Rheumatology Highlights 2012

Farhan Tahir MD, FACR

Rheumatology Division

Doylestown Hospital, Abington Memorial Hospital,
Rheumatic Disease Associates, Ltd.

Disclosure

- Speaker for Amgen, Abbott and Auxilium

Objectives

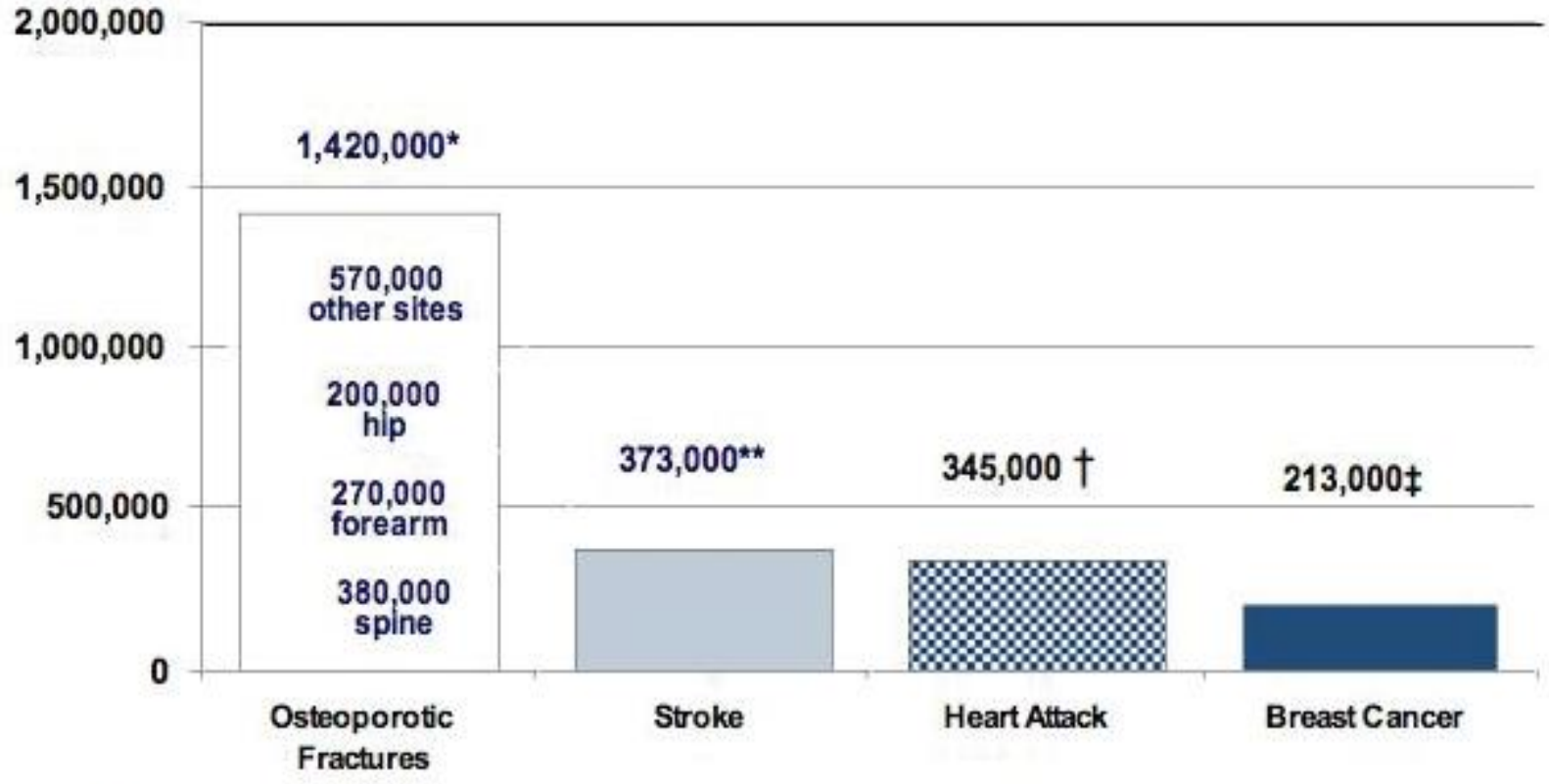
- Overview of current trends in osteoporosis management
- Belimumab (trade name *Benlysta*) for systemic lupus erythematosus
- Rituximab (trade name *Rituxan*) for ANCA associated vasculitis
- Tocilizumab (trade name *Actemra*) for rheumatoid arthritis
- Collagenase clostridium histolyticum (trade name *Xiaflex*) for Dupuytren's contracture
- Musculoskeletal ultrasound in rheumatology

Burden of Osteoporosis

- **Hip** fractures are the leading cause of serious complications
- **Mortality** ; first year after hip fracture > 30% for men and about 17% for women
- **> than half of hip fracture survivors** require skilled care and have permanent disability
- **Vertebral** and forearm fractures also cause major socioeconomic impact
- **2005 to 2025**, estimated osteoporosis-related fractures will increase from 2 million to 3 million, and cost will increase from $17 billion to $25 billion

ENDOCRINE PRACTICE Vol 16 (Suppl 3) November/December 2010

Burden on healthcare



* 2005 annual incidence all ages
** 2004 estimate
† 2004 estimate, new and recurrent
‡ 2006 new cases, women all ages

AACE

Executive summary recommendations

- Measures to prevent bone loss calcium, vitamin D (30-60ng/ml), limit alcohol, smoking & caffeine, weight bearing exercises, adequate protein intake
- Who needs to be screened Women 65 or older, younger with increased risks, secondary osteoporosis, prevalent vertebral fractures (VFA)
- Who needs treatment fx hip, spine; T score =/>-2.5, Tscore <-2.5 w/+FRAX (major fx risk>20%, hip>3%)
- What drugs to use: *First line*: alendronate, risendronate, zolendronic acid, denosumab; *2nd line*: ibendronate ; *2nd-3rd* raloxifene *; last*: calcitonin; *failure to bisphosphonates*: teriparatide

AACE
Executive summary recommendations

- Monitor DEXA 1-2 yrs until stable then 2yrs(more discussions to follow), spine & hip, ideal if same facility, machine, technologist; bone turnover markers
- How long should treatment last mild osteoporosis 4-5 years then drug holiday, if high risk 10 years treatment then 1-2 yr drug holiday; (my opinion switching MOAs)
- What are high risk for bone loss rheumatologic diseases, endocrinopathies, malabsoprtion, renal failure or hypercalciuria, medications, malnutrition, vitamin D deficiency, neuromuscular disorders
- Who is at risk of fall elderly, frail, impaired vision & hearing, sedatives, slipper rugs etc

NOF Guidelines

Therapy for Osteoporosis and NOF Guidelines

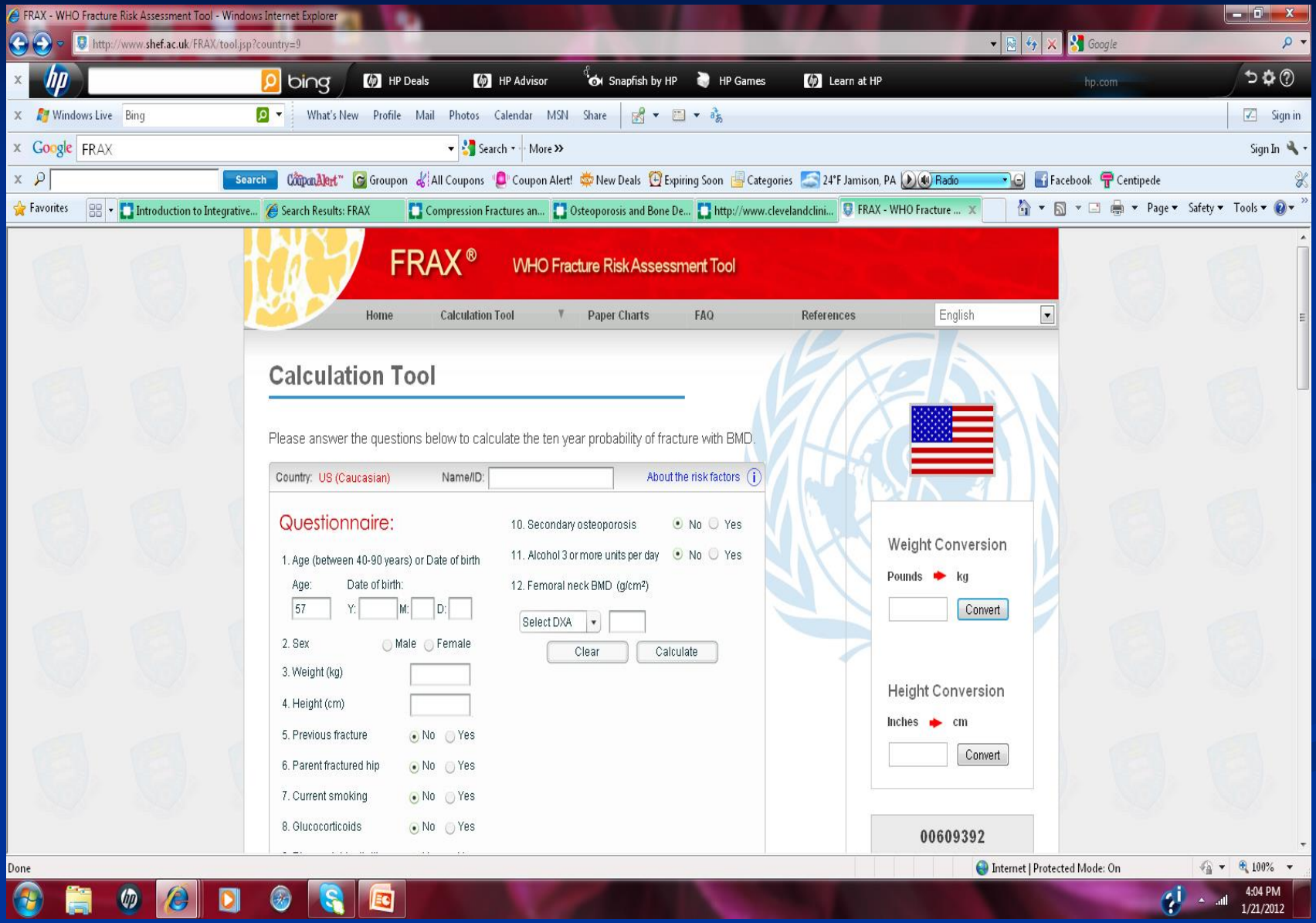
2008 NOF Guidelines: Treat 1) hip or spine fracture, 2) T-score hip or spine < -2.5, 3) If T-score -1.0 to -2.5 apply FRAX treat if 10-year hip fracture risk >3%, major osteoporotic fracture >20%

GLOW : Global Longitudinal Study of Osteoporosis in Women

NOF 2008 Guidelines		
By FRAX rise score- Treatment recommended		
	N (%) Treated	Odds Ratio
10 y probability of hip fracture > 3% and 10 y probability of major osteoporotic fracture > 20%	98 (64.1)	1.7 (1.1-2.6)
Either 10 y probability of hip fracture > 3% or 10 y probability of major osteoporotic fracture > 20%, but not both	70 (44.6)	0.8 (0.5-1.4)

Zhang, et al. ACR 2011. Abstract 1121.

FRAX


FRAX - WHO Fracture Risk Assessment Tool - Windows Internet Explorer
http://www.shef.ac.uk/FRAX/tool.jsp?country=9
FRAX®
WHO Fracture Risk Assessment Tool
Home
Calculation Tool
Paper Charts
FAQ
References
English
Calculation Tool
Please answer the questions below to calculate the ten year probability of fracture with BMD.
Country: US (Caucasian)
Name/ID:
About the risk factors
Questionnaire:
1. Age (between 40-90 years) or Date of birth
Age:
Date of birth:
57
Y:
M:
D:
2. Sex
Male
Female
3. Weight (kg)
4. Height (cm)
5. Previous fracture
6. Parent fractured hip
7. Current smoking
8. Glucocorticoids
10. Secondary osteoporosis
11. Alcohol 3 or more units per day
12. Femoral neck BMD (g/cm²)
Select DXA
Clear
Calculate
No
Yes
Weight Conversion
Pounds
kg
Convert
Height Conversion
Inches
cm
Convert
00609392
Done
Internet | Protected Mode: On
100%
4:04 PM
1/21/2012

FRAX in USA

- Consider therapies in postmenopausal women and men aged 50 years and older, if
- hip or vertebral fracture
- T-score ≤ -2.5 (exclude secondary causes)
- Low bone mass (T-score -1.0to -2.5) and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20%

Table 2: FRAX™ Risk Factors[6]

Age	Current smoking
Gender	Glucocorticoids
Weight	Rheumatoid arthritis
Height	Secondary osteoporosis
Previous fracture	Alcohol intake
Parent fractured hip	Femoral neck T score

Effectiveness Vs Adherence

- Postmenopausal osteoporosis screening, cost-effective, initiation at age 55 years Cost-Effectiveness of Different Screening Strategies for Osteoporosis in Postmenopausal Women

  Author(s): Nayak Smita , Annals of Int Medicine, Volume: 155 Issue: 11

- Patients are prepared to accept higher absolute fracture risk than doctors Differing perceptions of intervention thresholds for fracture risk: a survey of patients and doctors: Osteoporosis International Url: http://dx.doi.org/10.1007/s00198-011-1823-7

- Only a third of patients agree to second administration of Zolendronic acid Persistence with intravenous zoledronate in elderly patients with osteoporosis, Osteoporosis International, http://dx.doi.org/10.1007/s00198-011-1881-x

Fracture risk reduction

Summary of Evidence for Fracture Risk Reduction

Drug	Fracture risk reduction		
	Vertebral	Nonvertebral	Hip
Calcitonin (Miacalcin, Fortical)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Raloxifene (Evista)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Ibandronate (Boniva)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Alendronate (Fosamax)	Yes	Yes	Yes
Risedronate (Actonel)	Yes	Yes	Yes
Zoledronic acid (Reclast)	Yes	Yes	Yes
Denosumab (Prolia)	Yes	Yes	Yes
Teriparatide (Forteo)	Yes	Yes	No effect demonstrated[a]

[a] The lack of demonstrable effect at these sites should be considered in the context that the studies may not have been adequately powered.

HCP: Room for improvement

Treatment of Osteoporosis after Hip Fracture

- Hip fracture cases between 2000-2010
- 420 patients evaluated for osteoporosis treatment
- Median age = 80 (65-95)
- Male 27%
- 13.8% had DXA after discharge
- 19% received treatment (8.0% males, 23.1% females)
- Evaluation and treatment after hip fracture remains low

Antonelli, et al. ACR 2011. Abstract 870.

Poor Adherence

Adherence to Intravenous Zoledronic Acid (ZA) and Ibandronate (IB)

- Medicare database
  - 15,100 new users ZA
  - 7,120 new users IB
- 65.7% of ZA users persisted beyond 1-year
- 34.6% of IB users persisted beyond 1-year
- Persistance for ZA greater than oral bisphosphonates
- Factors associated with adherence
  - **Males, age 85+, GC use, prior fractures**
  - **Infusion by IM, Rheum, Endo vs Oncologist**

Curtis, et al. ACR 2011. Abstract 1101.

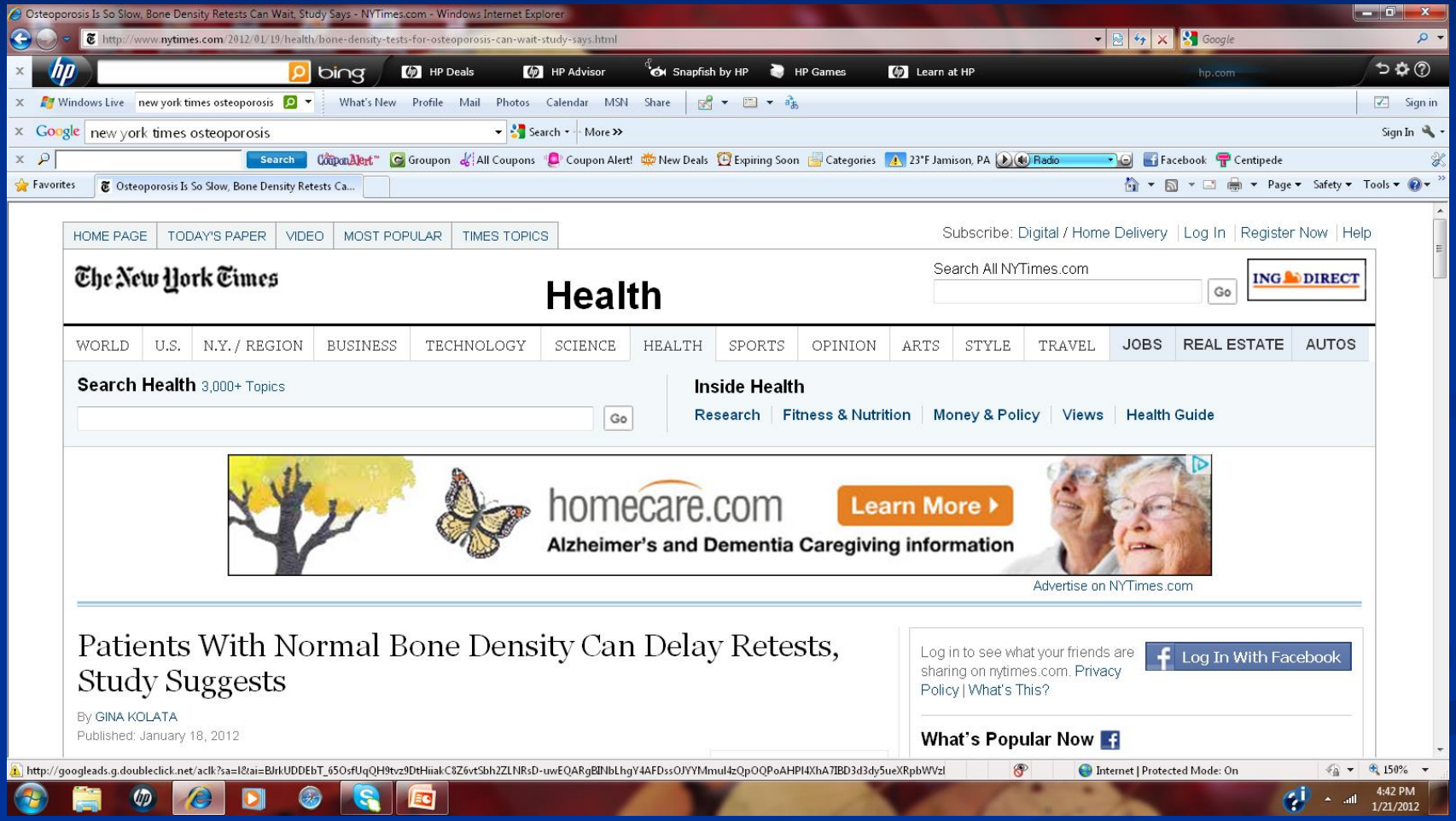
High Risk Population

- Bone mineral density (BMD) and clinical risk factors (CRFs) for fracture predict fracture risk better than BMD or CRFs alone
  - Fracture Risk Assessment in Clinical Practice: T-scores, FRAX, and Beyond; Clinical Reviews in Bone and Mineral Metabolism 2010-09-01

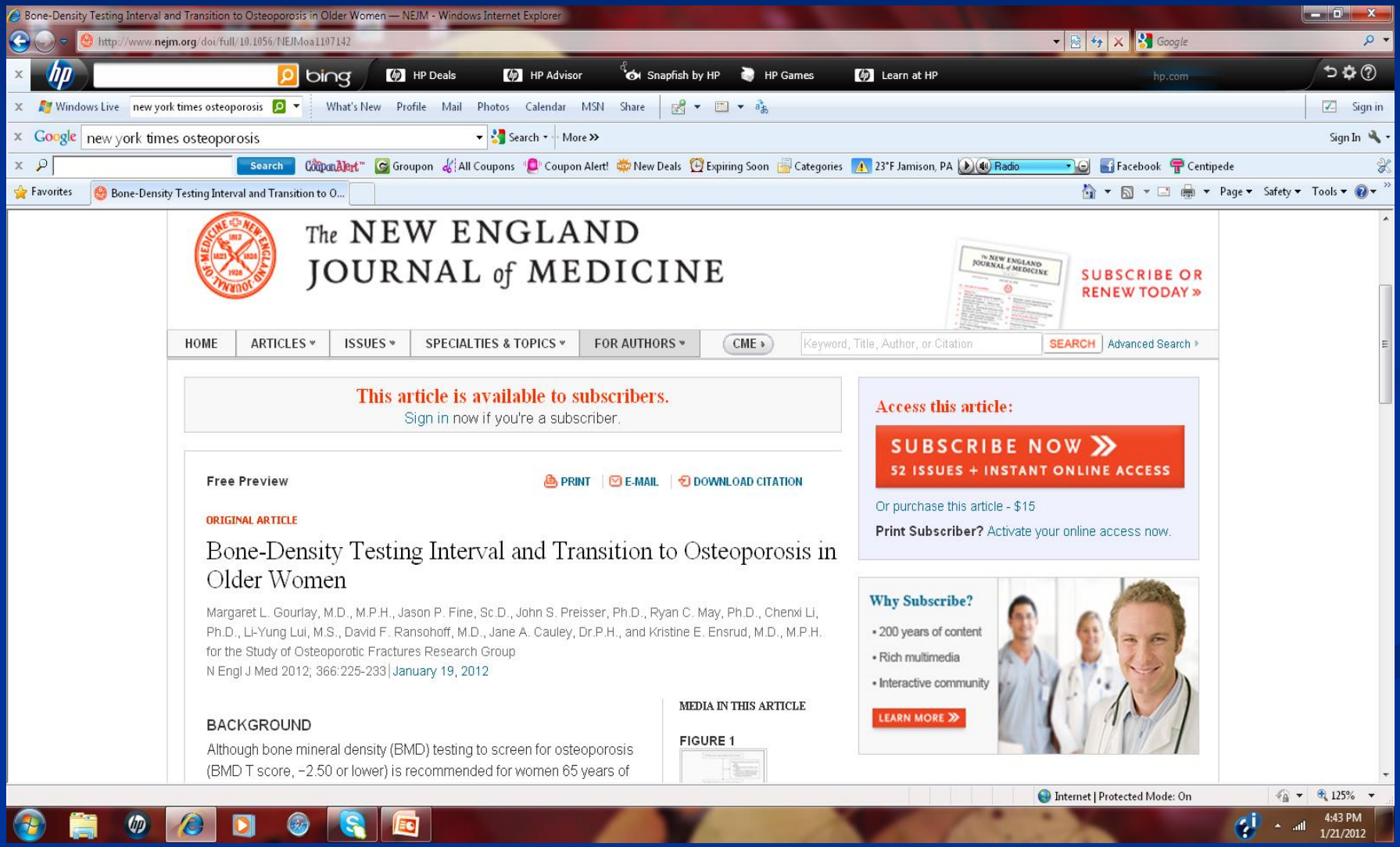
- Many CRFs; including women with CVD Women with Cardiovascular Disease Have Increased Risk of Osteoporotic Fracture, Calcified Tissue International http://dx.doi.org/10.1007/s00223-010-9431-7

- Hip fracture incidence was significantly higher in women having wide NSA (8.52%)- Older pts, debatable Prediction of incident hip fracture by femoral neck bone mineral density and neck-shaft angle: a 5-year longitudinal study in post-menopausal women *The British Journal of Radiology 57130600; published ahead of print November 17, 2011,*

DEXA in New York Times



Bone Density Testing



Bone-Density Testing Interval and Transition to Osteoporosis in Older Women

New England Journal of Medicine; Jan 19,2012

- **Aim:**
- To guide decisions about the interval between BMD tests
- **Methods :**
- 4957 women, 67 or older
- Normal BMD (T score femoral neck and total hip, −1.00 or higher)
- Osteopenia (T score, −1.01 to −2.49)
- No history of hip or clinical vertebral fracture
- No treatment for osteoporosis
- Followed 15 years

Margaret L. Gourlay, M.D., M.P.H.etal Study of Osteoporotic Fractures Research Group

Primary end point

- The BMD testing interval : Time for 10% to develop osteoporosis before having a hip or clinical vertebral fracture

- Three subgroups of osteopenia
  - Mild : -1.01 to -1.49
  - Moderate : -1.50 to -1.99
  - Advanced : -2.00 to -2.49

Results and Recommendations

- Time interval needed for 10% in the group to develop osteoporosis
  - 16.8 years for women with normal BMD
  - 17.3 for women with mild osteopenia
  - 4.7 years for women with moderate osteopenia
  - 1.1 years (95% CI, 1.0 to 1.3) for women with advanced osteopenia

- Retesting based on initial DEXA
  - 15 years for normal bone density or mild osteopenia
  - 5 years for women with moderate osteopenia
  - 1 year for women with advanced osteopenia.

