Soluble Fas and soluble Fas ligand in the joints of patients with rheumatoid arthritis and osteoarthritis: a Tunisian case-control study

Sirs,

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease characterized by abnormal synovial hyperplasia associated with local infiltration of various inflammatory cells leading to cartilage and bone destruction. A deficit in the physiological apoptotic process could be at the origin of rheumatoid synovitis (1, 2). The soluble form of Fas (sFas) and those of Fas ligand (sFasL) antigens are involved in apoptotic regulation (3-5) in RA. Conversely, in osteoarthritis (OA), there are no apoptosis abnormalities mediated by Fas/FasL interaction.

The objective of this study is to appreciate the role of apoptosis in the pathogenesis of RA through the comparison of sFas and sFasL concentrations in sera and in knee synovial fluid (SF) among 2 groups of patients, one with active form of RA, and another with flare-up of OA.

A case-control study was carried out, during the period from January 2001 to May 2003, by the department of Rheumatology of La Marsa hospital in collaboration with the Immuno-histology laboratory of the Faculty of Medicine of Tunis. The first group of 27 patients with active form of RA, according to the FDA and to the 1987 revised ACR criteria, is composed of 24 women and 3 men, with a median age of 48 years and median disease duration of 99.25 months. The second group of 8 patients, with flare-up of OA, is composed of 5 women and 3 men, with a median age of 50 years. All patients were enrolled after informed consent. Finally and to insure sFas and sFasL dosage validity in sera, a healthy control group, composed of 20 blood donors matched for age to the study groups, was selected. Concentrations of sFas and sFasL in sera and in SF have been determined using an Enzyme-Linked Immuno-Sorbent Assay (ELISA). Non parametric tests are used to compare the median concentrations, Mann-Whitney among 2 groups, and Kruskal-Wallis among 3 groups. A p value below 0.05 is considered as significant.

All results are summarized in Table I. In sera, sFasL and sFas levels in RA and OA groups are significantly higher than in the healthy controls group (both Kruskal-Wallis $p = 0.000$).

When comparing RA and OA groups, SF sFasL is significantly higher in the RA group ($p = 0.000$) while SF sFas, sera sFasL and sera sFas are not statistically different (respectively $p = 0.985$, $p = 0.203$ and $p = 0.580$). We can notice that, for both groups, sFasL levels are higher in SF than in sera (*e.g.* Fig. 1).

Table I. sFasL and sFas concentrations for each group of study.

Apoptotic markers	Study group	Valid cases	Median (25^{th} – 75^{th} percentiles)	p value	
sFasL in sera (pg/ml)	RA	23	380.00 (253.00 – 433.00)	0.203	0.000**
	OA	8	270.00 (260.00 – 317.50)		
	Healthy controls	20	166.50 (144.25 – 197.50)		
sFas in sera (ng/ml)	RA	23	5.70 (3.70 - 7.20)	0.580	0.000**
	OA	8	5.10 (3.725 - 5.675)		
	Healthy controls	20	2.35 (1.76 - 3.00)		
sFasL in SF (pg/ml)	RA	27	870.00 (730.00 – 975.00)	0.000**	
	OA	8	390.00 (300.00 – 517.50)		
sFas in SF (ng/ml)	RA	27	9.40 (7.60 – 11.20)	0.985	
	OA	8	9.20 (7.075 – 11.500)		

NB: ** p value highly significant.

