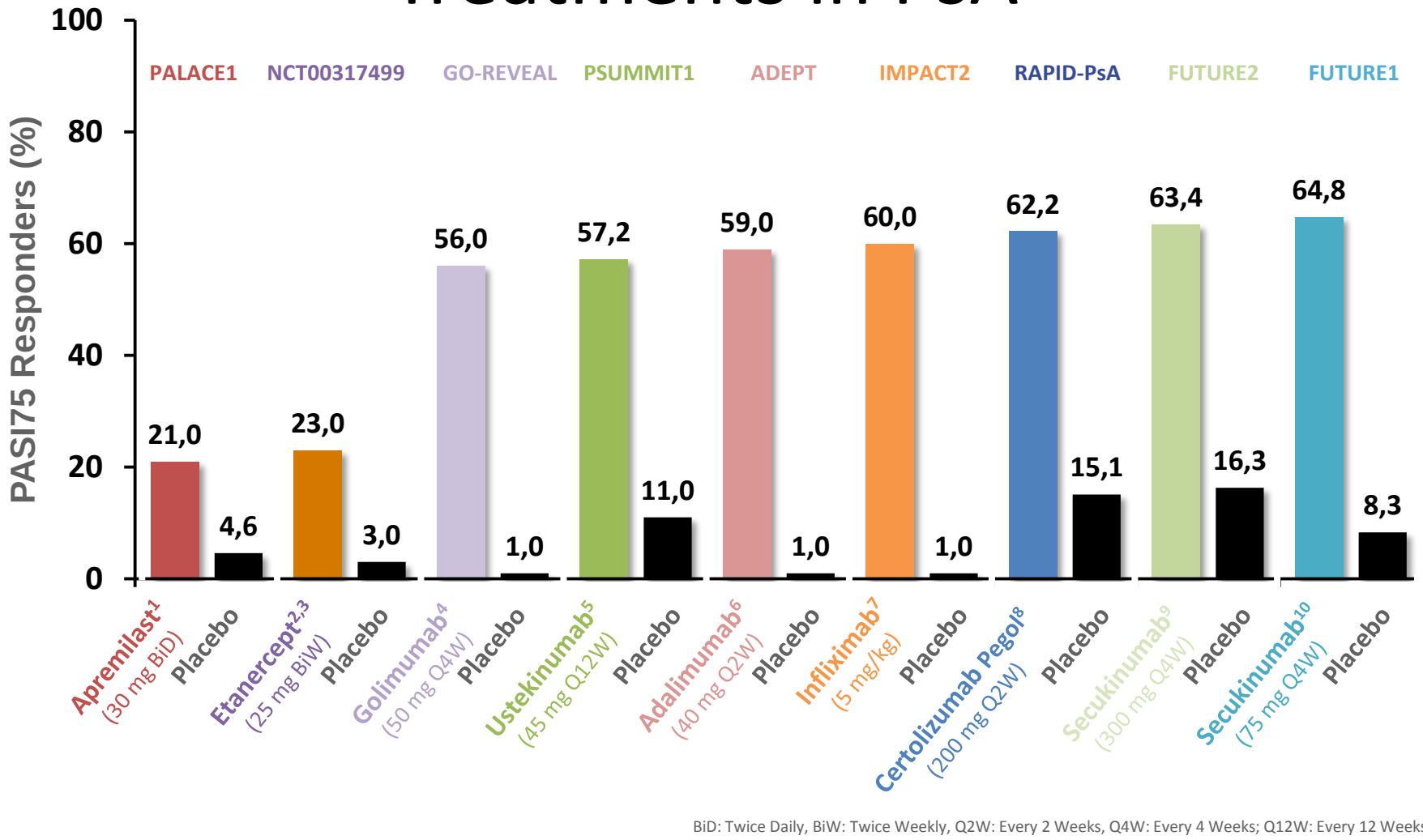


ACR20 Response at Week 24

BiD: Twice Daily, BiW: Twice Weekly, Q2W: Every 2 Weeks, Q4W: Every 4 Weeks; Q12W: Every 12 Weeks

Not a H2H comparison; direct comparisons cannot be made

Efficacy of Licenced Biologic Treatments in PsA



BiD: Twice Daily, BiW: Twice Weekly, Q2W: Every 2 Weeks, Q4W: Every 4 Weeks; Q12W: Every 12 Weeks

PASI75 Response at Week 24: In Patients with Psoriasis ≥3% BSA at Baseline

Pregnancy and anti-TNF

- Anti-TNFα **do not seem to carry any significant risk** of adverse pregnancy outcome.

- As the half-life of **monoclonal anti-TNF-α** antibodies is prolonged to several months in newborns, an **increased risk of infection in the child** exists during late pregnancy exposure.

