Prevalence of Autoantibodies to Various Tissue Antigens Before and During S2 – Complex Immunotherapy in Head and Neck Cancer Patients

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ABSTRACT :

BACKGROUND:

A total of 63 terminal untreatable stage IV head and neck cancer patients were investigated for clinical responses and presence of autoantibodies to various tissue antigens before and during S2- complex immunotherapy.

METHODS:

S2 –complex is a new low molecular weight biological response modifier (BRM) with a potant immunostimulating and anti tumor activities.

RESULTS:

Autoantibodies detected at pretreatment period were those directed towards the following antigens : nuclear, thyroid microsomal, epithelial cells, gastric parietal cells, smooth muscles, peripheral leukocytes, T-lymphocytes, B-lymphocytes, monocytes, thymus reticular epithelial cells and Hassall's corpuscles. Beside, autoantibodies with specificities to glomerular basement membrane and vascular endothelial cells were present at low incidence. Short term use of S2- complex induced a transient increase of the following autoantibodies: nuclear, thyroid microsomal, epithelial, parietal cells, smooth muscle, thymus reticuloepithelial cells, Hassal's corpuscles, thymocytes, peripheral blood leukocytes, T, B-lymphocytes, monocytes, as well as kidney glomerular basement membrane and vasculr endothelial cells.

DISCUSSION:

 In the later follow up period i.e. 2-6 months most of these autoantibodies responses returned to normal healthy control levels. Moreover, two exceptions were demonstrated which were the incidences of the antiglomerular basement membrane and vascular endothelial antibodies which remianed higher than the pretreatment frequencies. In addition, autoantibodies specific to mitochondria , thyroglobulin and red blood cells were only occasionally seen in our head and neck cancer patients both before and during S2- complex therapy.

KEY WARDS: Head and neck, Cancer, Autoantibodies.

INTRODUCTION:

Host immune response may play an important role in the origin and progression of head and neck cancer. Studies in the early 1970 revealed a depressed cell mediated immune response to cutaneaous antigenic stimulus of 2, 4 dinitrochlorobenzen (DNCB) skin testing (26). Various autoantibodies have been identified in the sera of patients with epithelial and hematological malignancies (1,2). Local recurrences and metastatic spread occurred more often among patients with autoantibodies (3). Another physiologic condition associated with increased titers of autoantibodies was aging (4,5).

Cancers are more prevalent in the elderly than in the younger individuals.Treatment of head and neck cancer is surgery, radiotherapy, chemotherapy and immunotherapy. These methods either used alone or in combination depending on the type, site, stage of tumor, patients age and general health. Immune therapy is a new type of cancer treatment that can boost or restore the body's immune system and act as an adjuvant after and / or with other three modalities of treatment(27). This can be achived by using immune adjuvants like levamisole, IL-2 and interferons.

S2-complex (Synthetic-2)is one of a new immune therapy used in this study. It is a low molecular weight synthetic organometalic complex (Iraqi classification No.6, International classification No.61K). It is submitted to the insurance of innocence of invention No.2836 in 15/1/1992.

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It is used in the treatment of advanced stages (stage III and stage IV) of HNC after surgery and / or radiotherapy or chemotherapy in the oncology unit. It had been found that immune therapy lead to production of auto antibodies in the patient serum like treatments with interferons lead to auto immune thyroiditis due to polyclonal activation so in this study, we try to demonstrate the incidence of various autoantibodies to different tissue antigens (Ags) in advanced head and neck cancer (HNC) patients stage IV before and during 6 months (ms.) of S2- complex immunotherapy to evaluate the effect of this immunotheraputic agent in exacerbation of auto immune responses.

PATIENTS & METHODS :

1. Patients group (treated with S2-complex):
Sixty three patients with advanced head and neck squamous cell carcinoma (HNSCC) , most of them failed the conventional forms of therapy (surgery, radiotherapy, chemotherapy) and refered to Oncology Unit in University Hospital of Iraqi Medical College o from year 1992 to 1994 for immunotherapy with S2-complex (0.1-0.5 mg/ kg body weight) for five consecutive days and then once at weekly interval for 6 months. Their aged ranged (13-79 ys.) Male to female ratio was 51/12. Most of them were heavy smokers. They had carcinoma of different sites in the head and neck area (larynx, hypopharaynx, parotid and maxillary sinus ..etc.).

