Anaemia, amyloidosis

Dr. Szekanecz Zoltán

DEOEC Reumatológiai Tanszék

REAKTOR, 2013. szeptember 26.

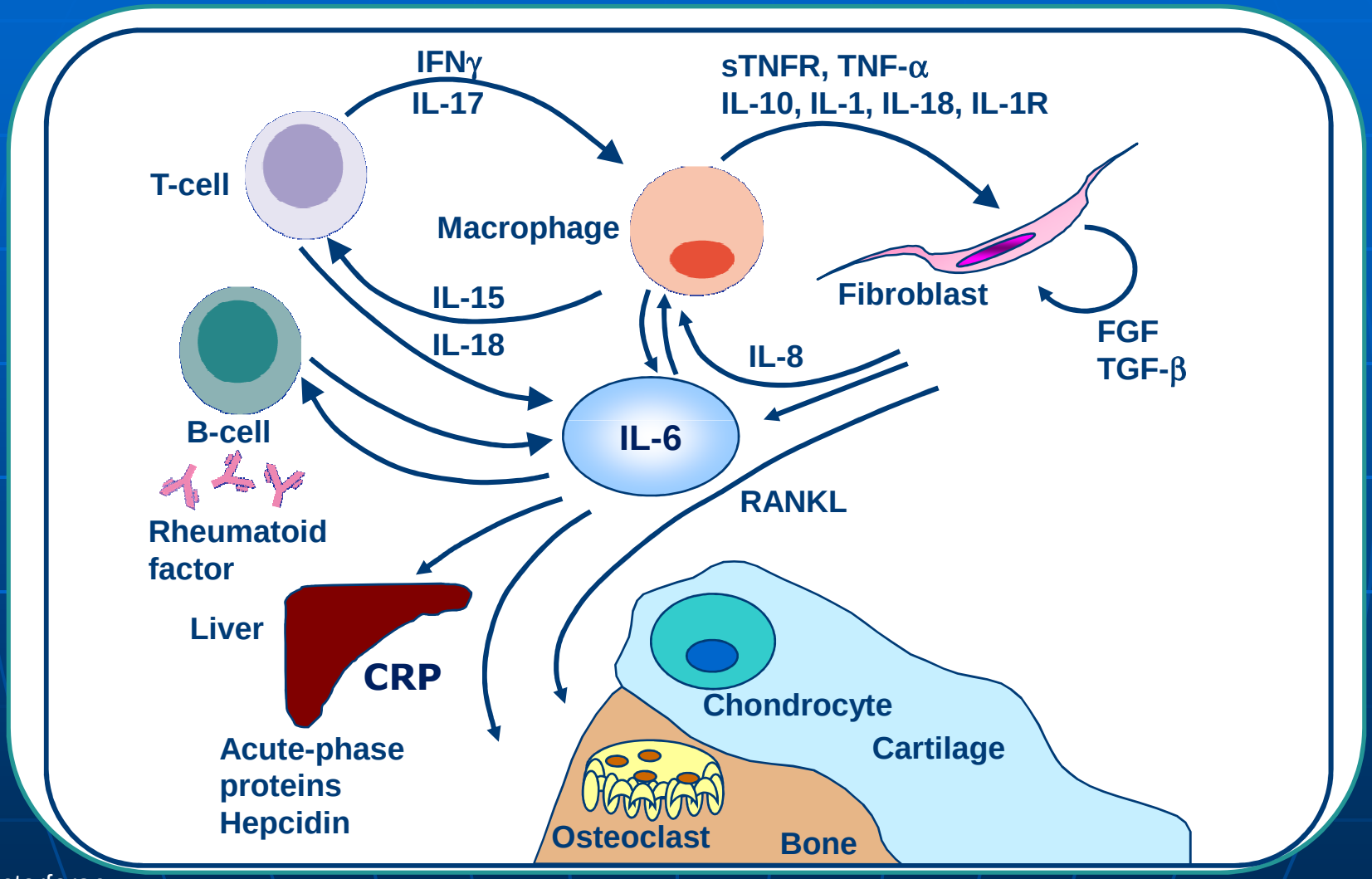
Systemic Consequences of Inflammation

Zoltán Szekanecz, György Kerekes

Disease	Estimated prevalence (%)
Inflammatory diseases Rheumatoid arthritis Systemic lupus erythematosus Vasculitis Sarcoidosis Inflammatory bowel disease	8–71
Acute and chronic infections	18–95
Malignancies Haematological Solid	30–77
Chronic renal failure	23–50

Table 1 Anaemia associated with chronic diseases

A cytokin hálózat rheumatoid arthritisben



IFN = interferon
sTNFR = soluble TNF receptor
TGF-β = transforming growth factor-β
FGF = fibroblast growth factor
RANKL = receptor activator for nuclear factor Kb ligand

1. Firestein GS. *Nature* 2003; **423**:356–361.
2. Smolen JS, *et al. Lancet* 2007; **370**:1861–1874.
3. Smolen JS & Steiner G. *Nat Rev Drug Disc* 2003; **2**:473–488.

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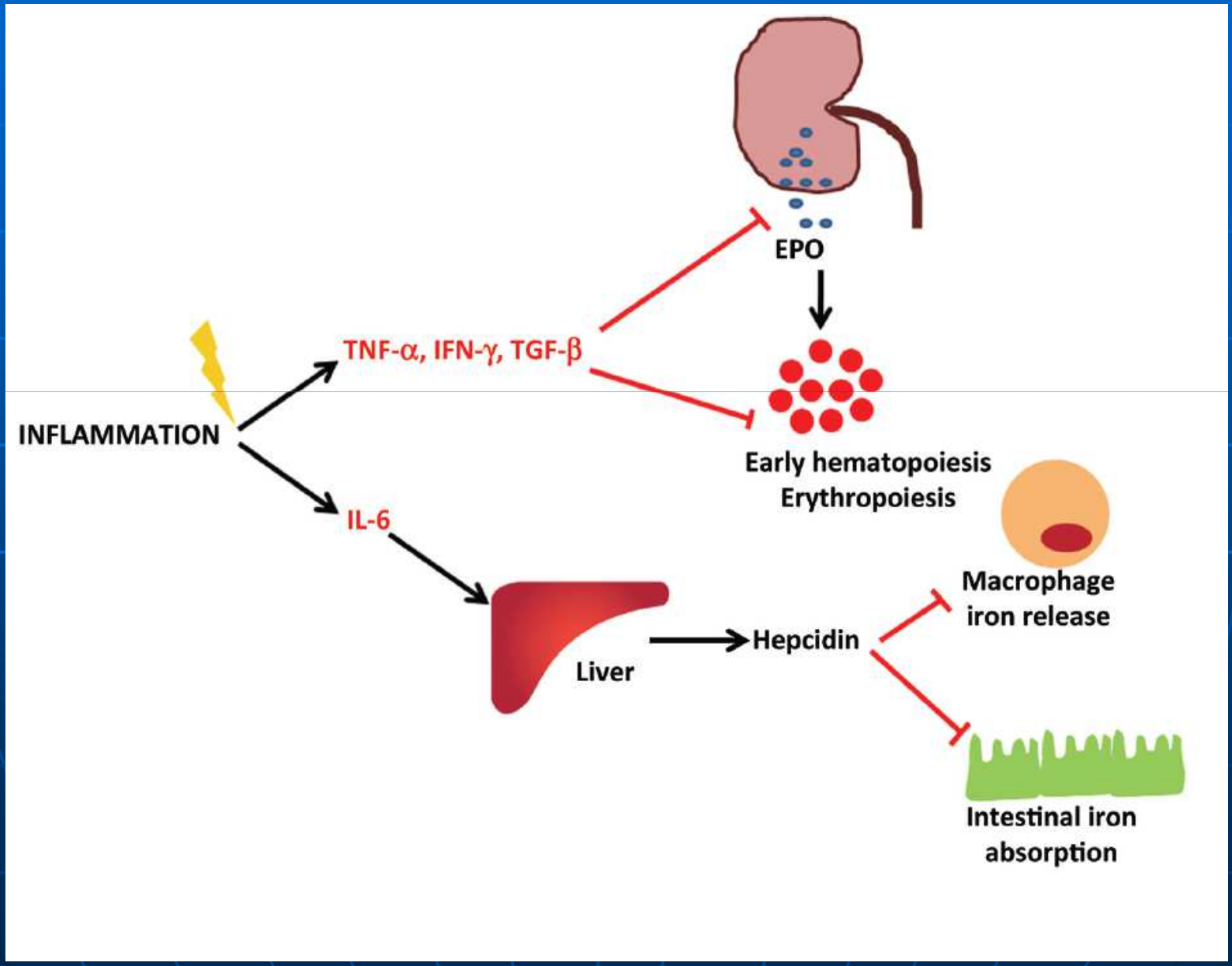
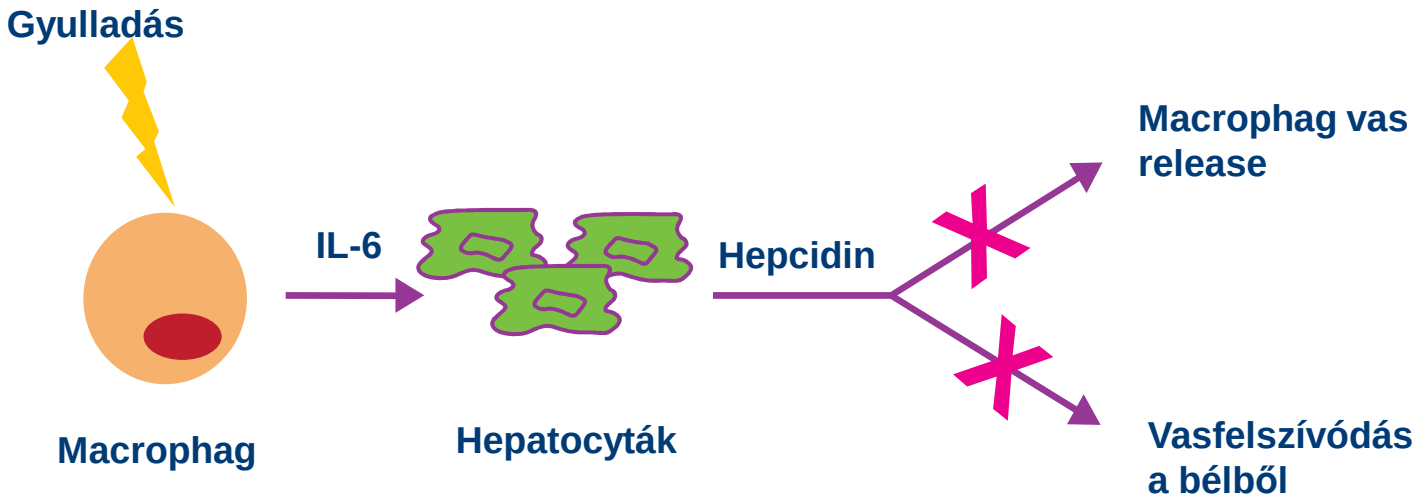


