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Telomerase activity in peripheral blood mononuclear cells from patients with SLE

Telomerase is a reverse transcriptase that adds the telomeric sequence to the terminal of chromosomes, prevents shortening of telomere, and maintains the complete telomeric structure.[1] It has been recently reported that an increase in telomerase activity is associated with the activation of lymphocytes,[2–7] and, in general, much attention has been paid to the role of telomerase in immunopathology. Katayama *et al* reported the telomerase activity in patients with systemic lupus erythematosus (SLE).[8] They analysed 17 patients with SLE, and the telomerase activity in peripheral mononuclear cells was increased to 64.7%. Thus, in this study, we divided patients with SLE into treated and untreated groups, and measured the telomerase activity of peripheral mononuclear cells.

Thirteen patients with SLE (1 man, 12 women) with a mean (SD) age of 30.7 (6.5) years (range 19–61) were enrolled in this study. All patients fulfilled the 1997 revised American Rheumatism Association criteria. As a control group, 10 normal volunteers, six women aged 19–41 and four men aged 30–37, were also included in the study. After informed consent had been obtained, 10 ml of peripheral blood was taken and heparinised. The mononuclear cell fraction was isolated from 10 ml of heparinised peripheral blood by Ficoll-Paque (Sigma Inc, St Louis, USA) density gradient centrifugation. A sample of 1.0×10^6 mononuclear cells was analysed by the TRAP assay method. The TRAP assay was performed with a TRAPeze telomerase detection kit produced by the Intergen Company (Purchase, NY, USA). The level of telomerase activity was expressed by a ratio of the entire TRAP ladders to an internal control band.

Table 1 shows the telomerase activity level data and clinical data used for determining the SLE Disease Activity Index (SLEDAI). Significant differences (p=0.006) were detected in the telomerase activity level between the control group, untreated SLE group, and treated SLE group by Kruskal-Wallis test with a significance level of 5%. For multiple comparisons the Mann-Whitney U test was used to evaluate intergroup differences after lowering the significance level using Bonferroni's technique. The p value was 0.002 between the control group and untreated SLE group, 0.005 between the untreated SLE group and treated SLE group, and 0.118 between the control group and treated SLE group. Compared with other groups, telomerase activity was significantly higher in the SLE untreated group. The Spearman rank correlation test with a significance level of 5% showed a significant positive relationship between telomerase activity and SLEDAI in the SLE group with a correlation coefficient of 0.872 and p value of 0.003. The relation between telomerase activity and clinical data in SLEDAI was also analysed using the Spearman rank correlation test with a significance level of 5% in the SLE group. The correlation coefficient and p value were −0.614 and 0.033 between telomerase activity and white blood cell count, −0.715 and 0.013 between telomerase activity and serum complement activity, and 0.637 and 0.027 between telomerase activity and serum IgG level, respectively, with a significance level of 5%. However, the relation between telomerase activity and other clinical data was not significant in the SLE group. Telomerase activity was measured before and after treatment and changes in the activity level were analysed.

SLEDAI decreased in all patients after treatment. Wilcoxon signed rank test with a significance level of 5% showed a significant decrease in telomerase activity (p=0.043) after treatment.

The treatment reduced the telomerase activity in peripheral mononuclear cells. We could not confirm whether the cause was due to the steroids or the reduction of disease activity. However, because the telomerase activity of peripheral mononuclear cells was correlated with SLEDAI, the peripheral blood telomerase activity may be useful in the evaluation of disease activity and in judging the therapeutic effects in SLE.

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Table 1 Telomerase activity and clinical laboratory parameters and SLE disease activity index (SLEDAI)

