

[Original]

Prednisolone Dosing Regimen for Treatment of Subacute Thyroiditis

Tadashi ARAO^{1*}, Yosuke OKADA², Keiichi TORIMOTO², Akira KUROZUMI², Manabu NARISAWA², Sunao YAMAMOTO² and Yoshiya TANAKA²

¹ *Department of Internal Medicine, Japan Labour Health and Welfare Organization Kyushu Rosai Hospital, Moji Medical Center, Japan. Moji-ku, Kitakyushu, 801-8502, Japan*

² *First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan. Yahatanishi-ku, Kitakyushu, 807-8555, Japan*

Abstract : The rate of recurrence of subacute thyroiditis (SAT) during prednisolone (PSL) therapy is approximately 10 to 20%. However, there is little or no information on the time period to relapse following administration of a tapered dose of PSL and the factors associated with such relapse. The aim of this study was to determine the correlation between SAT recurrence and PSL tapering regimen used in the treatment of SAT. This study was a medical record-based retrospective study and involved 26 patients (3 men, 23 women) who received PSL therapy for SAT. The primary endpoint was the association between recurrence and number of days required to taper daily PSL dose to 5 mg. The secondary endpoint was the relationship between recurrence and several variables including age, clinical score, free thyroxine, inflammatory reaction, thyroglobulin, total treatment time, total dose of PSL and presence or absence of creeping thyroiditis. The SAT recurrence rate was 15.3%. There was no significant difference in the initial PSL dose between the non-recurrence and recurrence groups (27.5 mg vs 24.5 mg, $P = 0.302$). However, for the primary endpoint, significant differences were found between the two groups in time required for tapering PSL to 5 mg/day (non-recurrence: 44.3 ± 15.3 days, recurrence: 19.0 ± 11.9 days, $P = 0.012$). None of the clinical variables evaluated correlated significantly with SAT relapse. In conclusion, to prevent recurrence of SAT, consideration should be given to the period required for PSL tapering to 5 mg/day.

Keywords : subacute thyroiditis, prednisolone, the recurrence rate, dosing regimen.

(Received December 19, 2014, accepted May 14, 2015)

Introduction

Subacute thyroiditis (SAT), also known as de Quervain thyroiditis or granulomatous thyroiditis, is an inflammatory disease caused by viral infection and has characteristic symptoms of fever, thyroid nodules with tenderness, and thyrotoxicosis, which includes palpitations and excessive sweating [1–3]. The prevalence of SAT is higher in women aged 40 to 50 years than

in men, with female patients accounting for 80% of individuals with the disease [1, 4, 5]. High erythrocyte sedimentation rate (ESR), and high levels of C-reactive protein (CRP) and thyroglobulin (Tg) during the acute phase, as well as reduced uptake of ¹³¹I on thyroid gland scintigraphy, are frequently used for differentiating SAT from Graves' disease.

Recurrence of SAT after completion of treatment is rare (approximately 2%) [4–6]. While studies have re-

*Corresponding Author: Tadashi ARAO, MD, PhD, Department of Internal Medicine, Japan Labour Health and Welfare Organization Kyushu Rosai Hospital, Moji Medical Center, Japan, 3-1 Higashiminato machi, Moji-ku, Kitakyushu City, Fukuoka 801-8502, Japan, Tel: +81-93-331-3461, Fax: +81-93-332-7234, E-mail: t-arao@med.uoeh-u.ac.jp

ported that the recurrence rate during treatment with prednisolone (PSL) is approximately 2.2% [7] or 35% [8], it is generally thought that the SAT relapse rate is approximately 10 to 20% [3, 9]. Clinically, a rapid tapering of PSL during treatment can increase the likelihood of a recurrence, and thus tapering schedules of 1 to 2 weeks are recommended [10]. However, there are no studies that have compared the number of days at which patients experience recurrence following PSL dose tapering and none has compared patients with recurrence and those without. In this study, we examined associations between recurrence episodes and methods of PSL dose tapering in patients with SAT.

