Original Article

Polydimethylsiloxane: An effective immune adjuvant and slow-release cytokine medium for local cancer treatment

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Abstract

Background and Aim: Silicone oil or gel has well-defined chemotactic properties on monocytes and lymphocytes in vitro. It results in fibrotic reaction when spread into the human tissues either incidentally or purposely and can slowly release any physically-enclosed lyophilized compounds due to its viscosity. Our aim is to investigate whether polydimethylsiloxane could be considered as an effective medium in the local treatment of cancer.

Materials and Methods: Our study was conducted between January 2004 and December 2006 on 15 patients with various types of cancer. The criteria for selection included patients with locally-advanced tumor that was rapidly growing and life threatening and those who had poor quality of life and general wellbeing. The patients were already discharged from the cancer centre before joining the study, after they had already received their chemoradiation protocol. Once a week for one month, different areas of the tumor were injected with 0.25 ml of polydimethylsiloxane medical grade (viscosity: 350 centistokes at 30°C), mixed with 300,000 units of lyophilized human IL-2. Tumor biopsies were taken before the study was started and one week after the last injection for the histopathological analysis of the percentage of severe inflammatory reaction using an image analysis system. CT scans of the tumor were taken before the injection cycle was started and one week after the last injection in order to determine the percentage change in the size of the tumor. The quality of life and general wellbeing of the patients was assessed at the beginning of the study, and one week after the study was over by using the Karnofsky performance test.

Results: Our treatment was well tolerated by the patients. They had a significant improvement in their quality of life and general wellbeing ($p = 0.0005$). The prognosis of the patients before the beginning of the study ranged between 1 and 6 months, while their overall survival after treatment was between 2 and 12 months, with three patients still remaining alive. A significant decrease in the tumor size was observed at the end of the study in 12 patients ($p < 0.0001$). Such a decrease was associated with a significant increase in the percentage of the tumor containing a severe immune reaction ($p < 0.0001$). A significant correlation was found between the percentage reduction in tumor size and the percentage of tumor immune reaction ($r^2 = 0.968; p < 0.0001$).

Conclusion: Polydimethylsiloxane could be used as an effective cytokine medium in the local treatment of cancer. When injected inside the tumor, it is capable of creating and modulating an effective, slow and persistent antitumor immune response. Moreover, it is capable of improving the overall survival as well as the quality of life and general well being of the cancer patients.

Keywords: Cancer immunology, polydimethylsiloxane
Introduction

Naoum and colleagues published an interesting histological and immunohistochemical study on silicone fluid being used for soft tissue augmentation. The authors reported that at a viscosity of 350 centistokes and at a temperature of 25°C, such a fluid was capable of soliciting mesenchymal and immunocompetent cell responses. The study involved the injection of very low doses (0.05–0.07 ml) of silicone, followed by serial punch biopsies after 2 and 13 days, and 1, 2, 3, 4, and 12 months. Both a short-term perivascular lymphocytic infiltration as well as a delayed hypersensitivity reaction were found to be present. Subsequently, IgG–IgA deposits were detected around the vessel walls and were associated with a significant fibroblastic reaction.

The chemotactic properties of polydimethylsiloxane (silicone oil) on lymphocytes, monocytes, and macrophages and its viscosity that allows the trapping of some molecules in between the silicone chains, thereby releasing them at a very slow rate, might, in our opinion, be an ideal adjuvant of the local administration of cytokine in cancer treatment. This is especially true for head and neck cancers, where it is necessary to counteract the tumor expansion, which, otherwise, could lead to the impairment of vital functions. Moreover, this is equally important in certain organs or anatomical regions (such as the pancreas, liver or abdominal wall), where primary and/or secondary nonresectable cancers might be infiltrated with such a compound to limit their growth and metastasis.

Recently, De Stefani and colleagues reported a long-term follow-up of 201 patients affected by resectable ORL cancer. The patients were treated with perilymphatic IL-2 injection (5000 U) ten days before surgery, five days after surgery, and monthly thereafter for one year. The authors reported that the treated patients had a longer disease-free survival time, and a better overall survival as compared to the untreated patients. Further, other studies have reported positive results in patients whose tumor mass was injected with IL-2.