2. Patients group without treatment:
70 patients with HNC. Sera were obtained from 30 patients with carcinoma of the larynx, 25 with carcinoma of hypopharaynx and nasopharaynx and the rest from other sites. Their age's ranged from 14-65ys., medianage was 50 ys.

3. Control group:
Consisted from twenty healthy individuals. Their age ranged (23-73ys.). All of them were in good general conditions, not smokers and did not take any medication. Sera of both groups were separated from the blood and used for detecting the presence of autoantibodies against different tissue antigens using indirect immunofluorescence method (6).

RESULTS:

The first autoantibody which had been detected in our study was antinuclear antibody (ANA) table -1- was detected in 65.07 % of head and neck cancer patients. S2- complex induced transient increase in this autoantibody then decrease to 40 %. The pattern of reaction was speckled in most of reactions. The predominant isotype was IgG and the titer was more than 1:20. the regression index increase early after treatment then decrease after 6ms. Of treatment. The same condition was noticed with other autoantibodies like antimicrosomal antibodies table-2-. There was a transient increase in the level of autoAbs then decrease after long period of follow up. The titer was also IgG type and the titer was 1:10. regarding antithyroglobulin Abs, It occurred only before treatment and after one mounth of treatment. Other autoAb was the antiepithelial antibodies (table-3-) also showed a transient increase in these autoantibodies and their titer mostly of 1:10 and also increase in minority of cases reaching 1:640. The isotype of these autoantibodies is of mixed types (IgM, IgG, IgA). In case of antiparietal cell antibodies (table-4-), there was a progress decrease in antipariatal cell Abs reaching 6.6% after 6ms. And decrease in the regression index in all periods of follow-up. The titer in most periods is 1:10 and of IgG type while antismooth Ms. AutoAbs, there was a decrease in a slower rate and increase in the regression index. The titer was 1:10 and of IgG type. Regarding anti basement membrane antibodies and antiendothelial cells as shown in table 5 and antireticular antibodies (table-6-) demonstraed a transient increase in these autoantibodies and then decrease after long period of follow-up . The titer was 1:10. In case of antierythrocytes antibodies and antimitochonderial antibody, they were not detected in both control and head and neck cancer patients (table -7-). Other Ab was Anti Hassale's corpusels antibody , completely disappeare after 6ms. And anti thymocytes Abs detected in very small percentages (table-6-). Lastly antileukocytes, anti T- cells and B- cells in table -8- showed slight increase in autoantibodies titers and then decrease after six months of follow - up .

Table 1: Antinuclear antibodies,immunoglobulin isotypes and antibody titers in head neck cancer patients before and during S2-complex treatment and in healthy controls.

Individual	Positive Reaction No. %	**Regression index over those of treatment responses %	Titer	NO. Of Sera	%	Isotype > 1:40 No. %	Pattern Of Reaction no. %
Control N=20	2 10	--------------	1:10	2	100	---------	Speckled 2 100
Before N =63	41 65.07	-------------	1:10 1:20 1:40 1:80	35 4 1 1	85.3 9.7 2.4 2.4	IgG 1 50 Mix 1 50	Speckled 8 19.5 Rim 9 21.9 Mixed 24 58.5
After 2 Weeks N=51	31 60.7	6.7 *	1:10 1:20 1:40	27 2 2	87.09 6.2 6.2	IgG 1 50 IgG 1 50	Speckled 21 65.6 Diffuse 1 3.1 Mixed 10 31.2
1 m. n=45	33 73.3	12.6 *	1:10 1:20	30 3	90.9 9.09	------------	Speckled 24 72.7 Rim 2 6.06 Mixed 7 21.2
2 m. n=32	24 75	15.2 *	1:10 1:20	23 1	95.8 4.1	------------	Speckled 22 91.6 Mixed 2 8.3
3m. n=24	21 87.5	34.4 *	1:10 1:20	20 1	95.2 4.7	--------	Speckled 12 57.1 Rim 2 9.5 Mixed 7 33.3
4m n=22	19 86.3	32.6	1:10 1:20 1:40	15 3 1	78.9 15.7 5.2	IgG 1 100	Speckled 11 57.8 Mixed 8 42.1
5 m. n=15	12 80	22.9	1:10 1:20	10 2	83.3 16.6	-----------	Speckled 6 50 Rim 3 25 Mixed 3 25
6m. n=15	6 40	38.5	1:10 1:40	5 1	83.3 16.6	gG 1 100	peckled 3 50 rim 2 33.3 mixed 1 16.6

*   increase,   decrease ▼   ** Regression index % = 1- $\dfrac{\text{Regression \% after treatment}}{\text{Regression \% before treatment}}$ x 100

Table 2: Antimicrosomal, antithyroglobulin antibodies and immunoglobulin isoytpes in head and neck cancer patients before and during S2 complex treatment and in healthy controls.