Anaemia: az RA gyakori velejárója

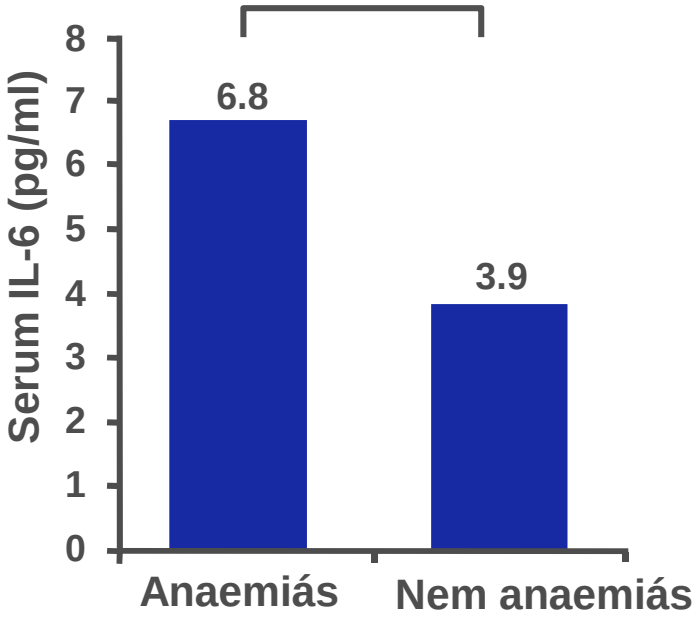
- **Hepcidin gátolja:**
  - A vas felszabadulását macrophagokból (reticuloendothelialis blokk)
  - A vas felszívódását (vashiány)

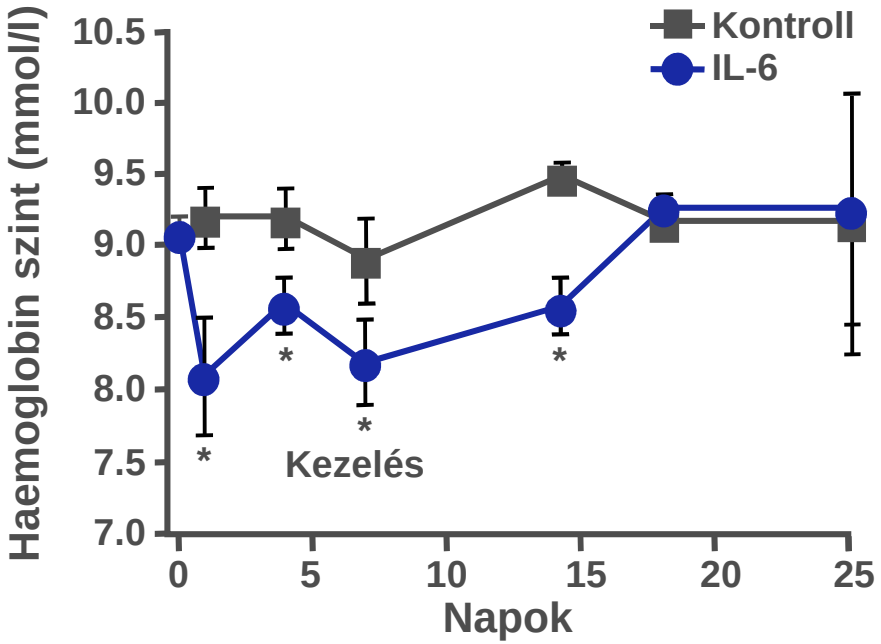


Adapted from: Andrews NC. *J Clin Invest* 2004; **113**:1251–1253.
Nemeth E, *et al. J Clin Invest* 2004; **113**:1271–1276.

Az IL-6 termelés korrelál az anaemiával

- RA: korreláció az IL-6 szint és anaemia közt[1]
- Patkány: IL-6 infusiok anaemiát indukálnak[2]





*p<0.01 vs. control

1. Voulgari P, *et al. Clin Immunol* 1999; **92**:153–160.
2. Jongen-Lavrencic M, *et al. Clin Exp Immunol* 1996; **103**:328–334.

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Iron biomarkers	Inflammatory anaemia	Iron-deficiency anaemia	Combination
Serum iron	↓	↓	↓
Transferrin	N or ↓	↑	↓
Transferrin saturation	↓	↓	↓
Soluble transferrin receptor	N	↓	N or ↑
Ferritin	N or ↑	↓	N or ↓

N = normal.

Table 2 Differential diagnosis of chronic inflammatory anaemia

Soluble Transferrin Receptors and Iron Deficiency, a Step beyond Ferritin. A Systematic Review

Anastasios Koulaouzidis[1], Elmuhtady Said[2], Russell Cottier[3], Athar A Saeed[4]

