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The effect of the immunomodulator agent AS101 on interleukin-2 production in systemic lupus erythematosus (SLE) induced in mice by a pathogenic anti-DNA antibody

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SUMMARY

The role of the synthetic immunomodulator AS101 on the production of interleukin-2 (IL-2) by spleen cells of mice with SLE was investigated. BALB/c female mice, in which SLE was induced by immunization with the pathogenic idiotype of anti-DNA antibody 16/6 Id were treated with AS101 for 7 weeks 2 and 4 months after induction of the disease. The ability of the splenocytes of the mice with SLE to produce IL-2 was restored after administration of AS101. This effect was particularly impressive when the 7-week AS101 treatment was initiated 4 months after immunization. Despite its beneficial effect on IL-2 production, AS101 exerted no influence on the titres of autoantibodies in the sera of the mice. It also had no effect on clinical parameters of SLE, such as the increased sedimentation rate, proteinuria and low white blood cell counts. Our data indicate that defective IL-2 production in SLE is probably secondary to other disease processes and is not necessarily associated with the production of autoantibodies in this disorder.

Keywords systemic lupus erythematosus lymphokines interleukin-2 autoimmunity idiotypes

INTRODUCTION

SLE is an autoimmune disorder characterized by B cell hyperactivity and impaired cell-mediated immunity (Decker *et al.*, 1979). T cell proliferation, T cytotoxic activity and natural killer (NK) cell cytotoxicity are decreased in SLE (Horwitz & Garrett 1977; Charpentier, Carnaud & Bach, 1979; Goto, Tanimotok & Horiughi, 1980; Katz *et al.*, 1982). These defects correlate with the reported decrease in the production of cytokines such as interleukin-2 (IL-2) in autoimmune mice and humans (Alcocer-Varela & Alarcon-Segovia 1982; Linker-Israeli *et al.*, 1983; Altman *et al.*, 1981; Wofsy *et al.*, 1981). Recently, we have described an experimental model in which SLE was induced in mice by immunizing them with a pathogenic idiotype of a human anti-DNA antibody 16/6 Id (Mendlovic *et al.*, 1988; Blank *et al.*, 1988; Shoenfeld *et al.*, 1989). The disease has also been induced by immunization with other antibodies carrying the 16/6 Id (Blank *et al.*, 1990a) and by a monoclonal anti-16/6 Id antibody (Mendlovic *et al.*, 1989). It was shown that the induction of the disease could be enhanced by estrogens and precluded by androgens (Blank *et al.*, 1990b). In preliminary results we noticed that the production of IL-2 in the mice with induced SLE was diminished. Modulation of IL-2 production and monitoring the effects on the progression of the disease can be observed in these mice in which the genetic background for developing autoimmune disorders is absent. Thus, the influence of IL-2 production on the pathogenecity of SLE can be evaluated.

This led us to consider treatment of the mice with experimental SLE with the synthetic immunomodulator AS101 (Sredni *et al.*, 1987, 1988; Nyska *et al.*, 1990). This immunomodulator has been found to have a potential therapeutic effect on various immune-mediated conditions, which is attributed to its ability to increase the production of IL-2 and colony-stimulating factor *in vivo* and *in vitro* (Sredni *et al.*, 1987). In this investigation we followed the effects of AS101 on SLE-like disease induced is mice and attempted to establish whether improved IL-2 production following treatment may have therapeutic effects on the course of the disease.

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MATERIALS AND METHODS

Mice

BALB/c female mice, aged 2 months, were obtained from Animal Resources, Sackler Medical School, Tel Aviv University, Israel.

Antibodies
SA-1, a monoclonal antibody derived from a patient with polymyositis at an active stage of the disease. This antibody binds to DNA and carries the 16/6 idiotype (Blank *et al.*, 1988).

Immunomodulator
The properties of AS101, a synthetic compound (ammonium trichloro dioxiethylene-O,O′-) tellurate) have been described earlier (Sredni *et al.*, 1987).