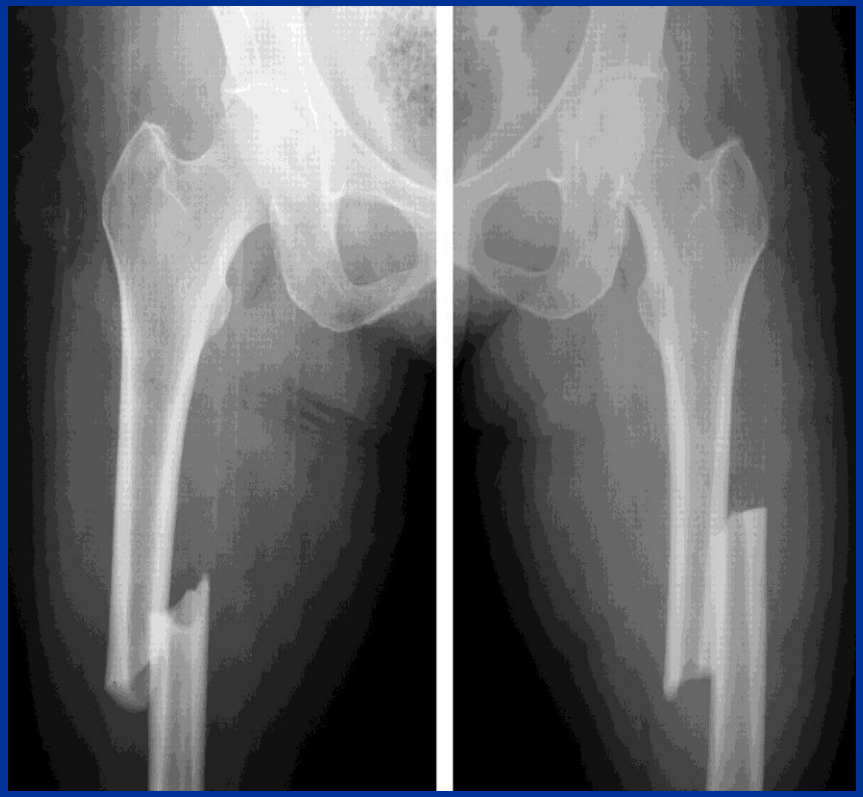
Myths and Facts Bisphosphonates

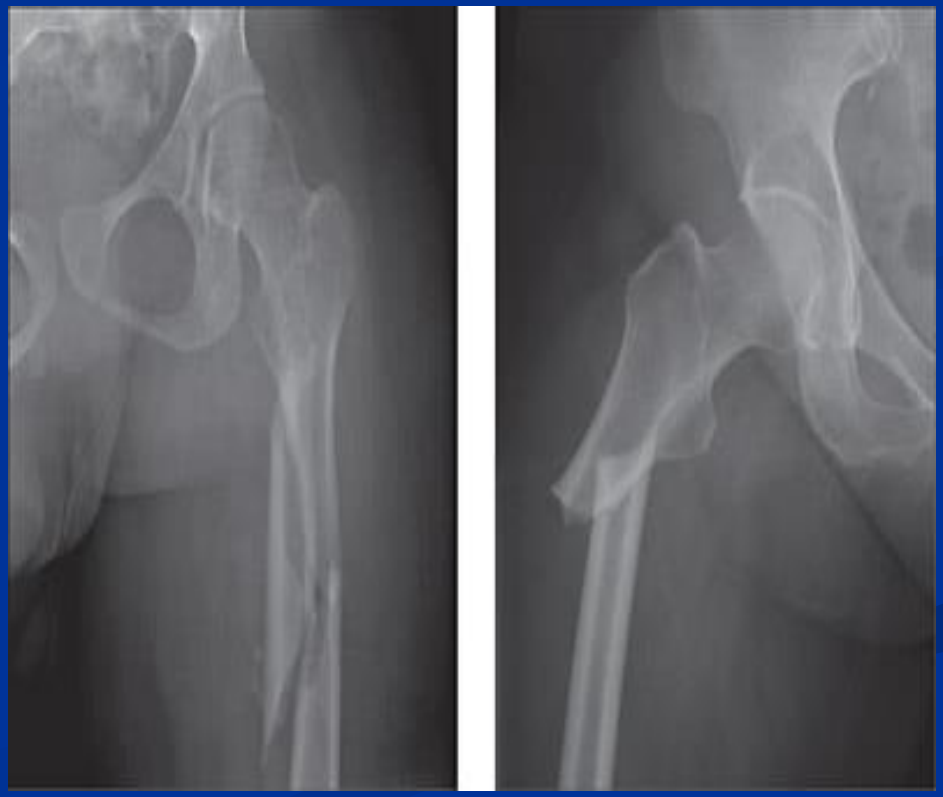
- Oteonecrosis of jaw (ONJ) High incidence in cancer pts; 2-11%, enhanced risk w/concomitant use of oral steroids, chemo, dental extraction, diabetes, tobacco use
- Bone Pain very uncommon adverse effects, resolves with discontinuation
- Atrial fibrillation no definitive association, incidental or underlying c.v. disease
  - Current Opinion in Rheumatology: July 2009 - Volume 21 - Issue 4 - p 363-368
- Cancer no rise in risk of cancer, avoid in Barrett's esophagus; ?protective breast, colorectal cancer Cardwell, (2012), Exposure to oral bisphosphonates and risk of cancer. International Journal of Cancer. doi: 10.1002/ijc.27389

Myths and Facts

- Subtrochanteric and femoral shaft fractures: affect elderly, incidence increased (2002 to 2009), obesity and dementia as risk factors Journal of Bone and Mineral Research, Vol. 27, No. 1, January 2012, pp 130–137
- Teriparatide and osteosarcoma: single case, association not established, 300,000 pt(baseline risk 1:250,000/yr)
- Vigilance, rather than alarm, is needed to manage adverse events associated with bisphosphonate use for osteoporosis Drugs & Therapy Perspectives: 1 February 2012 - Volume 28 - Issue 2 - pp 20-23

Atypical (low energy) fractures





The Journal of Bone & Joint Surgery. 2009; 91:2556-2561 doi:10.2106/JBJS.H.01774

How to decide

- Osteopenia associated with either low energy fracture(s) or very high risk for future fracture (assessed by FRAX) warrants therapy Treatment of osteopenia, Reviews in Endocrine & Metabolic Disorders
- Bone turnover markers (+BMD, CRF, FRAX) could best address the efficacy of treatment of osteoporosis Is There a Place for Bone Turnover Markers in the Assessment of Osteoporosis and its Treatment? Jean-Pierre Devogelaer, Rheumatic Disease Clinics of North America - August 2011 (Vol. 37, Issue 3, Pages 365-386, DOI: 10.1016/j.rdc.2011.07.002)
-

GIO and osteoporosis treatment

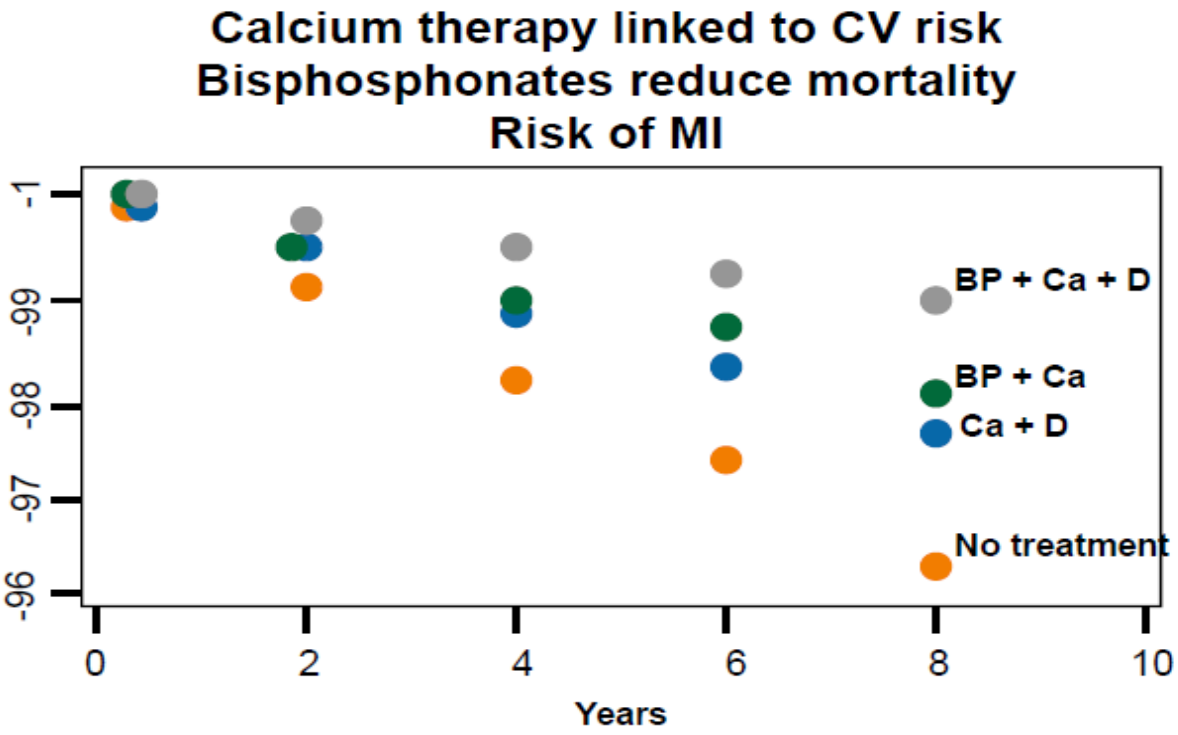
Use of Bisphosphonates for Prevention of GIO in RA

- Administrative data (Canada) identified 37,151 RA cases
- 21,547 GC courses >3m, >5mg
- 8,692 (40.3%) received a bisphosphonate (BP)
- 33.0% received a BP before 2000
- 46.7% received a BP after 2000
- 2010 ACR Guidelines recommend treatment in all subjects if dose >7.5mg >3m, and at lower doses based on FRAX 10-yr risk

Lacaille, et al. ACR 2011. Abstract 804.

Effects on Mortality

Reduction in MI in Bisphosphonate and Ca/Vit D Treated RA and SLE Patients



N = 155,750 semiannual observations in 23,228 RA (93%), SLE (7%) patients 2002-2010

Wolfe, et al. ACR 2011. Abstract 2589.

Newest FDA approved treatment

- Denosumab

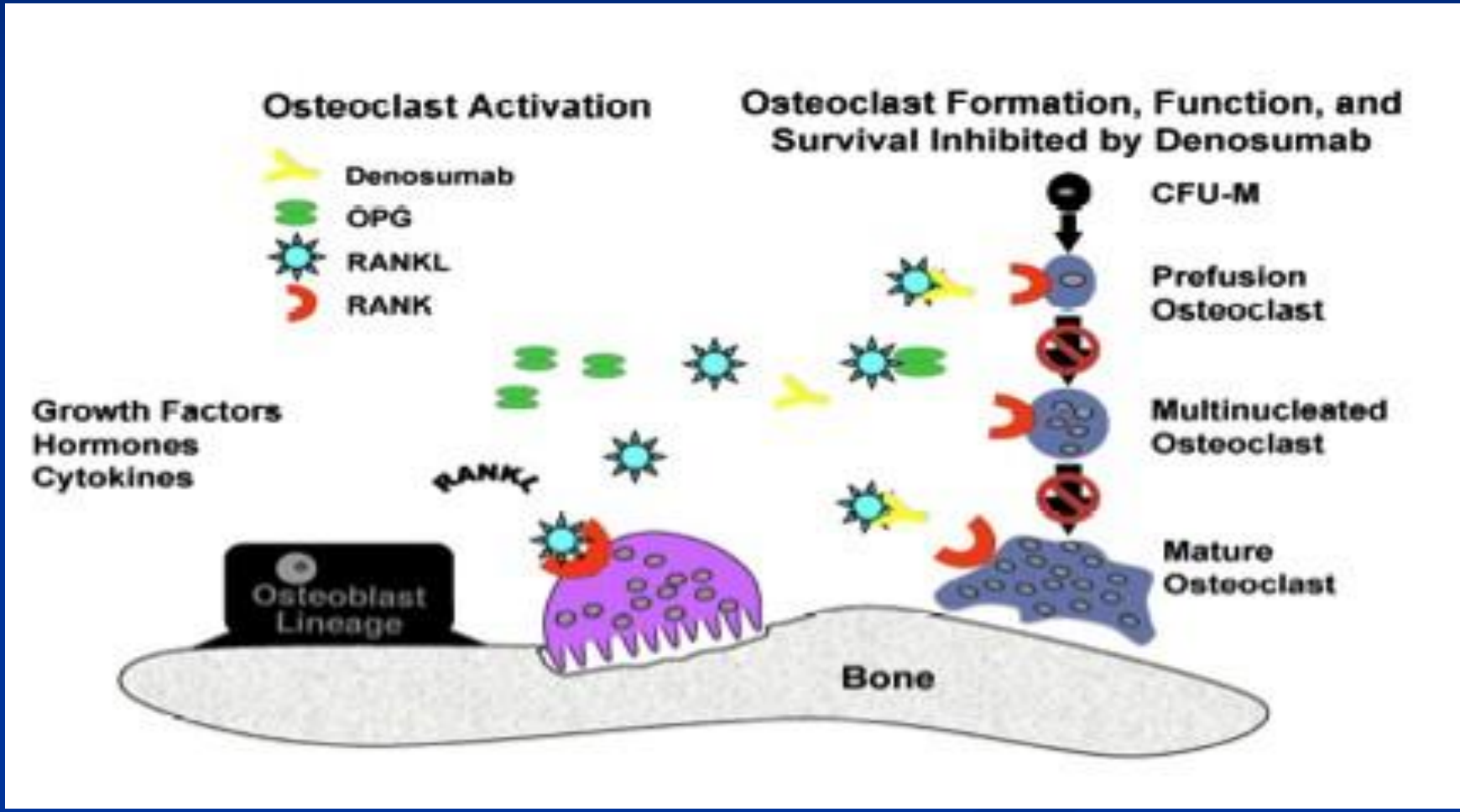
Denosumab

(*Trade name Prolia)*

- First biologic antiresorptive therapy for osteoporosis with efficacy and safety in patients with renal impairment The RANKL Pathway and Denosumab Robin K. Dore , Rheumatic Disease Clinics of North America - August 2011 (Vol. 37, Issue 3, Pages 433-452, DOI: 10.1016/j.rdc.2011.07.004)

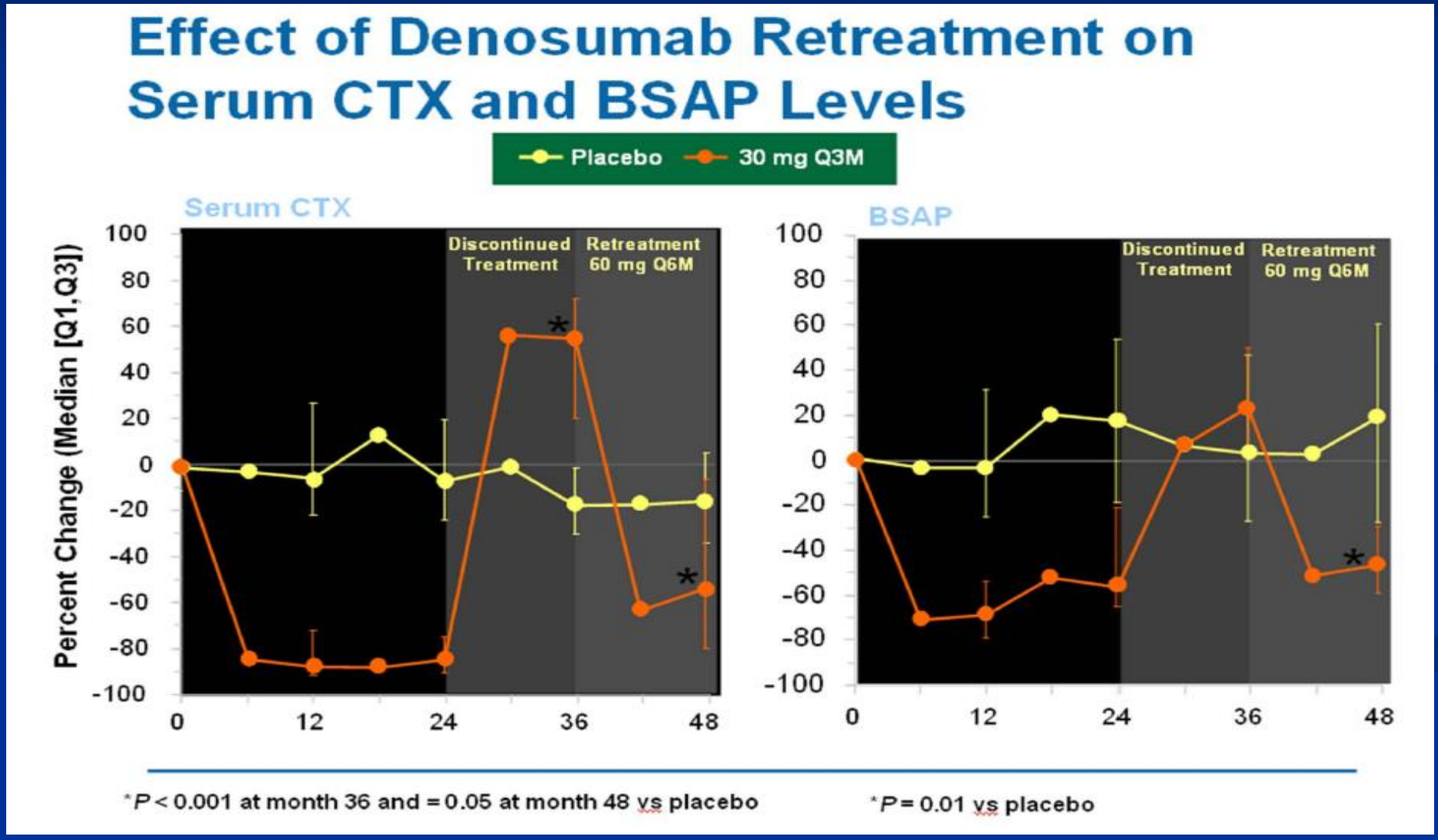
- Fully human monoclonal antibody against RANK ligand
- Released 6/2010
- Antiresorptive agent but rapid offset compared to Bps(which bind avidly to bone and remain in bone for extended time intervals)
- RANKL- RANK interaction, leads to osteoclastogenesis
- Denosumab reduces osteoclastogenesis to reduce resorption and improve bone density
- 60mg administered by subcutaneous injection every six months

Mechanism of Action



www.arcmesa.org/7153/monograph.php

Denosumab and Bone turnover



FREEDOM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

Steven R. Cummings, M.D., Javier San Martin, M.D., Michael R. McClung, M.D., Ethel S. Siris, M.D., Richard Eastell, M.D., Ian R. Reid, M.D., Pierre Delmas, M.D., Ph.D., Holly B. Zoog, Ph.D., Matt Austin, M.S., Andrea Wang, M.A., Stepan Kutilek, M.D., Silvano Adami, M.D., Ph.D., Jose Zanchetta, M.D., Cesar Libanati, M.D., Suresh Siddhanti, Ph.D., and Claus Christiansen, M.D., for the FREEDOM Trial*