Patient No	*Age*	*Sex*	*Telomerase activity*	*WBC*	*Lymph.*	*Plt. (×10³)*	*CH_{50}*	*IC (C1q)*	*dsDNA*	*u-prot.*	*ANA*	*IgG*	*IgA*	*IgM*	*SLEDAI*	*Symptom*	*Treatment (prednisolone)*
1	23	M	1.96	2700	800	158.0	31.2	1.5	5	(−)	640	14.69	3.05	0.53	10	2,4,5,6,8	None
			0.00	6500	1200	211.0	37.0	1.9	5	(−)	1280	—	—	—	2	None	20 mg/day
2	36	F	0.76	2900	900	48.0	23.6	9.3	165	(1+)	1280	12.82	1.68	0.65	12	2,4,8	None
			0.00	5800	1700	243.0	29.2	—	72	(−)	—	—	—	—	2	None	30 mg/day
3	28	F	0.82	3700	1000	226.0	31.6	1.5	77	(±)	640	18.98	3.89	1.98	10	2,5,8	None
			0.78	8000	700	253.0	28.1	1.5	32	(±)	1280	—	—	—	2	None	20 mg/day
4	61	F	0.47	3600	400	201.0	15.0	34.5	83	(±)	5120	31.37	3.44	0.76	16	2,3,4,5,8	None
			0.29	5800	600	200.0	34.8	9.9	12	(−)	5120	—	—	—	0	None	30 mg/day
5	19	F	0.85	4520	920	311.0	27.2	1.9	13	(3+)	320	15.60	3.54	2.24	21	1,2,4,5,8	None
			0.28	16130	1130	327.0	30.0	1.5	5	(1+)	40	6.44	1.84	1.79	0	None	30 mg/day
6	24	F	0.25	8700	1400	149.0	34.2	1.5	185	(2+)	5120	11.34	3.33	0.90	2	None	50 mg/day
7	53	F	0.40	5600	1200	13.0	36.2	1.5	5	(2+)	160	18.24	6.00	0.79	1	None	60 mg/day
8	39	F	0.05	6800	1300	248.0	35.6	1.9	5	(−)	40	9.80	2.09	0.55	0	None	15 mg/day
9	41	F	0.18	12400	400	247.0	47.6	1.6	5	(1+)	640	13.13	2.73	0.51	0	None	20 mg/day
10	36	F	0.06	7900	1400	209.0	41.0	1.5	12	(−)	80	11.89	1.71	0.88	0	None	5 mg/day
11	56	F	0.04	7900	1200	219.0	41.5	1.5	5	(1+)	40	12.19	4.17	0.66	0	None	10 mg/day
12	39	F	0.10	5600	600	134.0	34.2	1.5	7	(3+)	640	7.65	2.32	0.38	0	None	20 mg/day
13	36	F	0.58	9000	1100	138.0	24.0	1.5	21	(2+)	320	16.53	3.55	1.39	4	7	30 mg/day

WBC = white blood cell count (/μl); Lymph. = lymphocyte count (/μl); Plt. = platelet count ($\times10^3$/μl); CH_{50} = serum complement activity (U/ml); IC (C1q) = serum immune complex level with a C1q solid phase method (μg/ml),;dsDNA = anti-double stranded DNA antibody level (IU/ml); u-prot. = urine protein analysis with a test paper method; ANA = antinuclear antibody (titre); IgG = immunoglobulin G level (g/l), IgA = immunoglobulin A level (g/l); IgM = immunoglobulin M level (g/l); SLEDAI = SLE disease activity index.
Symptom: 1 = central nervous system lupus; 2 = arthritis; 3 = myositis; 4 = nephritis; 5 = new rash; 6 = alopecia; 7 = serositis; 8 = fever.

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Treatment of ankylosing spondylitis with infliximab

In January 2000 a 35 year old man presented with severe ankylosing spondylitis (AS), diagnosed in 1981. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was 6.0, the Bath Ankylosing Spondylitis Functional Index (BASFI) was 3.0, and on a 1–10 visual analogue scale (VAS) for pain in the previous two months he had a score of 6.

Schober's test was 0 cm (normal 4 cm), Ott's test 1 cm (normal 2 cm), finger-floor distance 16 cm, lateral flexion 3 cm, tragus-wall distance 21 cm, cervical rotation 30°.

C reactive protein (CRP) was 41 mg/l (normal <5), erythrocyte sedimentation rate (ESR) was 25 mm/1st h (normal <15), and HLA-B27 genotype was positive.

Conventional radiography showed typical signs of AS. Magnetic resonance imaging (MRI) detected inflammatory activity in the ileosacral joints[1] by contrast enhancement after gadolinium application in the apical portion of the right ileosacral joint in T_1 weighted sequences (fig 1).

We started treatment with infliximab,[2] a monoclonal antibody (IgG1) directed against tumour necrosis factor α (TNFα), at a dose of 5 mg/kg body weight. Intravenous infusions were given in weeks 0, 2, 6, and then continued at six weekly intervals for one year without any additional disease modifying drug.

Pain improved within 24 hours of the first infusion. Within six weeks the patient required no ibuprofen and CRP, ESR, BASDAI, BASFI, and VAS improved dramatically (fig 2). With the exception of CRP and ESR, all variables remain normal up to now. CRP and ESR increased mildly at week 12 owing to a mild upper respiratory tract infection. There were no other adverse events. Two mobility variables (cervical rotation and tragus-wall distance) had improved at the end of one year's treatment.

MRI of the ileosacral joints showed no contrast enhancement at weeks 14 and 41 of treatment (fig 1).

The patient denied any loss of effect at the end of the six weekly infusion intervals or after one year of treatment. Except for the mild upper respiratory tract infection, which abated after two weeks without specific treatment, there were no adverse events.