Induction of SLE
One microgram of the SA-1 (16/6 Id+) antibody in Freund's complete adjuvant (FCA) was injected intradermally into the hind foodpads of BALB/c females. Three weeks later a booster injection of 1 μg in phosphate-buffered saline (PBS) was administered to the hind foodpads. The presence of autoantibodies against ssDNA, dsDNA, poly(I), poly(G), histones (subfraction $H_{1\text{-}5}$), cardiolipin, Sm, RNP, SS-A (Ro), SS-B(La) and 16/6 idiotype in the serum was determined by ELISA (Mendlovic *et al.*, 1988; Shoenfeld *et al.*, 1983 a,b; Blank *et al.*, 1990c; Konikoff *et al.*, 1987).

Detection of SLE-associated pathological manifestations
The erythrocyte sedimentation rate was determined by diluting the heparinized blood in PBS at a ratio of 1:1. The diluted blood was then passed to a microsampling pipette and the sedimentation was measured 6 h later. Proteinuria was measured by a semi-quantitative way using Combistix Kit (Ames, Elkhart, IN).

AS101 treatment
Female mice immunized with SA-1 (16/6 Id+) were treated 2 and 4 months after immunization with 1·0 μg/mouse of AS101 intraperitoneally every second day for 7 weeks. After treatment the effect of AS101 on the different manifestations of SLE was determined.

Preparation of IL-2-containing supernatants
Splenocytes prepared from SLE mice with and without AS101 treatment (*in vivo* or *in vitro*), were tested for the ability to produce IL-2 *in vitro*. Nylon wool non-adherent splenocytes at a concentration of 1×10^6/ml were incubated in 24-well plates in RPMI 1640 supplemented with 5% heat-inactivated fetal calf serum (FCS), 2% glutamine, and 5×10^{-5} M mercapoethanol. The cells were exposed *in vitro* either to 5 μg/ml of concanavalin A (Con A) or to different concentrations of AS101 (10^{-2} to 10^1 μg/ml). After 24 h at 37°C in 5% CO_2, supernatants were collected, centrifuged and stored at −20°C until assayed for IL-2 activity.

Determination of IL-2 activity
IL-2 activity was tested on an IL-2 dependent T cell line (CTL-D, obtained from Dr R. Apte, Department of Immunology, Ben Gurion University, Beer Sheva, Israel). The cells (1×10^4/well), were placed in microtitre plates, with RPMI 1640 containing 5% FCS, 2% glutamine and 5×10^{-5} M mercaptoethanol. Volumes of 0·1 ml of serial dilutions of the supernatants to be assayed for IL-2 were added to each well. The microplates were incubated at 37°C in 5% CO_2 for 48 h with ^{3}H-thymidine (0·5 μci/well; Nuclear Research Center, Israel) and its incorporation was determined. The spleen cells from two mice were pooled; each result represents the mean ct/min of triplicate cultures. IL-2 units were calculated according to the methods of Gillis *et al.* (1987).

Table 1. Autoantibodies profile in sera of mice immunized with SA-1 (16/6+Id) antibody and treated with AS101 3 months after immunization

Antibody to	−16/6 Id		+16/6 Id	
	—	+AS101	—	+AS101
ssDNA	47±8	97±7	874±15	854±21
dsDNA	59±12	101±15	901±21	878±15
poly (I)	72±6	88±8	747±13	899±24
poly (G)	34±9	79±11	793±14	703±21
Histones	53±9	84±6	655±18	715±18
Cardiolipin	67±13	93±7	707±22	749±25
Sm	49±6	121±12	847±31	901±32
RNP	67±8	130±14	788±25	879±17
SS-A (Ro)	59±11	122±9	815±37	904±23
SS-B (La)	66±8	97±18	798±29	813±35
16/6	73±13	104±16	1147±43	1074±42
Anti 16/6*	61±8	131±11	561±27	635±31

Antibody responses expressed as mean ± s.d. of sera taken from five mice.