Materials and Methods

Informed consent and selection criteria
Our study was conducted between January 2004 and December 2006. It involved 15 patients (six males, and nine females) aged between 28 and 78 years [Table 1]. The study was approved by the human ethics committee at the University of Modena and Reggio Emilia, and conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). The study was clearly explained to the patients, and a signed informed consent was obtained stating that the patients agreed to voluntarily participate in the study and that they were free to withdraw from the study whenever they decide to do so. The patient selection criteria included the following:

1. Patients who have locally advanced and quickly growing cancer that is life threatening.
2. Patients who have already completed all the prescribed chemoradiation protocols and were already discharged from the cancer centre before joining the study.

Procedure

The patients were injected once a week for one month with 0.25 ml of polydimethylsiloxane medical grade (viscosity 350 centistokes at 30°C; Eurosilicone, APT, France). Polydimethylsiloxane was mixed with 300,000 units of lyophilized human recombinant IL-2 (Proleukin-Chiron) by strong and prolonged shaking at 37°C for 5 min. We chose IL-2 because of its reported safe and effective use at low doses in humans. The injection was performed under local anesthesia (1 ml 1% carbocaine + 1:100,000 Epinephrine injected with 21

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Table 1: Characteristics of the patients enrolled in the study

| Number of patients (N.) | Patient initials | Age | Sex | Diagnosis |
|------------------------|-----------------|-----|-----|-----------|
| 1                      | C.K.            | 28  | F   | Ethmoid cancer with skull and meningeal infiltration |
| 2                      | F.O.            | 68  | M   | Anaplastic thyroid cancer |
| 3                      | G.G.            | 42  | M   | Cancer of pyriform sinus with neck invasion |
| 4                      | Z.N.            | 74  | M   | Left maxillary sinus cancer, with orbit and nasal fossa infiltration. Pain and ocular globe extrusion by the tumor mass |
| 5                      | S.G.            | 72  | M   | Parotid cancer with multiple neck metastasis |
| 6                      | A.A.            | 62  | F   | Thyroid metastatic follicular cancer with a big local recurrence |
| 7                      | B.M.            | 65  | F   | Cancer of the tongue |
| 8                      | Z.G.            | 58  | M   | Cancer of parotid gland. Local relapse |
| 9                      | P.C.            | 51  | M   | Cancer of the larynx with left neck involvement |
| 10                     | F.R.            | 56  | F   | Pancreatic cancer with peritoneal involvement |
| 11                     | U.T.            | 52  | F   | Metastatic left neck mass from previous breast cancer |
| 12                     | M.M.H.          | 57  | F   | Pancreatic cancer |
| 13                     | P.T.            | 78  | F   | Bowel cancer with peritoneal involvement |
| 14                     | B.M.            | 45  | F   | Ovarian cancer with peritoneal involvement |
| 15                     | F.L.            | 40  | F   | Ovarian cancer with massive pelvic invasion |
Biopsies were taken from the tumor mass before the study was started and one week after the fourth injection. They were processed into paraffin blocks, and 4 µm sections were taken and examined by two independent pathologists for determining the percentage of the tumor containing a significant inflammatory reaction using an image analysis system (IAS). The occurrence of such a reaction was confirmed if bands of lymphocytes were present in the vicinity of the tumor and some of them infiltrated the actual tumor mass. This also included the presence of areas of dense fibrosis in the vicinity and within the tumor. Data obtained by the independent pathologists were then added up, and the average percentage was calculated. The inter-observer variability was very low (<0.03%) and estimation of the 95% confidence limits required a maximum of 15 randomly selected high-power fields (magnification: x400) to be analysed by each pathologist. The IAS consisted of an observer-interactive computerized image analysis (SAMBA microscopic image processor; Meylan, France), whose hardware and software have been described by Brugal and colleagues. This system is fitted with a standard Axioplan microscope with an automated stage (Carl Zeiss; Oberkochen, Germany) that allows a precise location of a particular field through XYZ axis plotting, a color video camera (Sony Corporation; Tokyo, Japan), an image analysis processor (Matrox; Montreal, QC, Canada), and a personal computer (Pentium 2, 166-MHZ processor; Intel; Santa Clara, CA).

CT scan imaging

CT scans of the tumors were performed one week after the study was over and were compared with the ones performed at the beginning of the study. CT scans were obtained and re-digitized using anatomy modeling software (Anatomy Modelling, Theraplan Plus). The tumors were evaluated and outlined on each image slice that contained a mass by consensus reached by two independent radiologists, both of whom were blinded to the study. The tumor volume was then calculated using a summation of areas technique with radiotherapy planning software (Theraplan Plus, version 3.18), taking into account the CT slice thickness.