J Gastrointestin Liver Dis
September 2009 Vol.18 No 3, 345-352

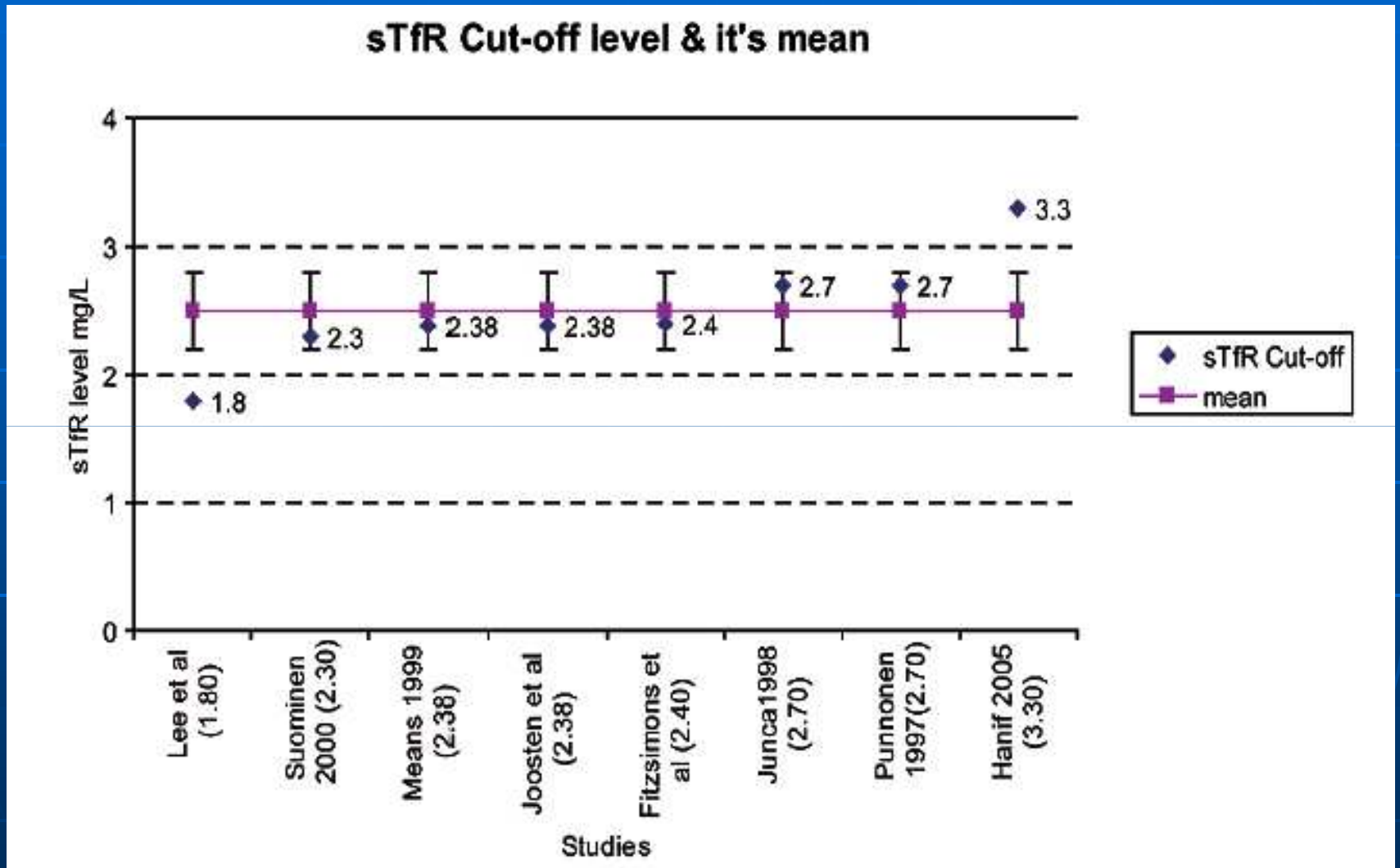


Fig 1. sTfR cut-off level and mean with its confidence intervals.

ARTHRITIS & RHEUMATISM
Vol. 43, No. 5, May 2000, pp 1016–1020

SINGLE VALUES OF SERUM TRANSFERRIN RECEPTOR AND TRANSFERRIN RECEPTOR FERRITIN INDEX CAN BE USED TO DETECT TRUE AND FUNCTIONAL IRON DEFICIENCY IN RHEUMATOID ARTHRITIS PATIENTS WITH ANEMIA

PAULI SUOMINEN, TIMO MÖTTÖNEN, ALLAN RAJAMÄKI, and KERTTU IRJALA

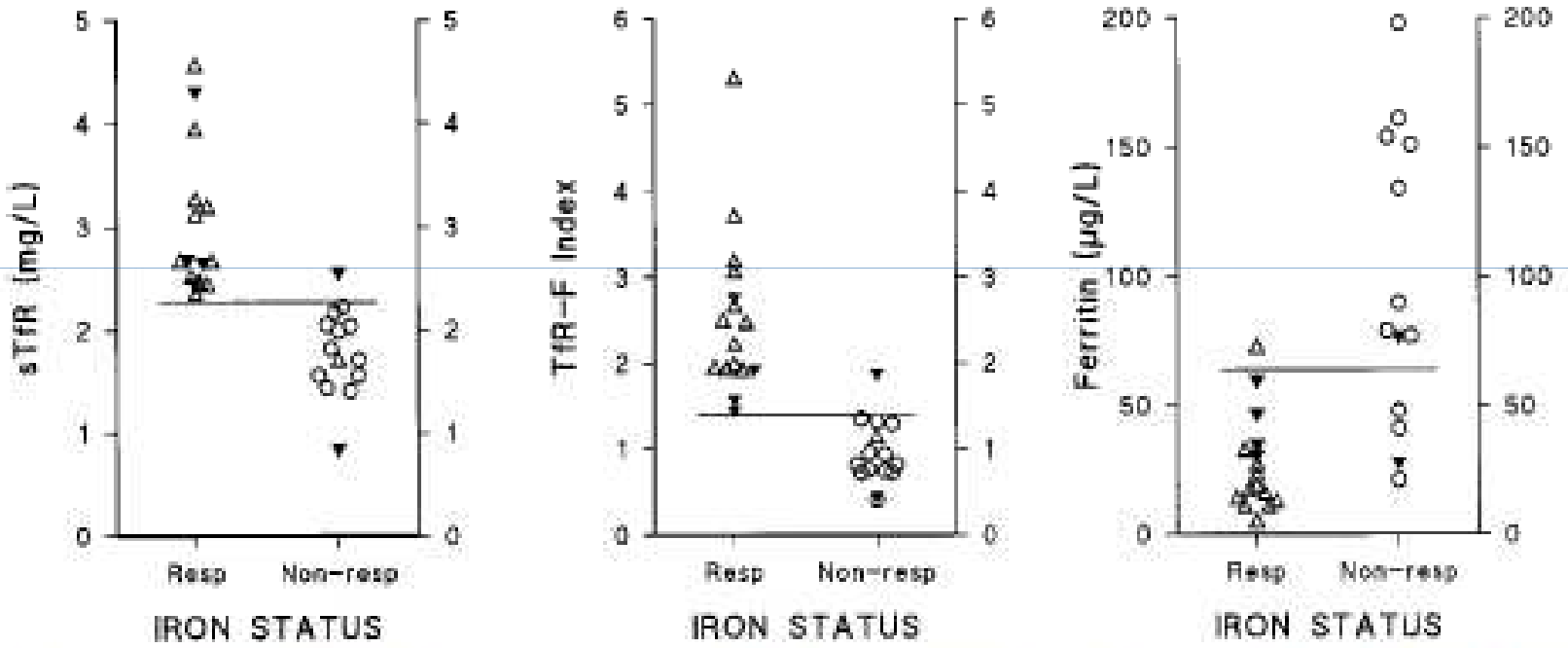


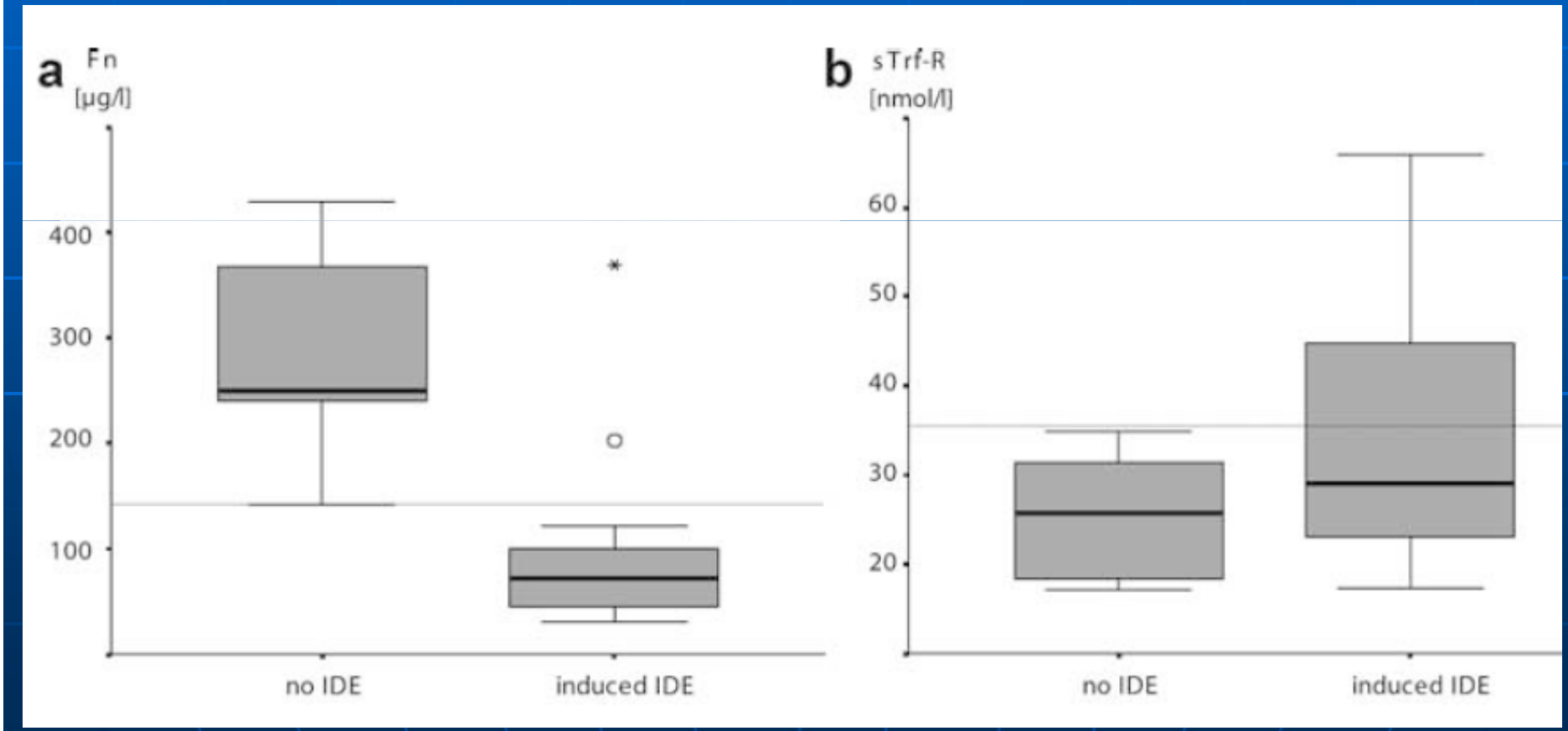
Figure 2. Prediction of response by baseline values. The scattergrams illustrate the capability of baseline values of sTfR, TfR-F Index, and ferritin to differentiate between iron-deplete and iron-replete patients. Solid horizontal lines represent the optimal cutoff values of each analyte. △ = BMI 0; ▼ = BMI +/++; ○ = BMI +++. Resp = responders; Non-resp = nonresponders (see Figure 1 for other definitions).