Sera were diluted 1:200 and the results are presented as OD_{405} nm × 10^3.

*Antibody to anti-16/6 Id represents the mouse 16/6 Id.

Detection of Tac antigen on splenocytes
Anti-Tac monoclonal antibody and IL-2 are known to recognize and compete for the same binding site on IL-2 receptor (Depper *et al.*, 1983)). T cells reactive with anti-Tac antibody were detected by the indirect immunofluorescence method, using the fluorescein isothiocyanate (FITC) conjugated $F(ab')_2$ fraction of goat anti-mouse IgG antibody (Becton Dickinson, Mountain View, CA) as the second antibody. Nylon wool non-adherent splenocytes (5×10^5) were incubated with 20 μl of anti-Tac monoclonal antibody (Becton Dickinson) in a final dilution of 1:25 for 30 min at 4°C. These cells were then washed twice with PBS containing 1% bovine serum, and then incubated with the FITC conjugated antibody for 30 min at 4°C. As a control, normal mouse IgG was used. The percentage of reactive cells in at least 500 lymphocytes was determined under Zeiss u.v. microscope (Tsudo *et al.*, 1982).

RESULTS

The effect of AS101 on the titres of autoantibodies in the sera of SLE mice
Table 1 shows that treatment with AS101, injected into mice every second day for 7 weeks, did not affect the titres of autoantibodies in the sera of the mice, recorded 3 months after SLE induction. Elevated levels of antibodies to DNA, histones, cardiolipin Sm, RNP, SS-A (Ro), SS-B (La), 16/6 Id, anti-16/6 Id, were consistently found in the sera. Similarly, AS101 had no effect on the clinical parameters (Table 2). Furthermore, no differences in the serological or clinical parameters were noted 5 months after disease induction (data not shown).

Table 2. Clinical manifestations in mice immunized with 16/6 Id and treated with AS101

	ESR (mm/6 h)	WBC (cells/mm^3)	Proteinuria (g/l)
Normal	0·5	6342±843	<0·3
Normal+AS101	0·7	7549±803	<0·3
3-month SLE*	8	3249±641	>3
3-month SLE+AS101†	11	3593±747	>3
Normal	0·2	6551±702	<0·3
Normal+AS101	0·4	7984±853	<0·3
5-month SLE‡	12	2645±579	>3
5-month SLE+AS101†	14	3499±651	>3

Mean±s.d. of five mice

*Data on mice 3 months after immunization with 16/6 Id prior to treatment with AS101.

†Data on mice after 7 weeks of treatment with AS101.

‡Data on mice 5 months after immunization with 16/6 Id prior to 7 weeks of treatment with AS101.

ESR, erythrocyte sedimentation rate; WBC, white blood cells.

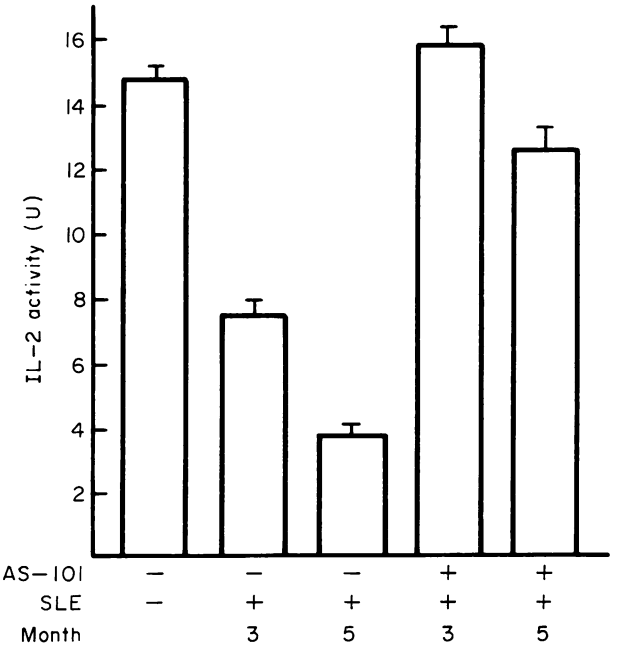

Fig. 1. Interleukin-2 (IL-2) secretion of splenocytes from SLE mice with and without *in vivo* AS101 treatment. Bars are s.d.