1ndividual	Anti Micro somal Abs +ve Reac Tion No %	Regre Ssion index %	Titer	no.	%	% iso type > 1:40	No %	Anti Thyro Globu Lin Ab +ve reac tion No.%	Titer	no.	%	% iso type > 1:40
Contr Ol N=20	3 15 (1)	--	1:10	3	100	--	--	--	--	--	--	--
Before N=63	41 65	--	1:10 1:20	33 7	80.4 17.07	IgG	1 100	--	--	--	--	--

Individual	No/%	Index	Titer	no	%			no/%	Titer			
	(1)		1:40	1	2.4							
After N=51	45 88	35.5	1:10 1:20	42 3	89.3 6.6	--	--	1 1.9	1:20 1:100	--	--	--
1m n=45	27 60	7.7 ↓	1:10 1:20 1:40	25 1 1	92.5 3.7 3.7	IgG	1 100	--	---	--	--	--
2ms n=32	22 68	5.5	1:10	22	100	--	--	1 3.1	1:10 1:100	--	--	--
3ms n=24	19 79	21.5	1:10 1:20	18 1	94.7 5.2	--	--	--	--	--	--	--
4ms n=22	15 68	4.6	1:10	15	100	--	--	--	--	--	--	--
5ms n=15	10 66	2.3	1:10	10	100	--	--	--	--	--	--	--
6ms n=15	5 33	48.8	1:10	5	100	--	--	--	--	--	--	--

↑ Increase   ↓ decrease   (1) p<0.005

Table 3: Ant epithelial antibodies and immunoglobulin isotypes in head and neck cancer patients before and during S2 complex treatment and in healthy controls.

1ndividual	+ve ReacTion No.	+ve ReacTion %	Regression index %	Titer	no.	%	Iso Type >1:40	no.	%
Control N=20	---	---	-----	-----	-----	-----	----	----	-----
Before N=63	30 *(4)	47.6	-----	1:10 1:20 1:40 1:80 1:640	19 6 1 2 2	63.3 20 3.3 6.6 6.6	IgG mix	4 1	80 20
After N=51	24	47.05	1.1 ↓	1:10 1:20 1:80 1:160	20 1 2 1	76.9 4.1 3.9 3.8	IgG mix	2 1	66.6 33.3
1m n=45	31	68.8	44.5 ↑	1:10 1:20 1:40 1:80	23 6 1 1	74.1 19.3 3.2 3.2	IgG	2	100
2ms n=32	21	65.6	37.8 ↑	1:10 1:20 1:40 1:80	15 1 2 3	71.4 4.7 9.5 14.2	IgG mix	4 1	80 20
3ms n=24	22 *(1,2,3,4)	91.6	92.4 ↑	1:10 1:20 1:40 1:80	13 6 2 1	59.09 27.2 9.09 4.5	IgG mix	2 1	66.6 33.3
4ms n=22	16 *(1)	72.7	52.7 ↑	1:10 1:20 1:40	11 4 1	68.7 25 6.2	IgG	1	100
5ms n=15	9 *(2)	60	26.05 ↑	1:10 1:20 1:160	6 2 1	66.6 22.2 11.1	IgG	1	100

| 6ms n=15 | 8 *(3) | 53.3 | 11.9 ↑ | 1:10 1:20 1:80 | 6 1 1 | 75 12.5 12.5 | IgG | 1 | 100 |

*(1): not significant,   (2): P<0.02,   (3): P<0.01,   (4):P>0.001

Table4: Antiparietal cell antibodies and anti smooth muscle antibodies and immunoglobulin isotypes in head and neck cancer patients before and during S2 – complex treatment and in healthy countrol.