- CZP differs from other anti-TNF-α in that it has **no Fc region** and is not actively transported through the placenta

- Confirmed Diagnosis of **Pregnancy → interruption of treatment** is advised but not compulsory

- Assessment of **Benefits/Risks Ratio** on a case-by-case basis (concurrent therapies risk– disease relapse – irreversible joint damage due to PsA).

M Ostensen Ann. N.Y. Acad. Sci. (2014) 1–7; U Mahadevan et al. 2013. Clin. Gastroenterol. Hepatol. 11: 286–292.; M Clowse et al. 2012 Arthritis Rheum. 64(Suppl 10): S702.; A Nesbitt et al. 2007. Ann. Rheum. Dis. 66(Suppl 2): 296.

Università di Roma Tor Vergata

Study Populations:

- **Inclusion criteria**: patients unresponsive or intolerant to conventional therapies or unresponsive to other biologics drugs

- **Exclusion criteria**: active or past serious medical conditions that contraindicate therapy with biologics.

- **Initial assessment:**
  PASI (severity of psoriasis index)
  DAS44 (joint involvement index)
  VAS (visual analogue scale of severity disease)

- **BASELINE : medical history and EO, haematological routine, hepatitis markers, TB Gold and chest X-ray, ECG, Echocardiogram.**

OUR STUDY POPULATION

Mean AGE	Sex	Naïve to Biologics	PSA	PSA/PSO
59.8±8	16 M; 25 F	14	5	36

- **41 patients**
- **32 patients (group A)** completed tree month of treatment
- **12 patients** completed six month of treatment **(group B)**

- Active rheumatic disease was considered if DAS44 >3.7
- Adequate clinical response was indicated by DAS44-ESR ≤2.4
- Remission was considered if DAS44 <1.6

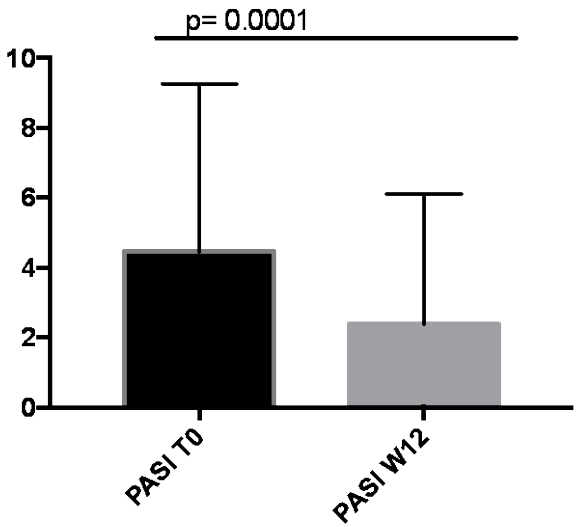
- **Dropped out:** 1 alopecia, 1 failure, 1 bariatric surgery complication

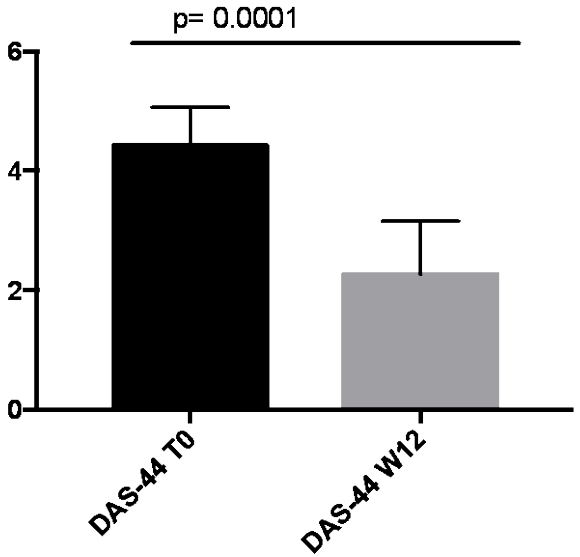
Università di Roma Tor Vergata

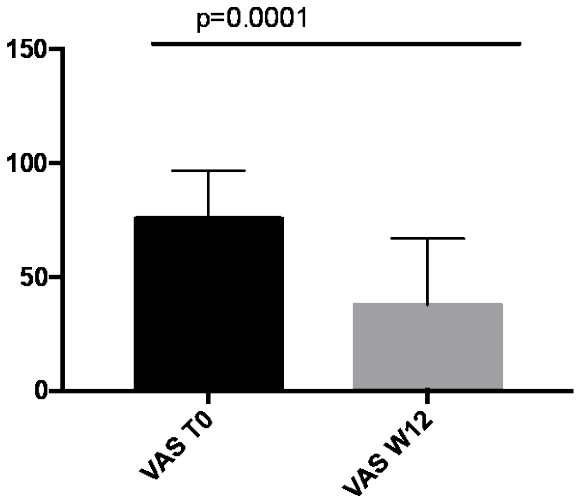
- The clinical efficacy was consistent on both cutaneous and rheumatic components as demonstrated by the reduction of :