Assessing the quality of life and general wellbeing of the patients

The quality of life and general wellbeing of the patients were objectively assessed at the beginning of the study and one week after the study was over by using the following standardized and validated Karnofsky performance scores:

- 0% – death.
- 10% – moribund, rapidly progressive fatal disease.
- 20% – very ill, urgently requiring admission, requires supportive measures or treatment.
- 40% – disabled, requires special care and help.
- 60% – requiring some help, can take care of most personal requirements.
- 80% – normal activity with some difficulty, some symptoms or signs.
- 70% – caring for self, not capable of normal activity or work.
- 90% – capable of normal activity, few symptoms or signs of disease.
- 100% – normal, no complaints, no signs of disease.

Statistical analysis

Statistical analysis was performed on the data obtained from the 15 patients using a statistical software package (SAS; SAS Institute; Cary, NC). The two-tailed student's t test was used to determine any significant difference between the Karnofsky scores before and after the treatment, between the size of the tumor on CT scan before and after the treatment, and between the percentage of tumor inflammatory reaction before and after the treatment. Results were calculated as mean ± SD, and a p-value < 0.05 was considered significant. The correlation coefficient (r²) was calculated using the Spearman method in order to determine any significant association between the reduction in tumor size and the tumor inflammatory reaction.

Results

The procedure was reported to be well tolerated by the patients, and the major side effects observed were fever (38-40°C) and mild to moderate pain, which were alleviated by the administration of tramadol and ketoprophen [Table 2]. In one patient with thyroid anaplastic cancer and cervical spine...
Table 2: Comparison of the changes taking place in the patients and their tumors before and after treatment

| N   | Percentage decrease in tumor size following treatment, as determined by CT scan (mm²) | Percentage of tumor immune reaction before treatment, as determined by IAS (µm²) | Percentage of tumor immune reaction after treatment, as determined by IAS (µm²) | Side effects accompanying treatment | Prognosis before treatment started (months) | Survival after treatment (months) | Performance Status (Karnofsky score) before treatment | Performance Status (Karnofsky score) after treatment | Cause of death |
|-----|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------|----------------------------------------|-------------------------------|------------------------------------------------|------------------------------------------------|----------------|
| 1   | 38                                                                                | 0                                                                              | 46                                                                                                      | Chills, and short-term fever        | 1                                      | 9                            | 30                                           | 100                                          | Cerebro-meningeal cancer |
| 2   | 30                                                                                | 0                                                                              | 42                                                                                                      | Neck pain requiring opioids in the last injection cycle; short-term fever. | 3                                      | 12                           | 70                                           | 100                                          | Metastasis to cervical spine and lungs |
| 3   | 35                                                                                | 2                                                                              | 40                                                                                                       | Short-term fever; pain at the end of injection cycle alleviated by administration of tramadol and ketoprophen. | 1                                      | 4                             | 80                                           | 100                                          | Sepsis               |
| 4   | 29                                                                                | 7                                                                              | 35                                                                                                      | Fever and chills; facial pain at the end of the injection cycle.         | 3                                      | 8                             | 30                                           | 80                                           | Hemorrhage |
| 5   | 20                                                                                | 0                                                                              | 30                                                                                                      | Mild fever, and late onset of moderate pain alleviated by administration of tramadol. | 1                                      | 6                             | 30                                           | 60                                           | Lung metastasis |
| 6   | 12                                                                                | 4                                                                              | 27                                                                                                      | Mild fever                        | 3                                      | 9                             | 60                                           | 90                                           | Acute pulmonary insufficiency due to lung metastasis |
| 7   | 0 (but, no increase in size)                                                      | 2                                                                              | 10                                                                                                      | Mild fever                        | 3                                      | Still alive                   | 60                                           | 100                                          | Liver metastasis, ascites, and pulmonary complications |
| 8   | 10                                                                                | 1                                                                              | 17                                                                                                      | Mild fever, and late onset of moderate pain alleviated by administration of tramadol. | 6                                      | 16                           | 60                                           | 90                                           | Liver insufficiency |
| 9   | 70                                                                                | 1                                                                              | 81                                                                                                      | Mild fever; none                  | 3                                      | Still alive                   | 20                                           | 100                                          | Cachexia, and heart failure |
| 10  | 39                                                                                | 2                                                                              | 50                                                                                                      | Mild fever; none                  | 1                                      | 2                             | 20                                           | 20                                           | Heart failure                                     |
| 11  | 25                                                                                | 2                                                                              | 36                                                                                                      | none                              | 1                                      | 6                             | 20                                           | 60                                           | Liver insufficiency |
| 12  | 0 (but, no increase in size)                                                      | 0                                                                              | 11                                                                                                      | none                              | 3                                      | 6                             | 40                                           | 80                                           | Cardiovascular insufficiency |
| 13  | 0 (but, no increase in size)                                                      | 0                                                                              | 14                                                                                                      | none                              | 1                                      | 2                             | 20                                           | 20                                           |                         |
| 14  | 22                                                                                | 1                                                                              | 38                                                                                                      | Mild fever; none                  | 6                                      | Still alive                   | 60                                           | 90                                           |                            |
| 15  | 39                                                                                | 1                                                                              | 44                                                                                                      | Mild fever; none                  | 1                                      | 8                             | 20                                           | 60                                           | Renal metastasis |