Fracture Reduction of Denosumab in Osteoporosis Every 6 Months

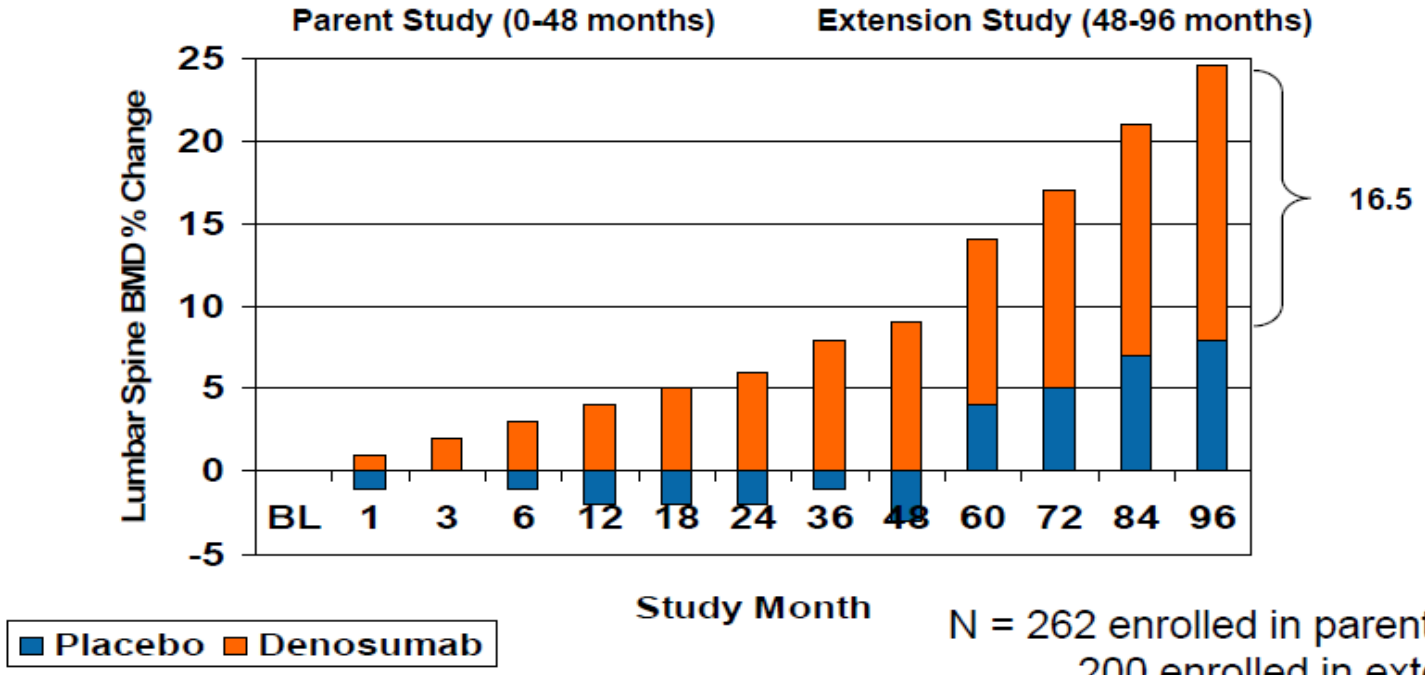
- Methods: 7868 women, lumbar/femoral T -2.5-4.0, D/P injection every 6 months for 36 months
- Primary end point: New vertebral fracture, non vertebral and hip secondary end points
- Results: Decrease
- Vertebral fractures 68% (2.3% vs. 7.2%, P<0.001)
- Hip fractures 40% (0.7% vs. 1..2%, P<0.04)
- Safety: No increase in risk of cancer, infection, delayed wound healing, ONJ, hypocalcaemia. Increase in eczema in 3%(P<0.001)

N Engl J Med 2009; 361;756-65

Lumbar BMD

Denosumab Lumbar Spine BMD Over 8 Years

Percent Change in Lumbar Spine BMD From Parent Study Baseline

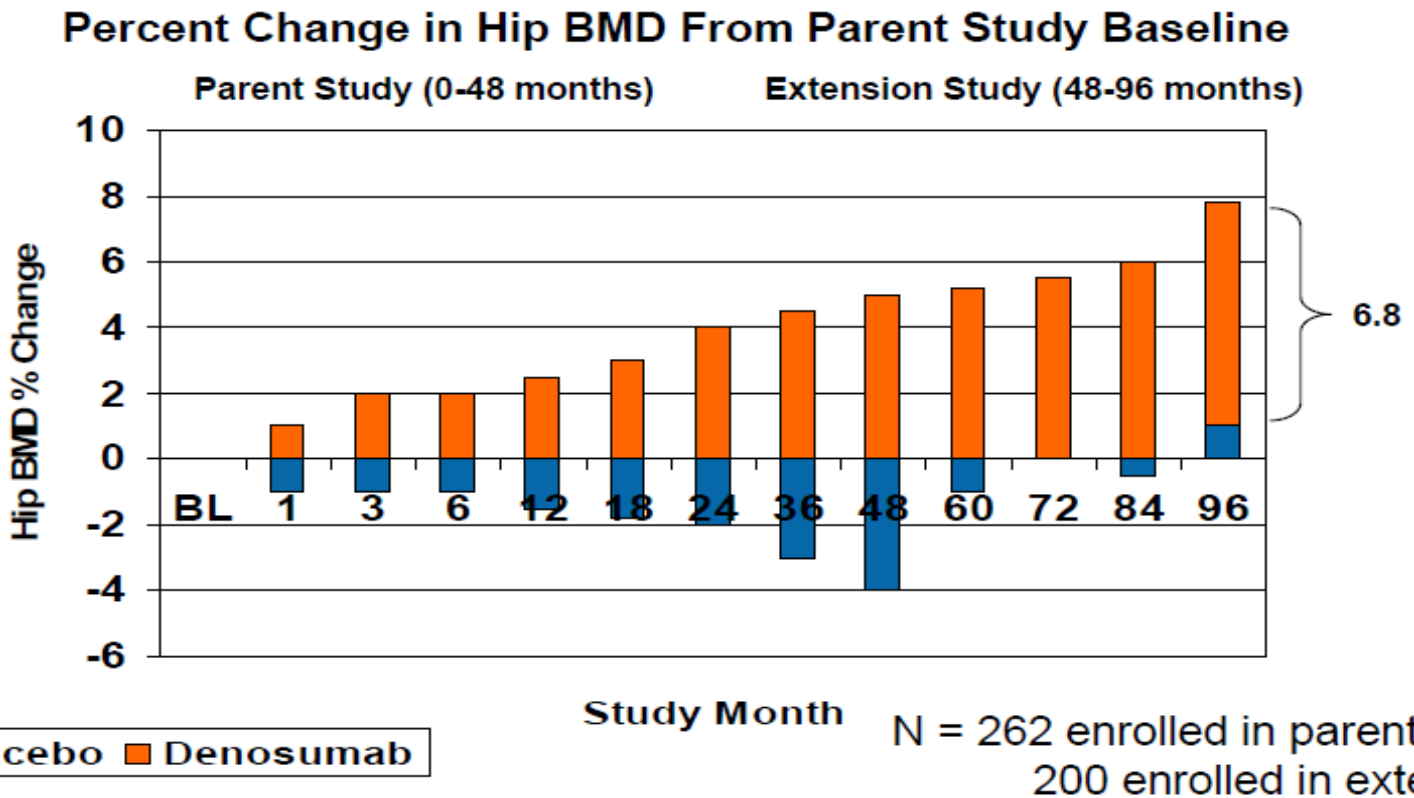


N = 262 enrolled in parent study
200 enrolled in extension
138 completed 8-years

McClung, et al. ACR 2011. Abstract 1107.

Hip BMD

Denosumab Total Hip BMD Over 8 Years



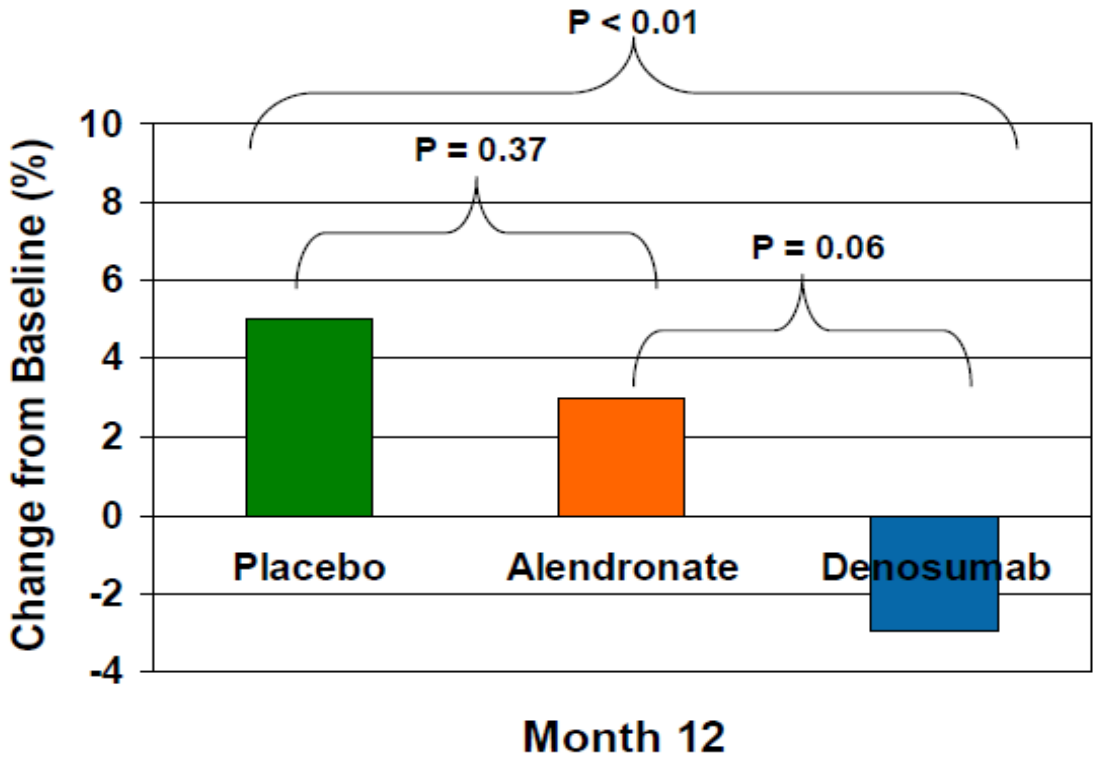
N = 262 enrolled in parent study
200 enrolled in extension
138 completed 8-years

McClung, et al. ACR 2011. Abstract 1107.

Cortical Bone Porosity

Denosumab Decreases Cortical Porosity

Denosumab Decreases Cortical Porosity at the Distal Radius in Postmenopausal Women with Low BMD



-8.18% vs PBO, -5.84% vs Aln

N = 247 women

Porosity calculated by HRpQCT

Libanati, et al. ACR 2011. Abstract 1631.

Freedom Extension Data

Late Breaking 8: Denosumab, FREEDOM Extension 3-Years

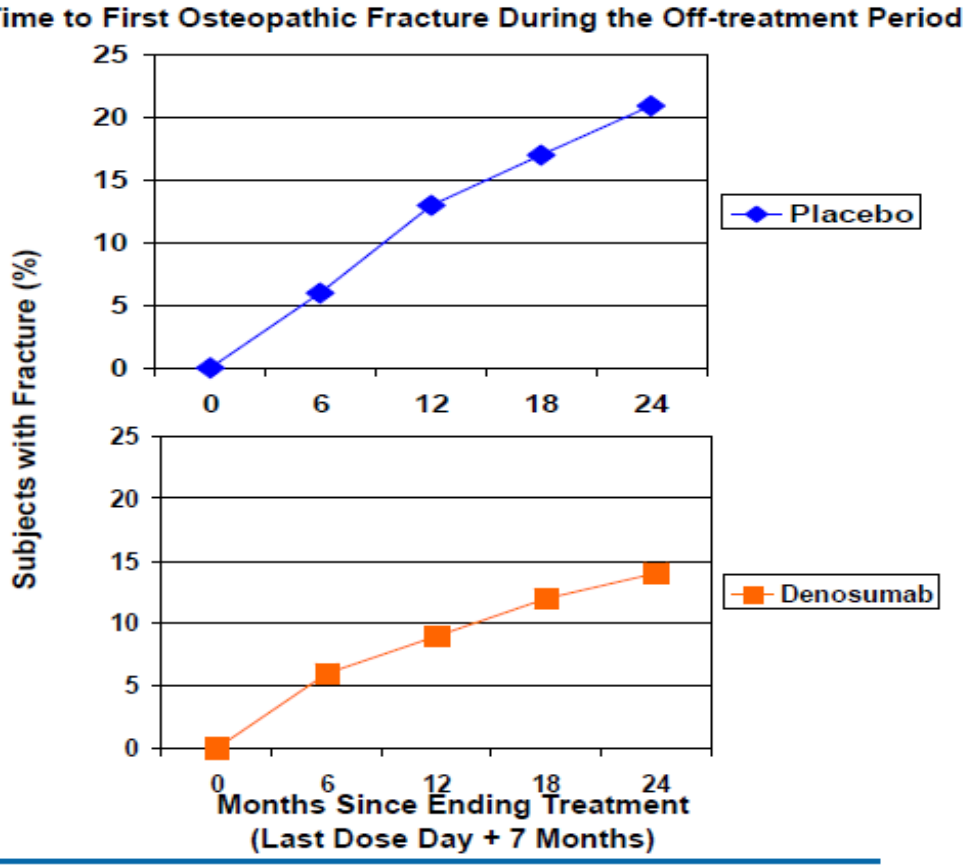
- Open-label, active-treatment FREEDOM Extension Study : 7-year extension of 3-year FREEDOM Trial
- 4550 women enrolled
- Cumulative 6-year gains:
  - **Lumbar spine = 15.2%**
  - **Total hip = 7.5%**
- 4 cases of ONJ through 6-years

Denosumab Discontinuation

Denosumab Discontinuation and Fracture Incidence in the FREEDOM Trial

FREEDOM : 3-year RCT of Denosumab

- 797 subjects received 2-5 doses and discontinued denosumab
- 42% PBO started alternative therapy, 28% denosumab



Brown, et al. ACR 2011. Abstract 1098.

Denosumab vs. Bisphosphonates

- Increased bone mineral density lumbar 6%, hip 9%, reduced risk of all type of fractures
- Blocks the formation, function and survival of osteoclasts vs. BNP block the function and survival but not formation
- Magnitude of vertebral risk reduction similar to IV Zolendronic acid and greater than oral bisphosphonates (same for non vertebral fractures in both options)
- Median reduction in bone resorption 86% in 1 month, more than other anti resorptive agents
- Better than IV Zolendronic acid (bone metastasis)
- Better adherence to oral agents, 50% pts stop oral agent in 1yr

Safety Data

Denosumab Adverse Events Years 4-5

Yearly Incidence of Serious Adverse Events of Infection

		Freedom			Extension	
		Year 1 r(n)	Year 2 r(n)	Year 3 r(n)	Year 1 r(n)	Year 2 r(n)
Cellulitis or Erysipelas	Cross-over (Pbo/DMab)	0	0	< 0.1 (1)	0	< 0.1 (1)
	Long-term (DMab/DMab)	0.1 (4)	< 0.1 (1)	0.2 (8)	< 0.1 (2)	< 0.1 (1)

r = exposure adjusted subject incidence per 100 subject years

Brown, et al. ACR 2011. Abstract 1103.

Safety Data

Denosumab Adverse Events Years 4-5

Yearly Incidence of Serious Adverse Events of Infection

		Freedom			Extension	
		Year 1 r(n)	Year 2 r(n)	Year 3 r(n)	Year 1 r(n)	Year 2 r(n)
All SAEs of Infection	Cross-over (Pbo/DMab)	1.1 (42)	1.4 (50)	1.4 (48)	1.5 (33)	1.6 (32)
	Long-term (DMab/DMab)	1.5 (56)	1.6 (58)	1.6 (54)	1.3 (30)	1.2 (26)

r = exposure adjusted subject incidence per 100 subject years

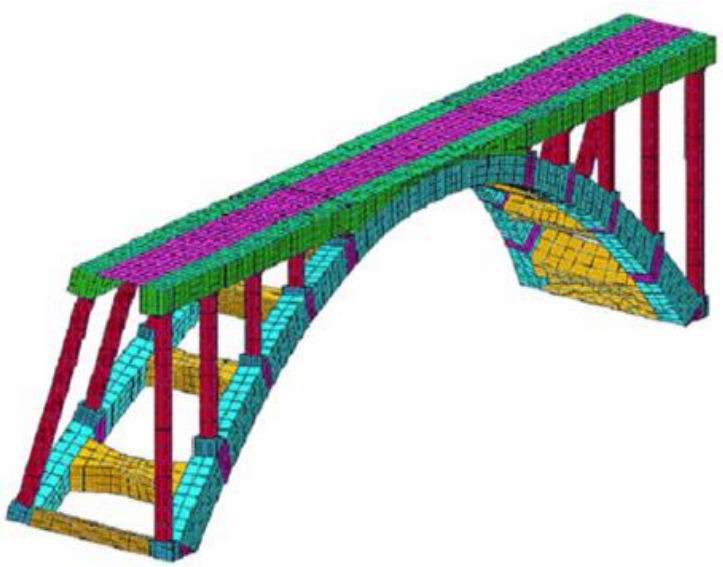
Brown, et al. ACR 2011. Abstract 1103.

Teriparatide

- FORTEO (teriparatide [rDNA origin] injection) for subcutaneous use, U.S. Approval: 2002
- Recommended dose is 20 mcg subcutaneously once a day
- Administered into the thigh or abdominal wall
- Maximum use of the drug no more than 2 years (life time)

Teriparatide-Anabolic agent

Finite Element Analysis



Model of a bridge with the different colors representing different material properties.

With permission: Igor Lozovitski of the Lozik Group

Teriparatide Finite Element Analysis Strength

Change from Baseline to Month 18 (%)

Median (interquartile range)		
Outcome	Vertebra (n=30)	Femur (n=26)
Strength	16.6 (7.4, 24.7)*	2.3 (-1.6, 6.8)*

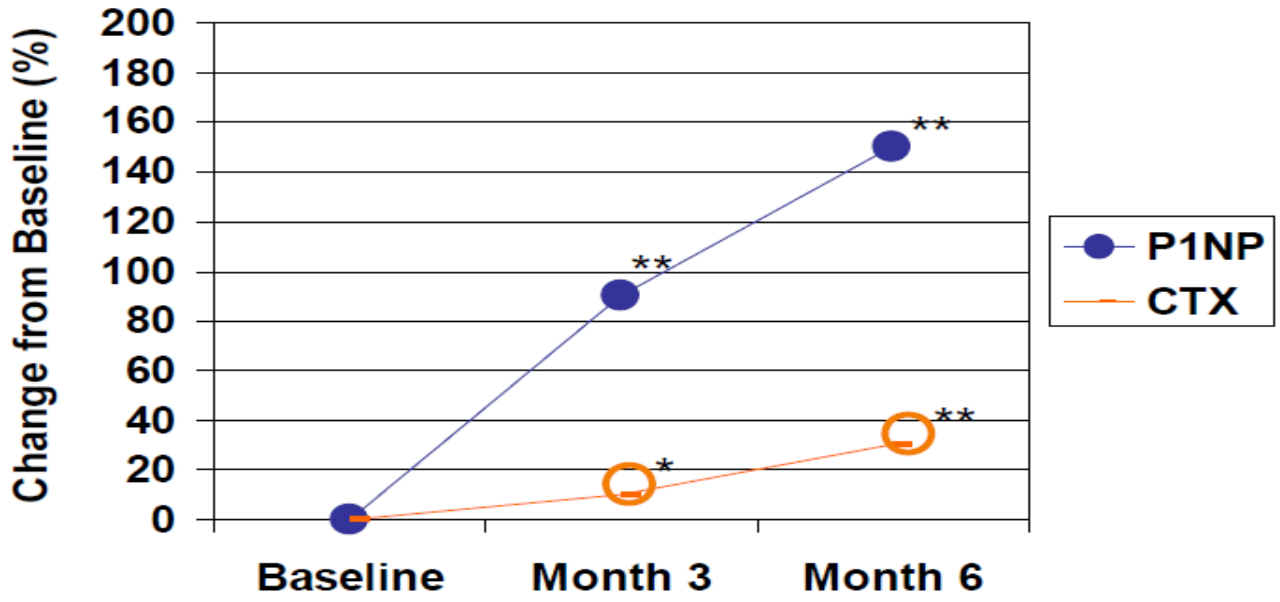
Mean (standard deviation)		
Areal BMD	Vertebra (n=25)	Femur (n=28)
Lumbar spine	6.3 (5.0)**	
Femoral neck		1.8 (4.8)
Total hip		0.2 (3.4)

*P<0.05 vs baseline
**P<0.0001 vs baseline

Keaveny, et al. ACR 2011. Abstract 1099.

Teriparatide
Anabolic agent

Teriparatide Bone Turnover Markers

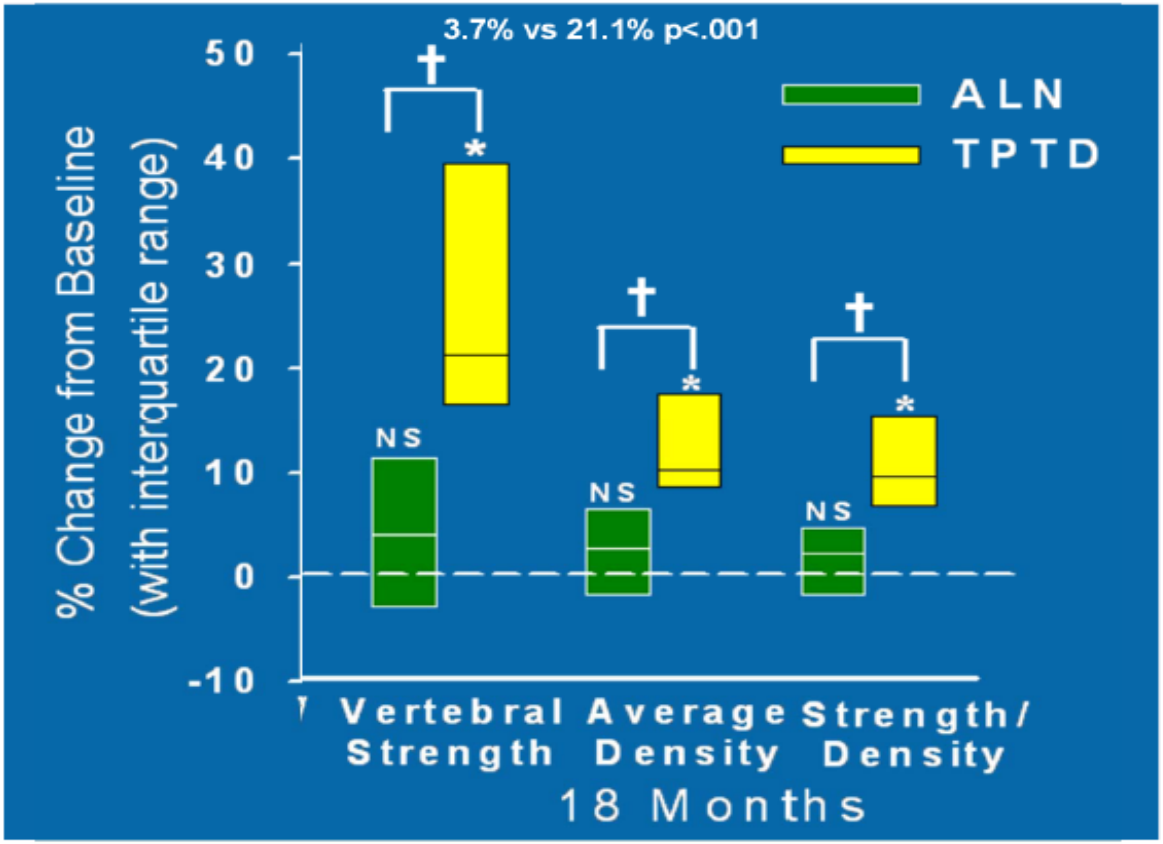


*P<0.05 vs baseline
**P<0.0001 vs baseline

Keaveny, et al. ACR 2011. Abstract 1099.