- **mean PASI** score from 4.4±4.7 at BL to 2.3±3.7 at W12 (group A) and from 5.1±5.7 at BL to 0.8±1.2 at W24 (group B)
- and decreasing of **DAS44-ESR** from 4.4±0.6 at BL to a mean of 2.2±0.9 at W12 (group A) and from 4.1±0.6 at BL to a mean of 1.9±0.5 at W24 (group B)

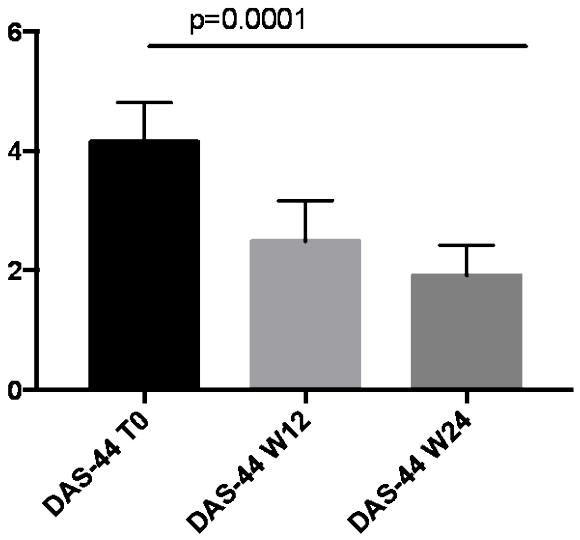
➢ GROUP A

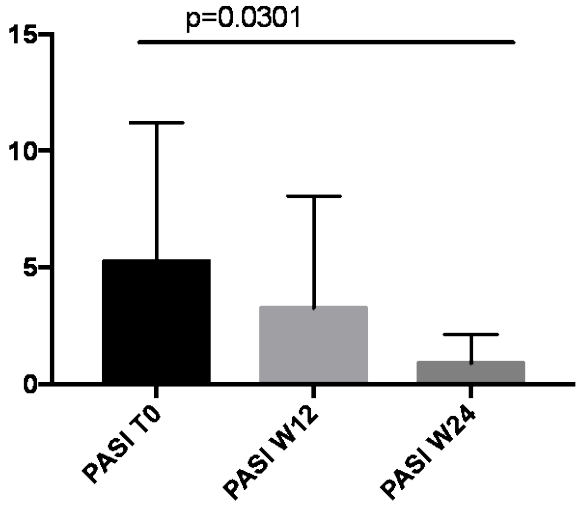

p= 0.0001
10
8
6
4
2
0
PASI T0
