IntAAC
International Anti Aging Conference 2.0

&

4th NATIONAL CONGRESS OF
PERDAWERI

SYMPOSIUM

Ago Harlim

SPEAKER

IntAAC 2.0
International Anti Aging Conference
"Tantangan dan Peluang Anti Aging Medicine Pada Era MEA"
Jakarta, 14 - 16 July 2017
PERDAWERI
Sekretariat : Jl. Dr. Samratulangi No. 29 Jakarta Pusat (10350) Indonesia,
Telp/Fax : 021-31937910 , 3155260. email: intaac2017@gmail.com

Jakarta, 16 Juni 2017

No. : 027/InTAAC/F.3/06/2017
Lamp :
Hal : **Permohonan Kesediaan sebagai Pembicara**

Kepada Yth.
DR. Dr. Ago Harlim, MARS, SpKK
di
Tempat

Dengan hormat,

International Anti Aging Conference (InTAAC) merupakan satu agenda kegiatan tahunan yang diselenggarakan oleh Perhimpunan Dokter Anti Penuaan, *Wellness*, Estetik & *Regeneratif* Indonesia (Perdaweri). Tahun ini merupakan tahun ke-2 pelaksanaan InTAAC 2017, yang bertemakan "***Challenges and Opportunities of Antiaging Medicine in AEC Era***", dan akan diselenggarakan pada tanggal 14 - 16 Juli 2017 di Hotel Sahid Jaya Jakarta.

Sehubungan dengan InTAAC ke-2, bersama ini kami mohon kesediaan sejawat menjadi pembicara dalam kegiatan yang akan dilaksanakan pada:

Hari/Tanggal	: Minggu, 16 Juli 2017 (Simposium)
Pukul	: 10.30-11.20 WIB
Topik 1 (20 menit)	: The Difference of Stemcell Product
Topik 2 (20 menit)	: Immunology Behind The Filler

Demikian kami sampaikan surat permohonan sebagai pembicara. Kiranya sejawat bersedia sebagai pembicara dalam kegiatan ini. Kami lampirkan formulir kesediaan, dan lembar kesediaan dapat dikirimkan melalui email intaac2017@gmail.com sebelum 28 Juni 2017.

Hormat kami,

Panitia InTAAC 2017

Dr. Putro Setyobudyo Muhammad
Ketua Panitia

Konfirmasi Kesediaan ke Sekretariat Panitia:
Ibu Iyek (08561938327) atau Evi (08567907503)

LEMBAR KESEDIAAN

Yang bertanda tangan dibawah ini:

Nama : Dr. dr. Ago Harlim MARS, Sp.KK

Institusi : Fakultas Kedokteran Universitas Kristen Indonesia

Jabatan : Kepala Bagian Kulit & Kelamin

Email : agoharlim@yahoo.com

No Telp/HP : 0816854083

1. Bersedia/tidak bersedia menjadi Pembicara dalam kegiatan ilmiah ***International Anti Aging Conference (InTAAC)*** **Perdaweri** yang ke 2 tahun 2017.
2. Memberikan CV
3. Memberikan materi presentasi

Mohon surat kesediaan ini ditandatangani dan diemail ke intaac2017@gmail.com

Jakarta, 17 Juni 2017

(Dr. dr. Ago Harlim MARS, Sp.KK)

Konfirmasi Kesediaan ke Sekretariat Panitia:
Ibu Iyek (08561938327) atau Evi (08567907503)

IntAAC 2.0
International Anti Aging Conference
"Tantangan dan Peluang Anti Aging Medicine Pada Era MEA"
Jakarta, 14 - 16 July 2017

PERDAWERI

Sekretariat : Jl. Dr. Samratulangi No. 29 Jakarta Pusat (10350) Indonesia,
Telp/Fax : 021-31937910 , 3155260. email: intaac2017@gmail.com

Jakarta, 28 Juni 2017

No. : 053/InTAAC/F.3/06/2017
Lamp : Rundown Acara
Hal : **Permohonan Power Point dan Abstrak Materi Pembicara**