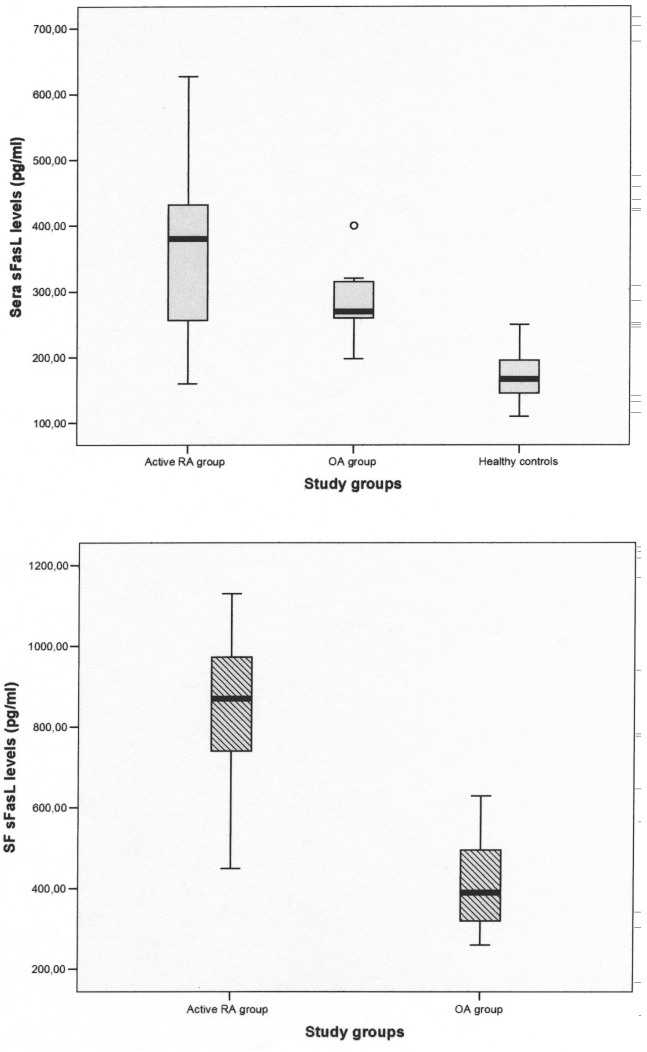

Fig. 1. Sera and SF sFasL levels comparisons among study groups.

Letters to the Editor

Our most important finding is that the SF sFasL levels of RA group are higher than those of OA group. Hashimoto *et al*. (6) find elevated levels only for SF sFasL in RA and OA groups. Whereas, Hasunuma *et al*. (7) report a higher concentration of SF sFas in RA group when compared to OA group but have found no difference in sera sFas concentrations.

Asahara *et al*. (8) consider that an over expression of FasL, on the surface of activated T lymphocytes located in the rheumatoid synovium, contribute to the induction of apoptosis in RA. The addition of anti-Fas IgM monoclonal antibodies (MAb) to cultured synoviocytes, obtained from RA and OA samples, leads to apoptosis only in RA patients (9). These findings show a sensitivity of rheumatoid synovium to anti-Fas IgM MAb and suggest that its therapeutic use might reduce the synovitis through apoptosis induction (10).

In conclusion, the increase of sFasL levels in SF appears to characterize active RA. As sFasL is an apoptotic marker, we might ask whether an elevated level of the SF sFasL could not be an expression of the synovium proliferation observed in active RA?

D. MRABET[1]
R. HAJRI[1]
K. HAMZAOUI[2]
N. ATTIA ROMDHANE[3]
L. ZAKRAOUI[1]

[1]Department of Rheumatology, Mongi Slim Hospital, La Marsa; [2]Laboratory of Immunohistology, Faculty of Medicine, Tunis; [3]Department of Neurology, Charles Nicolle Hospital, Tunis, Tunisia.

Address correspondence to: Dalila Mrabet, 12, Rue du 3 Septembre. Tunis 1007, Tunisia.
E-mail address: mrabetdalila@yahoo.fr

Competing interests: none declared.