PASI W12

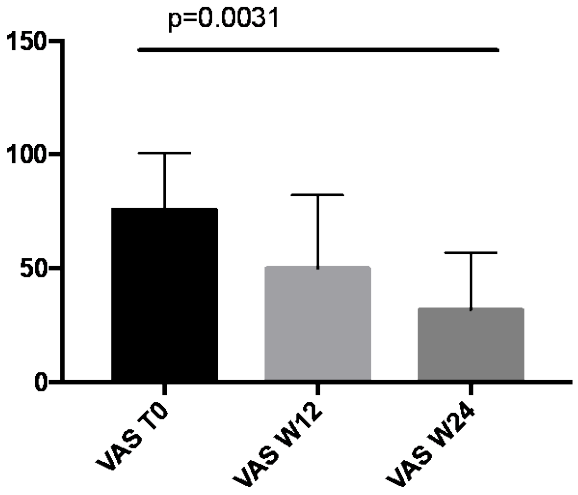

p= 0.0001
6
4
2
0
DAS-44 T0
DAS-44 W12


p=0.0001
150
100
50
0
VAS T0
VAS W12

➢ GROUP B

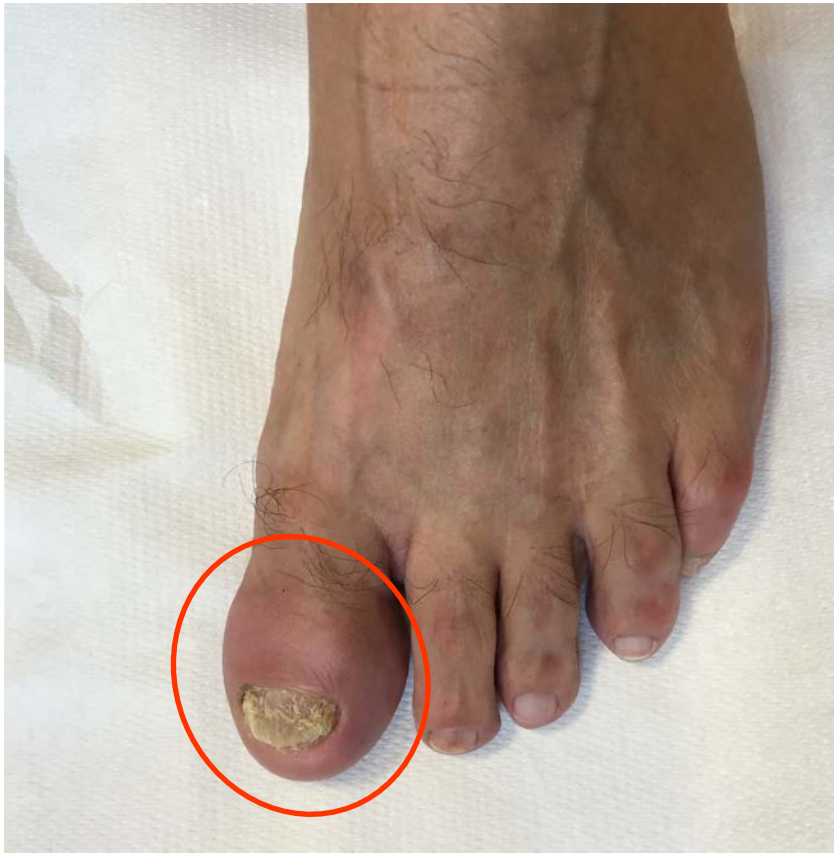

p=0.0001
6
4
2
0
DAS-44 T0
DAS-44 W12
DAS-44 W24


p=0.0301
15
10
5
0
PASI T0
PASI W12
PASI W24

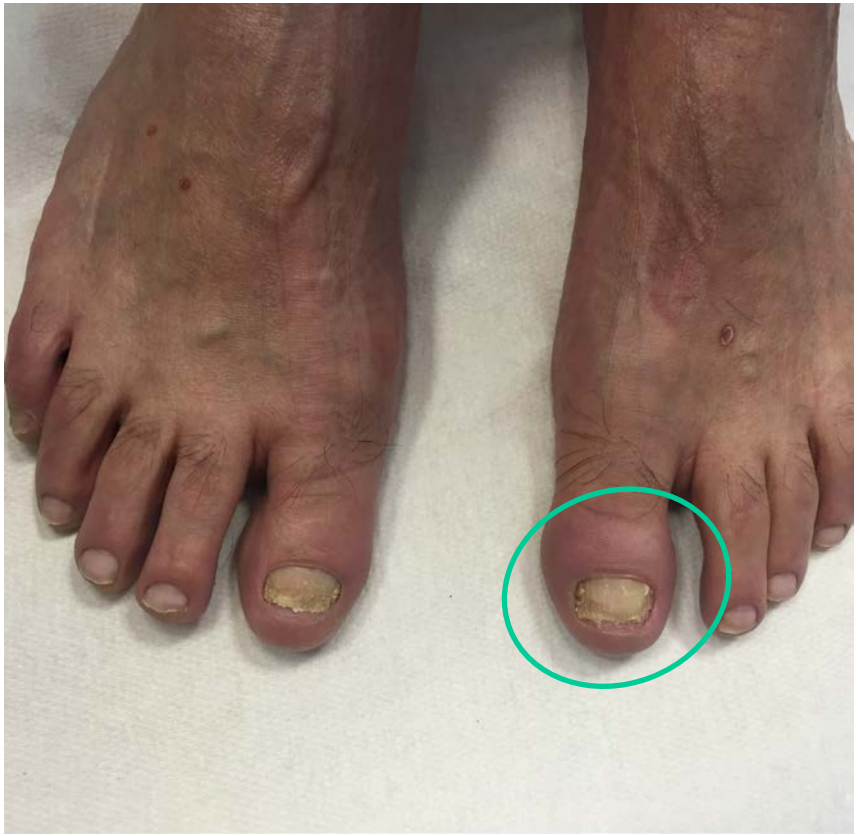

p=0.0031
150
100
50
0
VAS T0
VAS W12
VAS W24

Our experience result :case 1 (naive)