1ndividual	Anti Parietal Abs No.	Anti Parietal Abs %	Regre Ssion index %	Titer	No.	%	Isotype >1:40 No.	Isotype >1:40 %
ControOl N=20	------	-------	-------	-------	--------	-------	--------	-------
Before N=63	12	19.4	------	1:10 1:20 1:40	9 1 2	75 8.3 16.6	IgG 2	100
After N=51	5	9.8	48.5 ↓	1:10 1:20	4 1	80 20	-------	------
1m n=45	5	11.1	41.7 ↓	1:10	5	100	--------	------
2ms n=32	-----	0	---- ↓	------	------	-----	-----	-----
3ms n=24	3	12.5	43.3 ↑	1:10	3	100	--------	------
4ms n=22	2	9.09	52.2 ↑	1:10 1:40	1 1	50 50	IgG 1	100
5ms n=15	3	20	5.04	1:10	3	100	------	--------
6ms n=15	1	6.6	65.3	1:10	1	100	-------	-----

1ndividual	Anti Smooth Abs No.	Anti Smooth Abs %	Regre Ssion index %	Titer	No.	%	Isotype >1:40 No.	Isotype >1:40 %
ControOl N=20	------	-------	-------	-------	--------	-------	--------	-------
Before N=63	15	23.8 (1)	------	1:10 1:40 1:60	11 3 1	73.3 20 6.6	IgG 4	100
After N=51	26	50.9	113.8 ↑	1:10	26	100	-------	-------
1m n=45	26	57.7	142.4 ↑	1:10	25	96.1	IgG 1	100
2ms n=32	11	34.3	44.1 ↑	1:10	11	100	----------	----------
3ms n=24	12	50	110.08 ↑	1:10	12	100	------------	---------
4ms n=22	12	54.5	7.07 ↑	1:10 1:20 1:40	10 10 1	83.3 8.3 8.3	IgG 1	10

| 5ms n=15 | 9 | 60 | 152.1 ↑ | 1:10 | 9 | 100 | ------------ | ---------- |
| 6ms n=15 | 5 | 33.3 | 39.9↑ | 1:10 | 5 | 100 | ------------ | ------------ |

(1) not significant

Table 5: Antibasement membrane , antiendothelial and antimitochondrial antibodies in head and neck cancer Patients before and during S2- complex and in healthy controls.

1ndividual	Anti Base Ment Membrane Abs+ve Reaction No. %	Regre Ssion index %	Titer	no.	%	Anti Endo Thelial Ab +ve reaction No. %	Regre Ssion index %	Titer	no.	%	Anti Mito Chon drial Abs +ve Reaction No. %
Contr Ol N=20	--	--	--	--	--	--	--	--	--	--	--
Before N=63	1 3.1 (1)	--	1:10	2	100	3 4.7 (4) (2)	--	1:10	3	100	--
After N=51	13 25.4 (1)	719.3 ↑	1:10	13	100	11 21.5 (3) (2)	357.4	1:10	11	100	--
1m n=45	14 31	903.2 ↑	1:10	14	100	3 6.6 (3)	40.4 ↑	1:10	3	100	--
2ms n=32	5 15.6	403.2 ↑	1:10	5	100	5 15.6	231.9 ↑	1:10	5	100	--
3ms n=24	8 33.3	974.1 ↑	1:10	8	100	5 20.8	342.5 ↑	1:10	5	100	--
4ms n=22	7 31.8	925.8 ↑	1:10	7	100	3 13.6	189.3 ↑	1:10	3	100	--
5ms n=15	2 13.3	329.03 ↑	1:10	2	100	3 20	325.5 ↑	1:10	3	100	--
6ms n=15	3 20	545.1 ↑	1:10	3	100	4 26.6	465.9 ↑	1:10	4	100	--

(1) : $p<0.001$,   (4) (2) : $p<0.01$,   (3) : $p<0.05$

Table6: Antireticular, anti Hassall's corpuscles and anti thymocytes antibodies in head and neck cancer patients before and during S 2 –complex treatment and in healthy controls.

1ndividual	Anti Reticular + reaction No.	Anti Reticular + reaction %	Regress Ion Index %	Anti Hassal's Corpus -cles Abs + Reaction No.	Anti Hassal's Corpus -cles Abs + Reaction %	Regress Ion Index %	Anti Thymo- Cyt Abs + Reaction No.	Anti Thymo- Cyt Abs + Reaction %
Contr Ol N=20	--------	-------	--------	--------	--------	--------	--------	-------
Before N=63	47	74.6	-------	15	23.8	------	-------	------
After N=51	34	66.6 (1)	10.7 ↓	23	45.09 (2)	89.4 ↑	8	15.6
1m n=45	31	68.8	7.7 ↓	24 (2)	53.3	123.9 ↑	2	4.4
2ms n=32	20	62.5	16.3 ↓	5	15.6	34.4 ↓	1	3.1

3ms n=24	13	54.1	27.4	8	33.3	39.9	2	8.3
4ms n=22	10	45.4	39.0	1	4.5	81.09	1	4.5
5ms n=15	4	26.6	64.3	----	-----	0	1	6.6
6ms n=15	1	6.6 (1)	91.1	-------	-----	0	2	13.3

(1): P<0.005   (2): not significant

Table7: Antierythrocytea antibodies in head and neck camcer patients before and during S2-complex treatment and in healthy controls.