The mean reduction in tumor size was 0% at the beginning of the study, as compared to 24.6% ± 18.9 SD one week after the study was over (p < 0.0001). The mean percentage of the tumor displaying a severe immune reaction was 1.53 ± 1.88 SD at the beginning of the study, while it was 34.73 ± 18.28 SD one week after the study was over (p < 0.0001). The mean value of Karnofsky score was 41.3 ± 21.3 SD at the beginning of the study, while it was 76.7 ± 27.4 SD one week after the study was over (p = 0.0005).
infiltration, a significant increase in neck pain was observed during treatment, and this was relieved using morphine (30 mg/ daily).

Comparison of the Karnofsky scores revealed that the quality of life and general well being of the patients improved significantly at the end of study [Table 2]. The mean value of such score was 41.3 ± 21.3 SD at the beginning of the study, while it was 76.7 ± 27.4 SD at its end; \( p = 0.0005 \). This was associated with improved survival, whereby the prognosis of the patients before the beginning of the study ranged between 1 and 6 months, while their overall survival after treatment was between 2 and 12 months with three patients still remaining alive [Table 2, Figure 1].

Comparison of the CT scans of the patients’ tumor at the beginning of the study and at its end revealed that a significant decrease in tumor size was observed in 12 patients [Table 2]. Such a reduction reached 70% in one patient. In the remaining three patients, although there was no reduction in the tumor size, such tumors stopped growing completely. Accordingly, the mean reduction in tumor size observed in our study was 0% at the beginning of the study as compared to 24.6% ± 18.9 SD one week after the study was over; \( p < 0.0001 \).

The abovementioned CT scan results were further confirmed by the results obtained from the histopathological analysis of the multiple biopsies taken from the tumor at the beginning of the study and one week after its end using an IAS. Examination of the tumor site following treatment revealed a rapid or delayed accumulation of fluid inside the tumor, which was associated with an intense inflammatory fibrotic reaction enveloping and penetrating the tumor mass. The results obtained by the two independent pathologists who performed the analysis revealed that the mean percentage of the tumor displaying a severe immune reaction was 1.53 ± 1.88 SD at the beginning of the study, while the mean percentage was 34.73 ± 18.28 SD one week after the study was over; \( p < 0.0001 \) [Table 2]. In the three patients whose tumor did not decrease in size, but had also stopped growing completely, the pathologists observed the presence of a dense rim of fibrotic tissue encircling the tumor. A significant correlation \((r^2 = 0.968; \ p < 0.0001)\) was found between the percentage reduction in tumor size and the percentage of tumor immune reaction one week after the study was over [Figure 2].

**Discussion**

There are several risks associated with the continuous growth of the cancer mass, such as compression and infiltration of vital structures, which often result in functional impairment in the patients. Our results showed that multiple injections with silicone oil that was mixed with IL-2 in different regions of the tumor resulted in a significant reduction in the tumor size in most of the cases, while it resulted in confining the tumor in others. This was achieved by acute and chronic recruitment of lymphocytes and monocytes to the tumor, thereby resulting in inflammation, edema, and fibrosis of the injected areas and
their surroundings. This ability of the silicone oil to cause both acute and chronic recruitment of lymphocytes and monocytes could be explained by its ability to slowly release IL-2 due to the hydrophobic surface of silicone that will cause the denaturing of proteins absorbed into it. In our study, in addition to be able to successfully recruit monocytes to the injections sites, such monocytes were also able to react to the silicone oil by increasing their cytokine production.