BASELINE

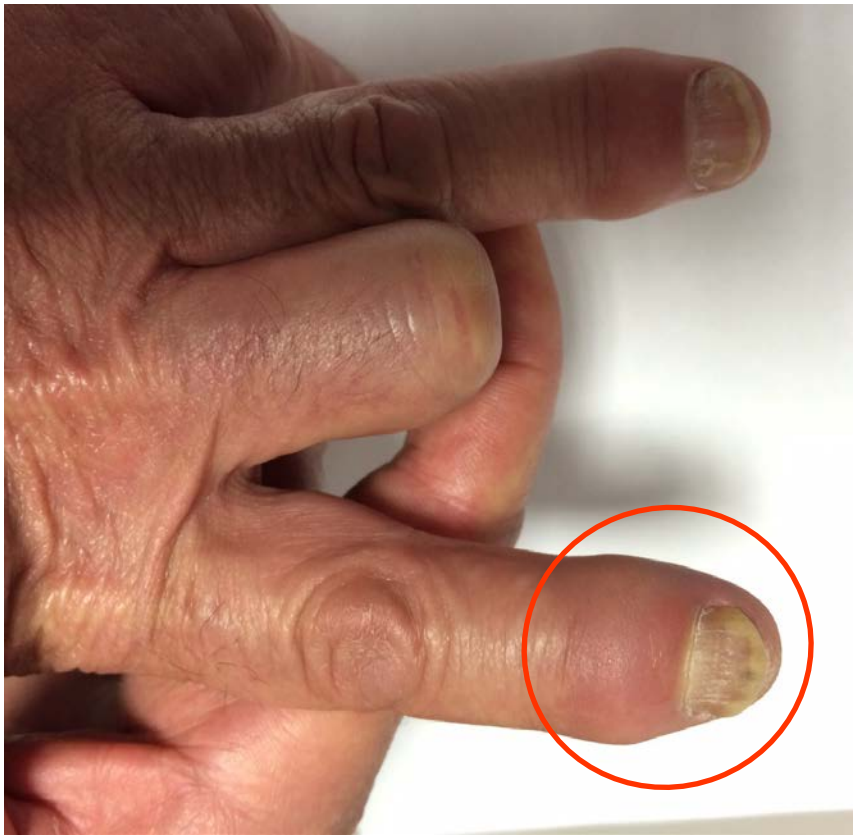


W 12



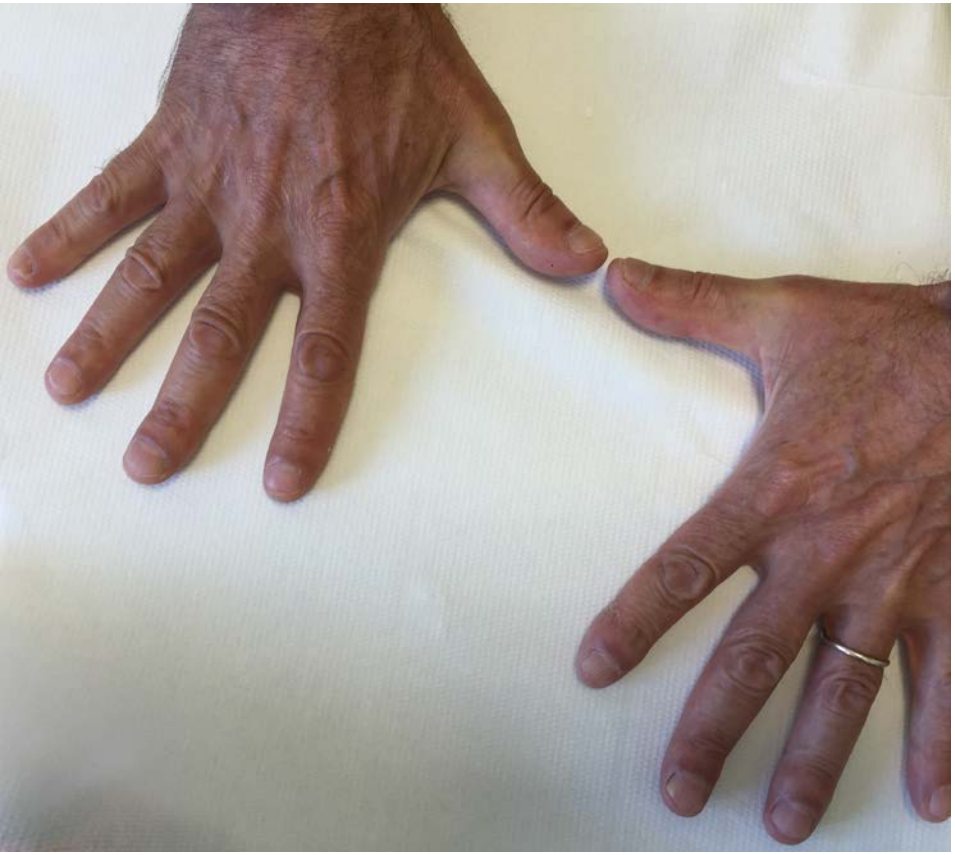