Subjects and Methods

Subjects

This study included 26 patients (3 men, 23 women) who received PSL treatment for SAT between January 2004 and July 2013 at our hospital (Table 1).

Methods

Relapse was defined as the development of goiter with tenderness at the neck, fever, and re-elevation of inflammatory markers during PSL tapering. The following variables were recorded: i) non-recurrence or recurrence of SAT, number of days to recurrence, and the presence or absence of creeping thyroiditis; ii) clinical score, thyroid function (thyroid stimulation hormone [TSH], free thyroxine [FT4]), and Tg levels; iii) inflammatory reactions (CRP, ESR, leukocyte count); iv) PSL dose until reduction to 5 mg/day; all patients in the recurrence group experienced SAT recurrence by the time PSL was tapered to 5 mg/day (Table 2); v) treatment period and total dose of administered PSL.

The primary endpoint was the correlation between recurrence and number of days to tapering PSL to 5 mg/day. The secondary endpoint was the correlation among recurrence episodes and several variables including age, clinical score, FT4, inflammatory reaction, Tg level and presence or absence of creeping thyroiditis. The clinical scoring system was calculated using 1 point for fever (over 38.0°C), 1 point for neck pain, 1 point for thyroid gland enlargement, and 1 point (over 20 mm/hr) or 2 points (over 60 mm/hr) for high ESR.

This is a retrospective study. The setting of primary dose and tapering of PSL reached by the judgment of the chief physicians. We had diagnosed subacute thyroiditis based on the subacute thyroiditis diagnostic criteria (2010) of the Japan Thyroid Association (Table 3) [11]. This study was approved by the ethics committee of University of Occupational and Environmental Health, Japan.

Laboratory evaluation

The concentrations of serum TSH and FT4 were measured by chemiluminescent immunoassay using assay kits (Architect TSH, Architect FT4). The normal ranges for TSH and FT4 for our hospital are 0.34-6.50 $\mu\text{U}/\text{mL}$ and 0.97-1.79 ng/mL , respectively (Abbott Japan Co., Tokyo, Japan). Serum Tg (normal range: < 32.7 ng/mL ; ECLIA, Elecsys 2010, Roche Diagnostics Japan Co.) was measured with a double-antibody chemiluminescence assay.

Statistical analysis

Results are expressed as mean \pm standard deviation. Comparison of two groups was performed using the Wilcoxon signed rank test. For categorical data, Fisher's exact probability test was employed. The odds ratio and 95% confidence interval are used for all data. Statistical analysis was performed using SPSS Statistical Software 21.0 (SPSS Inc., Chicago, IL), and P value < 0.05 was considered significant.

Results

Table 1 summarizes the clinical features recorded at the onset of SAT. The mean age was 49.0 ± 11.3 years (range, 31.0 - 76.0 years), the body temperature (BT) was $37.0 \pm 0.6^\circ\text{C}$, and the pulse rate was 98.2 ± 20.5 /min. Symptoms of thyrotoxicosis, presence or absence of creeping thyroiditis and preceding upper respiratory infection were observed in 57.7%, 15.4% and 38.5% of patients, respectively. The mean clinical score was 3.8 ± 0.8 (range, 2.0-5.0). At baseline, TSH was 0.03 ± 0.01 $\mu\text{U}/\text{mL}$ ($n=26$), FT4 was 4.0 ± 1.9 ng/mL , CRP was 7.0 ± 5.4 mg/dL ($n=26$), ESR was 79.6 ± 25.1 mm/hr ($n=22$), leukocyte count was 8287.2 ± 2736.5 $/\mu\text{L}$ ($n=25$) and Tg was 928.2 ± 1414.3 ng/mL ($n=22$) (Table 1).

In comparison of the non-recurrence and recurrence

groups, the non-recurrence group: 10 patients took 30 mg/day PSL, 1 patient took 25 mg/day, 10 patients took 20 mg/day, and 1 patient took 15 mg/day. The recurrence group: 3 patients took 30 mg/day PSL, and 1 patient took 20 mg/day (Fig. 1. A). The number of days required to taper PSL to 5 mg/day was 41.0 ± 16.3 days (Fig. 1. B).