Teriparatide and Vertebral strength

Effects of Teriparatide and Alendronate on Parameters of Vertebral Strength



Keaveny, et al. *J Bone Min Res* 2007;22(1):149-57.

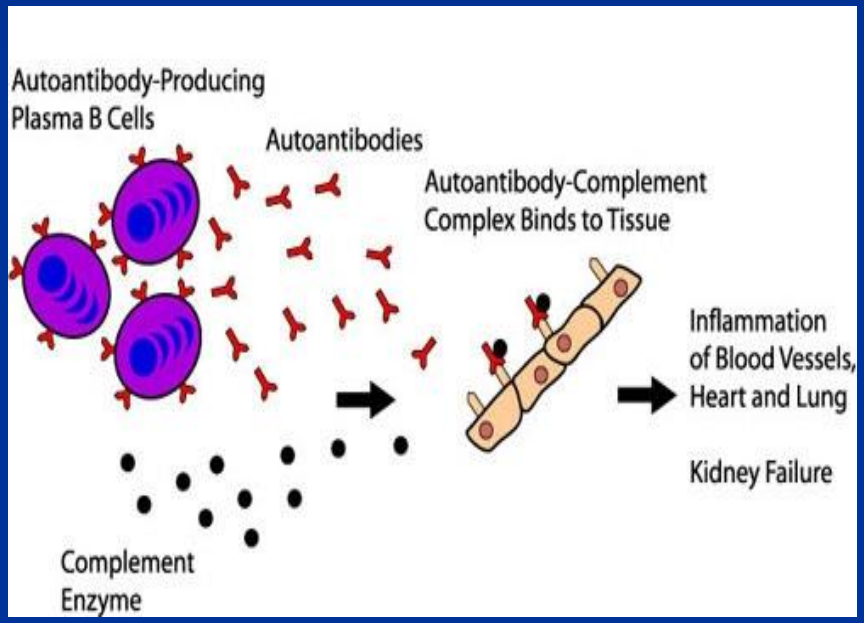
Belimumab for SLE

Belimumab

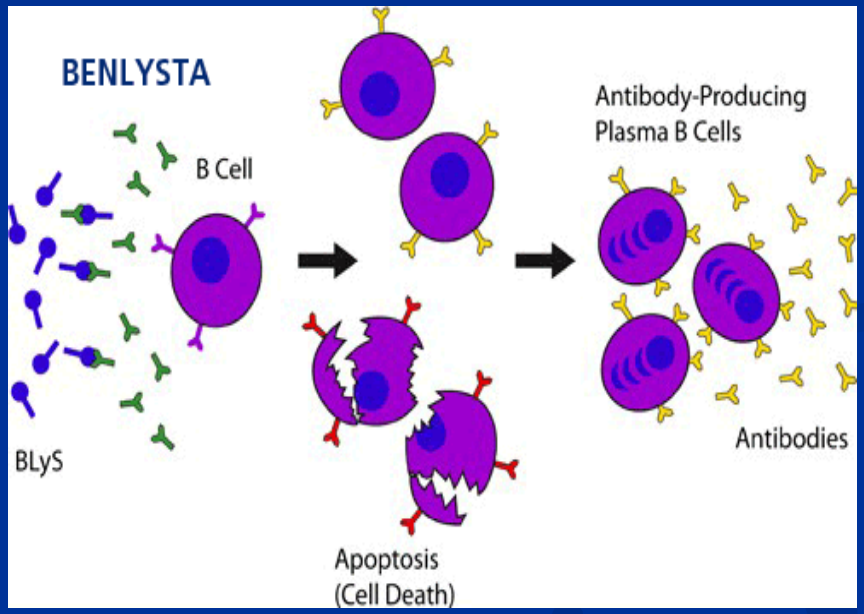
- B-lymphocyte stimulator (BLyS)-specific inhibitor
- BLyS-specific inhibitor blocks the binding of soluble BLyS, a B-cell survival factor
- Does not bind B cells directly, but by binding BLyS and inhibits the survival of B cells
- Reduces auto reactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells

Mechanism of action

Pathophyiology



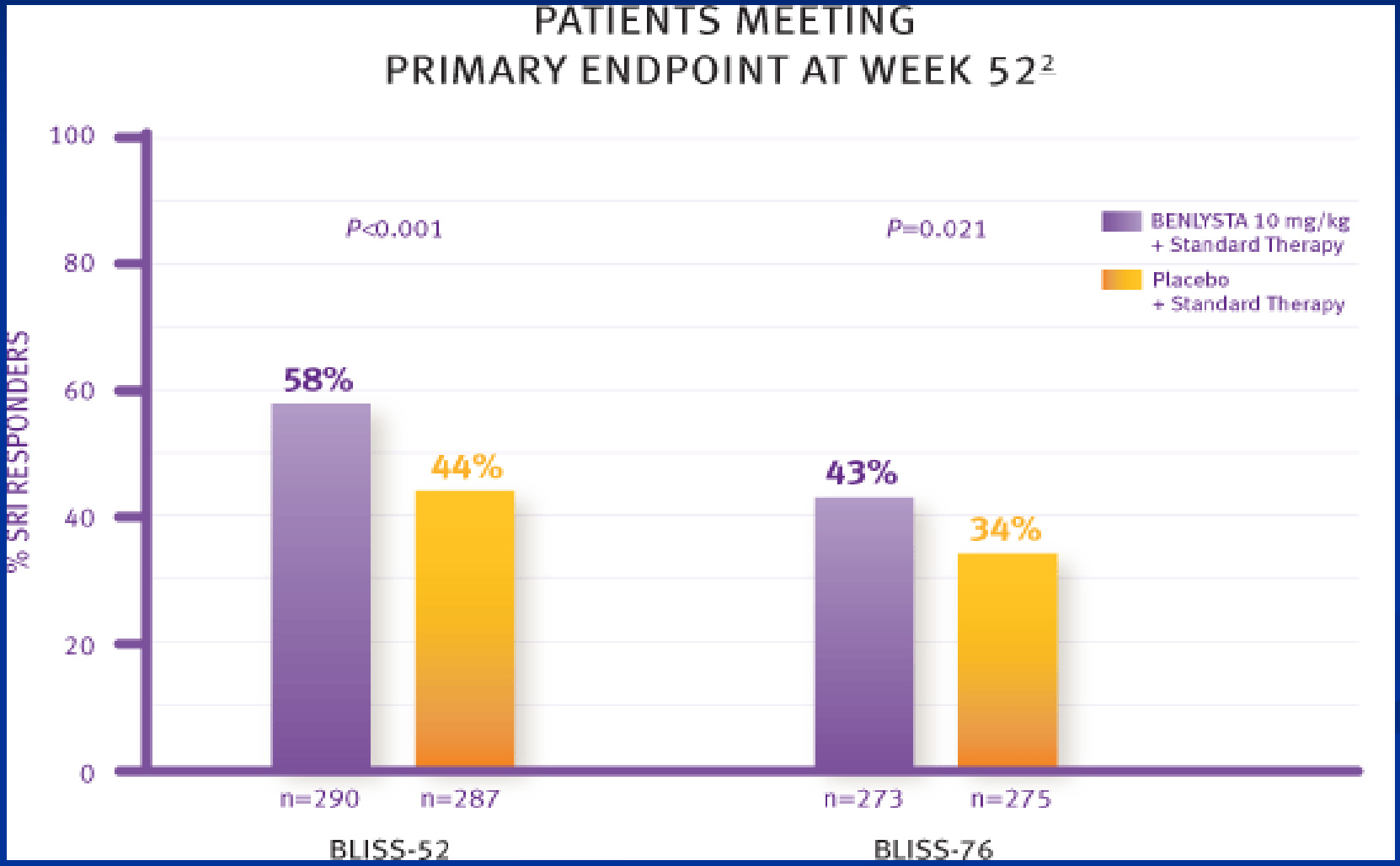
Blys binding



Clinical Trials

- >50% of pts 3 or more active organ systems , mucocutaneous, immunology, musculoskeletal
- Randomly assigned to receive Belimumab 1 mg/kg, 10 mg/kg, or placebo in addition to standard of care.
- Intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for 48-72
- The primary efficacy endpoint : SLE Responder Index or SRI to suggest worsening
- Trial 2 and 3 rd met the endpoints, Placebo versus 10mg/kg dose; 34% vs 43%; 34% vs 58%

Clinical Trials



Summary

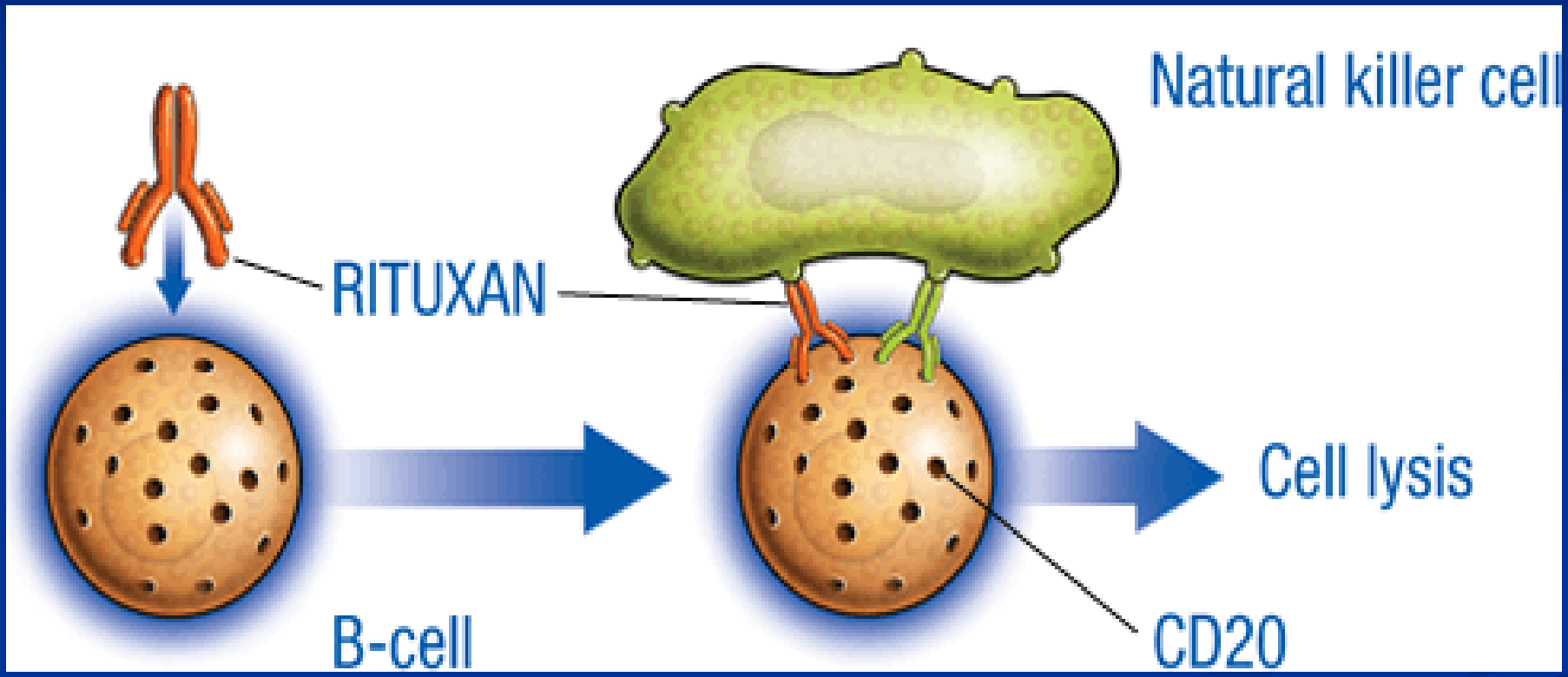
- Active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy
- Not indicated in severe active lupus nephritis or severe active lupus cerebritis
- Intravenous10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals
- Adv events and Caution; prophylactic medications reduce infusion reaction and risk of immunogenicity

Rituximab in ANCA vasculitis

Rituximab in autoimmune disorders

- B cell depleting monoclonal antibody, attacks B cells CD 20+lymphocytes
- FDA approved for RA (SLE, Sjogren's syndrome, HCV cryoglobulinemic vasculitis, Antiphospholipid syndrome and ANCA vasculitis)
- Replaced "standard of care" Cyclophosphamide in ANCA associated vasculitis, effective but has high rates of death and adverse events
- Small series showed remission -80 to 90% in refractory ANCA vasculitis with better safety profile
- Two pivotal NEJM published RCTs

Mechanism of Action



www.rituxan.com/lymphoma/hcp/MOA/index.m

RAVE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

Rituximab versus Cyclophosphamide for ANCA-associated vasculitis

- Design: US based ,197 pts
- Methods: 375mg/m2 once a week for 4 weeks, control group (oral cyclophosphamide 2mg/kg), 1-3 pulse solumedrol followed by prednisone 1mg/kg
- Primary end point was remission of disease without prednisone at 6 months
- Results: 64% patients in Rituximab arm and 53% in control arm reached primary end point and met criteria of non inferiority P<0.001

Stone JH - *N Engl J Med* - 15-JUL-2010; 363(3): 221-32

RAVE

- Safety: No significant differences in adverse effects
- Conclusion: Rituximab was non inferior
- More effective is inducing remission for refractory relapsing disease, 67% (34/51) vs. 42% (21/50) in control group
- Same efficacy as cyclophosphamide in major renal disease or alveolar hemorrhage

Stone JH - *N Engl J Med* - 15-JUL-2010; 363(3): 221-32

RITUXVAS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 15, 2010 VOL. 363 NO. 3

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Rachel B. Jones, M.R.C.P., M.D., Jan Willem Cohen Tervaert, M.D., Ph.D., Thomas Hauser, M.D., Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Matthew D. Morgan, M.R.C.P., Ph.D., Chen Au Peh, F.R.A.C.P., Ph.D., Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Mårten Segelmark, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Pieter van Paassen, M.D., Ph.D., Dorothy Walsh, B.S.C.N., Michael Walsh, M.D., F.R.C.P.(C.), Kerstin Westman, M.D., Ph.D., and David R.W. Jayne, M.D., F.R.C.P., for the European Vasculitis Study Group

Take home message

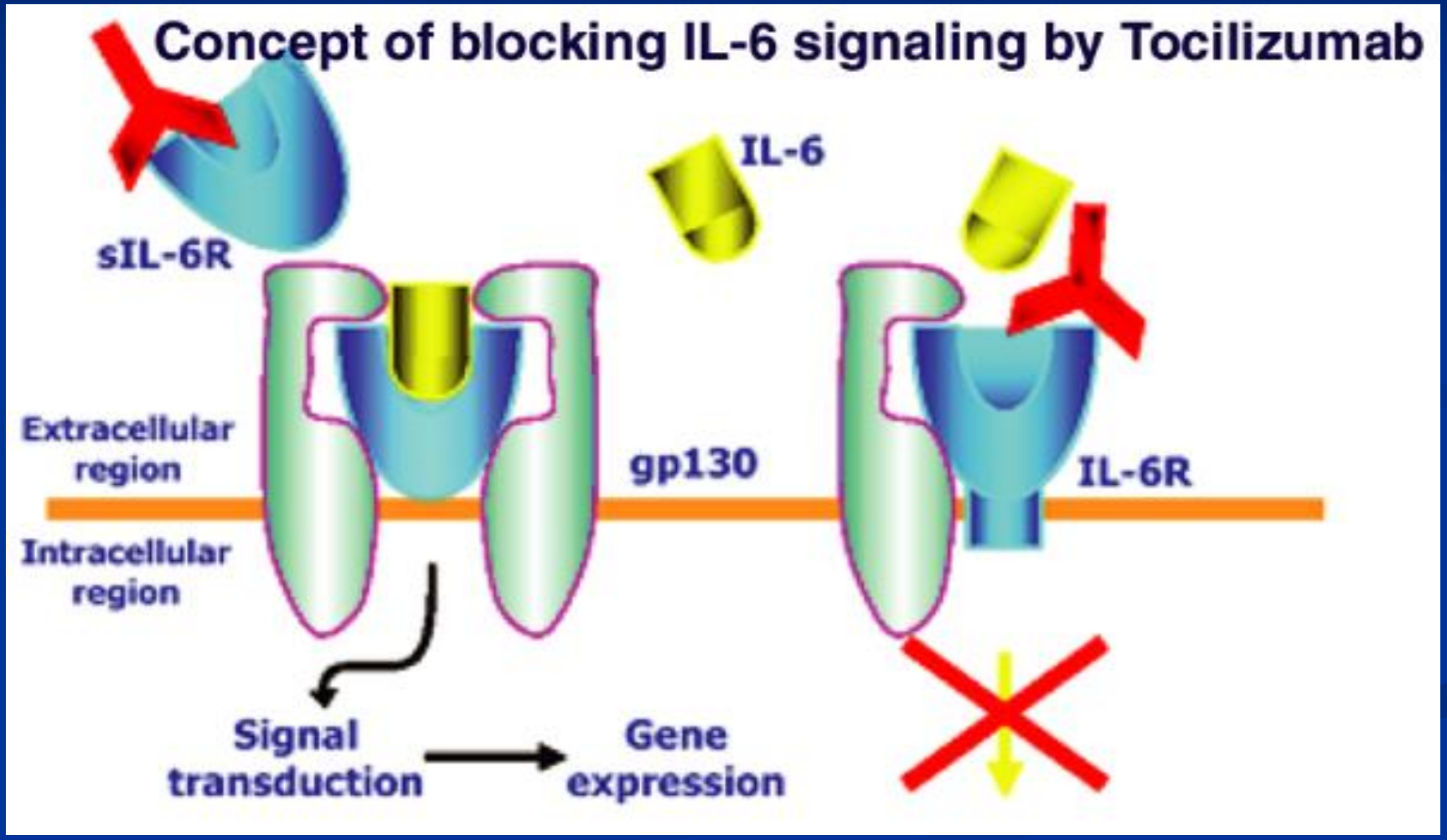
- Rituximab was efficacious in inducing remission particularly for refractory relapsing cases
- Adverse effect profile
- First line and even better for induction of refractory cases
- Azathioprine appears to be reasonable choice for maintenance

Tocilizumab

Tocilizumab for rheumatoid arthritis

- Chronic inflammation leads to production of IL-6; cytokine with its receptor expressed on effectors cells
- Effector cells cause and prolong inflammation
- Humanized anti IL-6 receptor IgG1 inhibits IL-6 binding to receptor and interferes cytokine effects.
- Its an IV infusion administered over one hour
- Potent inhibitor of CRP production and improves inflammation induced anemia
- Approved for RA patients who are TNF non responders, marketed as "Actemra"

Mechanism of Action



Arthritis Research & Therapy 2006 **8**(Suppl 2):S2 doi:10.1186/ar1916

RADIATE

- Design: Double blind, RCT, Europe and USA
- Methods: 500 pts
- Primary outcome: ACR 20 @ 24 wks, secondary outcomes ACR50/70, DAS and HAQ
- Results: Primary and secondary end points
- 50% in MTX+ 8mg/kg vs. 10% in control
- Conclusion: Tocilizumab plus MTX is effective in achieving rapid and sustained improvement in TNF non responders

Ann Rheum Dis 2008. doi:10.1136/ard.2008:092932

Good Safety Profile

- Reversible elevation of transaminases 3ULN- 6% in MTX + Tocilizumab
- Serious infections/100 pts : 3, 6 vs. 2.3 compared to MTX
- Elevated serum cholesterol (large molecule, not @MI)
- Transient neutropenia
- Gastrointestinal adverse events including diverticular perforation, may suppress and delay detection of diverticulitis