Ann Hematol (2005) 84: 159–166
DOI 10.1007/s00277-004-0950-z

ORIGINAL ARTICLE

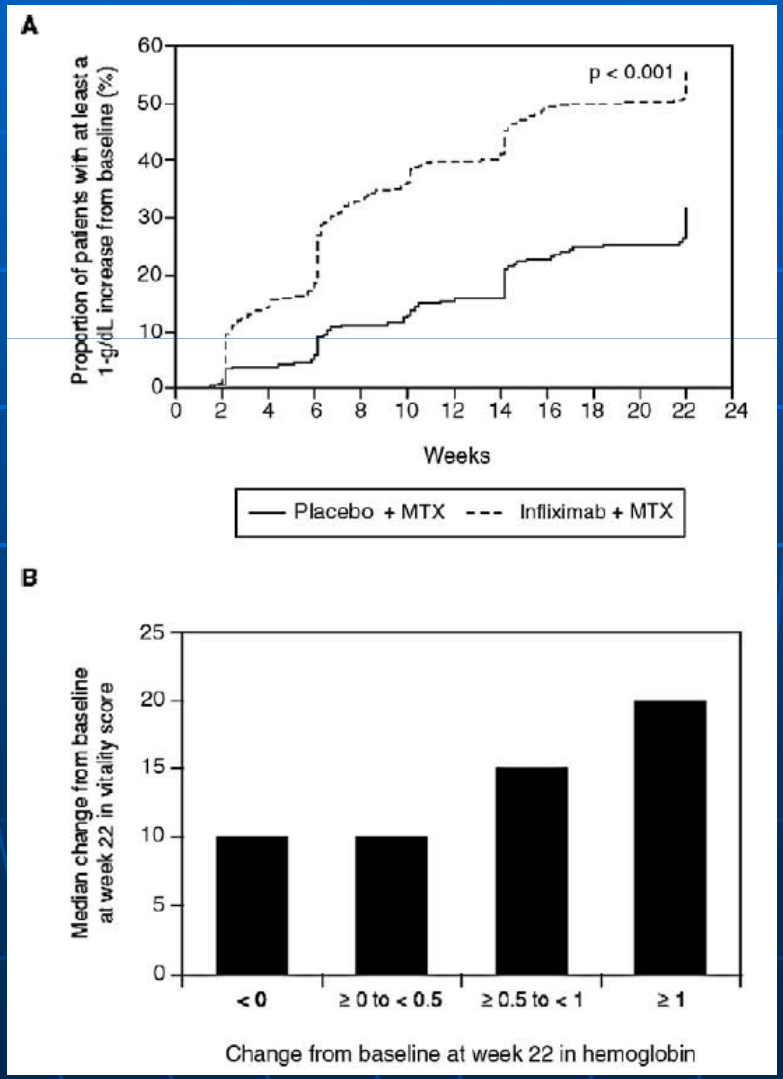
U. Arndt · J. P. Kaltwasser · R. Gottschalk · D. Hoelzer · B. Möller

Correction of iron-deficient erythropoiesis in the treatment of anemia of chronic disease with recombinant human erythropoietin

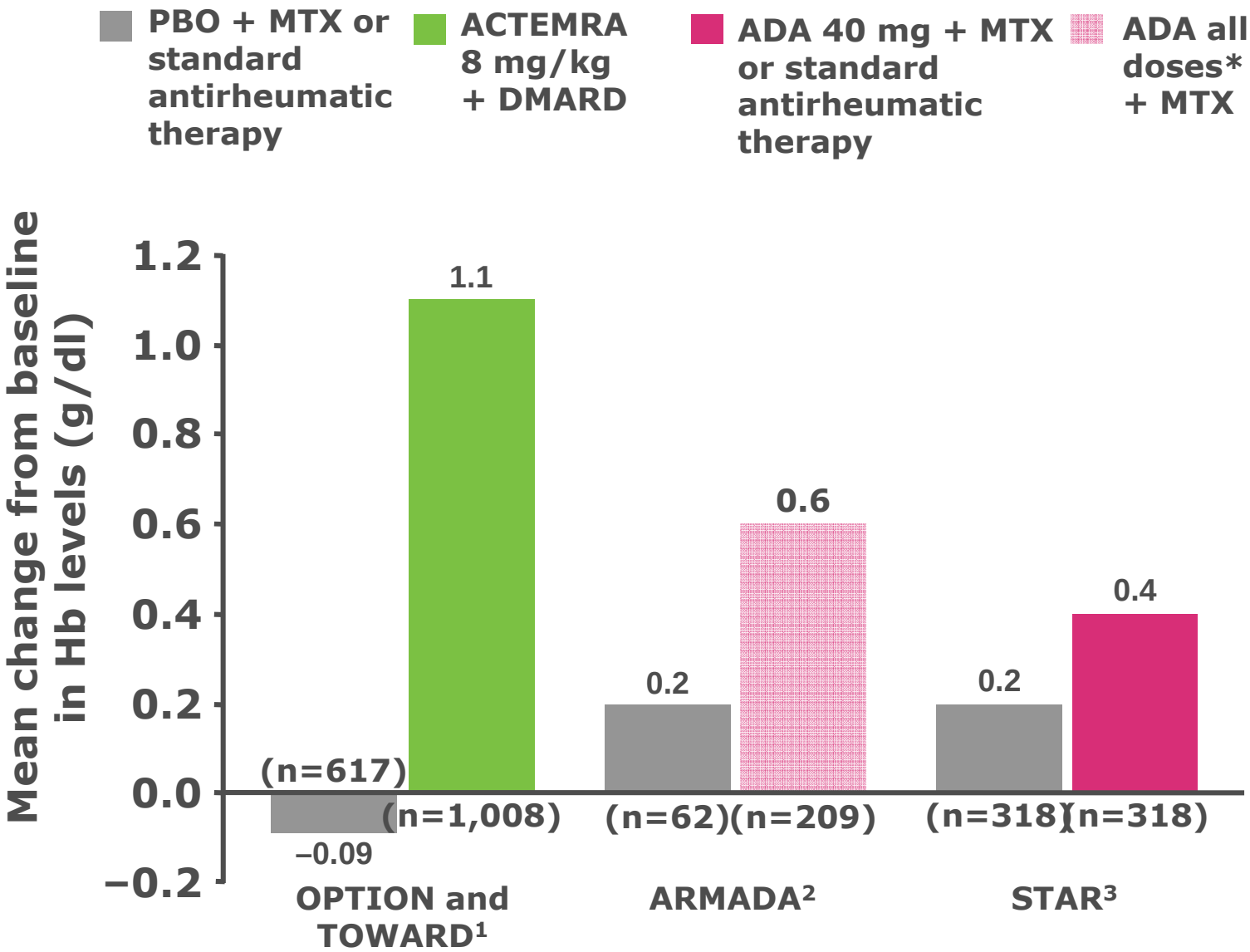


Treatment with Infliximab plus Methotrexate Improves Anemia in Patients with Rheumatoid Arthritis Independent of Improvement in Other Clinical Outcome Measures—A Pooled Analysis from Three Large, Multicenter, Double-Blind, Randomized Clinical Trials

Mittie K. Doyle, MD,* Mahboob U. Rahman, MD, PhD,†
Chenglong Han, PhD,‡ John Han, PhD,§ Jon Giles, MD,¶
Clifton O. Bingham III, MD,‖ and Joan Bathon, MD**



Biológiai terápia hatása az anaemiára



* ADA all doses = ADA (20, 40 or 80 mg pooled analysis) subcutaneously every other week.