Kepada Yth.
DR. dr. Ago Harlim, MARS, SpKK
di
tempat

Dengan hormat,

Sehubungan dengan semakin dekatnya waktu pelaksanaan **International Anti Aging Conference - InTAAC ke-2**, bersama ini kami mohon kesediaan sejawat untuk dapat memberikan power point dan abstrak materi pembicara, yaitu dengan jadwal dan topik sebagai berikut:

Hari/Tanggal : Minggu, 16 Juli 2017

Tempat : Hotel Sahid Jaya, Jakarta

Waktu (Sesi) : 09.30 – 10.20 WIB (Simposium Sesi 6)

Topik 1 (20') : The Difference of Stemcell Products

Topik 2 (20') : Immunology Behind The Filler

Demikian kami sampaikan surat permohonan power point dan abstrak materi pembicara serta informasi update susunan acara terbaru. Kiranya sejawat bersedia mengirimkan materi tersebut sebelum Rabu, 5 Juli 2017 melalui email intaac2017@gmail.com dan menginformasikannya kepada sekretariat InTAAC 2017 dengan Sdri Evi (08567907503) atau Sdri Sri Handayani (08561938327). Atas perhatian dan kerjasamanya kami ucapkan terima kasih.

Hormat kami,

Panitia InTAAC 2017

Dr. Putro Setyobudyo Muhammad
Ketua Panitia

Konfirmasi Kesediaan ke Sekretariat Panitia:
Ibu Iyek (08561938327) atau Evi (08567907503)

2nd International Antiaging Conference IntAAC 2017
RUNDOWN SIMPOSIUM Day 1
SABTU, 15 JULI 2017
HOTEL SAHID JAYA JAKARTA

Sesi /Jam		Tema
08.00 - 08.30		Registrasi Peserta
Sesi 1 (08.30-09.20)		**Nutraceuticals**
		Moderator : dr. Henti Widowati, M.Biomed (AAM)
08.30 - 08.50	20'	Personalized Nutrition for Healthy Condition & Rejuvenation
		Prof.DR.dr. Nurpudji Astuti Taslim, MPH, SpGK(K)
08.50 - 09.10	20'	Nutraceuticals for Anti Aging
		DR.med. Dr. Maya Surjadjaja, M.Gizi, SpGK
09.10 - 09.20	10'	Discussion
Coffee Break (09.20-09.30)		**Coffee Break**
Pembukaan (09.30-10.25)		**Pembukaan**
09.30 - 09.35	5'	Menyanyikan lagu Indonesia Raya
09.35 - 09.40	5'	Sambutan Ketua Panitia
09.30 - 09.40	10'	Sambutan Ketua Perdaweri
09.40 - 09.55	15'	Sambutan Ketua PB IDI
09.55 - 10.25	30'	Pembukaan dan Keynote Speech Menteri Kesehatan
		Kebijakan Pemerintah dalam Upaya Pengembangan Antiaging Medicine and Health Tourism di Indonesia pada Era MEA
Panel (10.25-12.05)		**Panel : Future Challenges for Anti Aging Physicians**
		Moderator : Dr. dr. Supriyantoro, Sp.P, MARS
10.25 - 10.45	20'	Konsep dan Implementasi Pemberian Kewenangan Tambahan oleh Ketua KKI
		Prof. Dr. Sukman Tulus, SpA
10.45 - 11.05	20'	Peluang dan Tantangan Pengembangan Antiaging/Aesthetic Health Tourisme di Indonesia
		Perdaweri
11.05 - 11.25	20'	Peran Wellness and Health Tourisme Khususnya Aesthetic Health Tourism dalam Mendukung Destinasi Wisata
		Kementerian Pariwisata RI
11.25 - 11.45	20'	Diskusi
Lunch & Prayer (11.45 - 13.00)		**Lunch & Prayer**
Sesi 2 (13.00 - 13.50)		**Rejuvenation**
		Moderator : Dr. Freddy Wilmana, MFPM, SpFK
13.00 - 13.20	20'	Hormone Therapy for rejuvenation
		Dr. Anoop Chaturvedi, BSc, MBBS, DA, MD, PhD
13.20 - 13. 40	20'	Update on telomerases
		DR. Drs. Andi Wijaya, Apt
13. 40 - 13. 50	10'	Discussion
Sesi 3 (13.50-14.40)		**New Modalities In Antiaging and Aesthetic**
		Moderator : Dr. Djauhery
13.50 - 14.10	20'	Metformin Update in Anti-Aging
		Dr. Freddy Wilmana, MFPM, SpFK
	5	Discussion
14.15 - 14.35	20'	Sculptra & Combination Treatment
		Dr. Darryl Chew
14.35 - 14.40	5	Discussion
Coffee break (14.40 - 15.00)		**Coffee break**
Sesi 4 (15.00-15.50)		**Silent Inflammation**
		Moderator : dr. Rita Lahirin
15.00 - 15.20	20'	SAMe nutrient for antiaging (detoxification and neurotransmitter balancing)
		DR. Dr. Gaga Irawan Nugraha, M.Gizi, SpGK
15.20 - 15.40	20'	Anti-Inflammation Diet Plan and Supplementation
		Dr. Siti Nur Fatimah, MS, SpGK
15.40 -15.50	10'	Discussion