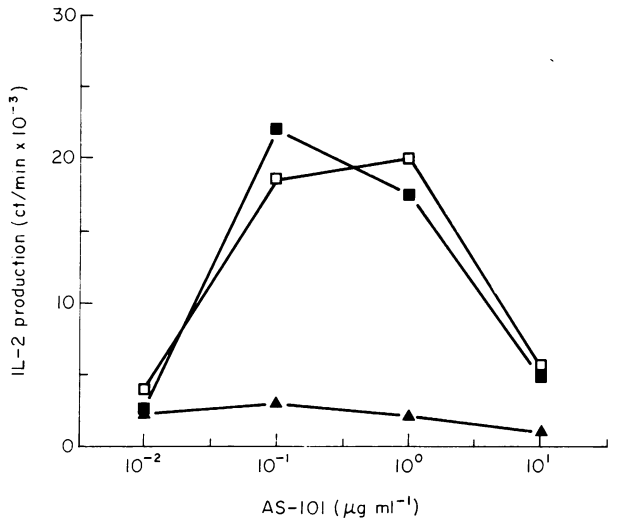

Fig. 2. Interleukin-2 (IL-2) secretion of splenocytes from SLE mice treated with AS101. *in vitro*. □, Production of IL-2 by splenocytes from normal mice ($n=5$) in the presence of AS101; ■, production of IL-2 by splenocytes from mice 3 months after SLE disease induction, in the presence of AS101; ▲, production of IL-2 by splenocytes derived from mice 3 months after SLE induction in the absence of AS101.

Reconstitution of IL-2 secretion by spleen cells from SLE-induced mice treated with AS101

Since it was previously shown that treatment with AS101 leads to increased secretion of IL-2 by mouse spleen cells (Sredni *et al.*, 1987), we attempted to establish whether the pathogenesis of SLE induced in mice would be affected by treatment with AS101 through the IL-2 pathway.

Mice in which SLE had been induced were killed 3 and 5 months after induction of the disease and subsequent to a 7-week treatment with AS101. A significant diminution ($P<0·002$) in IL-2 secretion by the splenocytes of SLE mice, both 3 and 5 months after induction of the disease was detected (Fig. 1): 3 months after immunization with the anti-DNA idiotype (16/6$^+$ Id) the ability of splenocytes to secrete IL-2 had decreased by 50%, and after 5 months by 75%. Treatment of the SLE mice with AS101, every second day for 7 weeks restored the ability of the splenocyte to secrete IL-2. Splenocytes derived from mice after 3 months of treated SLE had restored their ability to secrete IL-2 to normal levels, while splenocytes derived from 5 months of treated SLE restored their ability to IL-2 production to 83% of normal control levels (Fig. 1).

Splenocytes derived from mice after 3 months of SLE improved their capacity to produce IL-2 in the presence of AS101 *in vitro* to normal levels, as seen in Fig. 2.

Restoration of Tac antigen on splenocytes of AS101-treated mice with induced SLE

The expression of IL-2 receptor (Tac antigen) on T cells is known to be the key to T cell proliferation in the presence of IL-2 (Tsudo *et al.*, 1982; Cantrel & Smith, 1983). The expression of Tac antigen on splenocytes from mice 3 and 5 months after induction of SLE and treatment with AS101, was studied using anti-Tac antibody. Table 3 shows that Tac antigen as determined by indirect immunofluorescence appeared on 37% of T cell splenocytes from normal mice treated with AS101, and on 29% and 32% of T cells from AS101-treated mice with induced SLE of 3 and 5 months' duration, respectively. Cells from normal mice displayed low levels of Tac antigen which increased following treatment with AS101. Similarly, cells derived 3 and 5 months after SLE induction and AS101 treatment exhibited elevated levels of Tac positive cells (12% of T cells 3 months and 18% of T cells 5 months after disease induction). Treatment with AS101 augmented the number of Tac positive cells by more than