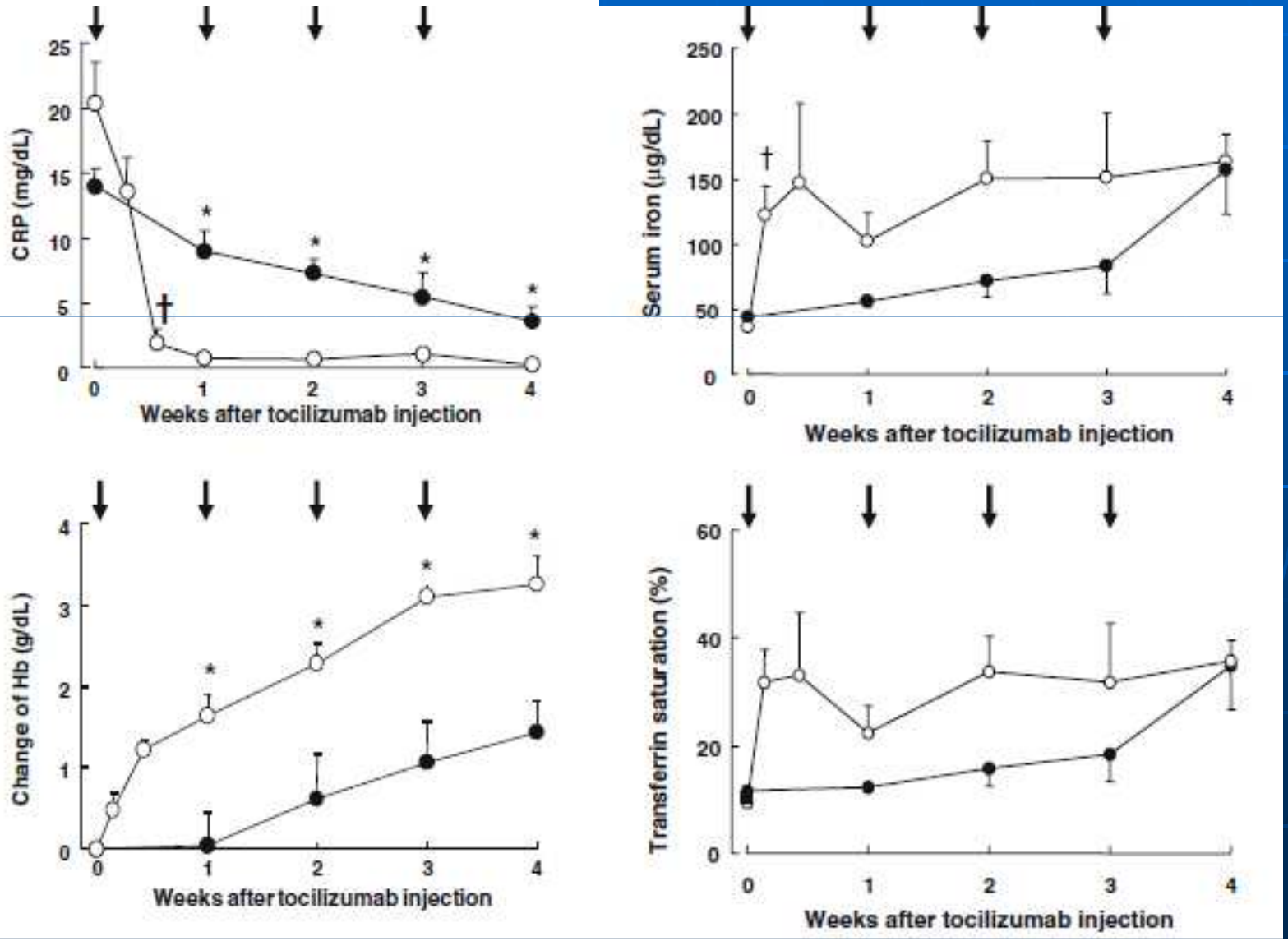
1. F. Hoffmann-La Roche. Data on file. Pooled analysis (OPTION, TOWARD).
2. Weinblatt ME, *et al. Arthritis Rheum* 2003; **48**:35–45.
3. Furst DE, *et al. J Rheumatol* 2003; **30**:2563–2571.

Rheumatol Int (2010) 30:917–923
DOI 10.1007/s00296-009-1075-4

ORIGINAL ARTICLE

Tocilizumab, a humanized anti-interleukin-6 receptor antibody, improved anemia in monkey arthritis by suppressing IL-6-induced hepcidin production

Misato Hashizume · Yasushi Uchiyama · Naoto Horai · Naohisa Tomosugi · Masahiko Mihara



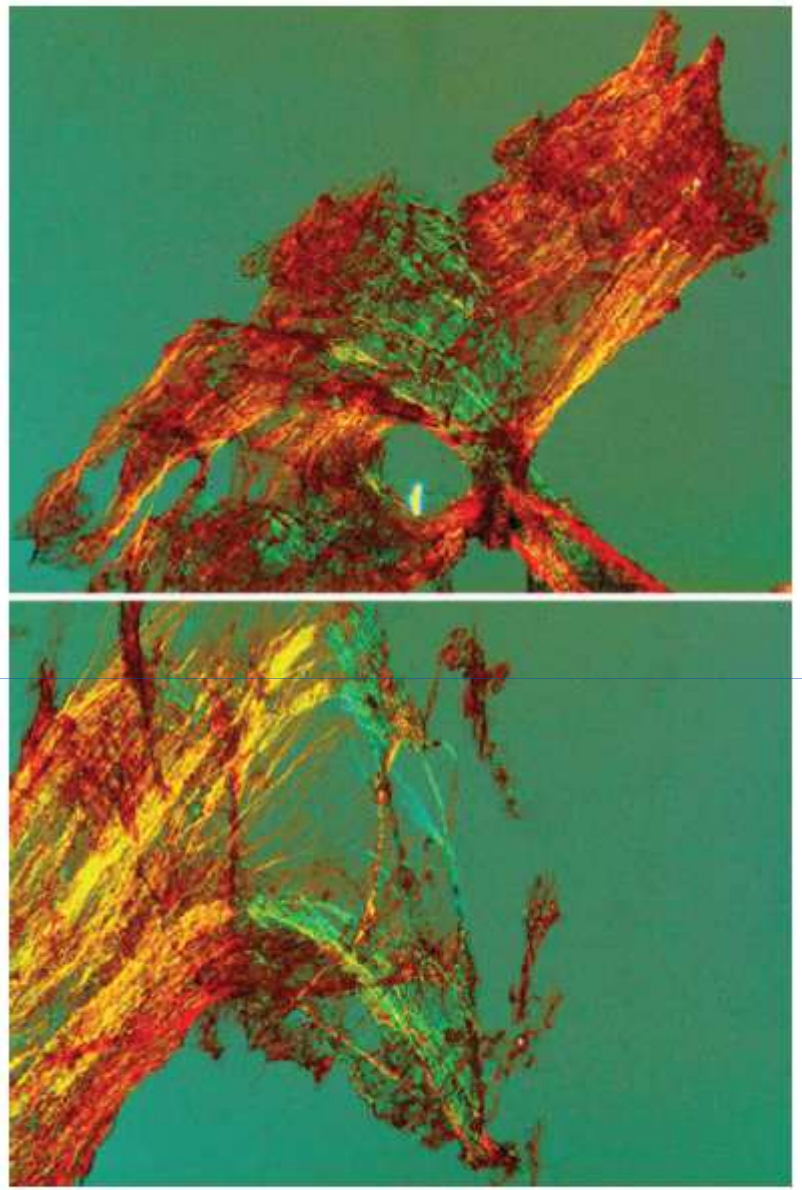


Figure 1 | Appearance of amyloid protein deposit on microscopic examination. Subcutaneous fat aspirate stained with Congo red and viewed under polarized light shows the characteristic apple-green birefringence.

Systemic amyloidosis: a challenge for the rheumatologist

Federico Perfetto, Alberto Moggi-Pignone, Riccardo Livi, Alessio Tempestini, Franco Bergesio and Marco Matucci-Cerinic