2nd International Antiaging Conference IntAAC 2017

RUNDOWN SIMPOSIUM Day 2

MINGGU, 16 JULI 2017

HOTEL SAHID JAYA JAKARTA

Sesi/Jam	Jam	Tema
08.00 - 08.30		Registrasi
Plenary (08.30-09.30)		**Plenary**
08.30 - 08. 50	**20'**	Medical Ethics (MKEK IDI)
		Dr. M. Nasser, Sp.KK, LLM DLaw
08. 50 - 09. 10	**20'**	Patient Safety (PB IDI)
		PB IDI
09. 10 - 09.30	**20'**	Complement and Alternative Medicine in Indonesia
		Dr. Merdias Almatsier (Ketua Pokja Kemkes ttg CAM)
Sesi 5 (09.30 - 10.20)		**Antiaging : Economic Perspective**
		Moderator : Dr. Dyah Agustina Waluyo
09.30 - 09.55	25'	Entrepreneurship: Anti Aging as The New Startup Frountier
		dr. Bayu Prawira Hie
09.55 - 10.15	20'	Antiaging Lab Test
		Dr. George A. Mantiri, MLM, SpPK
10.15 - 10.25	10'	Discussion
Coffee Break (10.25-10.30)		**Coffee Break**
Session 6 (10.30-11.20)		Stemcell
		Moderator: dr. Henti Widowati, M.Biomed (AAM)
10.30 - 10.50	20'	The Difference of Stemcell Products
		DR.dr. Ago Harlim.MARS., SpKK
10.50 - 11.10	20'	Immunology Behind The Filler
		DR.dr. Ago Harlim.MARS., SpKK
11.10-11.20	10	Discussion
Sesi 7 (11.20 -12.10)		**Lifestyle Modification**
		Moderator: Dr. Putro S Muhammad
11.20 - 11. 40	**20'**	Management Obesity: Fight Obesity for Healthy Life
		DR.med, Dr. Maya Surjadjaja, M.Gizi, SpGK
11.40-12.00	20'	The Miracles of Aloe Vera
		Dr. Freddy Wilmana, MFPM, SpFK
12.00-12.10	10'	Discussion
Lunch & Prayer (12.10 - 13.00)	**50'**	**Lunch & Prayer**
Sesi 8 (13.00-13.50)		**Lifestyle Selection**
		Moderator : Dr. Siti Nur Fatimah, MS, Sp.GK
13.00 - 13.20	20'	Lifestyle for Uterine Cervical Health
		Prof. Dr. Antonius Kurniawan, Sp.PA (K)
13.20 - 13.40	20'	Rational Use of Probiotics in Daily Practice
		Dr. Abdullah Firmansah, SpGK. Mkes
13.40 - 13.50	10'	Discussion
Sesi 9 (13.50 - 14.40)		**Better Neurologic life style**
		Moderator : Dr. Kishanty Hardaningtyas
13.50 - 14.10	20'	Specific Exercise for Relax
		Dr. Grace Tumbelaka, SpKO
14.10 - 14.30	20'	Melatonin Contribution in Sleep and Quality of life
		Dr. Widya Murni, MARS
14.30 - 14.40	10'	Discussion
(14.40 - 15.10)	20'	**Coffee Break & Medikamentoring**
Sesi 10 (15.10-16.00)		**Hormone Therapy**
		Moderator : Dr. Yenni Zuharini, M. Gizi, Sp.GK
15.10 - 15.30	20'	Hormonal Changes & Sexual Function in Aging Women
		Dr. Widya Murni, MARS
15.30 - 15.50	20'	Climacteric & Post Menopause Symptoms and Management
		Dr. Prima Progestian, SpOG
15.50 - 16.00	10'	Discussion
Closing ceremony (16.00-16.15)		**Closing ceremony, doorprize**