Our experience result :case 1

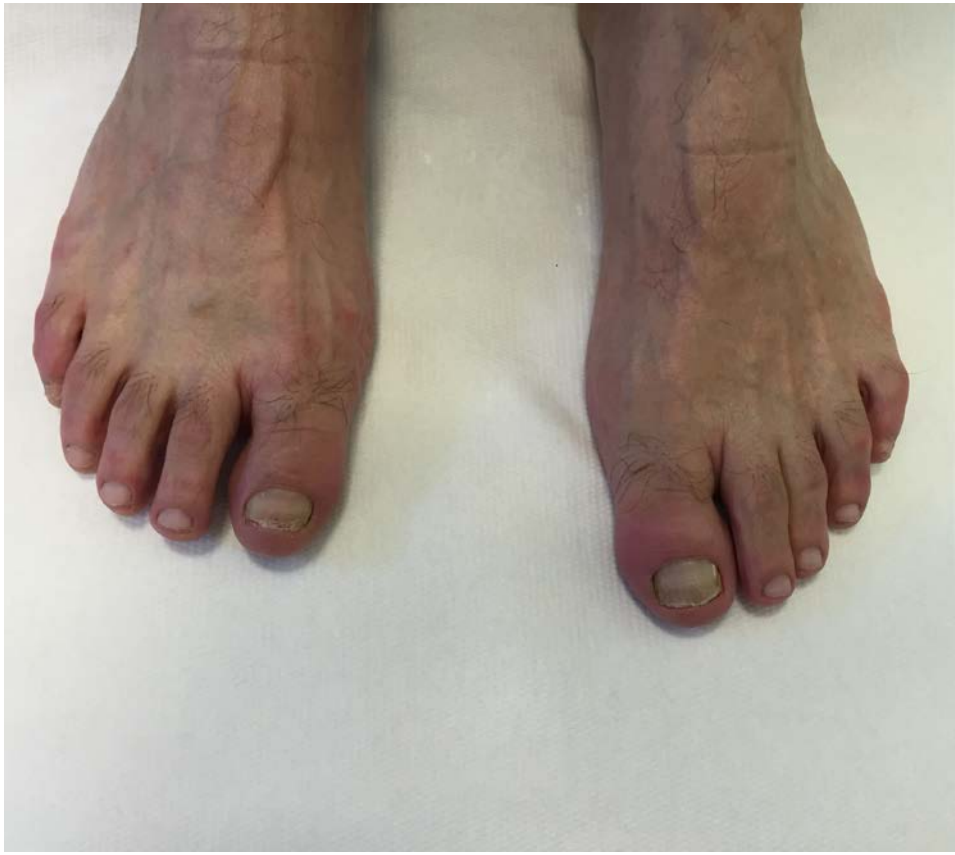
BASELINE



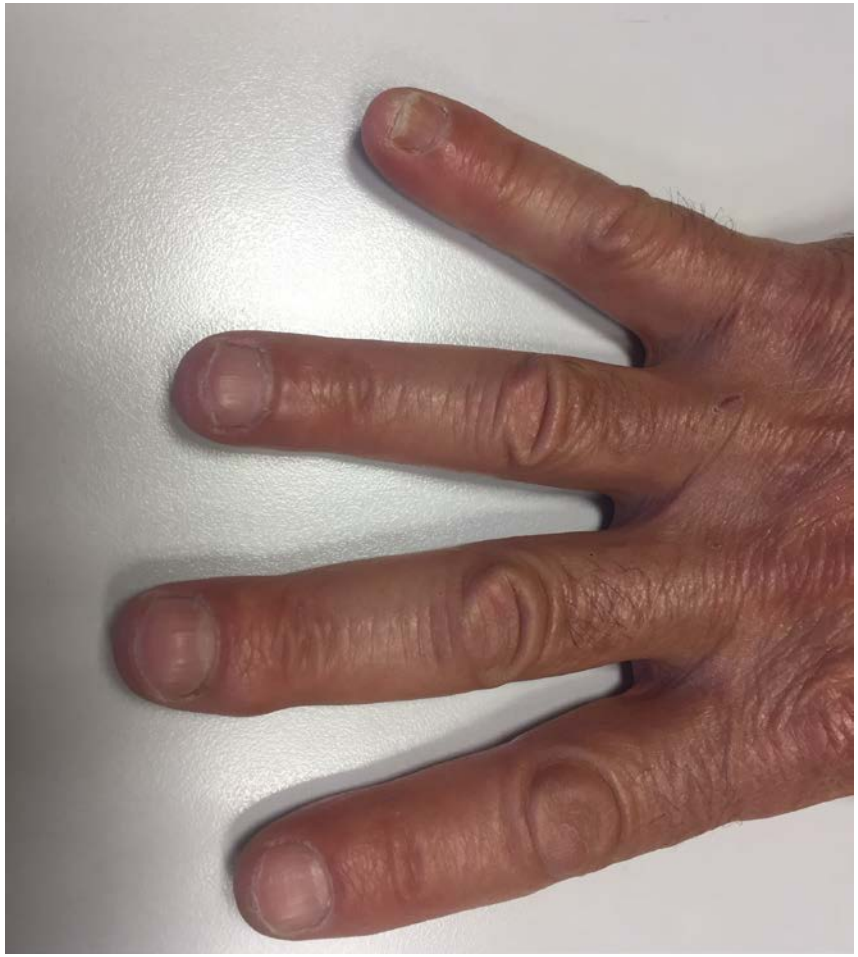