This case report documents the first long term application of infliximab in a patient with AS. Two previous studies reported effective treatment of a total of 22 patients with AS with three infusions of infliximab at a dose of 5 mg/kg body weight.[3 4]

The pharmacological basis for TNFα inhibitory treatment in AS is the detection of TNFα-mRNA and TNFα protein in biopsy specimens of ileosacral joints of patients with active AS.[5] In rheumatoid arthritis (RA) and Crohn's disease (CD), several TNFα inhibitors seem to be successful in significantly reducing inflammatory activity.[6 7]

Theoretically, up regulation of the TNFα receptors and subsequent tachyphylaxis might be expected upon constant blockade of the agonist. This has not been noted in studies on infliximab, etanercept, and D2E7 in RA, CD, and psoriatic arthritis (PA) during long term treatment, even when constant therapeutic plasma levels are maintained.[7–9] This case report suggests this is true also for patients with AS.

In summary, we present the case of a patient with AS effectively and safely treated with infliximab over a period of more than one year. This indicates that treatment of AS with TNFα inhibiting substances may have equal long term safety and long term benefits on peripheral and spinal joint function as does treatment of RA, CD, and PA. Randomised controlled double blind studies are needed to investigate this in further detail.

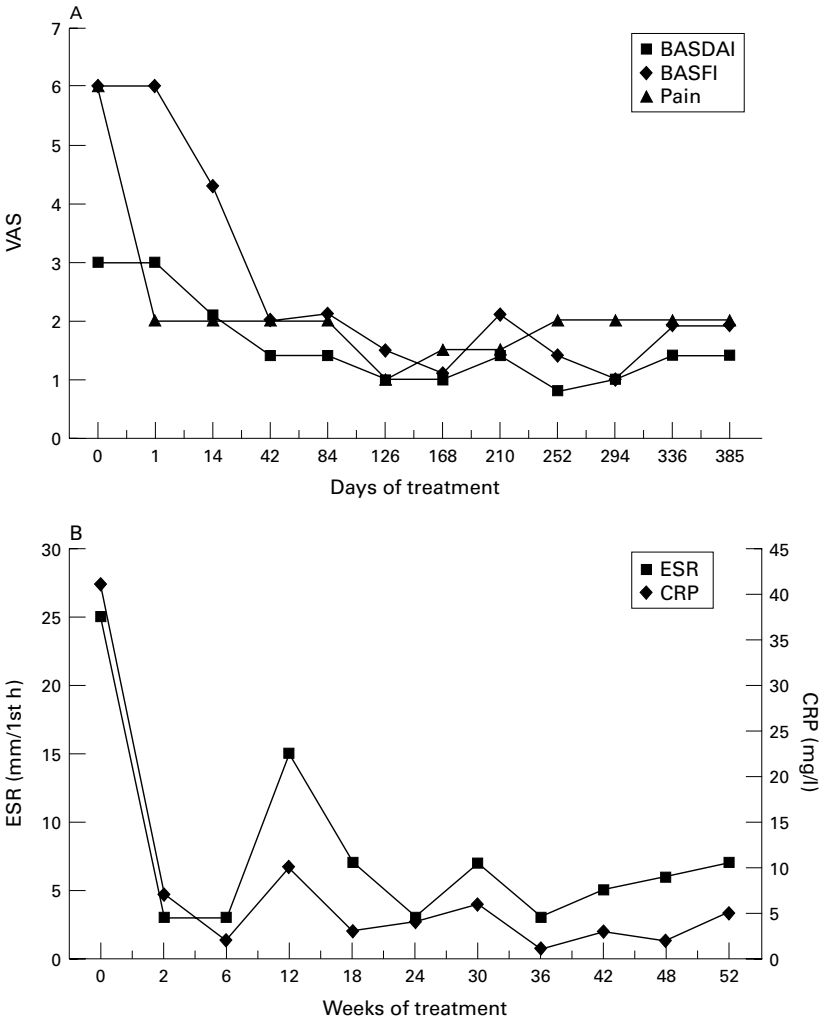

Figure 2 Self assessment of pain on a 1–10 visual analogue scale (A) and CRP and ESR (B).

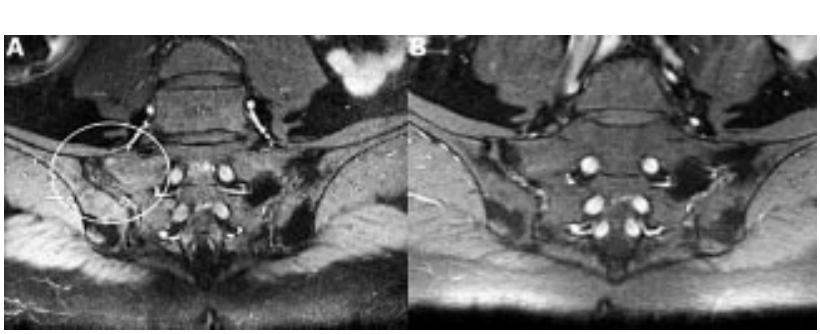

Figure 1 Gadolinium contrast enhanced T_1 weighted magnetic resonance imaging before treatment with infliximab (A) showing contrast enhancement in the right ileosacral joint, and (B) in week 41 of treatment showing no contrast agent uptake.