INTAAC 2017

Permohonan Power Point dan Abstrak Materi Pembicara InTAAC 2017

To: Dr hadim sl al al. Cc: Freddy Wilmana, Maya Surjadjaja, Andalusia Adnar, [illegible], Yanni Rufadi, siti fatimah

30 June 2017 17.03

Details

Jakarta, 28 Juni 2017

No. : 053/InTAAC/F.3/06/2017
Lamp : Rundown Acara
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Topik 1 (20') : The Difference of Stemcell Products

Topik 2 (20') : Immunology Behind The Filler

2nd International Anti Aging Conference IntAAC 2017
Jumat,14 Juli 2017
Hotel Sahid Jaya Jakarta
RUNDOWN WORKSHOP

WORKSHOP I		**Update in Fat Loss Management**
(09.00 - 11.00)		**Moderator: Prof. Dr. Antonius Kurniawan, Sp.PA (K)**
09.00 - 09.30	30'	Hunger Craving Weight Gain its all in The Brain
		Dr. Anoop Chaturvedi, BSc, MBBS, DA, MD, PhD
09.30 - 10. 00	30'	Hormone Diet: How To Do a Good Hormonal Diet
		DR.med, Dr. Maya Surjadjaja, M.Gizi, SpGK
10.00 - 10.30	30'	Bioidentical Hormones for Fat Loss
		Dr. Anoop Chaturvedi, BSc, MBBS, DA, MD, PhD
10.30-11.00	30'	Q n A
11.00-11.15		**Coffee Break dan Registrasi WS II**
WORKSHOP II		**Dysbiosis Fact – Relationship of Gut with Skin Health**
11. 15 - 12.15		**Moderator: Dr. Freddy Wilmana, MFPM, SpFK**
11.15 - 11.45	30'	Overview of Gut-Brain-Immune
		Dr. Anoop Chaturvedi, BSc, MBBS, DA, MD, PhD
11.45 - 12. 15	30'	Intestinal Barrier Dysfunction (Leaky Gut)
		DR. Dr. Aris Wibudi, SpPD
12.15 - 13.00		**ISHOMA**
WORKSHOP II (lanjutan)		**Dysbiosis Fact – Relationship of Gut with Skin Health**
13.00 - 14.00		**Moderator: Dr. Freddy Wilmana, MFPM, SpFK**
13.00 - 13.30	30'	Relevance of Hormonal Therapy with Dysbiosis
		Dr. Anoop Chaturvedi, BSc, MBBS, DA, MD, PhD
13.30 - 14.00	30'	Q n A
14.00-14.15		**Coffee Break dan Registrasi WS III**
WORKSHOP III		**Update On Minimal Invasive Acne Management**
14.30 - 16.30		**Moderator : Dr. Erdina Pusponegoro, SpKK**
14.30 - 15.00	30'	Etiopatogenesis Acne
		DR. Dr. Irma Bernadette, SpKK(K) FINS DV
15.00 - 15.30	30'	Update on Acne Treatment (Management Akne Update di Indonesia)
		Dr. Lili Legiawati, SpKK(K) FINSDV FAADV
15.30 - 16.00	30'	Managemen HPA dan SPA update
		Dr.Lilik Norawati, SpKK FINSDV FAADV
16.00 - 16.30	30'	Q n A