W 12

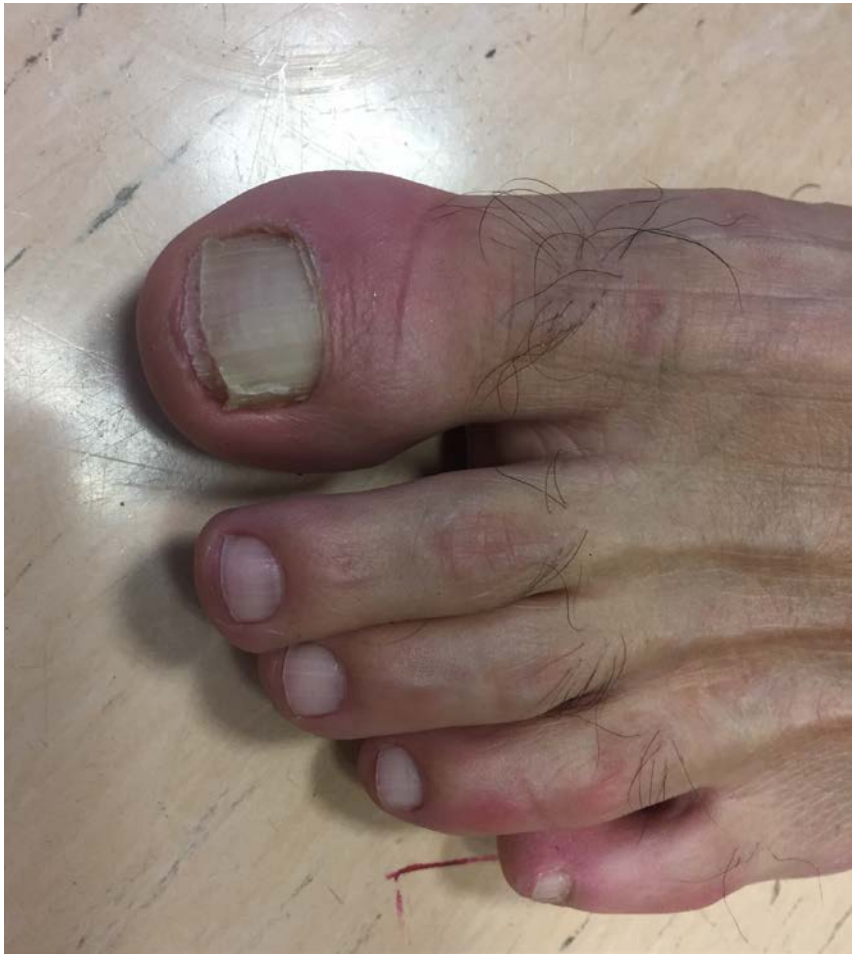
12 months



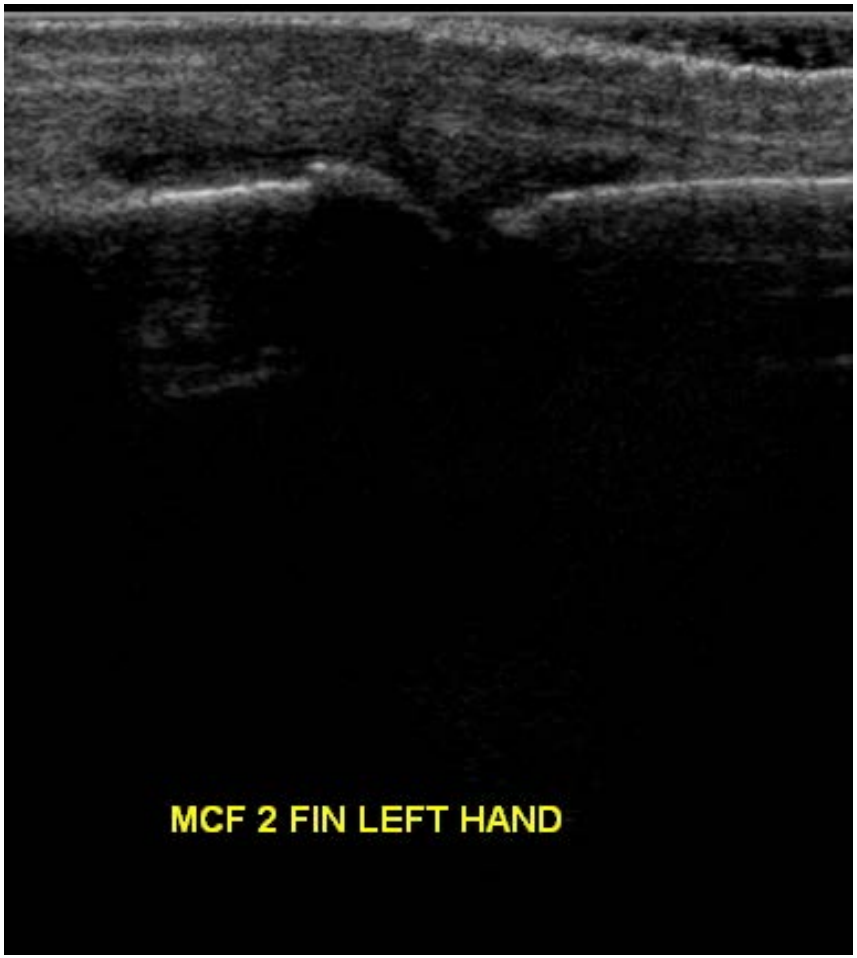