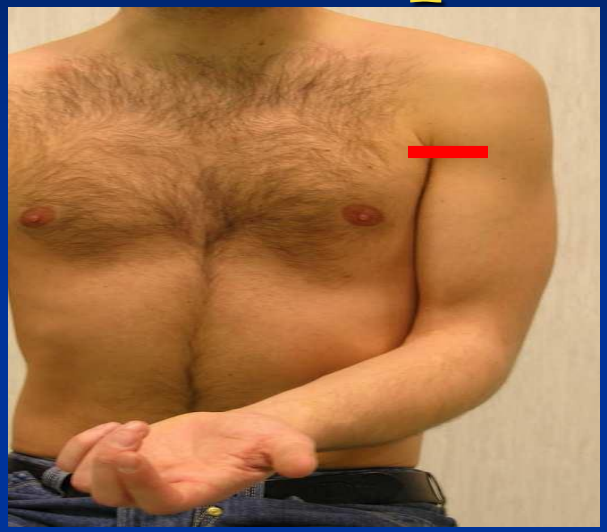
Musculoskeletal Ultrasound

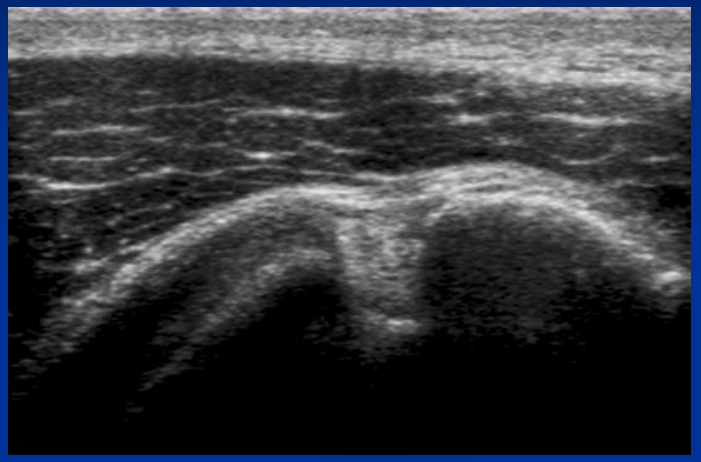
Musculoskeletal Ultrasound

- Tool for real time examination of musculoskeletal structures of interest
- In trained hands, serves a great diagnostic tool with fraction of the cost and radiation
- RCTs have shown improved injections technique and provided objective assessment of response to treatment
- Useful in assessment of tendinopathy, tenosynovitis, bursitis and joint effusions which are difficult to assess on physical exam
- Neovasculization of synovial tissues with doppler images help detect active disease related to inflammation

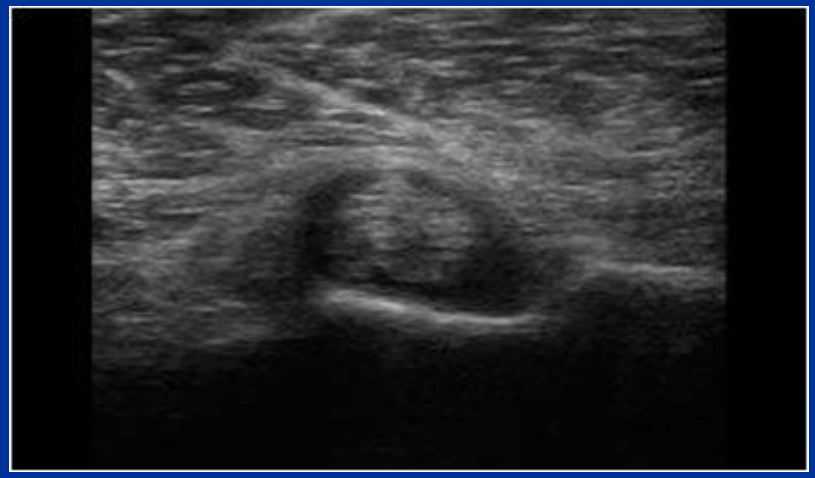
Image source http://www.ultrasoundcases.info/, http://www.essr.org/cms