IMMUNOLOGY BEHIND THE FILLER

inTAAC 2017

Ago Harlim

Universitas Kristen indonesia

1. BACKGROUND

Silicone injection for cosmetics and surgery is still widely practiced in Indonesia. The result of Indonesian Association of Plastic Surgeons survey start from 2004 to 2007, found 249 cases of silicone complications.[1] Epidemiological data in other countries was not clear because silicone injection had been banned. In 1990, more than 100,000 patients in United States had received silicone injection in their face.[3] In Indonesia, there had been no research on silicone injection and its complications, although the cases were abundant. The use of silicone injection for cosmetic treatment had been banned by Federal Food, Drug & Cosmetic America (FDA) since 1992.[3] Liquid silicone which was injected into the skin can migrate and cause morphological changes and uncontrolled inflammatory response. Liquid silicone in the tissue is persistent, so it will lead to chronic inflammation and granulomas formation, if severe, it could be followed by infection, necrosis, and abscess.[2-4] Silicone granuloma is difficult to evacuate and is still able to form new granuloma after the evacuation. Immune response of granuloma is mediated by T cells, Th1 secreted pro inflammatory cytokines and Th2 secreted anti inflammatory cytokines.[18] The new theory of immune tolerance played by Tregs ($CD4^+CD25^+$) and Indoleamine-2,3-dioxygenase enzyme might be explained obviously the pathogenesis of granuloma formation due to silicone injection.[21-24] Until now, the pathogenesis of silicone granuloma has been studied, but the result are still controversial. The aimed of this study is to analyse the phatogenesis of silicone granuloma in respect to immune inflammatory response and tolerance.

2. METHOD OF STUDY

Descriptive analytic method was conducted in this study, which included: **(1)**. Cross-sectional study, to compare immune response in three groups, namely the chin granuloma tissue,

submental skin and skin tissue from healthy individuals (control), and to assess the clinical correlation, histopathological, and immune responses. Samples were 31 cases of silicone granulomas tissue and submental skin, and 37 normal skin tissue. All tissues were examined histopathologically (HE staining) to see the degree of foreign body reaction (FBR) and immunohistochemistry to assess the expression of TNF-α, IFN-γ, IL-10, IDO, and Treg cells $CD4^{+}CD25^{+}$; **(2).** Laboratory experimental performed to assess blood cytokine levels with: (a) Culturing whole blood cells from granuloma patient and normal individuals, using RPMI medium, RPMI stimulated by PHA, and stimulated by 3% of silicone industry. (b) Examined cytokine levels from cell culture supernatant on day 3, included TNF-α, IFN-γ, and IL-10. All analyzed with Luminex and IDO with ELISA. The research was conducted in specialist clinics, Faculty of Mathematics and Sciences University of Indonesia, Faculty of Medicine University of Indonesia, Faculty of Medicine Airlangga University, and Eijkman Institute, start from November 2012 until September 2014.

3. RESULT AND DISCUSSION

Generally, patients with silicone injections in their chin were injected in the salon. They came for treatment approximately 12.5 years after injection, shape of chin changed in 4^{th} years, the color of the skin changed in 5^{th} years. Nose and chin were main area of silicone injections, 54.8% of patients with silicone injection complications were not know that the injected substance was liquid silicone. Silicone was also present in normal skin with statistical mean 44,07μg/g, while the silicone level in the submental skin (944 μg/g) was significantly higher than the silicone level in the granuloma (688 μg/g).

There was no significantly difference in the levels of TNF-α, IFN-γ, IL-10 and IDO from blood cultures stimulated by 3% of liquid silicone compared with negative control. Differences seen significantly between negative control and the positive control (PHA), ($p<0.001$).

There was significantly difference in the expression of TNF-α, IFN-γ, IL-10 and IDO on inflammatory cells surface in normal skin compared with granuloma or submental skin of granuloma ($p<0.001$). However, there was no significantly difference between granuloma and submental skin of granuloma. In contrast, There was no significantly difference in Tregs population between granuloma and normal skin, but there was significantly difference between normal skin and submental skin of granuloma ($p<0.001$).

Histopathological features (with HE staining) of normal skin tissue showed that giant cells and fibrosis area was not found. Histopathologic features of granuloma showed that granuloma tissue more inflammative than submental skin of granuloma tissue.

Correlation between immune response in chin granuloma due to silicone injections, submental skin and blood.

Based on a significant correlation between the expression of cytokines TNF-α, IFN-ɣ, IL-10 and IDO on inflammatory cell surface in chin granuloma, submental skin of granuloma and normal skin with cytokines levels in blood, thus the **minor hypothesis 1**.

Correlation between immune response in chin granuloma due to silicone injections with submental skin.