Systemic Consequences of Inflammation

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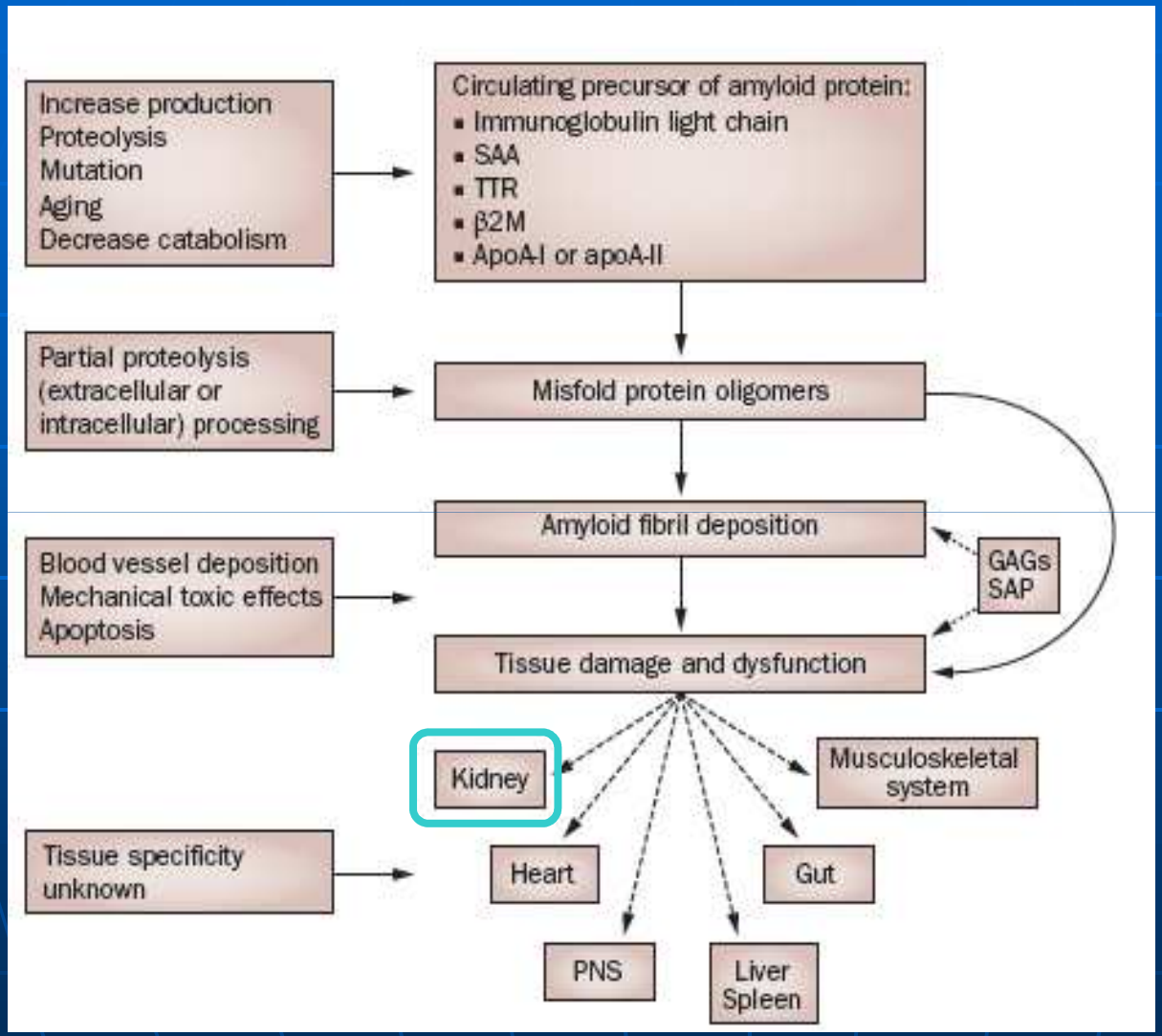
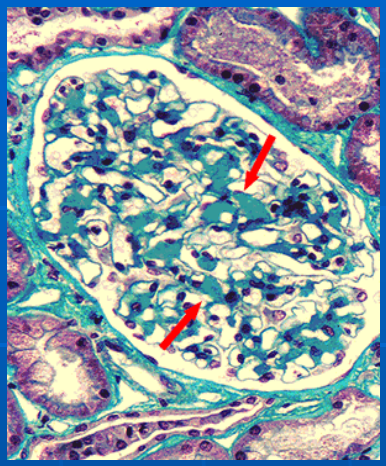
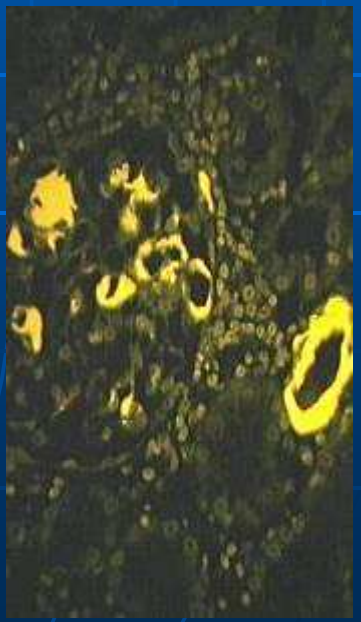
Amyloid type	Fibril protein precursor	Clinical syndrome
AL	Monoclonal immunoglobulin light chains	Associated with plasma cell dyscrasias
AH	Monoclonal immunoglobulin heavy chains	Associated with plasma cell dyscrasias
AA	Serum amyloid A protein	Associated with chronic inflammatory conditions
$A\beta_2M$	β_2-Microglobulin	Associated with chronic haemodialysis
ATTR	Genetically variant transthyretin	Familial (autosomal dominant) amyloid polyneuropathy
ATTR-SSA	Wild- type transthyretin	Senile systemic amyloidosis
ACys	Genetically variant cystatin	Hereditary cerebral haemorrhage with cerebral and systemic amyloidosis
AGe	Genetically variant gelsolin	Familial (autosomal dominant) systemic amyloidosis Cranial nerve involvement, lattice corneal dystrophy
ALys	Genetically variant lysozyme	Familial (autosomal dominant) systemic amyloidosis Non-neuropathic, prominent visceral involvement
AApoAI	Genetically variant apoA-I	Familial (autosomal dominant) systemic amyloidosis Non-neuropathic, prominent visceral involvement
AApoAII	Genetically variant apoA-II	Familial (autosomal dominant) systemic amyloidosis Non-neuropathic, prominent renal involvement
AFib	Genetically variant fibrinogen A α chain	Familial (autosomal dominant) systemic amyloidosis Non-neuropathic, prominent renal involvement

Szisztémás amyloidosis







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Amyloid type	MSS	Renal	CV	PNS	ANS	Liver	Spl	Skin	GI	Thy	Adr	Eye	Test	Tong	FX def.
AA	-	+++	+	-	++	++	++	-	+	+	+	-	-	±	-
AL	++	+++	+++	++	++	++	+	±	++	+	+	-	±	+++	+
$A\beta_2M$	+++	-	±	-	-	±	±	-	-	±	±	-	-	-	-
ATTR	±	+	+++	+++	+++	-	-	-	-	-	-	++	-	-	-
ATTR-SSA	-	-	+++	+	-	-	-	-	-	-	-	-	-	-	-
ALys	-	+++	±	-	-	++	+	-	++	-	-	-	-	-	-
AApoAI	-	++	++	+	-	++	++	-	-	-	-	-	++	-	-
AApoAII	-	++	+	-	-	-	-	-	-	-	-	-	-	-	-
AFib	-	+++	+	-	-	+	+	-	-	-	-	-	-	-	-

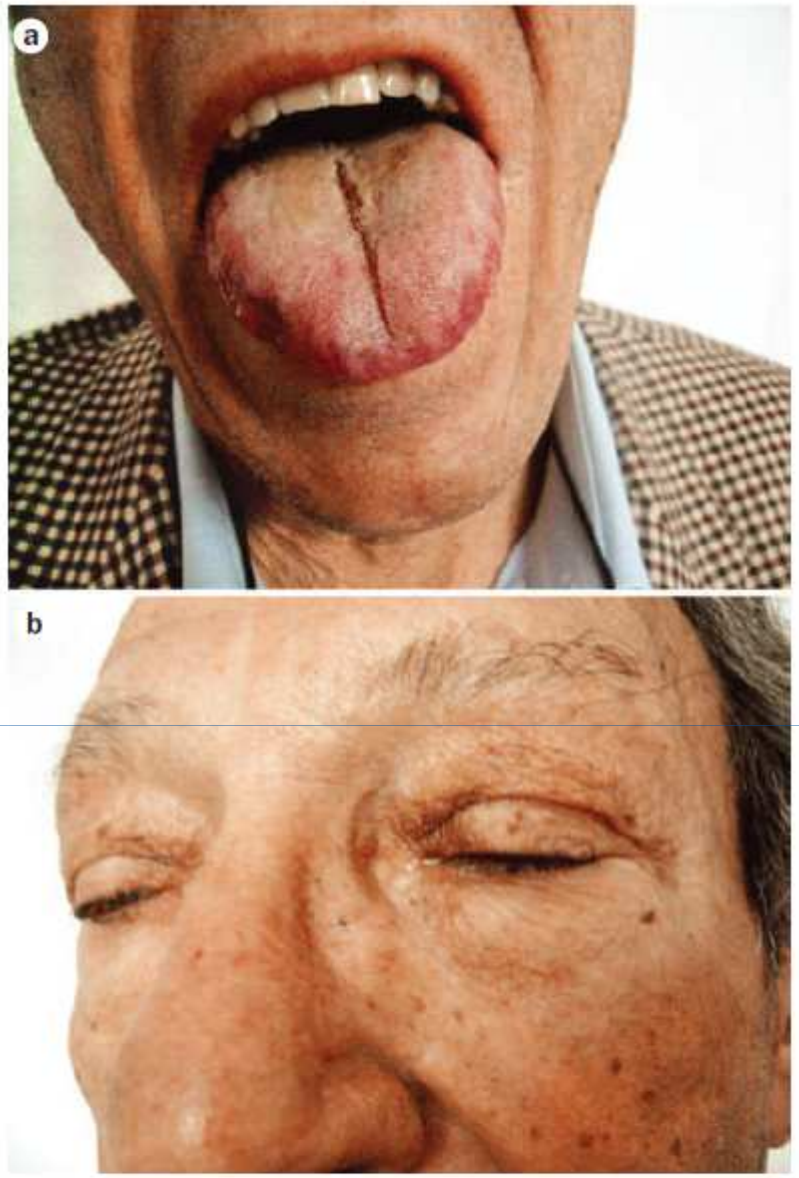

Figure 3 | Clinical features of AL amyloidosis. **a** | Macroglossia in a patient with AL amyloidosis. The tongue is firm to palpation. Note the nonreducible impression in the tongue caused by the teeth. **b** | Periorbital purpura in the same patient. Purpura is frequently bilateral. The patient gave no history of trauma to the area of ecchymosis.