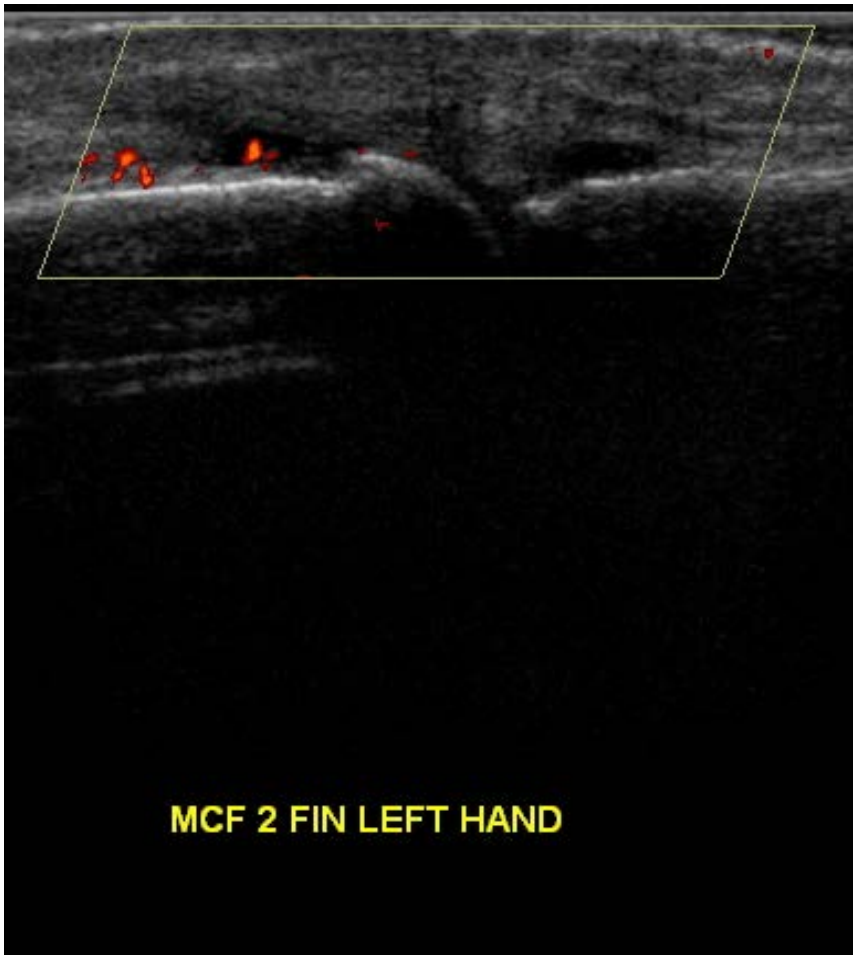
16 months





US BL





US after 6 months