Table 3. Expression of Tac antigen in mice with induced SLE, treated with AS101 *in vivo*

Mice	T cells Tac (+)	cells
Normal	Untreated	3±1%
	AS101	37±4%
3-months SLE	Untreated	12±1%
	AS101 (+)	29±5%
5-months SLE	Untreated	18±1%
	AS101 (+)	32±3%

Mean ± s.d. for five mice.

50%, both 3 and 5 months after disease induction and AS101 treatment.

The restoration of IL-2 receptors was observed in SLE animals treated *in vivo* with AS101, 3 and 5 months after immunization and treatment.

DISCUSSION

Autoimmune diseases are characterized by decreased production of and/or response to IL-2 (Alcocer-Varela, Laffon & Alarcon-Segovia, 1984; Bellamy *et al.*, 1985; Cathely, Amor & Fournier, 1986). Several studies have documented low levels of IL-2 in SLE in animal models as well as in humans (Altman *et al.*, 1981; Alcocer-Varela *et al.*, 1984; Bellamy *et al.*, 1985; Cathely *et al.*, 1986; Murakawa *et al.*, 1985; Linker-Israeli *et al.*, 1985; Bocchieri, Knittweiss & Seaton, 1984; Huang You-Peng *et al.*, 1988). At present there is no definitive concept concerning the diminished secretion of and the low response to IL-2 in SLE explaining whether these are secondary to pathological processes in the disease or whether they contribute to the induction of the disease via the IL-2 effect on T and B cell functions (Decker *et al.*, 1979; Bellamy *et al.*, 1985; Murakawa *et al.*, 1985; Huang You-Peng *et al.*, 1988). The development of an experimental animal model using mice in which SLE was induced by immunization with a pathogenic anti-DNA idiotype lead to the investigation of the role of IL-2 in experimental SLE. In addition, the synthetic immunomodulating substance, AS101, which mainly affects IL-2 production, enabled this problem to be studied both *in vitro* and *in vivo*.

We found that splenocytes derived from mice with experimentally induced SLE have a decreased ability to produce IL-2. This parallels the behaviour of mice with a strong genetic tendency to develop autoimmune disorders which develop SLE spontaneously (Altman *et al.*, 1981; Bocchieri *et al.*, 1984). The decreased ability of splenocytes to secrete IL-2 in association with increased production of autoantibodies by the mice is in accordance with the data reported in the literature (Blaese, Greyson & Steinberg, 1980; Bocchieri *et al.*, 1984; Huang You-Peng *et al.*, 1988). Similarly, the elevated levels of Tac antigen on the lymphocytes of our experimental SLE model concord with the established pattern of T cell activation known to take place in SLE (Huang You-Peng *et al.*, 1988).

From our study employing the immunomodulator AS101 in the mice it was clearly shown that the decreased secretion of IL-2 is the result and not the cause of SLE in mice. Although IL-2 production and Tac antigen expression in the treated mice as well as the untreated mice (*in vitro*) were restored to normal levels by AS101, the serological parameters and the clinical course of the disease remained unaffected. We therefore believe that the low IL-2 production in SLE is most probably connected with and secondary to other immunological processes.

The results of Alarcon-Varela *et al.* (1989) studying the *in vitro* effect of AS101 on peripheral blood lymphocytes of SLE patients support this contention. In view of this the authors addressed the question whether SLE patients should be treated with AS101 or with exogenous IL-2. Although it is difficult to project from the available studies on mice with SLE on to humans, we feel that the results of our *in vitro* experiments indicate that a much larger body of relevant data is warranted before the unqualified use of exogenous IL-2 for treating SLE patients can be recommended.

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