Based on the correlation between the expression of cytokines TNF-α, IFN-ɣ, IL-10 and immune tolerance (Treg cells ($CD4^+CD25^+$), IDO in chin granuloma and submental skin of granuloma, **minor hypothesis point 2 was accepted**.

1. There was a significant correlation between histopathologic features of granulomas with submental skin of granuloma (p=0.004, r=0.507), due to silicone spreading, thus the foreign body reaction also occured in the submental skin of granuloma (Table 2).
2. Anti inflammatory cytokines in submental skin of granuloma were significantly correlated with cytokines level in granulomas tissue. Level of IL-10 in submental skin of granuloma correlated significantly with IL-10 in granuloma tissue (p=0.021, r=0.412), IDO in submental skin of granuloma significantly correlated with almost all cytokines (TNF-α p=0.009, r=0.460; IFN-γ p=0.003 r=0.512; IL-10 p=0.012; r=0.445; IDO p=0.026 r=0.399). Population of Treg cells in submental skin of granuloma was significantly correlated with the expression of IDO on inflammatory cell surface in granuloma (p=0.034, r=0.381) (Table 3). Based on these results, the submental skin of granuloma occurs immune tolerance to prevent damage due to inflammation by silicone.

Histopathological features of chin granulomas and submental skin of granuloma related with period of injection, silicone levels and the degree of clinical severity

Based on correlation of histopathological features of chin granulomas and submental skin with period of injection, silicone levels and clinical severity, so the **hypothesis minor 3 points 2, 3, 4 are accepted.**

1. Clinical severity was not associated with and silicone levels in patient with chin granuloma caused by silicone. The degree of clinical severity was not determined by period of silicone injection or silicone level, but by individual immune response.
2. Histopathologic features with three phases of granuloma significantly associated with clinical severity ($p=0{,}020^{ch}*$). When clinical features became more severe, histopathological features tends to be fibrosis ($r=0.456$, $p=0{,}010^{s}*$, $R^2=0.207$) (Figure 4)
3. Histopathological features with eight stages of granuloma significantly associated with period of silicone injection in granuloma tissue ($p = 0.020$), and submental skin of granuloma ($p=0.046$) (Figure 5). Peak of inflammation was reached around 10-19 years after silicone injection and decreased after 19 years due to individual immune tolerance.
4. Histopathological features with eight stages of granuloma significantly associated with higher levels of silicone in submental skin of granuloma ($p=0.047$), but not in the granuloma tissue. it can be seen in figure 4.10, that the inflammation increased concomitantly with silicone level in submental skin of granuloma and shifted toward fibrosis gradually when silicone started to be decreasing.[20,23,27] Silicone level in submental skin of granuloma was more stable than in granuloma tissue.

The role of pro inflammatory and anti inflammatory cytokines to the occurrence of immune tolerance in patients due to silicone injections into their chin, which is assessed in granuloma tissue, skin and blood

Based on the correlation between Treg ($CD4^+CD25^+$) population as immune tolerance properties, expression of IDO on inflammatory cell surface in granuloma tissue and submental skin with period of silicone injection and silicon level, the **minor hypothesis 4 was accepted**, described in table 4 and 5.

Expression of IDO on inflammatory cell surface did not correlate with period of silicone injection and silicone level. Population of Treg cells did not correlate with period of silicone injection, but Treg population in granuloma tissue correlated significantly with silicone level ($p=0.033$, $r=0.383$), (Table 4 and 5). Each individual have a difference immune tolerance,

depend on antigen level. Silicone need plasma proteins on its surface to trigger immune responses. Phases of protein adsorption on silicone surface are dynamic process and difficult to be predicted.[31] Patients with chin silicone injection have delayed-type hypersensitivity (DTH) reaction which would recruit lymphocytes. Silicone captured by lymphocytes via its receptor, then lymphocytes secreted both proinflammatory and antiinflammatory cytokines, and then, in this process, Treg played a role to mantain homeostasis, thus the silicone level correlated with Treg population in granuloma tissue. [27]

Based on the correlation between the expression of IDO on inflammatory cell surfacein granuloma tissue, submental skin of granuloma and blood with clinical and histopathologic severity, then the **minor hypothesis 5 was accepted** and can be seen in table 6.