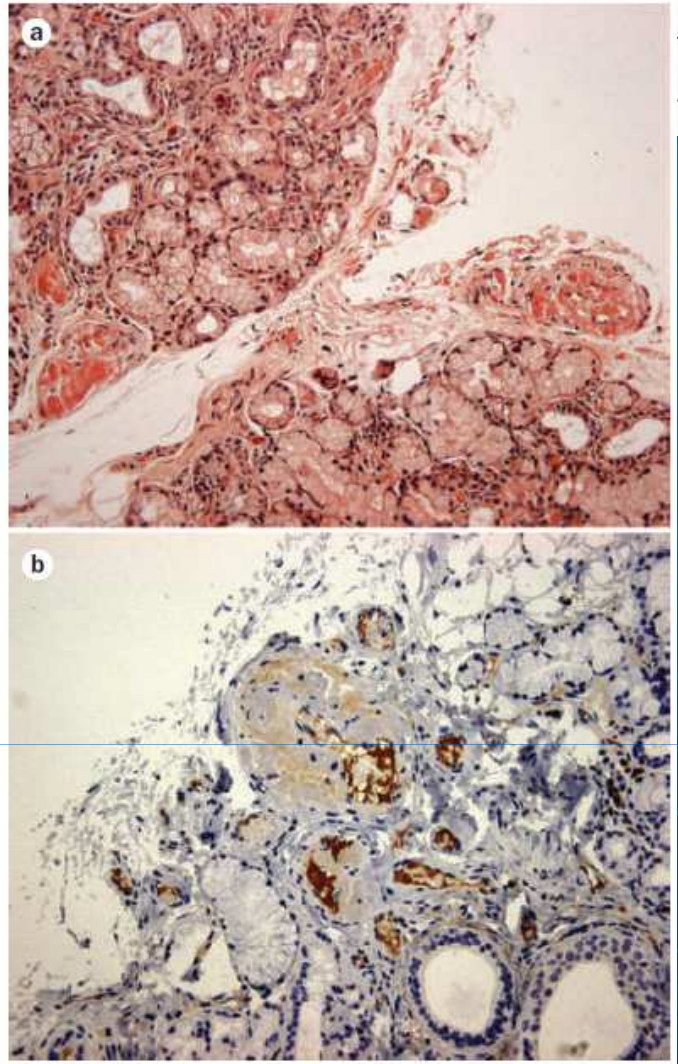

Figure 5 | Minor salivary gland biopsy of a patient with AL amyloidosis. **a** | A specimen obtained via biopsy of the minor (labial) salivary gland shows amyloid deposits mainly in the interstitium (Congo red staining). **b** | Using immunohistochemical analysis, the amyloid deposits are positively stained with anti-λ light-chain antibody.

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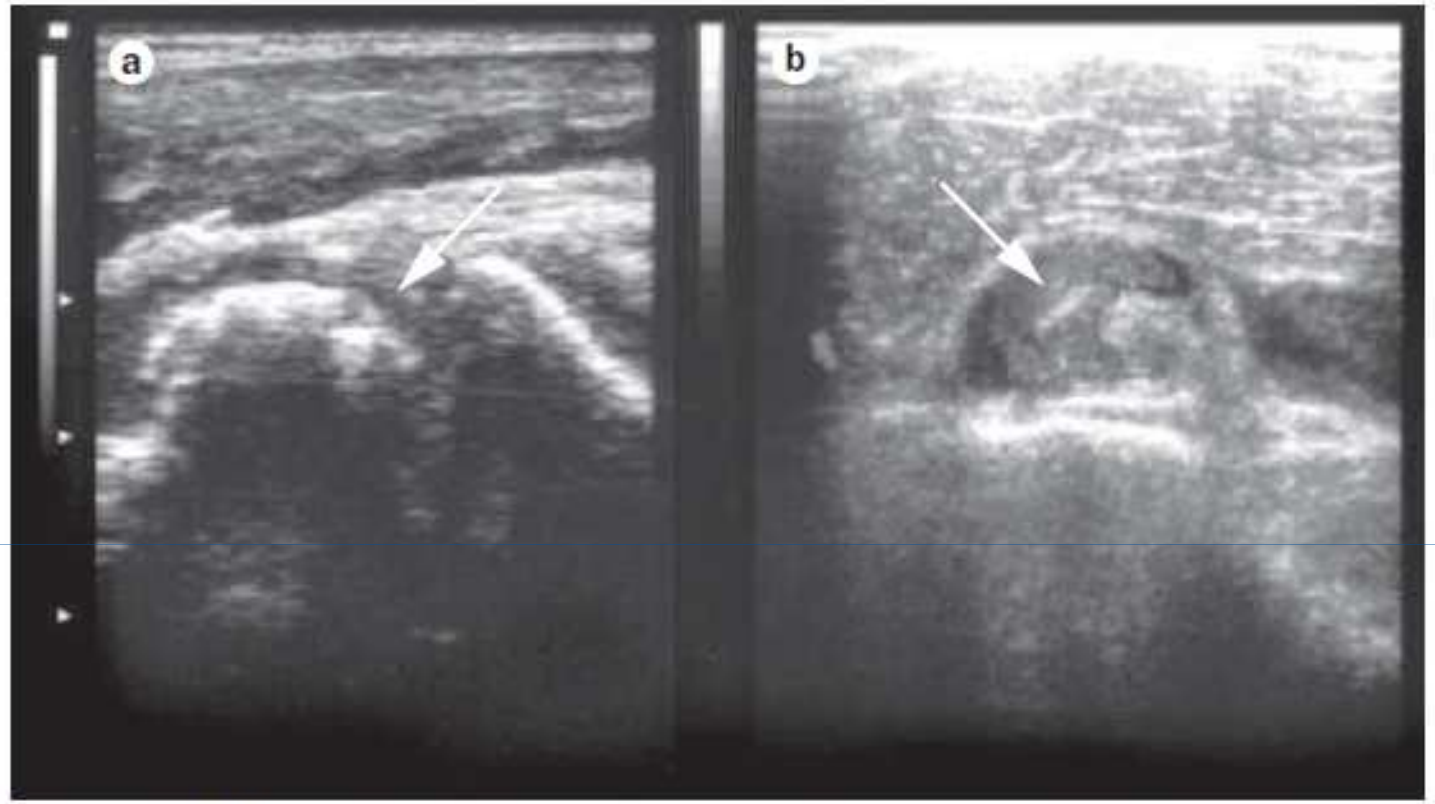

Figure 4 | $A\beta_2M$ amyloid arthropathy of the shoulder and wrist in a patient undergoing long-term hemodialysis. **a** | In the shoulder, the biceps tendon is enlarged, with an inhomogeneous echo texture that indicates amyloidosis (arrow) without hypervascularization on power Doppler analysis. **b** | In the wrist, imaging reveals stretching of the joint capsule with solid and heterogeneous content and with cortical irregularity of the metacarpal bone (arrow).

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1. Characteristic patients	• Chronic rheumatic disease • Long-term dialysis • Monoclonal gammopathy
2. Characteristic clinical manifestations	• Non-diabetic nephrotic syndrome • Low voltage on ECG • Echocardiography showing left ventricular hypertrophy • Hepatomegaly, abnormal levels of alkaline phosphatase, γ-glutamyl; transferase • Hower–Jolly bodies in peripheral blood smear • Splenomegaly • Chronic demyelinating polyneuropathy and/or orthostatic hypotension • Macroglossia, 'shoulder pad' sign, cutaneous ecchymosis • Xerostomia, joint involvement, jaw claudication, skin involvement
3. Biopsy-histology	• Abdominal subcutaneous fat aspiration with Congo red staining • Other biopsies (rectal, renal, liver, salivary gland)
4. Additional laboratory tests to identify type of amyloidosis	• Immunofixation of serum and urine, Ig free light chain assay (AL amyloidosis) • Serum amyloid A assay (AA amyloidosis) • Genetic testing (ATTR amyloidosis) • Serum β_2-microglobulin level (Aβ2M amyloidosis)
5. Imaging	• Echocardiography • Abdominal ultrasound (kidney, liver, spleen) • Musculoskeletal ultrasound (joints) • CT, MRI (spinal involvement in β2M amyloidosis) • EMG/nerve conduction study (carpal tunnel syndrome, polyneuropathy)