Recurrence was diagnosed in 4 out of 26 patients, with an estimated recurrence rate of 15.3% (Table 2). Table 2 shows details of prednisolone medication in the four patients with recurrence. SAT recurrence did not correlate with sex, age, concomitant drug, first dose of PSL, PSL dose at recurrence, total time until recurrence, PSL dose after recurrence, total treatment time on PSL and total amount of PSL.

Furthermore, all 4 patients experienced recurrence at the time when the PSL dose was 5 mg/day. Analysis of the non-recurrence and recurrence groups showed no significant differences in the initial PSL dose between the non-recurrence (24.5 ± 5.3 mg) and recurrence groups (27.5 ± 5.0 mg, $P = 0.302$; Fig. 2. A). However, the number of days required to taper the PSL dose to 5 mg/day was significantly shorter in the non-recurrence group (44.3 ± 15.3 days, $P = 0.012$; Fig. 2.B) than in the recurrence group (19.0 ± 11.9 days). As shown in Table 4, there were no significant differences between the two groups in age, clinical score, FT4, CRP, ESR, leukocyte count, Tg, first dose of PSL, total treatment time, total dose of PSL and presence or absence of creeping thyroiditis.

Table 1. Baseline characteristics of 26 patients with SAT

Clinical features and data	mean \pm SD	range
males / females	3 / 23	
Age (years)	49.0 ± 11.3	31.0 – 76.0
Clinical score	3.8 ± 0.8	2.0 – 5.0
Body temperature (°C)	37.0 ± 0.6	36.0 – 38.2
Pulse rate (bpm)	98.2 ± 20.5	66.0 – 168.0
Symptoms of thyrotoxicosis (%)	57.7 (15 / 26)	
Presence or absence of creeping thyroiditis (%)	15.4 (4 / 26)	
Preceding upper respiratory infection (%)	38.5 (10 / 26)	
TSH (μ U/ml)	0.03 ± 0.01	0.01 – 3.48
FT4 (ng/ml)	4.0 ± 1.9	1.8 – 8.7
CRP (mg/dl)	7.0 ± 5.4	0.5 – 23.0
ESR (mm/hr)	79.6 ± 25.1	21.0 – 118.0
Leukocyte count ($/\mu$ l)	8287.2 ± 2736.5	3280.0 – 14800.0
Tg (ng/ml)	928.2 ± 1414.3	26.3 – 6490.0

TSH: thyroid stimulating hormone, FT4: free thyroxine, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SAT: subacute thyroiditis, Tg: thyroglobulin

Table 2. Details of prednisolone medication in the four patients with recurrence

Case	Sex	Age (years)	Concomitant drug	First dose of PSL (mg)	PSL dose at recurrence (mg/day)	Total time until recurrence (days)	PSL dose after recurrence (mg/day)	Total treatment time on PSL (days)	Total amount of PSL (mg)
1	F	48	NSAID	30	5	14	10	114	1357
2	F	52	NSAID	30	5	34	10	48	785
3	F	44	None	30	5	23	30	66	855
4	F	56	None	20	5	22	20	92	975

PSL: prednisolone, NSAID: non-steroidal anti-inflammatory drugs

There were no complications with prednisolone in the 26 cases, and there was no difference for the complications with prednisolone between the two groups.

non-steroidal anti-inflammatory drugs (NSAIDs) was used in 11 of 22 cases (50%) in the non-recurrence group and in 2 of 4 cases (50%) in the recurrence group.

Table 3. Guidelines for the diagnosis of subacute thyroiditis (acute phase)[11]

Findings

a) Clinical findings

Swelling with pain and tenderness in the thyroid gland.

b) Laboratory findings

1. Elevation of C-reactive protein and/or erythrocyte sedimentation rate.
2. Elevation of serum free thyroxine (FT4) and suppression of serum thyroid stimulating hormone (TSH) : less than 0.1 μ U/m/
3. Hypoechoic lesion at a painful portion of the thyroid gland confirmed by ultrasonography.