Shoulder pathologies
Bicepital tendinosis

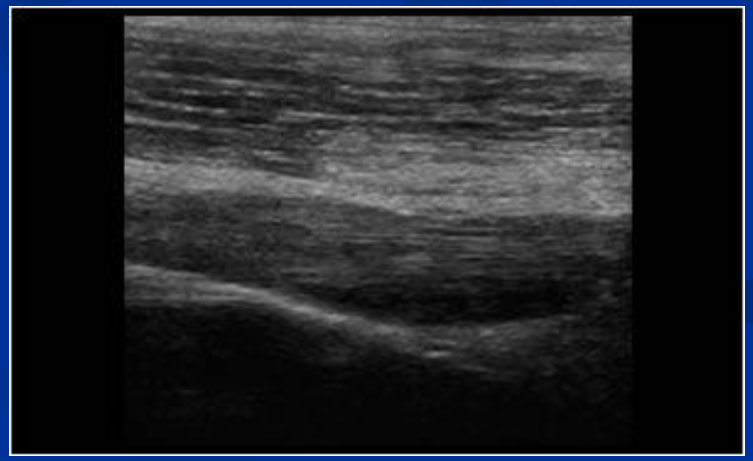




Normal Transverse

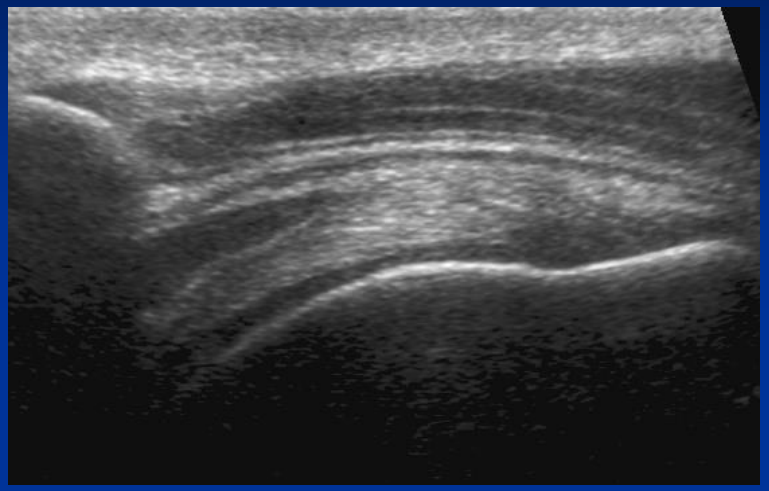


Transverse

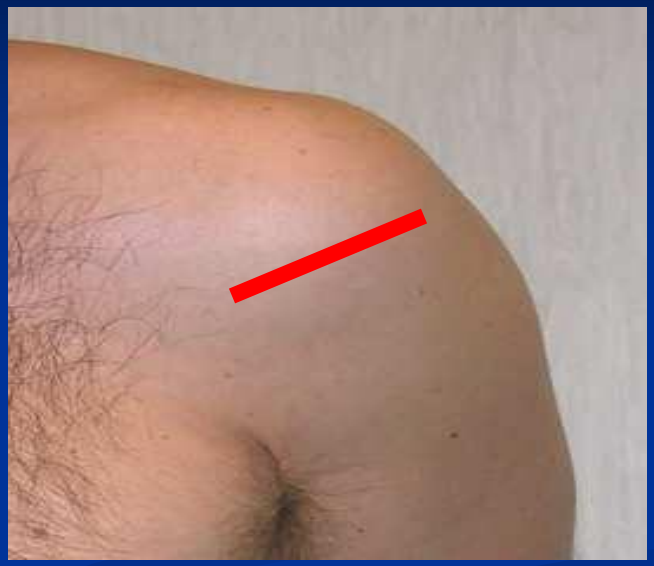


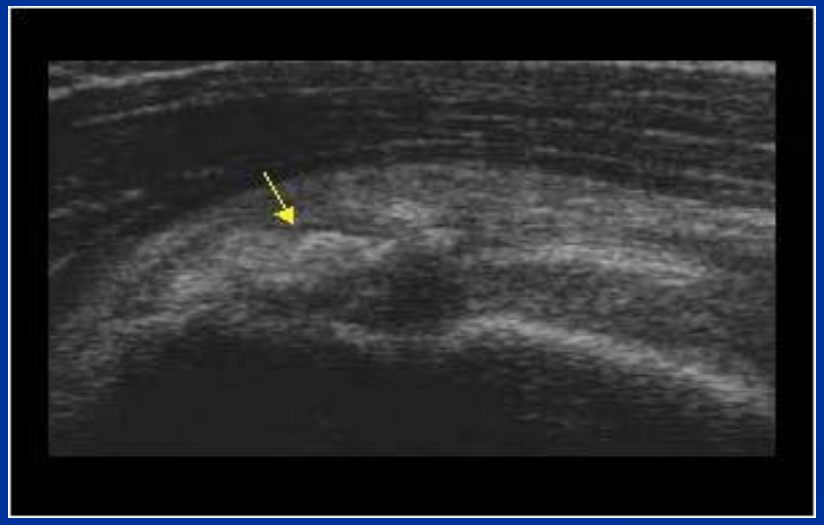
Longitudinal

Supraspinatus calcification

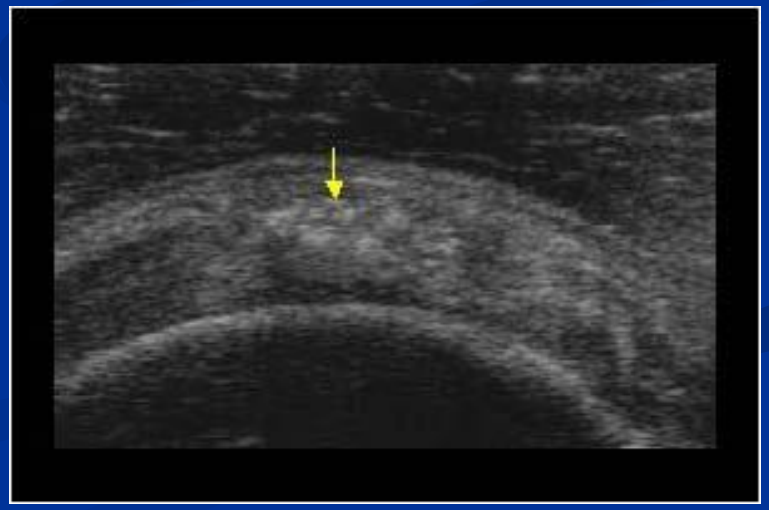


Normal



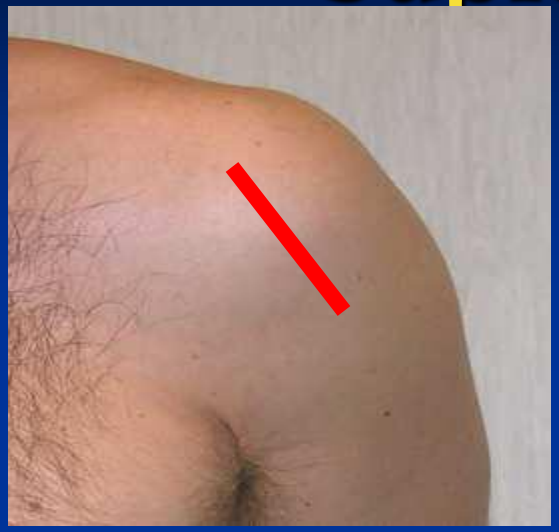


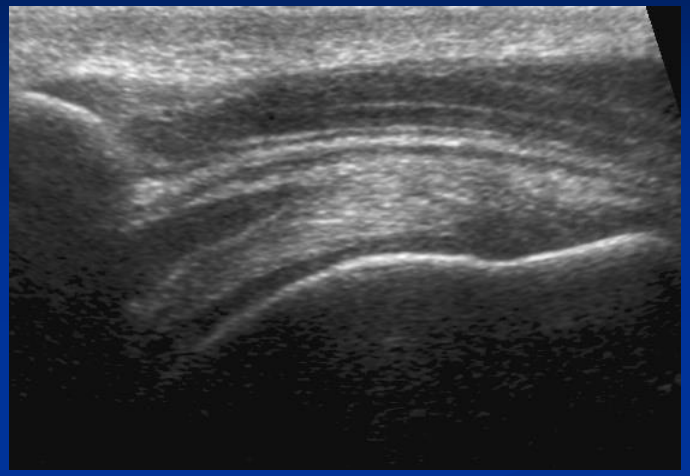
Longitudinal



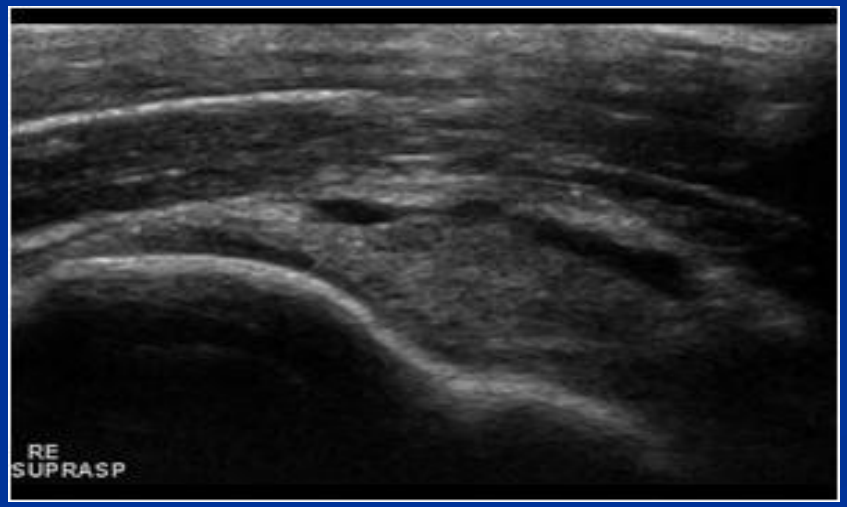
Transverse

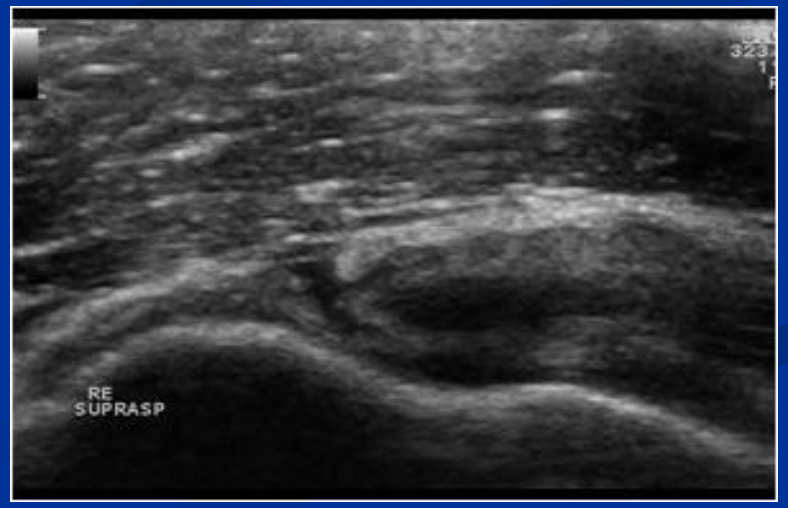
Supraspinatus tear





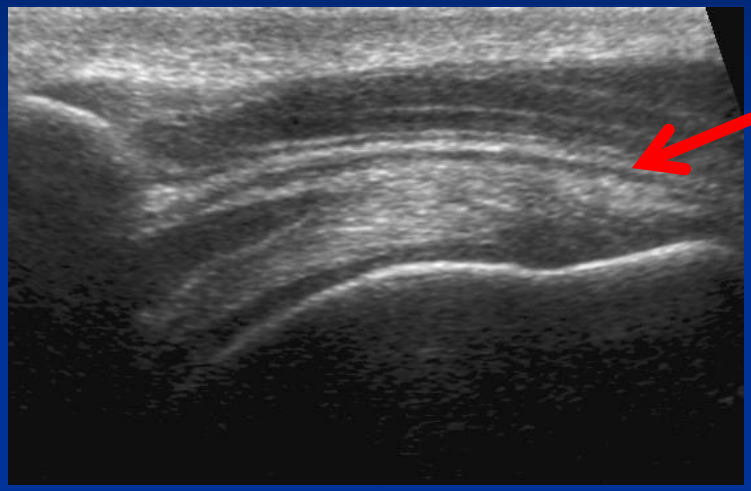
Normal

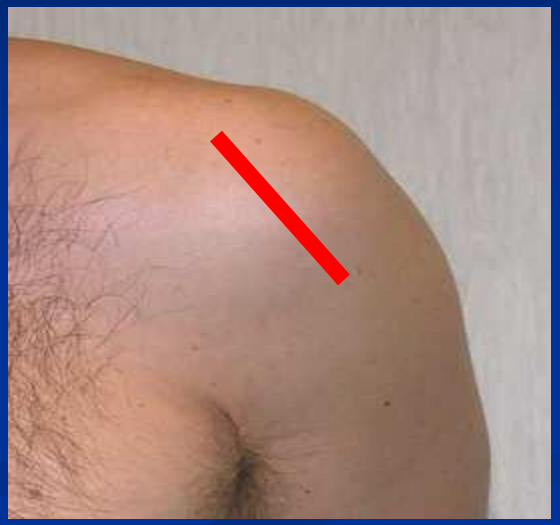


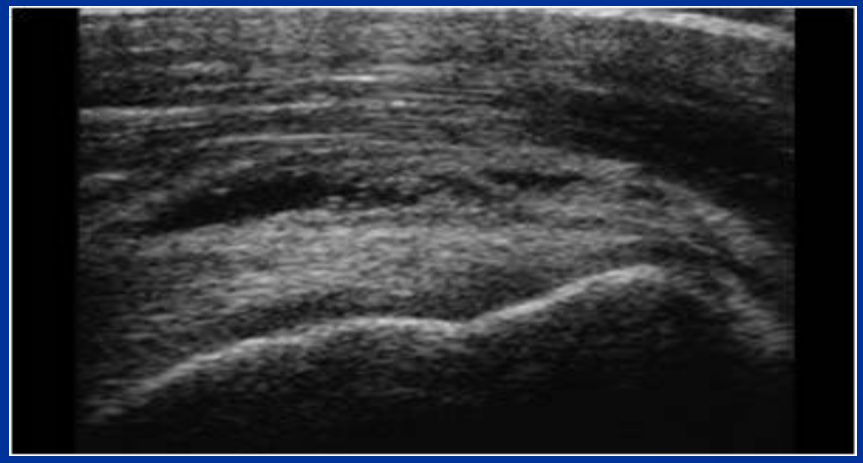


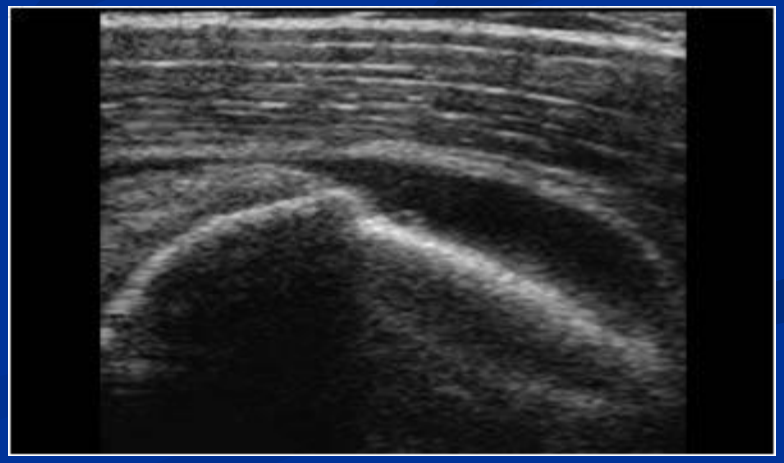
Longitudinal

Subacromail bursitis

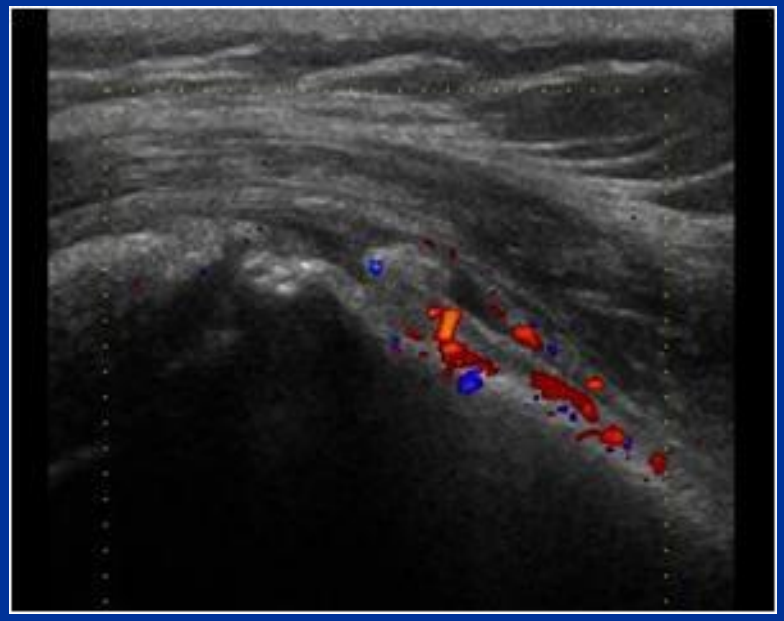


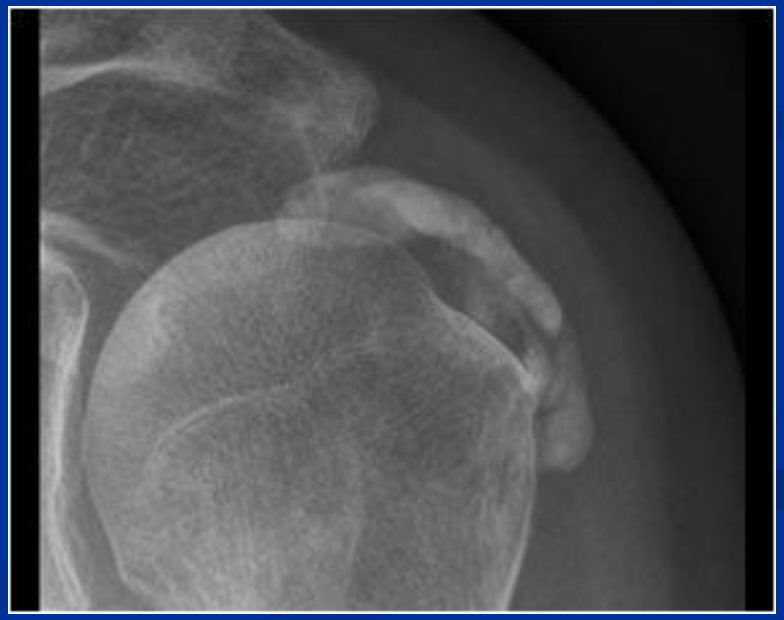




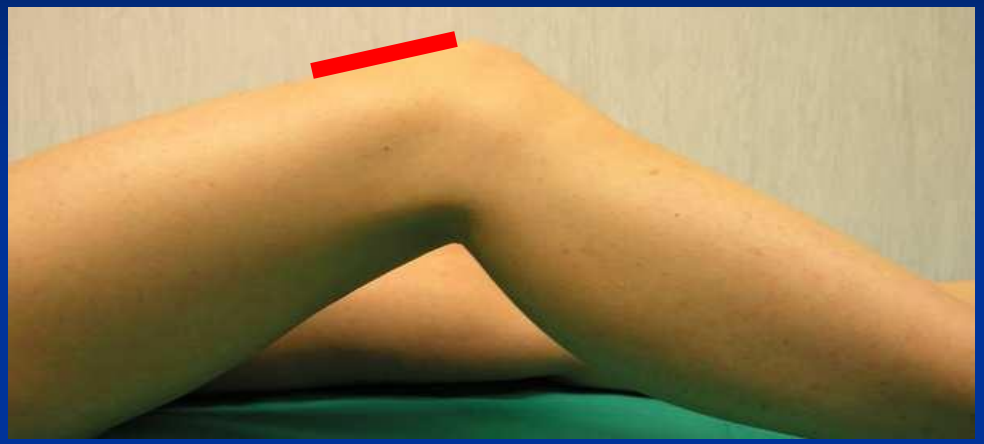


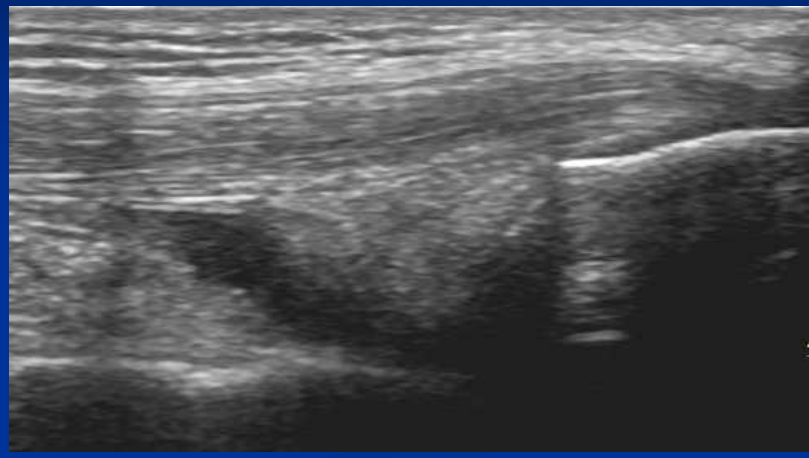
Calcification of bursa



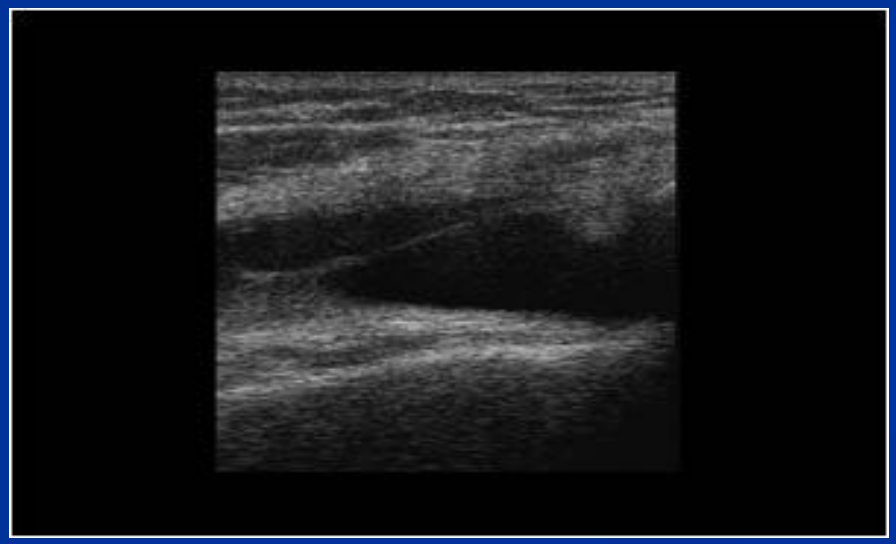


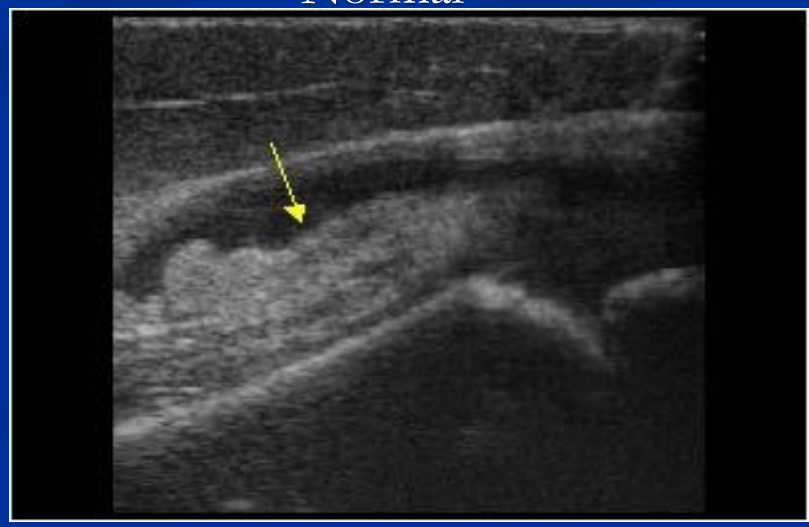
Anterior recess effusion of Knee





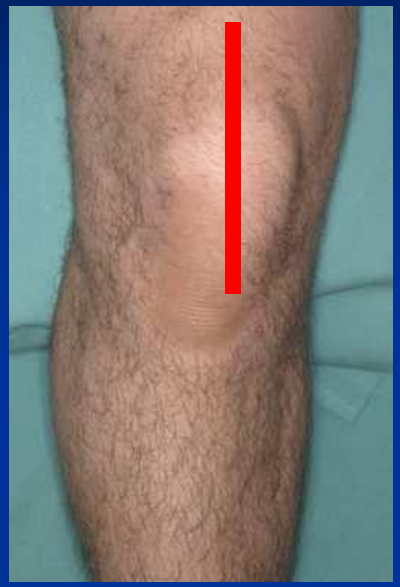
Normal

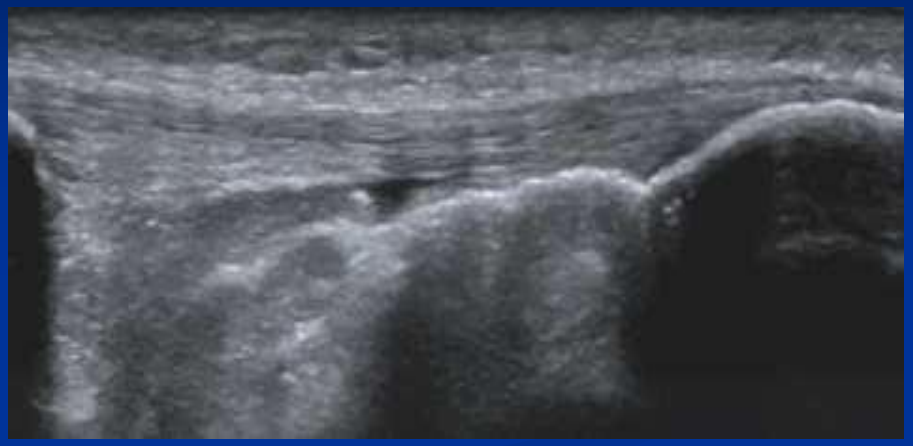




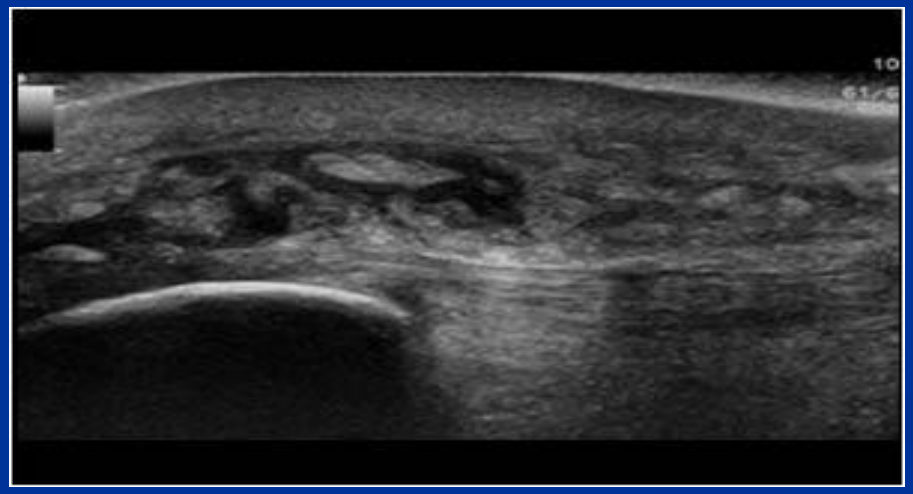
Longitudinal

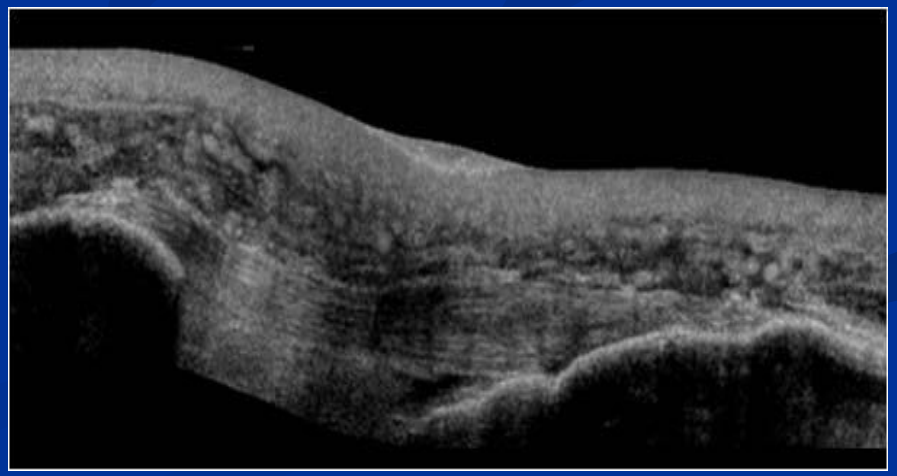
Prepatellar bursitis





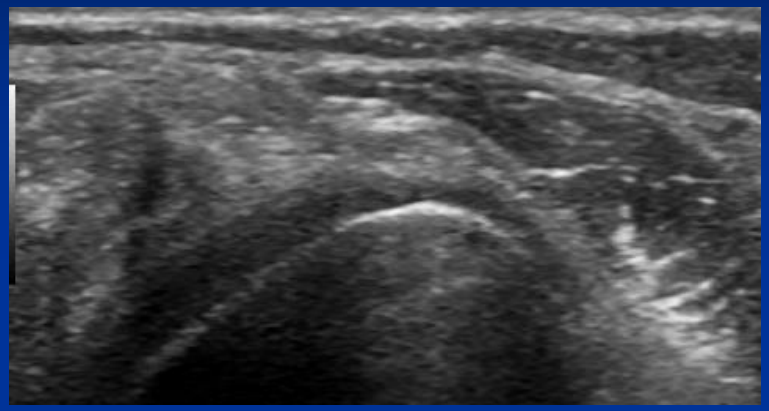
Normal



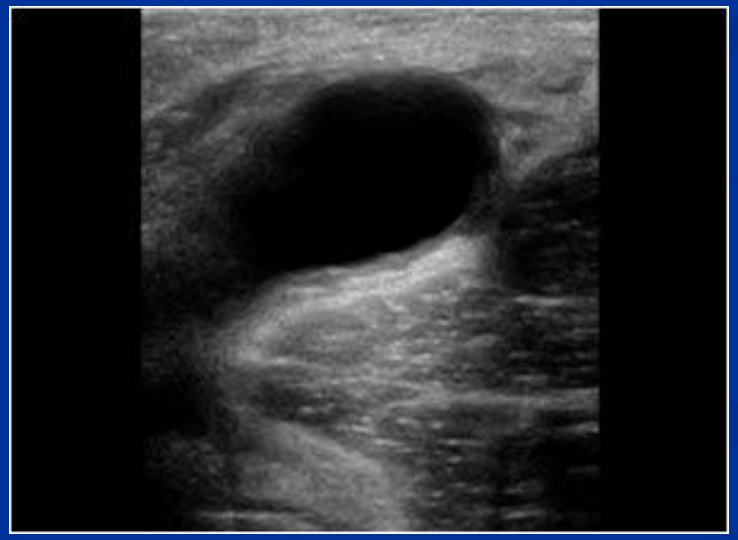


Longitudinal

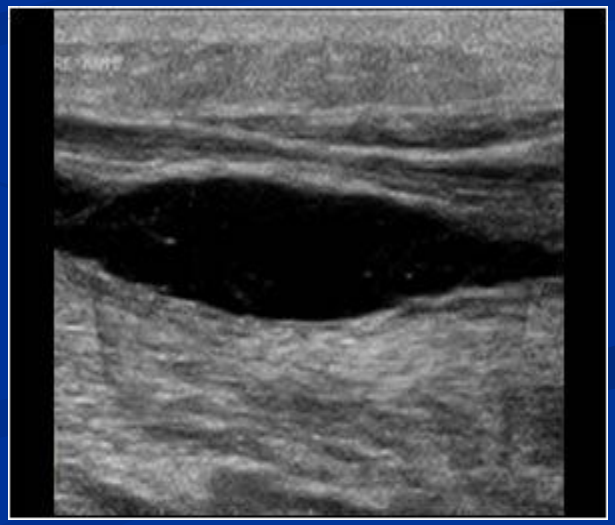
Baker's Cyst



Normal

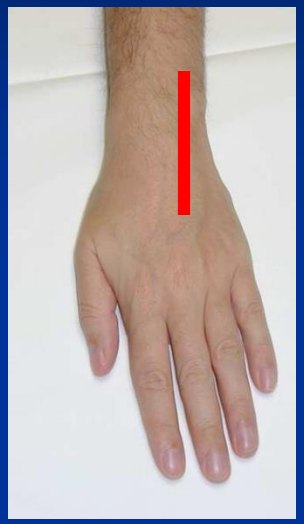


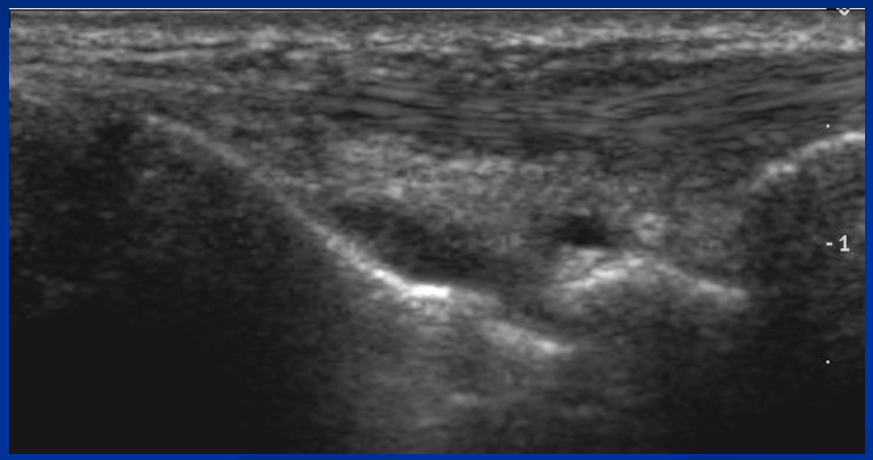
Transverse



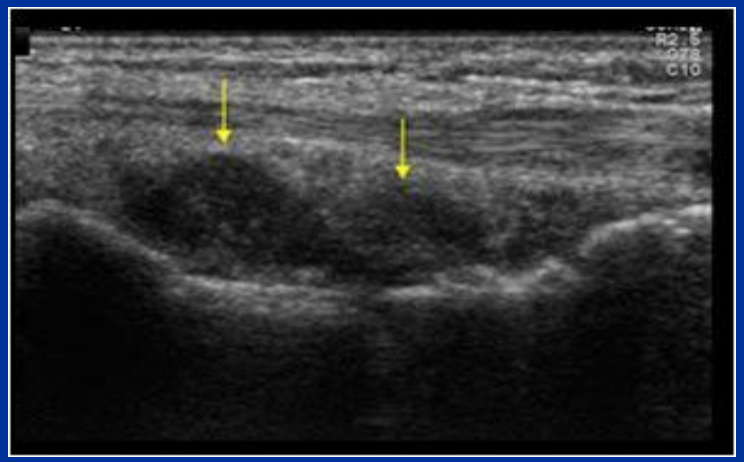
Longitudinal

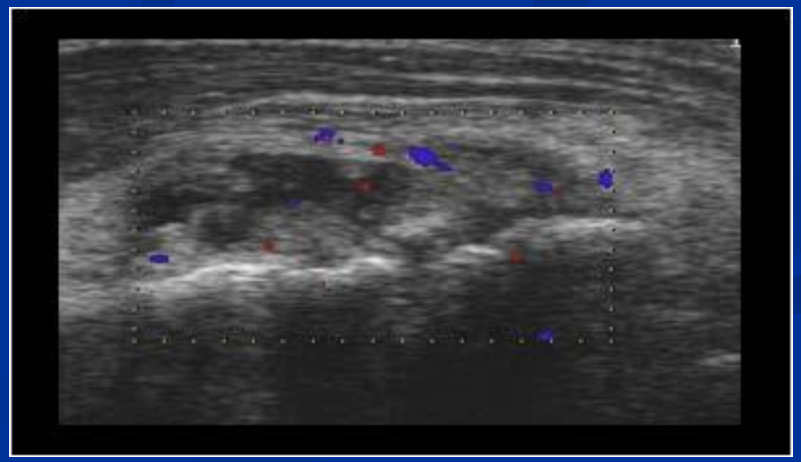
Rheumatoid Arthritis
Wrist : Thickened synovitis