1ndividu	+ reaction No.	+ reaction %
Control N=20	-------------	---------------------
Before N=63	---------------	-----------------------
-After N=51	---------------	-----------------------
1m n=45	1	2.2
2ms n=32	--------------	---------------------
3ms n=24	1	4.1
4ms n=22	----------------	-----------------------
5ms n=15	----------------	-------------------------
6ms n=15	-----------------	-------------------------

Table8: The mean (pluse, minuse -,+) standered error mean (SEM) of anti leukocytes, monocytes, T and B cells antibodies in head and neck cancer patients before and during S2-complex treatment and in healthy controls.

Tests done	Control No.=20	Before No.=63	After 2 weeks No.=51	1m. No.=45	2Ms. N0.=32	3Ms. No.=42	4Ms. No.= 22	5Ms. No.=15	6Ms. No.=15
Positive leukocytes	2+0.1-	129-+16.06	71-+12.8	47-+9.08	12-+6.11	6-+1.34	3-+1.07	2-+.07	37-+19.6
p-value	--------	1	1	---------	---------	---------	--------	----------	----------
% increase or decrease 0ver before treatment	------	--------	-44.9	-63.5	-90.6	-95.3	-97.6	-98.4	-71.3
Positive T cells	2-+.-0.5	15-+4.3	26-+6.1	31-+5.6	4-+0.7	2-+0.3	2-+0.4	2-+0.5	3-+0.5
P value	2	2	--------	--------	-------	---------	---------	---------	---------
% increase or decrease 0ver before treatment	---------	---------	+73.3	+106.6	-73.3	-86.6	-86.6	-86.6	-80
Positive B cells	3-+0.09	22-+4.7	21-+4.9	28-+6.9	8-+5.5	9-+7.3	2-+0.1	2-+0.2	6-+3.9
P value	3	3	--------	-------	----------	---------	----------	---------	--------
% increase or decrease 0ver before treatment	--------	---------	+4.5	+27.2	-63.6	-59.09	-90.9	-90.9	-72.7
Positive monocytes	5-+1.2	45-+6.01	52-+7.2	39-+6.6	72-+12.7	33-+7.4	24-+7.8	20-+6.7	33-+10

P value	4	4	----------	---------	----------	----------	---------	-----------	----------
% increase or decrease 0ver before treatment	---------	--------	+15.5	-13.3	+60	-26.6	-46.6	-55.5	-26.6

(4,3): P>0.001   (1):P<0.02,   (2):P<0.005
- :decrease,   +:increase

Table 9: Incidence of autoantibodies in head and neck cancer patients with or without recurrences and without S2-complex immunotherapy.

Autoantibodies	Patients with recurrence No.=55		Patients free from recurrence No.=15		Control No.= 20	
	No.	%	No.	%	No.	%
Antinuclear Abs	30 P=0.005	54.5	2 N.S.	13.3	1	5
Antismooth muscle Abs	20 P=0.005	40	2 N.S.	13.3	--	--
Antiglomerular Abs	6 N.S.	10.9	1 N.S.	6.6	--	---
Antimitochonderial Abs	---	---	---	--	--	----

DISCUSSION:

The incidence of autoantibodies in head and neck cancer (HNC) patients is significantly higher than in the control group. Our results were in agreement with other investigators (7,8). The autoantibodies in sera of patients directed against: nuclear, thyroid microsomal, epithelial cells, gastric parietal cells, smooth muscles, leukocytes, T cells, B cells, monocytes, thymus reticular tissues and Hassall's courpuscles. Besides, antibodies (Ab) at low incidence towards glomerular basement membrane and vascular endothelial tissues were also detected. The concept that autoimmune abnormalities may facilitate tumor growth are present in animal model(9). In our study the participation of autoimmune status in the immune alterations in patients with HNC had not been previously suggested. The presence of these autoAbs in sera of HNC confirmed the previous finding that cytotoxic drugs, radiotherapy, surgery, alone or in combination induced cellular destruction leading to release and denaturation of self antigens (Ag)e.g. DNA (10). This medication might be involved in triggering the immune response to self Ags. The presence of high level of antinuclear Abs in agreement with other results (11). High incidence of antimicrosomal Abs in our patients are in agreement with other results in breast cancer after radiotherapy or interferone therapy (12). Antiparietal cells Abs. Were detected for the first time in HNC patients. Previous reports showed no remarkable differences in patients with breast cancer and contro group(13). In case of antismooth muscle Abs which present in HNC patients may be due to change in the malignant cell membrane (7). The other auto Ab which was detected in our study is antiepithelial autoAbs It adds to the list of malignancies (skin, thymus, prostate, bladder and chronic lymphocytic leukemia). This is due to a common antigenic determinants on malignant cells that might stimulate immune system to produce cross reactive Abs with both tumor and normal skin (14). In addition to that, there is no significant difference in the incidence of antimitochondrial and antithyroglobulinin HNC which is in agreement with other results in breast cancers (13). Anti red blood cells (RBC) Abs were not detected in HNC but only detected in ovarian tumor, bronchogenic carcinoma (15). The other autoAbs which were detected in small frequency were antiglomerular basement membrane and renal vascular endothelial Abs in HNC patients. In recent years, interest in the development of immunologic approaches to malignancies has increased and there is good evidence that the growth of renal cell carcinoma can be modulated by the host immune system using interleukin-2 and B7-1 gene modified tumor cell as vaccine in the treatment of this disease (20). Immune therapy is another method of treatment HNC in addition to other methods. It acts as adjuvant to other methods. In our study we used S2 –complex which is a low molecular weight, synthetic compound. It stimulates the immune system (16,17).S2-complex treatment inducing transient increase in the incidence of these

autoAbs. This is due to activation of local immunological reactions in the HNC area. This might be due to cross reaction with kidney tissues resulting in autoAbs stimulation. Our report document the occurrence of autoAbs to thymus compounds which may contribute in the HNC pathogeneses. There were also autoAbs reactive with peripheral leukocytes, T, B cells and monocytes in serum samples from advanced HNC patients treated by conventional modalities. These autoAbs were present in other diseases like systemic lupus erythematouses and rheumatoid arthritis (18). Other studies reported that antimitochondrial and glomerular autoAbs were formed as a consequence of hepatic damage of certain liver diseases (25). The most exciting observations in our study were the transient increase of various autoAbs after S2 –complex treatment which last in most cases between 2-8 weeks. Moreover, long term use of S2-complex resulted in inhibition of the various temporally stimulated autoAbs response which was pronounced after 6 months of S2-complex treatment. Our present data may seem to indicate that S2-complex probably may play a role in the positive control of lymphocytes infiltration and class II Ag expression in many tissues . We think that additional experiments and clinical studies were warranted to prove that S2-complex can induce class II Ags expression in head and neck as well as other tissues. The promotion of tumor by induction of autoAbs had been only reported in experimental models (19). Some autoAbs were examined for their presence in patients serum with HNC and without treatment as shown in table-9-. Patients with recurrence showed increased frequencies of these autoAbs while patients who were free from recurrence showed decreased in autoAbs level. These autoAbs were formed due to accelerated lysis either spontaneous or theraputically induced, these led to shed large quentities of related Ags. This led to formation spesific Abs that cross-react with normal tissue components and disequilibirium of the normal immunoregulatory balances (10). Interferon is one of immune modulator used in the treatment of many conditions as immune therapy . It had been reported that treatment with alpha interferon induced autoimmune lesion of thyroid in patients with chronic viral hepatitis (21) and dermatomyositis in patients with melanoma (22) . Treatment with alpha interferon also induced polyarthritis (seropositive rheumatoid arthritis) in patients with chronic myelogenous leukemia and hairy cell leukemia (23). In addition, treatment with beta interferon induced autoimmune

thyroiditis in patients with multiple sclerosis (24). In our study , S2-complex were not induced such autoimmune diseases as a result of induction of autoantibodies.

CONCLUSION:
S2 - complex as a new immune modulator did not induce a long term high titer of autoantibodies which might induce autoimmune diseases as a result of poly clonal activation .

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