Criteria

- 1) A patient shall be said to have subacute thyroiditis if he/she has satisfied all 4 criteria.
- 2) A patient shall be said probably to have subacute thyroiditis if he/she has satisfied clinical criterion a), and 2 laboratory criteria b)-1 and b)-2.

Exclusionary conditions

A patient may not be said to have subacute thyroiditis if he/she is experiencing:

- acute exacerbation of chronic thyroiditis
- bleeding into a thyroid cyst
- acute suppurative thyroiditis
- thyroid anaplastic carcinoma

[Notes]

1. Patients often have preceding episodes of upper respiratory inflammation and high fever.
2. Pain and tenderness often moves gradually (creeps) to the opposite lobe of the thyroid gland.
3. Anti-thyroid autoantibodies are usually negative, but may rarely become weak-positive transiently during the course.
4. Polynuclear giant cells are observed in cytological or histological examinations, but neither tumor cells nor any findings characteristic of chronic thyroiditis are noted.
5. Radioactive iodine (or $^{99m}\text{TcO}_4^-$) uptake to the thyroid gland is decreased in the acute phase.

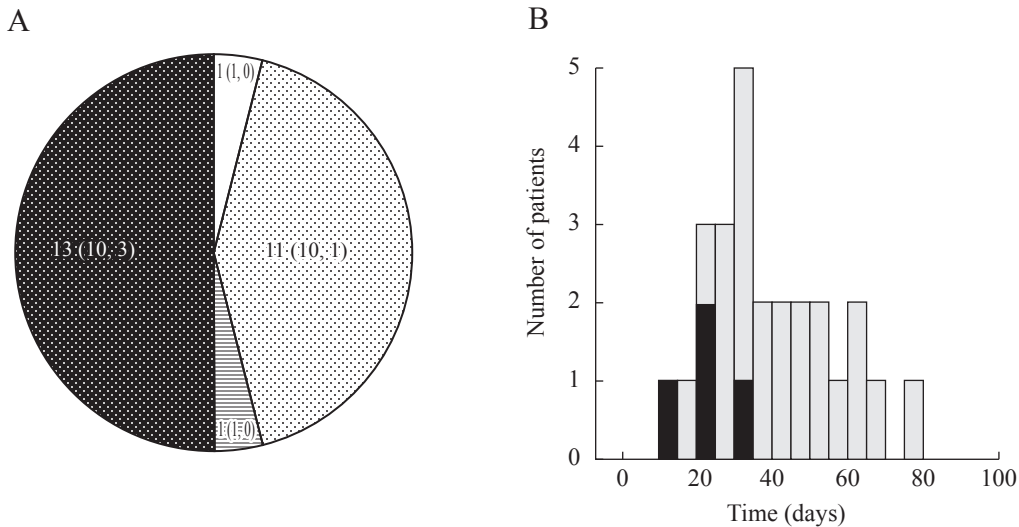


Fig. 1. Protocol used for administration of prednisolone. A: The initial PSL dose was 30 mg/day in 13 patients, 25 mg/day in 1 patient, 20 mg/day in 11 patients, and 15 mg/day in 1 patient. □: 15 mg, ▨: 20 mg, ▩: 25 mg, ▤: 30 mg, (): (left: value of non-recurrence, right: value of recurrence), B: The time required to taper PSL to 5 mg/day was 41.0 ± 16.3 days (n = 26). ■: recurrence group, ▨: non-recurrence group.

Discussion

Nishihara *et al* previously examined the clinical characteristics of 852 untreated patients with SAT, and reported that 28.2% of the patients were febrile (body temperature $\geq 38^{\circ}\text{C}$ in 19.2%), and that $\geq 60\%$ had clinical symptoms and signs of thyrotoxicosis at the

onset of the disease [12]. In our study, the mean body temperature was $37.0 \pm 0.6^{\circ}\text{C}$ ($\geq 38^{\circ}\text{C}$ in 19.2%), and symptoms of thyrotoxicosis were observed in 57.7% of the patients. These results point to similarities of the phenotype in the two studies, though with slightly lower rates of these two features of SAT in our group of patients.