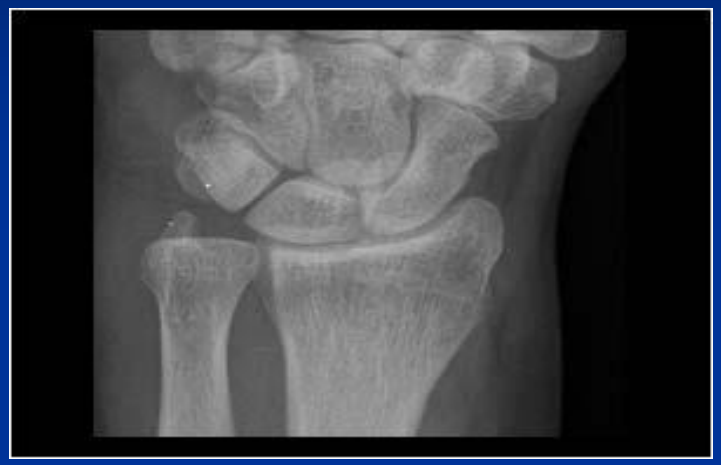
Normal

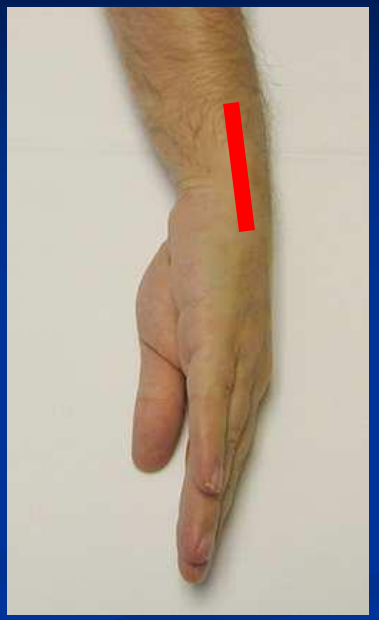


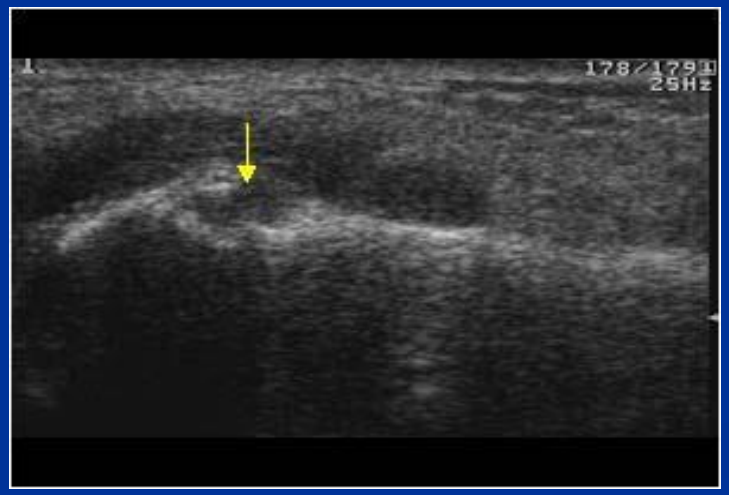


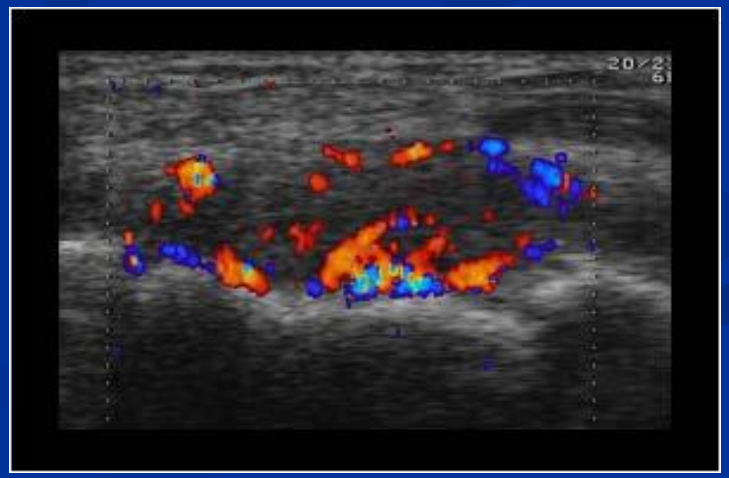
Longitudinal

Detecting Erosions and Hypervascularity



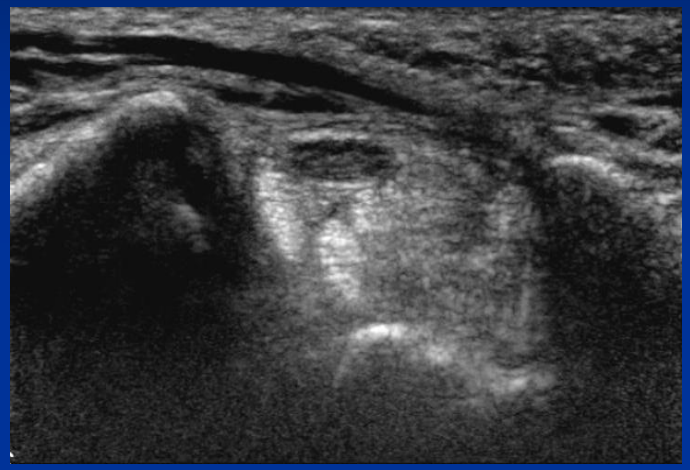




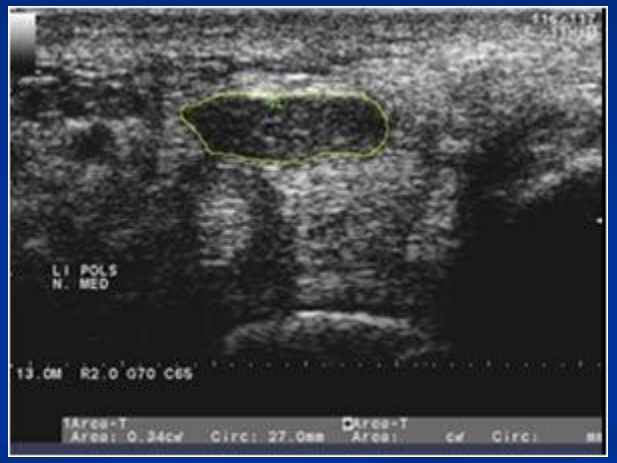


Longitudinal

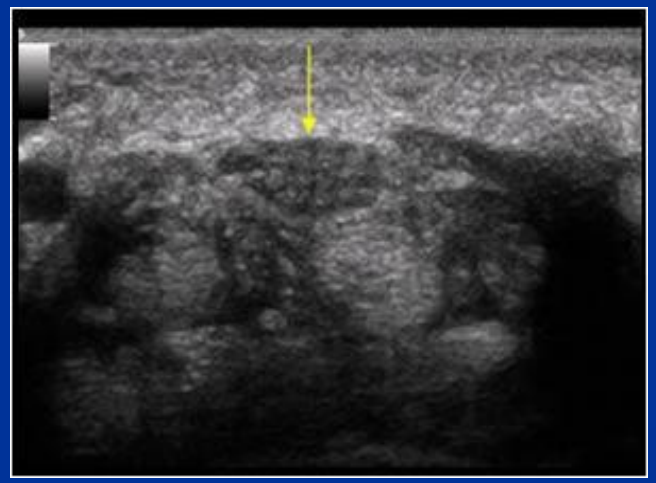
Median Nerve
Carpal tunnel syndrome



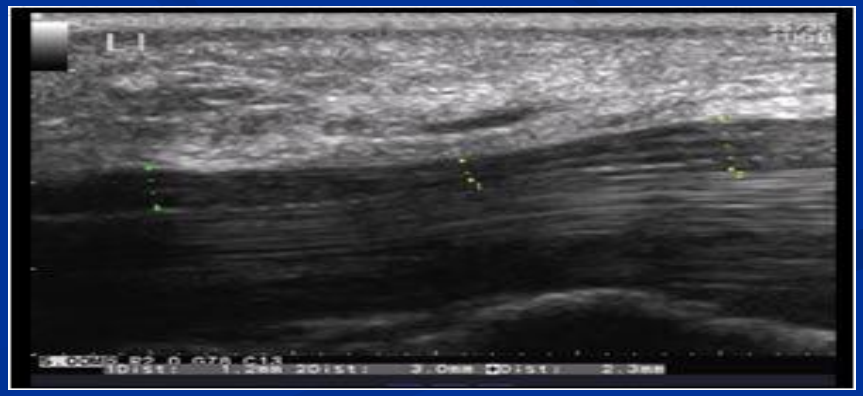
Normal



Transverse



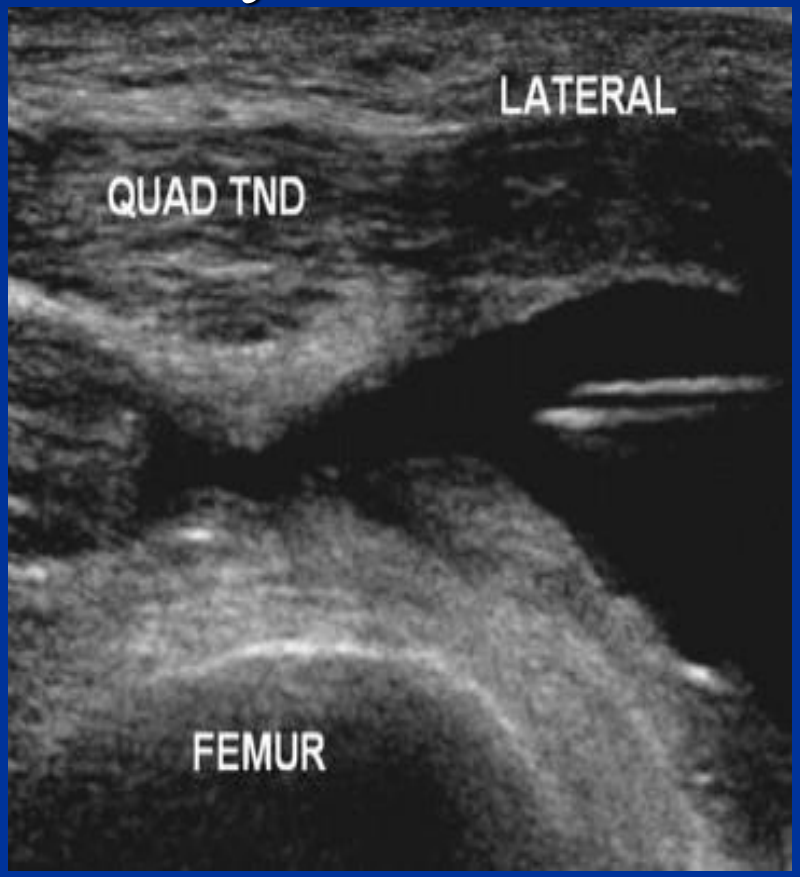
Transverse



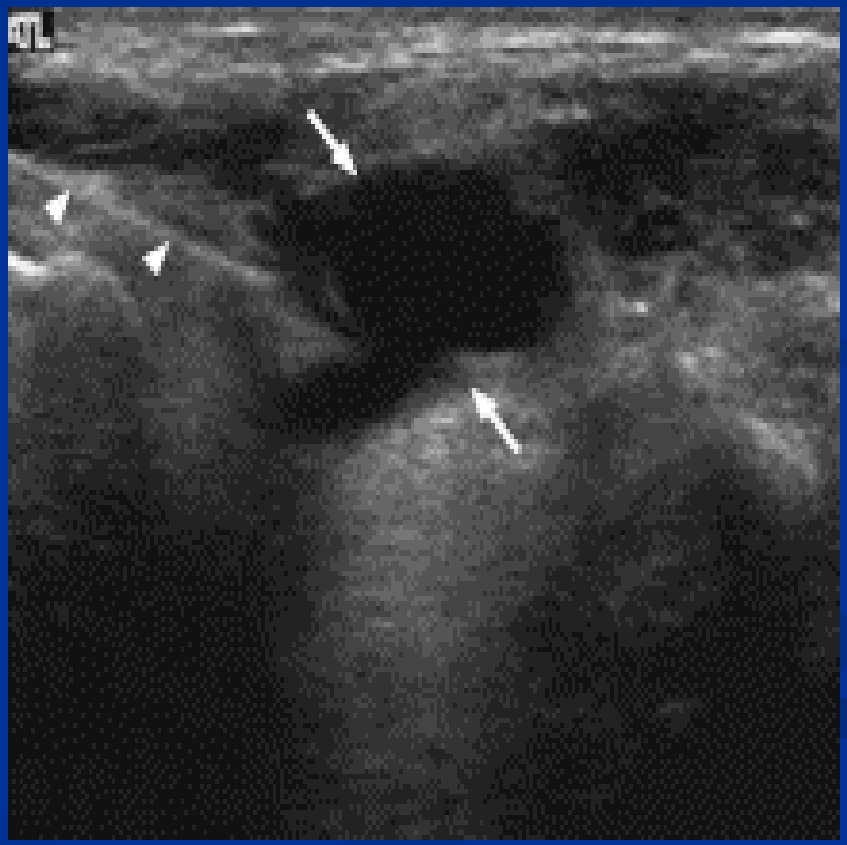
Longitudinal

Ultrasound guided injections

Knee Joint

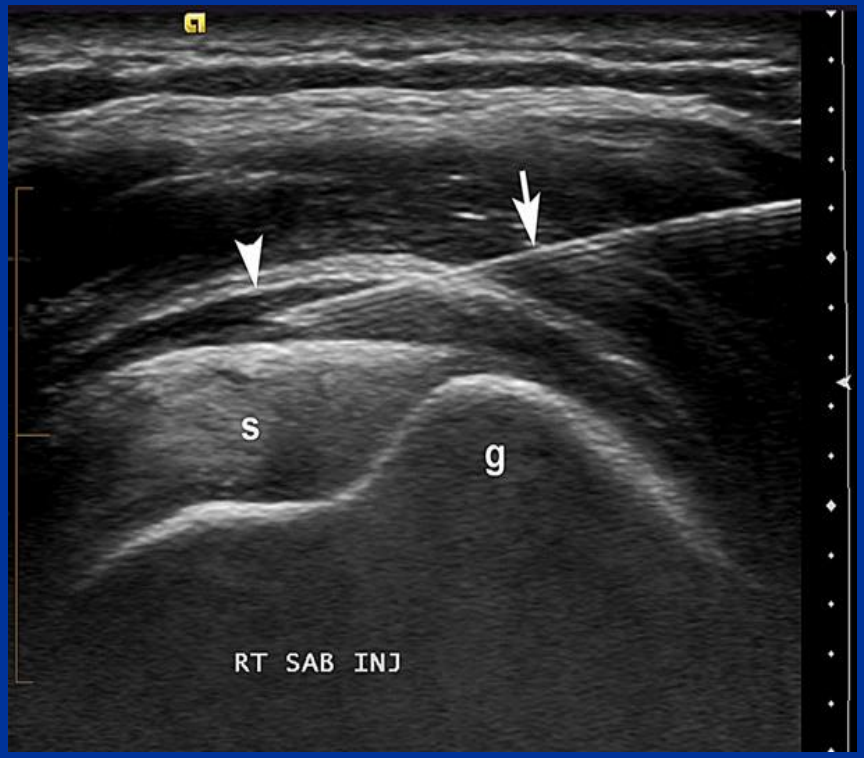


Baker's cyst



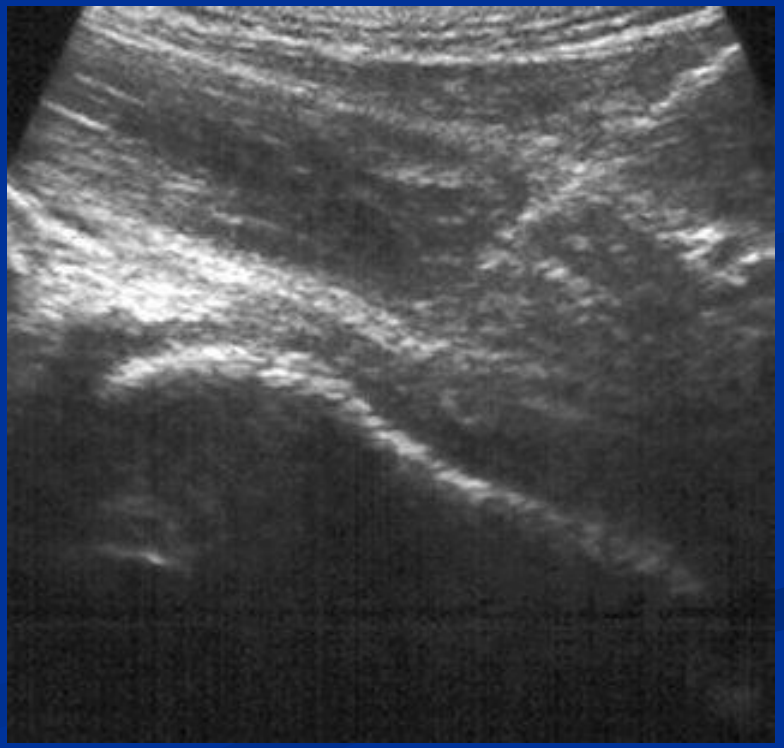
Ultrasound Guided Musculoskeletal Procedures,
Ultrasound Clinics, Volume 2, Issue 4, October 2007

Subacromial bursitis



AJUM May 2010; 13 (2):11-15

Hip joint



http://www.orthohealing.com/2007/10/

Clostridium Collagenase Histolyticum

Dupuytren's contracture Injectable Collagenase Clostridium

- DC is a progressive genetic disorder of pathologic collagen production and deposition
- Nodules coalesce to form cord, extending longitudinally causing shortening and flexion contracture
- Surgical fasciectomy has been the only treatment which had significant complication risk and suboptimal success
- First series of 35 patients with 44 affected joints published in J Hand Surg;24(4):629-36 showed potential of clostridial collagenase injections as first non surgical treatment
- In 2007 a RCT of 33 cases proved efficacy of Collagenase injection, 16/23 received 0-5 degree extension with 1 injection and 21/23 with 3 injections

CORD I

N Engl J Med 2009;361:968-79

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Injectable Collagenase Clostridium Histolyticum for Dupuytren's Contracture

Lawrence C. Hurst, M.D., Marie A. Badalamente, Ph.D., Vincent R. Hentz, M.D., Robert N. Hotchkiss, M.D., F. Thomas D. Kaplan, M.D., Roy A. Meals, M.D., Theodore M. Smith, Ph.D., and John Rodzvilla, M.D., for the CORD I Study Group*

CORD 1

- Method
  - 308 patients
  - 2: 1 Ratio
  - 3 injection allowed
- Primary end point
  - Reduction in primary contracture 0-5 of full extension

Results

- 64% contractures achieved primary point compared to 6.8% in placebo, P<.002.
- Mean time : 56 days
- MCP had better success rates than PIP (76% vs. 40%)
- mean change in contracture was 48 degrees
- success was 89% when contracture was less than 50 degrees

- Adverse effects
  - Local
  - No meaning full systemic adverse reaction

Mean degree of improvement

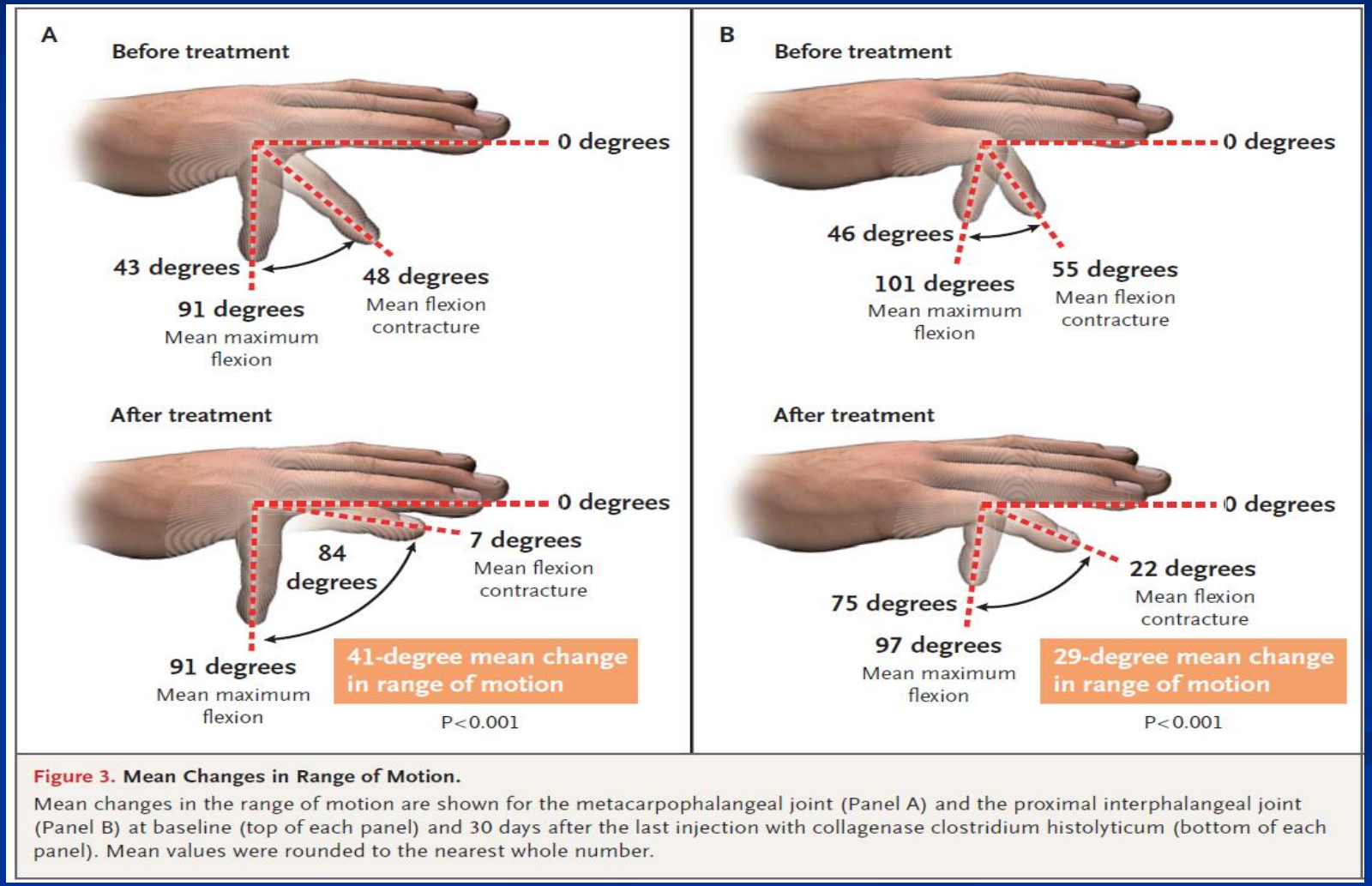
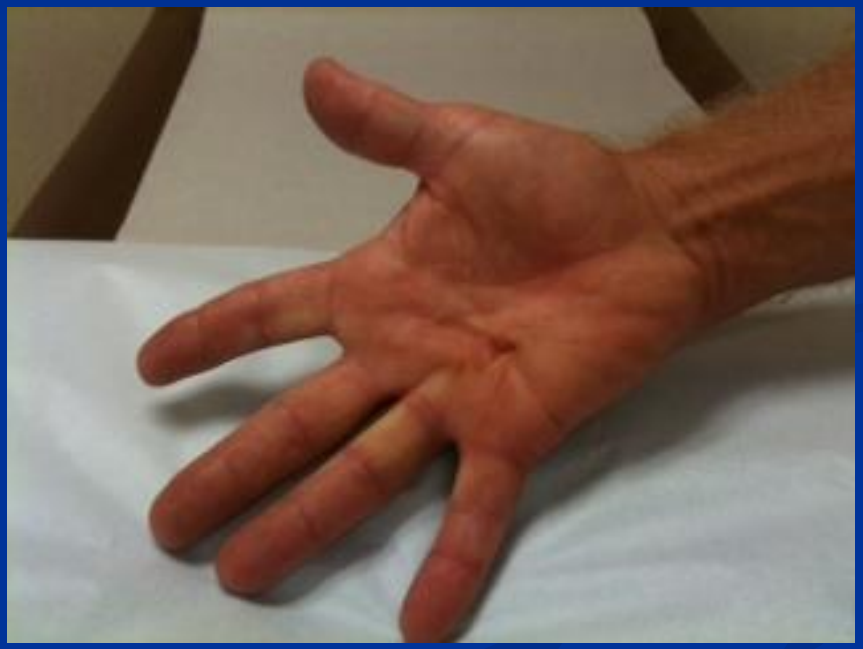
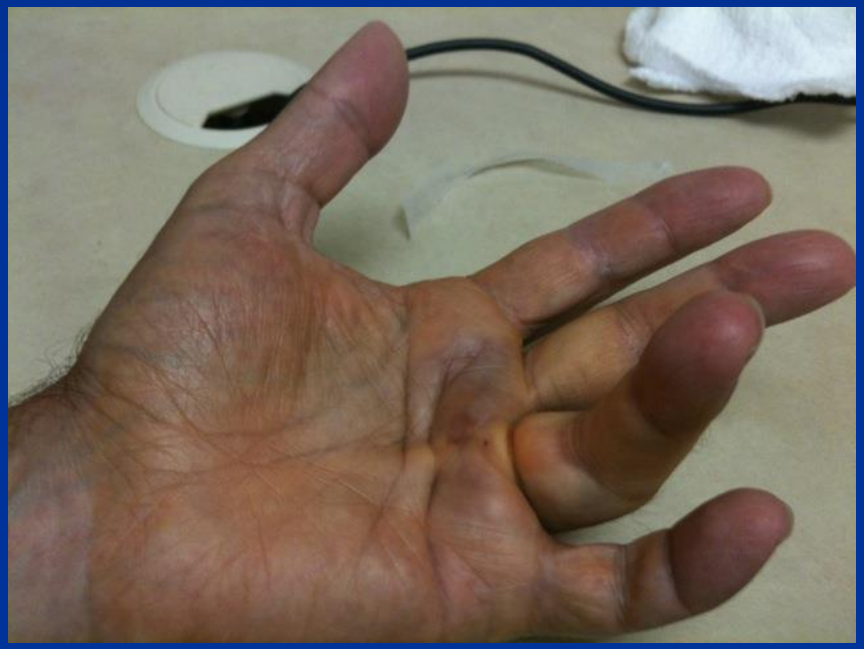


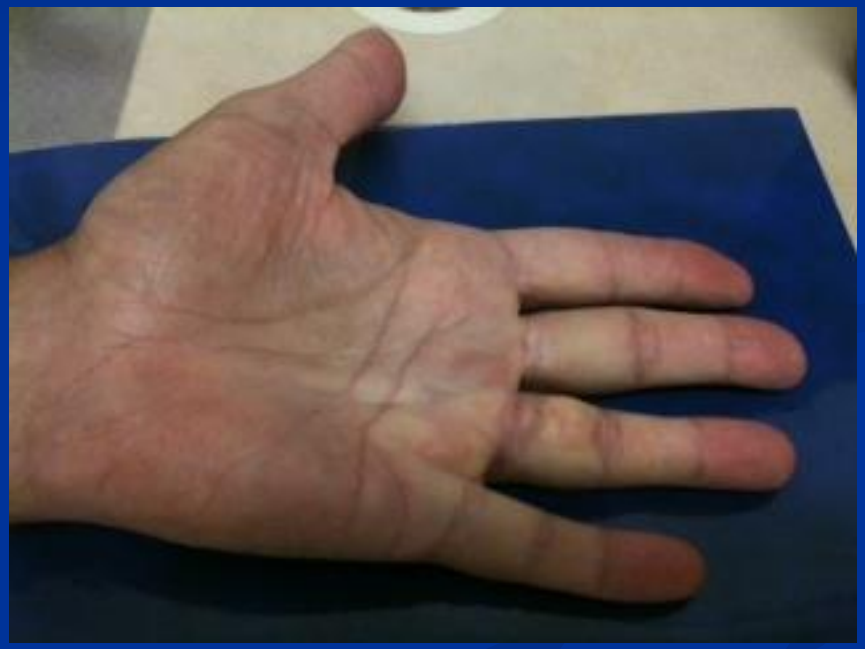
Figure 3. Mean Changes in Range of Motion.