The hypothesis to mix medical-grade silicone oil with cytokines in order to induce both chemotaxis and slow cytokine release, thereby improving the biologic effect of the cytokine is quite intriguing. Some experimental studies have investigated the effect of silicone itself or silicone mixed with complete or incomplete Freund's adjuvant. Naim and colleagues investigated the induction of hypergammaglobulinemia and macrophage activation by silicone oil in female ASW mice, showing that intraperitoneal injection of 0.5 ml of this oil resulted in an increase in the total serum IgM and IgG. Furthermore, the peritoneal macrophages of these mice produced higher levels of IL-1β, IL-6, and tumor necrosis factor alpha (TNF-α) as compared with the control. Similar findings were reported in another study where human monocytes were challenged in vitro with silicone oil as compared with the tissue culture polystyrene. On the other hand, Chang and co-workers reported that injecting Lewis rat model intraperitoneally with silicone in conjuction with heat-killed Mycobacterium tuberculosis and tumor cells (EL4) failed to enhance the immune response directed against the EL4 cells in the peritoneal cavity. Picha and Goldstein evaluated both the adjuvant and antigenic properties of low molecular weight silicone and fumed silica, which were variously mixed with complete and incomplete Freund's adjuvant. In this experimental model that was followed up for 120 days, the silicone oil was not an effective adjuvant and the fumed silica was not an effective antigen. Nevertheless, a delayed immune reaction was observed.

In our study, we used low dosages of highly pure medical-grade silicone oil that was moderately viscous so that it does not engulf the immunocompetent cells. The silicone used had a glucose-linked polydimethylpolysiloxane polymer chain. It has been argued that polydimethylsiloxane could be capable of producing an immune response in guinea pigs, as demonstrated by the macrophage-inhibiting technique. Heggars and colleagues hypothesized that macrophages may convert silicone to silica by means of NADP-dependent pathway, which results in the production of superoxide radicals. The latter may attack the silicone methyl bond of siloxane, thus releasing silica inorganic ion. Smith and colleagues detected silicone molecules in the Golgi apparatus, rough endoplasmic reticulum and at both ends of the lymphocyte-macrophage bridges.

These findings support the hypothesis about the intracellular involvement of this compound as well as about its interactive role between lymphocytes and macrophages. Wedler, and Lavey and Pearl attempted to characterize this silicone-protein interaction, suggesting the hypothesis of an induction hapten-like molecular complex.

From the experimental results and hypotheses reported earlier, it seems that there could be a good rationale behind endorsing the usage of silicone oil as a locally injected cytokine amplifier within the tumor. According to this and on the basis of the results obtained in this study, one could argue that a better exposure of the cytokine molecules on the silicone oil framework, as well as their slow bioavailability in the tumor microenvironment, might enhance the immunological response against the tumor. Moreover, silicone itself might allow to effectively expose the tumor antigens so that the latter could become better targets for the killer lymphocytes and macrophages. Silicone oil is also capable of eliciting a humoral-type immune response, as demonstrated by the increase in the blood titers of certain immunoglobulins.

TNF-α is a cytokine often released by macrophages during the chemotactic response, and it has a strong antitumor effect. Accordingly, we will be mixing this cytokine with silicone oil and injecting the mixture into different tumor areas in further studies that will be conducted at our laboratory. Rathjen and Aston recently patented designing ligands that could bind to human TNF-α resulting in modifications of its biological activity. Such modifications included inhibition of the TNF-α-induced endothelial procoagulant activity, enhancement of fibrin deposition inside the tumor and enhancement of the cytotoxicity and the receptor binding activity of the TNF-α on the tumor cells. Similarly, Kettling and co-workers recently patented their study that focused on specific proteases, fragments, and derivatives that could affect the TNF-α binding ability.

**Conclusion**

Our study demonstrated the effectiveness of the use of silicone oil as a slow cytokine-release adjuvant in reducing tumor size, confining local tumor growth and improving survival and general wellbeing of the cancer patients. This technique, according to our protocol, is relatively painless and safe. It is capable of significantly eliciting a rapid and delayed swelling engulfing and penetrating the tumor, caused by heavy lymphocytic and mononucy infiltration of the tumor as well as by intra and extra tumor edema and fibrosis. Further laboratory investigations are urgently required for the enhanced definition of the mechanism(s) of action of the injected mixture in our study and to potentially use such mechanism(s) for inducing effective...
tumor regression. In addition to expanding on the current study with IL-2, we propose that other biological compounds such as TNF-α could be dispersed in polydimethylsiloxane as a single drug or as a sequential multidrug schedule for local tumor immunotherapy.