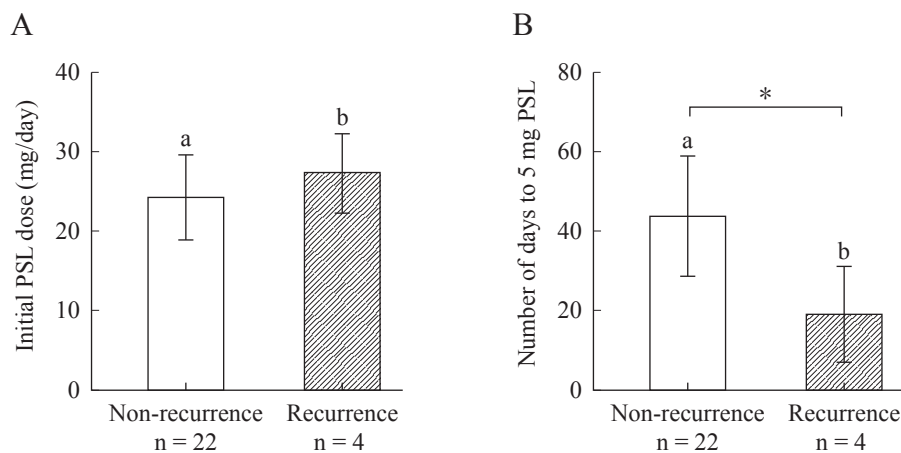


Fig. 2. The initial dose of PSL and time period required to taper PSL to 5 mg/day. A: The initial PSL dose was not different between the non-recurrence and recurrence groups. PSL: prednisolone, a: 24.5 ± 5.3 , b: 27.5 ± 5.0 , $P = 0.302$. B: The time required for PSL tapering to 5 mg/day was significantly shorter in the recurrence group compared with the non-recurrence group (*: $P < 0.05$, by Wilcoxon test), a: 44.3 ± 15.3 , b: 19.0 ± 11.9 , $P = 0.012$.

Table 4. Correlation between recurrence and various clinical parameters

Clinical features and data	Non-recurrence (n=22)	Recurrence (n=4)	<i>P</i> value
Age (years)	49.0 ± 12.2	50.0 ± 5.2	0.851*
Clinical score	3.8 ± 0.8	3.7 ± 0.6	0.817*
FT4 (ng/ml)	4.2 ± 2.0	3.3 ± 1.4	0.512*
CRP (mg/dl)	7.2 ± 5.8	6.0 ± 3.1	0.626*
ESR (mm/hr)	80.2 ± 25.4	76.3 ± 28.0	0.703*
Leukocyte count ($/\mu\text{l}$)	8213.0 ± 2485.0	9300.0 ± 4172.0	0.871*
Tg (ng/ml)	938.0 ± 1516.0	864.0 ± 560.0	0.685*
First dose of PSL (mg/day)	24.5 ± 5.3	27.5 ± 5.0	0.302*
Total treatment time (days)	58.0 ± 22.6	56.0 ± 32.6	0.135*
Total dose of PSL (mg)	761.0 ± 339.0	982.0 ± 196.0	0.076*
Presence or absence of creeping thyroiditis (%)	18.2	0.0	0.417**

Data are mean \pm SD, *P* values determined by Wilcoxon sign rank test (*) or Fisher's exact Test (**)

FT4: free thyroxine, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, Tg: thyroglobulin, PSL: prednisolone

The recurrence rate of 15.2% noted in the present study was similar to that reported in previous studies (ranging from 10 to 20%) [3, 9]. Mizukoshi *et al* [9] noted that the breaking point for recurrence may occur at a 10 mg PSL dose, and suggested that extending the period under treatment with 10 mg PSL may help reduce the recurrence rate [9]. In our study, recurrence was also observed when the PSL dose was tapered from 10 to 5 mg/day, which was in agreement with the above results reported by Mizukoshi *et al* [9].