Histopathologic features of granulomas were not associated with the expression of IDO on inflammatory cell surfacein granulomas, and whole blood culture with all stimulants, but histopathologic with eight phases in submental skin of granuloma was associated significantly with the expression of IDO on inflammatory cell surface in the submental skin of granuloma ($p=0.038$, Table 6). Expression of IDO on inflammatory cell surface in the submental skin of granuloma correlated with almost all cytokines in granuloma tissue. It is not surprising if IDO also correlated significantly with histopathological features. IDO seems to play an important role in the submental skin of granuloma so that IDO can be used as predictive tool for immune tolerance to silicone injection.

Treg did not associate with histopathologic and clinical severity, but Treg population in submental skin of granuloma significantly associated with clinical severity ($p=0.011$, Table 7). **Minor hypothesis 6 is accepted**, so, Treg population in the submental skin of granuloma can be used as predictive tool for observing the immune response and clinical features.

Based on the correlation between IDO and TNF-α and IFN-ɣ, in chin granuloma, submental skin of granuloma, as well as the blood level of cytokines, then the minor hypothesis at point seven is accepted and can be seen in Table 8.

1. Level of pro inflammatory cytokines, TNF-α and IFN-γ, in whole blood culture is not associated with the expression of IDO on inflammatory cell surface in both tissues but the expression of proinflammatory cytokines, TNF-α and IFN-γ, in granuloma significantly correlated with the expression of IDO in both tissues (TNF-α, $r=0.592$, $p<0.001$; IFN-γ, $r=0.603$, $p<0.001$, table 8). IDO has a primary role in submental area for controlling

inflammation from silicone-consuming macrophages with IDO secretion and helps to mantain immune tolerance, so tissue damage caused by inflammation could be prevented.[32-34] IDO activity can be used as predictive tool for observing immune response in granuloma.

2. Treg population did not correlate with TNF-α and IFN-γ in granuloma tissue and submental skin of granuloma, also in blood plasma, as well as silicone-stimulated blood, but Treg population in granuloma inversely correlated with TNF-α and IFN-γ in PHA-stimulated blood (TNF-α, r= -0.450, p=0.011; IFN-γ, r= -0.367, p=0.042). Lymphocytes will be stimulated by PHA. Treg cells are subset of lymphocytes that will mantain immune tolerance in granuloma caused by silicone injection. Inverse correlation happen because Treg works as an anti inflammatory, whereas TNF-α and IFN-γ are pro inflammatory cytokines.[17,27]

Based on the correlation between Treg population ($CD4^{+}CD25^{+}$) and IDO with ratio TNF-α/IL-10 and IFN-γ/IL-10 in whole blood culture and both tissue, then minor hypothesis at point eight is accepted and described on the table 9.

1. IDO in granuloma and submental skin of granuloma did not correlate to the ratio of TNF-α/IL-10 and IFN-γ/IL-10 in blood plasma and PHA-stimulated blood, as well as granuloma tissue but the IDO in granuloma significantly correlated with the ratio of TNF-α/IL-10 in silicone-stimulated blood and submental skin of granuloma (blood, r=0.418, p=0.019; submental skin of granuloma, r= -0.363, p=0.045). Based on data, IDO activity correlated with Treg function, thus the expression of IDO on inflammatory cell surface in granuloma can predict immune responses.
2. Treg population in granuloma and submental skin did not correlate to the ratio of TNF-α/IL-10 and IFN-γ/IL-10 in PHA-stimulated blood and silicone-stimulated silicone, as well as in granuloma and submental skin, but Treg population in granulomas inversely correlated with the ratio of TNF-α/IL-10 in blood plasma (r= - 0.460 p=0.009). This data prove that Treg function work through IL-10.

The level of cytokines ratio in blood for granuloma prediction

By assessing and comparing the inflammation that was occured with ability of the body to inhibit inflammation with anti inflammatory cytokines or tolerance mechanism, as played by IL-10 and IDO, the ratio of TNF-α/IL-10 or TNF-α/IDO would be more accurate to be used as predictive tool. Relationship between ratio of TNF-α/IL-10 and TNF-α/IDO with period of

silicone injection can be seen in table 10. The ratio of TNF-α/IL-10 in PHA-stimulated blood and blood plasma and TNF-α/IDO in silicone-stimulated blood and blood plasma can be used as predictive tool. Inverse correlation means that the lower the ratio, the longer onset period of granuloma.