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References

1. Naoum C, Dasiou-Plakida D, Pantelidaki K, Dara C, Chrisanthakis D, Perissios A. A histological and immunohistochemical study of medical-grade fluid silicone. Dermatol Surg 1998;24:867-70.
2. De Stefani A, Forni G, Ragona R, Cavallo G, Bussi M, Usai A, et al. Improved survival with perilymphatic interleukin 2 in patients with resectable squamous cell carcinoma of the oral cavity and oropharynx. Cancer 2002;95:90-7.
3. Pizza G, Severini G, Mennti D, De Vinci C, Corrado F. Tumour regression after intralesional injection of interleukin 2 (IL-2) in bladder cancer: Preliminary report. Int J Cancer 1999;84:359-67.
4. Den Otter W, Balemans L, Battersmann JJ, Bemsen MR, Cadee JA, Dobrowolski Z, et al. Local low-dose IL-2 therapy. Hepatogastroenterology 1999;46:1280-6.
5. Blankenstein T. The role of inflammation in tumour growth and tumour suppression. In: Cancer and Inflammation. In: Chadwick D, Goode J, editors. Chichester UK: John Wiley and Sons Ltd; 2004. p. 205-14.
6. Brugal G, Garbay C, Giroud F, Adelh D. A double scanning microphotometer for image analysis: Hardware, software and biomedical applications. J Histochem Cytochem 1979;27:144-52.
7. Mukherji SK, O'Brien SM, Gerstle RJ, Weissler M, Shockley W, Castillo M. Tumor volume: An independent predictor of outcome for laryngeal cancer. J Comput Assist Tomogr 1999;23:50-4.
8. Bussels B, Mes A, Flamen P, Lambin P, Evrken K, Hermans R, et al. Dose-response relationships within the parotid gland after radiotherapy for head and neck cancer. Radiother Oncol 2004;73:297-306.
9. Hermans R, Pameijer FA, Mancuso AA, Parsons JT, Mendenhall WM. Laryngeal or hypopharyngeal squamous cell carcinoma: Can follow-up CT after definitive radiation therapy be used to detect local failure earlier than clinical examination alone? Radiology 2000;214:683-7.
10. Hermans R, Bouillon R, Laara K, D'elae PR, Foor BD, Marchal G, et al. Estimation of tumour volume by spiral computed tomography. Eur Radiol 1997;7:214-6.
11. Kereftsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Meldred CM, editor. Evaluation of chemotherapeutic agents. Columbia Univ Press; 1949. p. 196.
12. Sengers T, L'Imoli JP, Baldwin CM Jr, Lau DR. Human adjuvant disease, possible autoimmune disease after silicone implantation: A review of the literature, case studies, and speculation for the future. Plast Reconstr Surg 1986;78:104-14.
13. Chang YH. Adjuvanticity and arthritogenicity of silicone. Plast Reconstr Surg 1993;92:469-73.
14. Picha GJ, Goldstein JA. Investigation of silicone oil and fumed silica in an adjuvant animal model. Plast Reconstr Surg 1997;100:643-52.
15. Naim JO, Ippolito KM, van Oss CJ. Adjuvancy effect of different types of silicone gel. J Biomed Mater Res 1997;37:534-8.
16. Naim JO, Satoh M, Buehner NA, Ippolito KM, Yoshida H, Nasu D, et al. Induction of hypergammaglobulinemia and macrophage activation by silicone gels and oils in female ASW mice. Clin Diagn Lab Immunol 2000;7:366-70.
17. Naim JO, van Oss CJ, Ippolito KM. In vitro activation of human monocytes by silicones. Colloids Surf B Biointerfaces 1998;11:79-86.
18. Smith DJ Jr, Szaz JA, Crisman J, Niu XT, Robson MC, Heggers JP. Immunogenic potential of cellular implants. J Surg Res 1990;48:13-20.
19. Heggers JP, Kassovsky N, Parsons RW, Robson MC, Pelley RP, Rain E. Biocompatibility of silicone implants. Ann Plast Surg 1983;11:13-45.
20. Wedler FC. Analysis of biomaterials deposited on soft contact lenses. J Biomed Mater Res 1997;25:325-35.
21. Lavey EB, Pearl RM. Inflammation in a silicone-induced granuloma caused by a tuberculosis skin test. Ann Plast Surg 1981;7:152-4.
22. Rathjen DA, Aston R. Patent number: US Patent US20070280932.
23. Ketting U, Koltermann A, Haupts U, Barbach M, Tebbe J, Votsmeier C, et al. Patent number. European Patent EP1847600.