The initial PSL dose varied from 15 to 30 mg/day, but there was no significant difference in the initial PSL dose between the non-recurrence (24.5 ± 5.3 mg/day) and recurrence groups (27.5 ± 5.0 mg/day). Kubota *et al* conducted a prospective study of SAT in which PSL was administered at an initial dose of 15 mg/day, and tapered to 5 mg/day over a 2-week period. The results indicated that 113 patients out of 219 (51.6%) achieved remission within 6 weeks, while 61 patients (27.9%) went into remission within 7 to 8 weeks, and none experienced recurrence. Based on these findings, they concluded that PSL tapering from a starting dose of 15 to 5 mg/day over a period of 2 weeks was a safe and efficacious method for PSL administration in Japanese patients [10]. Our study showed no correlation between the initial dose of PSL and recurrence rate. The results also showed a significantly shorter treatment-to-relapse period in the recurrence group. In other words, the average period required for PSL tapering to 5 mg/day was greater than 6 weeks but less than 7 weeks in the non-recurrence group, while it was greater than 2 weeks but less than 3 weeks in the recurrence group. Based on these findings, we recommend a period greater than 6 weeks at least before tapering PSL to 5 mg/day in order to prevent recurrence during PSL therapy, irrespective of the initial dose of PSL.

With regard to the secondary endpoints, our results showed no correlation between recurrence frequency and the variables measured in the present study, which included age, clinical score, FT4, inflammatory reactions, Tg levels and presence or absence of creeping thyroiditis. Previous studies used blood Tg concentrations as a marker of the early phase of SAT [13–15]. Another study identified high blood concentrations of interleukin-6 in thyrotoxic patients, but the levels returned to within the normal range after remission [16].

In another study of 36 patients with SAT [9] in which the initial dose of 25 or 30 mg/day of PSL was tapered to 5 mg/day weekly over a period of 5 to 6 weeks, the relapse rate was 22%, with no differences in pretreatment levels of ESR, leukocyte count, C-reactive protein (CPR), Tg, FT3 and FT4 between the non-recurrence and recurrence groups [9]. Our results confirm the findings of the above study [9] and point to the importance of tapering PSL over a relatively long period of time.

This study has several limitations. First, this is a retrospective study. The settings of primary dose and tapering of PSL are different according to the judgment of the chief physicians. Second, this study included a small sample size, particularly the number of patients in the recurrence group; the results should be verified in a larger sample size.

In summary, the results of the present study showed that the SAT recurrence rate during PSL therapy correlated with the number of days required for tapering the dose of PSL to 5 mg/day, but not with the starting dose of PSL. A relatively long period of time for PSL tapering to 5 mg/day is important to prevent recurrence of SAT.

Conflict of interest

The authors declare no conflict of interest.

References

1. Singer PA (1991): Thyroiditis. Acute, subacute, and chronic. *Med Clin North Am* 75: 61–77
2. Pearce EN, Farwell AP & Braverman LE (2003): Thyroiditis. *N Engl J Med* 348: 2646–2655
3. Volpe R (1993): The management of subacute (DeQuervain's) thyroiditis. *Thyroid* 3: 253–255
4. Fatourechi V, Aniszewski JP, Fatourechi GZ, Atkinson EJ & Jacobsen SJ (2003): Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. *J Clin Endocrinol Metab* 88: 2100–2105
5. Benbassat CA, Olchovsky D, Tsvetov G & Shimon I (2007): Subacute thyroiditis: clinical characteristics and treatment outcome in fifty-six consecutive patients diagnosed between 1999 and 2005. *J Endocrinol In-*