References

1. MICHAEL V, KOSCH ALISA E: Cell cycle implication in the pathogenesis of rheumatoid arthritis. *Frontiers in Bioscience* 2000; 5: 594-601.
2. LIU H, POPE RM: The role of apoptosis in rheumatoid arthritis. *Curr Opin Pharmacol* 2003; 3: 317-22.
3. POPE RM: Apoptosis as a therapeutic tool in rheumatoid arthritis. *Nat Rev Immunol* 2002; 2: 527-35.
4. MATSUNO H, YUDOH K, WATANABE Y, NAKAZAWA F, AONO H, KIMURA T: Stromelysin-1 (MMP-3) in synovial fluid of patients with rheumatoid arthritis has potential to cleave membrane bound Fas ligand. *J Rheumatol* 2001; 28: 22-8.
5. AINOLA MM, MANDELIN JA, LILJESTRON MP, LI TF, HUKKANEN MV, KONTTINEN YT: Pannus invasion and cartilage degradation in RA: involvement of MMP-3 and interleukin-1beta. *Clin Exp Rheumatol* 2005; 23: 644-50.
6. HASHIMOTO H, TANAKA M, SUDA T *et al*.: Soluble Fas ligand in the joints of patients with rheumatoid arthritis and osteoarthritis. *Arthritis Rheum* 1998; 41: 657-62.
7. HASUNUMA T, KAYAGAKI N, ASAHARA H *et al*.: Accumulation of soluble Fas in inflamed joints of patients with rheumatoid arthritis. *Arthritis Rheum* 1997; 40: 80-6.
8. ASAHARA H, HASUMUNA T, KOBATA T *et al*.: Expression of Fas antigen and Fas ligand in the rheumatoid synovial tissue. *Clin Immunol Immunopathol* 1996; 81: 27-34.
9. NISHIOKA K, HASUNUMA T, KATO T, SUMIDA T, KOBATA T: Apoptosis in rheumatoid arthritis: a novel pathway in the regulation of synovial tissue. *Arthritis Rheum* 1998; 41: 1-9.
10. SMITH MD, WALKER JG: Apoptosis a relevant therapeutic target in rheumatoid arthritis? *Rheumatology* (Oxford) 2004; 43: 405-7.

Erratum corrige

In an article in our previous issue, T. Nakamura *et al*. 2007; 25(**4**): 518-522, the authors have brought to our attention a mistake in Table I, page 520, under the column: **SAA1 gene polymorphism**. Here below is Table I with the corrected figures in bold.

Table I. Patients' characteristics.

Patient/ Age/ Sex	Disease duration RA/Amyloidsis (years)	SAA1 gene polymorphism	Prior DMARDs	Associated Prednisolone (mg/day)	Organ involvement	Proteinuria (g/day) Initial*	Proteinuria (g/day) Last**	Serum creatinine (mg/dl) Initial*	Serum creatinine (mg/dl) Last**	Follow-up (weeks)
1/53/F	12/11	1.3/1.3	CYC, MTX BU, SASP	0	Kidney	2.6	0.6	4.3	4.5	68
2/57/F	25/2	1.1/1.3	CYC, MTX GST, CyA TCR, SASP	5	Kidney Digestive tract Thyroid	3.2	1.2	5.3	3.6	56
3/70/M	43/5	1.3/1.3	GST, BU MTX, AU	10	Kidney	1.9	1.7	2.3	2.2	20
4/60/F	37/9	**1.5**/1.3	MTX, IM CYC, BU LEF, SASP	2	Kidney Heart, thyroid Bladder Digestive tract	1.8	0.3	0.9	0.9	37
5/59/F	6/2	**1.5**/1.3	BU, D-p, AU TCR, CYC MTX	5	Kidney Thyroid Digestive tract	2.5	1.2	4.0	3.8	32
6/72/F	4/2	1.3/1.3	CYC, MTX BU, CyA	10	Kidney	1.2	0.3	0.5	0.4	37
7/54/F	15/4	1.3/1.3	BU, MTX SASP, TCR CYC	3	Kidney Thyroid Digestive tract	2.9	0.8	2.6	2.4	54

CYC: cyclophosphamide; MTX: methotrexate; BU: bucillamine; SASP: sulfasalazine; GST: sodium aurothiomalate; CyA: cyclosporine; TCR: tacrolimus; AU: auranofin; IM: azathioprine; LEF: leflunomide; D-p: D-penicillamine.
*,** The value of initial (before etanercept) - and last (the index time) - visit following treatment with etanercept between follow-up periods.