Clin Rheumatol
DOI 10.1007/s10067-010-1469-4

ORIGINAL ARTICLE

Etanercept

Etanercept can induce resolution of renal deterioration in patients with amyloid A amyloidosis secondary to rheumatoid arthritis

Tadashi Nakamura · Syu-ichi Higashi · Kunihiko Tomoda · Michishi Tsukano · Masahiro Shono

Table 2 Surrogate markers between initial and last visit following treatment with etanercept

Parameter	Initial visit	Last visit	*P* value
DAS28-ESR	5.99±0.69	2.99±0.15	<0.01
CRP (mg/dl)	4.68±0.87	0.48±0.29	<0.01
SAA (μg/ml)	250±129	26±15	<0.01
Proteinuria (g/day)	2.24±0.81	0.57±0.41	<0.01
Serum creatinine (mg/dl)	2.54±1.38	2.50±2.21	0.896

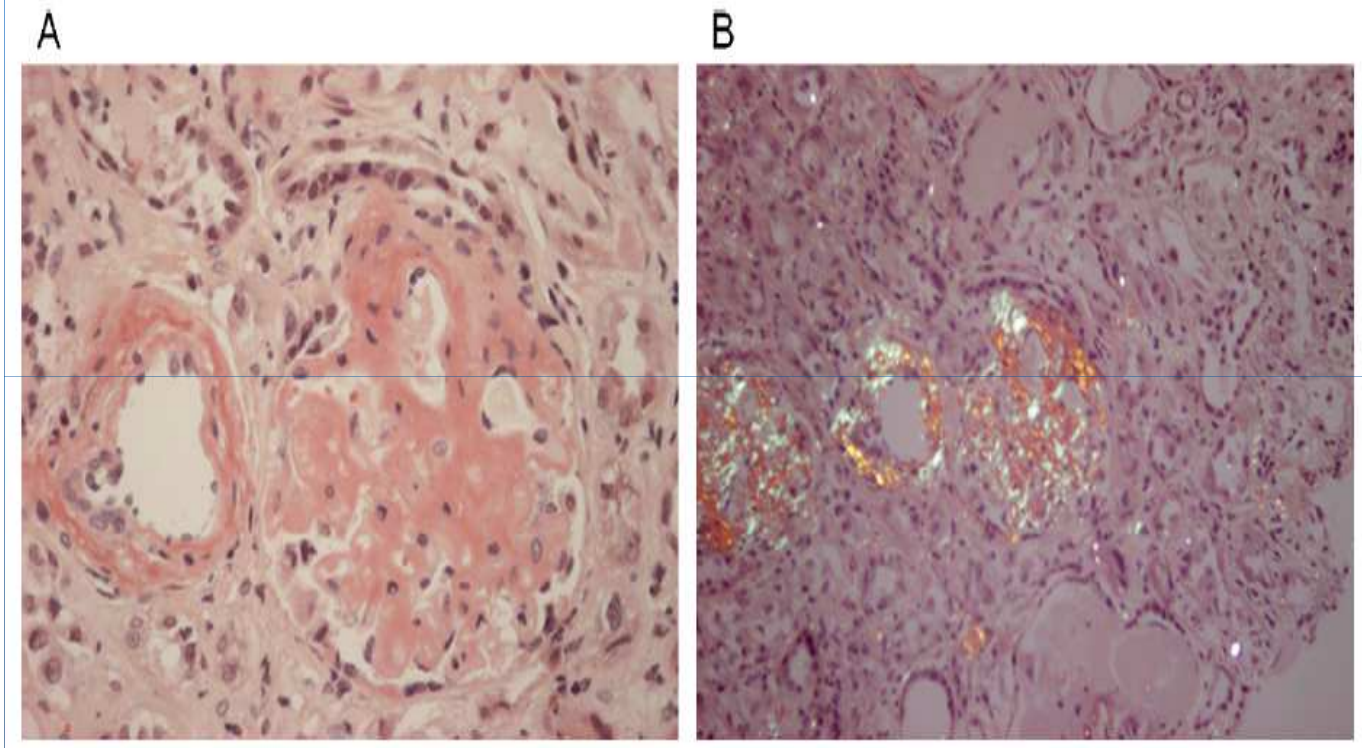


Figure 2 Renal amyloid deposition in a patient with AA amyloidosis secondary to rheumatoid arthritis. (A) Congo red staining. (B) Green birefringence under polarisation microscope. (Courtesy of Dr J Kovács, Department of Pathology, University of Debrecen Medical Center, Debrecen, Hungary).

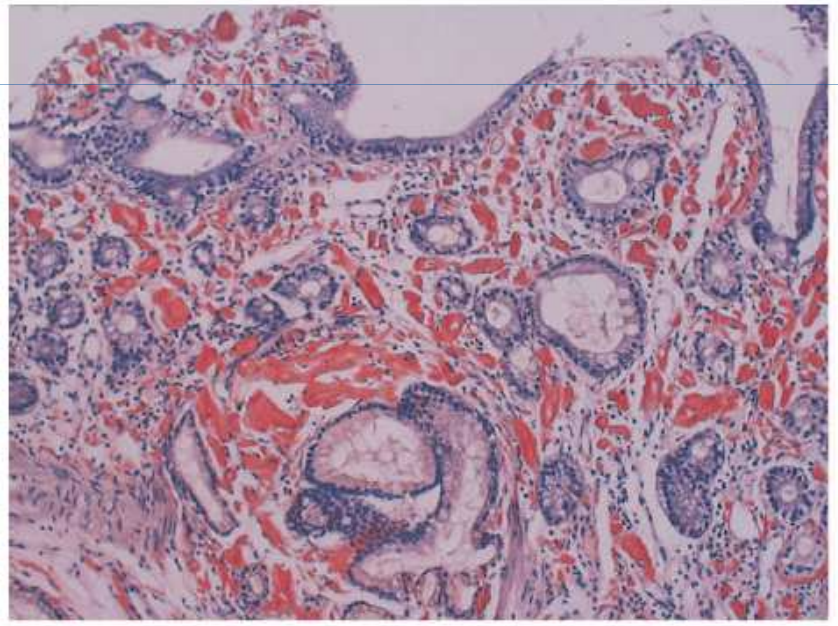
TCZ RA-hoz társuló szekunder amyloidosisban

Clin Rheumatol (2009) 28:1113–1116
DOI 10.1007/s10067-009-1185-0

CASE REPORT

Tocilizumab dramatically ameliorated life-threatening diarrhea due to secondary amyloidosis associated with rheumatoid arthritis

Hiroe Sato · Takehito Sakai · Toshiaki Sugaya · Yasuhiro Otaki · Kana Aoki · Katsushi Ishii · Hidehiro Horizono · Hiroshi Otani · Asami Abe · Noboru Yamada · Hajime Ishikawa · Kiyoshi Nakazono · Akira Murasawa · Fumitake Gejyo



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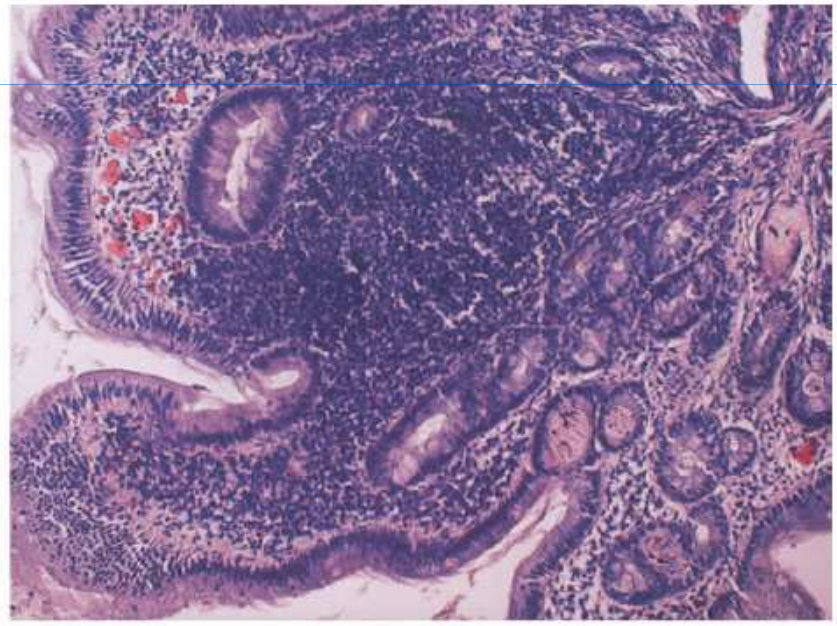

B

Figure 2. Results of gastrointestinal biopsy before and after tocilizumab therapy. **A,** Massive amyloid A protein deposits were observed in duodenal mucosa and submucosa before the start of tocilizumab therapy. **B,** Marked regression of amyloid A protein deposits was seen in duodenal mucosa and submucosa after tocilizumab treatment. (Congo red stained; original magnification × 200.)

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