- vest 30: 631–635
6. Iitaka M, Momotani N, Ishii J & Ito K (1996): Incidence of subacute thyroiditis recurrences after a prolonged latency: 24-year survey. *J Clin Endocrinol Metab* 81: 466–469
 7. Vagenakis AG, Abreau CM & Braverman LE (1970): Prevention of recurrence in acute thyroiditis following corticosteroid withdrawal. *J Clin Endocrinol Metab* 31: 705–708
 8. Bennedbaek FN & Hegedüs L (1997): The value of ultrasonography in the diagnosis and follow-up of subacute thyroiditis. *Thyroid* 7: 45–50
 9. Mizukoshi T, Noguchi S, Murakami T, Futata T & Yamashita H (2001): Evaluation of recurrence in 36 subacute thyroiditis patients managed with prednisolone. *Intern Med* 40: 292–295
 10. Kubota S, Nishihara E, Kudo T, Ito M, Amino N & Miyauchi A (2013): Initial treatment with 15 mg of prednisolone daily is sufficient for most patients with subacute thyroiditis in Japan. *Thyroid* 23: 269–272
 11. Guideline for the diagnosis of subacute thyroiditis (acute phase): Japan Thyroid Association Guidelines. www.japanthyroid.jp/en/guidelines
 12. Nishihara E, Ohye H, Amino N, Takata K, Arishima T, Kudo T, Ito M, Kubota S, Fukata S & Miyauchi A (2008): Clinical characteristics of 852 patients with subacute thyroiditis before treatment. *Intern Med* 47: 725–729
 13. Madeddu G, Casu AR, Costanza C, Marras G, Arras ML, Marrosu A & Langer M (1985): Serum thyroglobulin levels in the diagnosis and follow-up of subacute 'painful' thyroiditis. A sequential study. *Arch Intern Med* 145: 243–247
 14. Yamamoto M, Saito S, Sakurada T *et al* (1987): Effect of prednisolone and salicylate on serum thyroglobulin level in patients with subacute thyroiditis. *Clin Endocrinol (Oxf)* 27: 339–344
 15. Yamamoto M, Saito S, Sakurada T *et al* (1988): Recurrence of subacute thyroiditis over 10 years after the first attack in three cases. *Endocrinol Jpn* 35: 833–839
 16. Bartalena L, Brogioni S, Grasso L, Rago T, Vitti P, Pinchera A & Martino E (1994): Interleukin-6: a marker of thyroid-destructive processes? *J Clin Endocrinol Metab* 79: 1424–1427
-

亜急性甲状腺炎に対するプレドニゾロン投与方法の検討

新生 忠司¹, 岡田 洋右², 鳥本 桂一², 黒住 旭², 成澤 学², 山本 直², 田中 良哉²¹独立行政法人 労働者健康福祉機構 九州労災病院 門司メディカルセンター 内科²産業医科大学 医学部 第1内科学講座

要 旨：亜急性甲状腺炎(SAT)に対するプレドニゾロン(PSL)治療中の再燃率は約10 - 20%である。しかしSATの再発に至るまでの期間においてPSLの減量方法や再発に伴う因子に関する報告は無い。今回の研究ではPSLにて加療を行ったSATに対するPSLの減量方法と再燃との相関について検討することを目的とした。試験デザインは、カルテベースの後ろ向き研究で、対象は2004年1月から2013年7月にSATに対してPSLを投与した26名(男3名, 女23名)。主要評価項目は、再燃とPSL 5 mgに減量するまでに要した日数との関係、副次評価項目は再燃と年齢, clinical score (活動性), free thyroxine, 炎症反応, Thyroglobulin, 総治療期間, 総PSL量, Creepingの有無との関係とした。再燃率は15.3%であった。非再燃群と再燃群ではPSL初期投与量(27.5 mg vs 24.5 mg, $P = 0.302$)に有意差を認めない。しかし, 主要評価項目：PSL 5 mgに減量するまでの日数(非再燃群：44.3 ± 15.3日 vs 再燃群：19.0 ± 11.9日, $P = 0.012$)に有意差を認めた。副次評価項目：その他の臨床的項目とSATの再燃との間に有意な相関は認めなかった。結論として, SATの再燃を起こさないためには, PSL減量日数に留意すべきであり, PSL 5 mgまでの減量には十分時間をかけるべきである。

キーワード：亜急性甲状腺炎, プレドニゾロン, 再燃率, 投与方法。