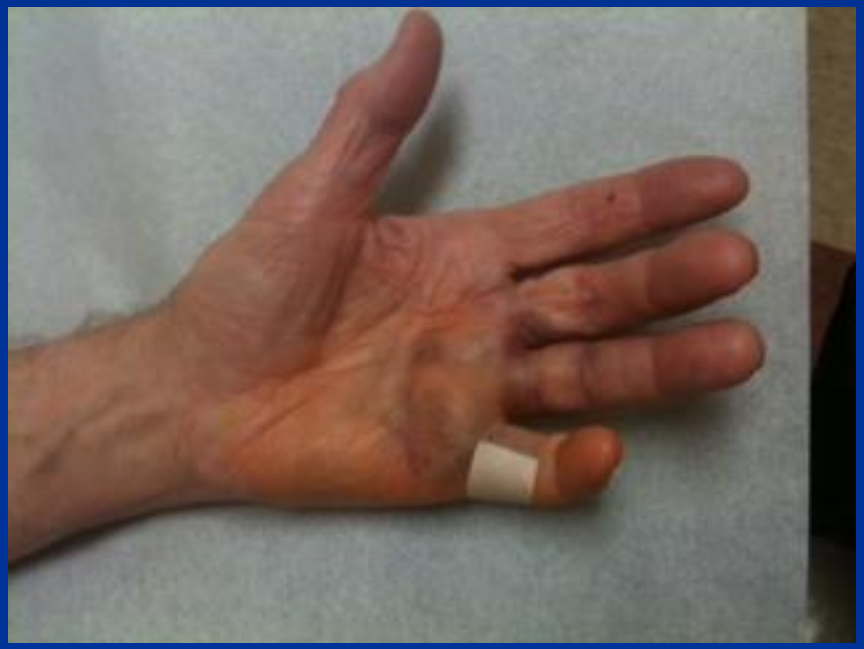
Mean changes in the range of motion are shown for the metacarpophalangeal joint (Panel A) and the proximal interphalangeal joint (Panel B) at baseline (top of each panel) and 30 days after the last injection with collagenase clostridium histolyticum (bottom of each panel). Mean values were rounded to the nearest whole number.

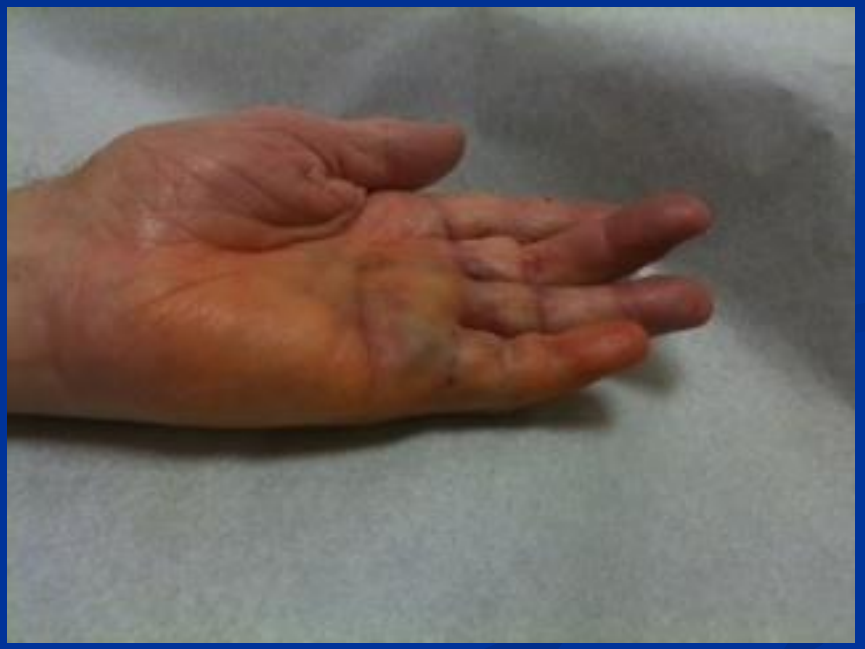
Case series



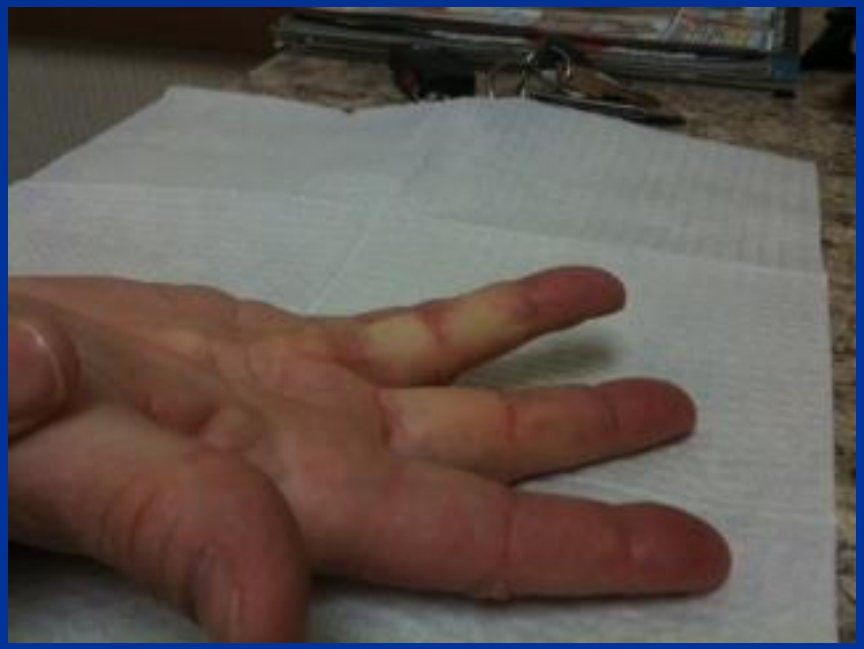


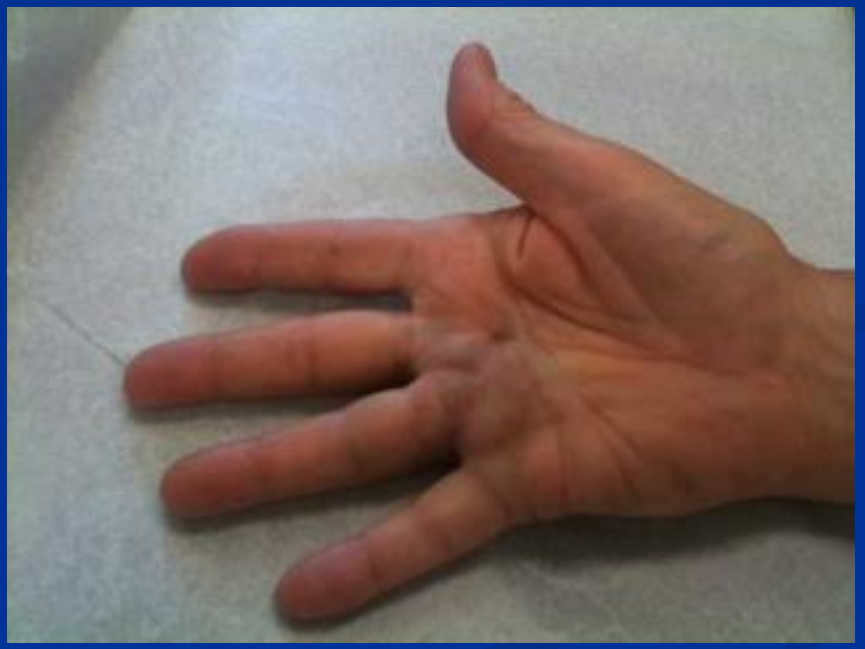


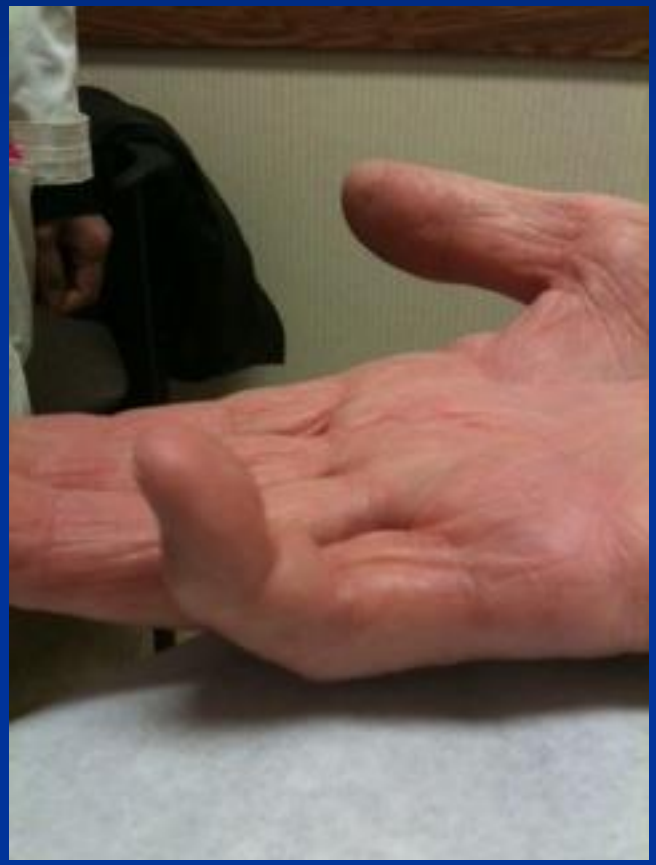





DELL

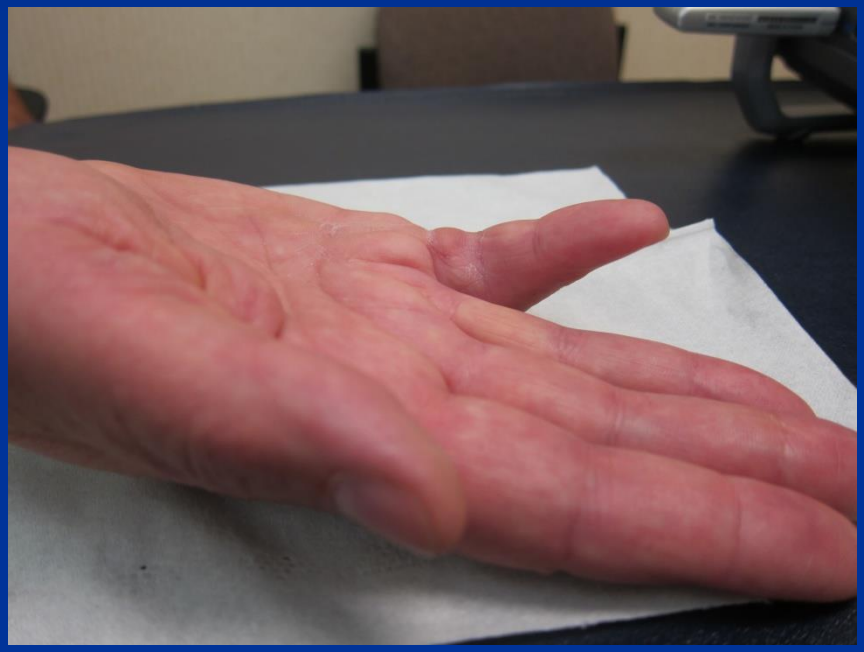




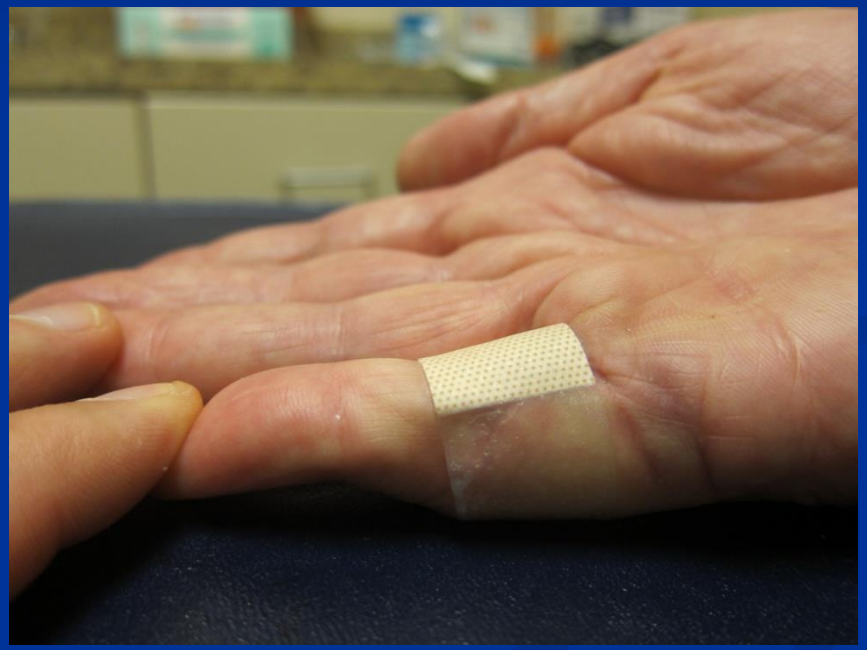


Series of Three Cases

Before (~25 degrees)



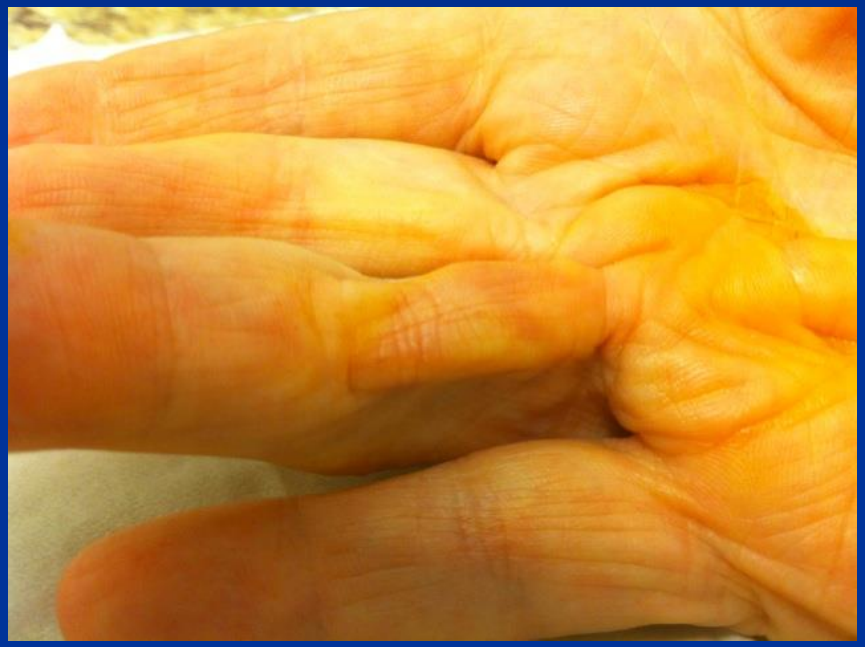
After- full extension



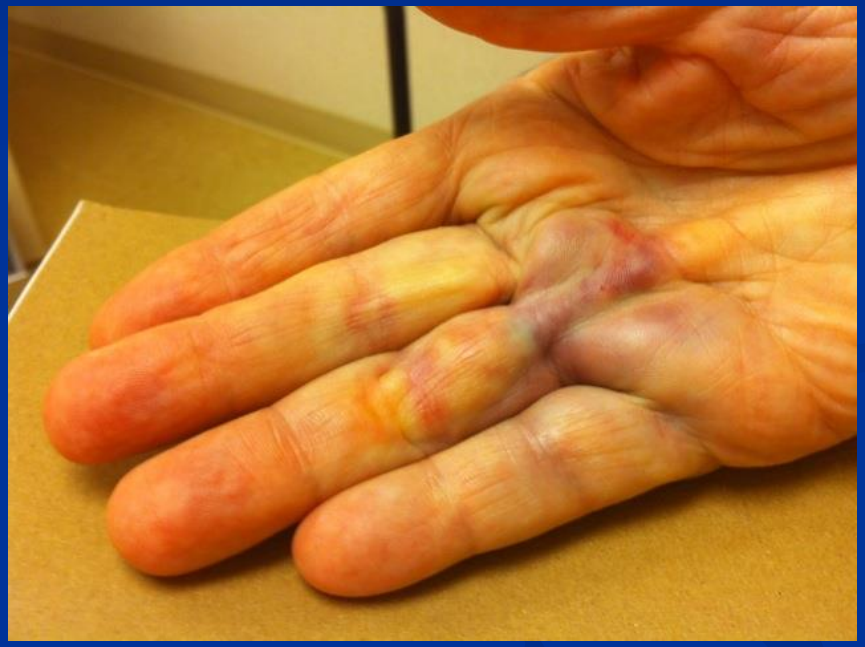
Courtesy Dr C. Michael Franklin M.D.

Patient # 2

Pre-Xiaflex



Post Xiaflex full extension

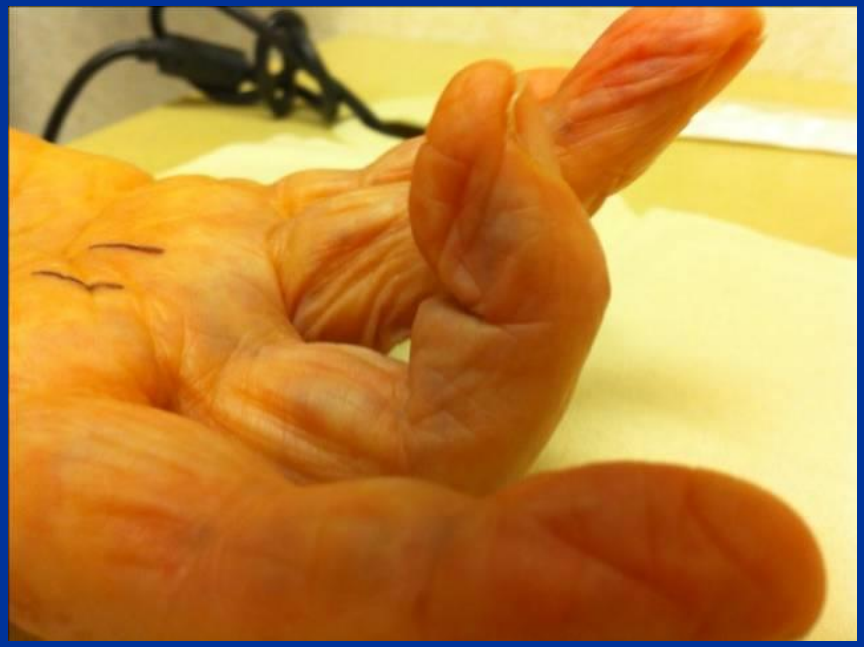


Note post injection ecchymosis

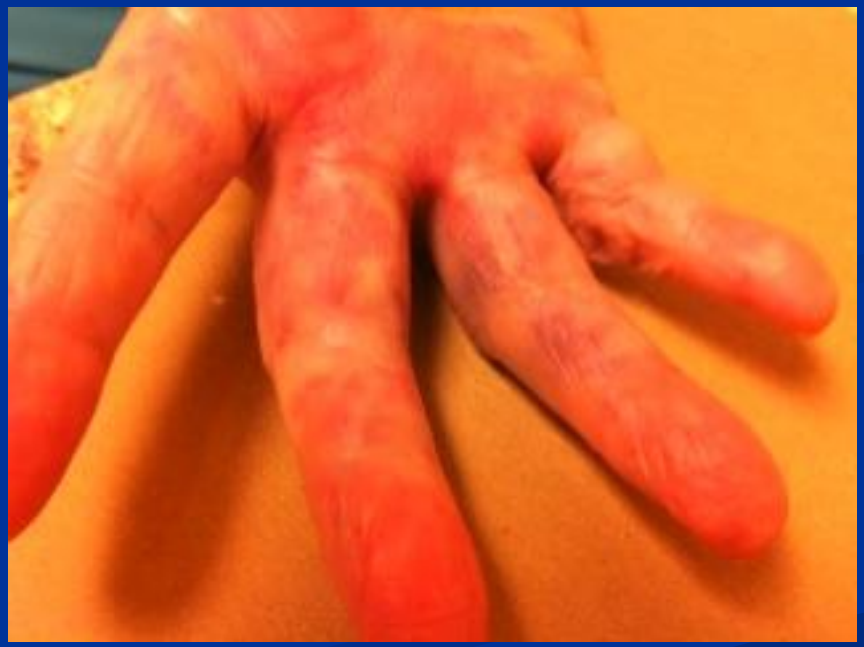
Courtesy Dr C. Michael Franklin M.D.

Patient # 3

90 degree flexion contracture



Post Xiaflex –full extension



Courtesy Dr C. Michael Franklin M.D.

Thanks for your attention

ftahir@arthritispa.com