According to the table 10, the ratio of TNF-α/IL-10 and TNF-α/IDO in blood plasma can be used as predictors of the onset period of granuloma (p=0.038; p=0.028). Table 1 showed the significant difference between the normal and granuloma patients. Ratio of TNF-α/IL-10 in blood plasma of normal patients differ significantly with granuloma patients (p=0.002). Ratio of TNF-α/IDO in blood plasma of normal patients differ significantly with granuloma patients (p=0.008).

The level of cytokines in tissue for granuloma prediction

Tissue examination is required if there are any indecision in the existing examination, either physical or blood cytokine examination.

Based on the results, in table 11, there was seen some cytokines correlated with clinical features and period of silicone injection. TNF-α expression on inflammatory cell surface in granuloma tissue significantly correlated with clinical features and period of silicone injection, but clinically most patients do not want to do the biopsy, i.e. at chin, so the submental skin of granuloma areas should be selected to represent the immune response that was occured.

Based on table 11, Treg and IL-10 in submental skin of granuloma can be used as predictors of immune response that would happen. In accordance with the results, table 7 showed Treg had a significant correlation with clinical severity of submental skin of granuloma, whereas IL-10 in submental skin of granuloma significantly correlated with IL-10 in the granuloma tissue.

The numerical data need to be transformed to categorical data to measure prediction by mean of multivariate logistic regression. Treg population in submental skin of granuloma were splitted into two category with a cut-off limit 0.5 based on ROC analysis between Treg with the clinical features.

Result of multivariate logistic regression analysis between clinical severity with IL-10 were obtained (IL-10 p=0.028 and Treg p=0.057). It was concluded that IL-10 in submental skin of granuloma can be used as the best predictor. Based on ROC analysis between IL-10 in

submental skin of granuloma and clinical features, expression limit of IL-10 in submental skin of granuloma is 138.

The higher degree of fibrosis showed immunologically improvement, but also became a problem for patients. IL-10 is an anti inflammatory cytokine and one of the cytokines produced by Treg, in addition to TGF-β.[20,27,28] TGF-β played a role in fibrosis. If IL-10 level more than 138 in submental skin of granuloma, granuloma did not need to be evacuated, actually. Evacuation procedure can be done on cosmetic indications, and must be followed-up through a standard blood test of normal patient, if IL-10 level less than 138, the patient should be recommended to treat with anti TNF-α or immunomodulatory, in order to avoid granuloma formation due to remaining-silicone in tissue.

Based on these data, cut off point for prediction of granuloma was establish. The median of ratios of granuloma patients can be used as cut-off point for predicting the onset of granulomas. Cut off point ratio of TNF-α/IL-10=3.8 and TNF-α/IDO=0.1 as a lowest level. If the ratio below the cut off, so we need follow up every 6 month, if above the cut off, therpy anti TNF-α is needed.

4. CONCLUSIONS

1. Generally, patients with chin granuloma due to silicone injection were injected in the salon. They came for treatment approximately 12.5 years after injection, the shape of chin changed in 4th years, the color of the skin changed in 5th years.
2. Level of pro inflammatory cytokines tend to be higher in patients with granuloma due to silicone injection compared to the normal patients, while anti inflammatory cytokines levels of blood tend to be lower than normal patients. Histopathological features of granuloma caused by silicone are more inflammation, while nomal skin were more fibrosis.
3. There is a significant correlation between proinflammatory cytokines TNF-α, in blood with TNF-α expression on inflammatory cell surface in granuloma tissue. Level of TNF-α in blood can be used as predictor to assess the immune response due to silicone injection.
4. IL-10 in submental skin of granulomas significantly correlated with cytokines in granulomas. IL-10 played a role in submental skin of granuloma and can be used as the best predictor to assess the immune response in submental skin due to silicone injection.

5. Clinical severity is significantly correlated with histopathological features of granuloma. Period of injection related with histopathologic features in granulomas and submental skin. Histopathological features in submental skin of granuloma associated with higher level of silicone.
6. TNF-α played a role in immune response due to inflammation in granuloma, while IL-10. Treg cells and enzime IDO played a role in immune tolerance due to silicone injection.

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