# The effect of Hochu-ekki-to for chronic idiopathic thrombocytopenic purpura and the immunological study of its effect

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## Abstract

Chronic idiopathic thrombocytopenic purpura (ITP) is characterized by persistent thrombocytopenia caused by a circulating anti-platelet factor.

Many immunosuppressants or splenectomies have been raised as candidates to treat refractory ITP. The authors used Hochu-ekki-to (Tsumura & Co. Japan) traditional Chinese medicine, for four cases of ITP. Within one to three weeks the platelet counts of all patients significantly increased ($p<0.001$) and platelet-associated IgG decreased with the increases in platelet counts. Serum interferon-$\alpha$ was increased after administration of this medicine. This medicine is thought to decrease the antibodies for platelets or suppress binding of antibodies to platelets by introducing interferon.

No adverse reactions were reported in any of the cases. This medicine can be considered for treatment of patients with ITP.

**Key words** ITP, Hochu-ekki-to, interferon-$\alpha$.

**Abbreviations** ITP, Chronic idiopathic thrombocytopenic purpura ; PA-IgG, platelet-associated IgG ; IFN, interferon ; Hochu-ekki-to, Bu-Zhong-Yi-Qi-Tang, 補中益気湯 ; Kami-kihi-to, Jia-Wei-Gui-Pi-Tang, 加味帰脾湯.

## Introduction

Chronic idiopathic thrombocytopenic purpura (ITP) is characterized by persistent thrombocytopenia caused by anti-platelet antibody and platelets are destructed by the reticuloendothelial system. But it is difficult to make clear the antigen or anti-platelet antibody of the patients with ITP. It is only understood that platelet-associated IgG (PA-IgG) is a significant factor.[1-3]

Many immunosuppressants or splenectomies are considered as candidates for the treatment of ITP. In recent years, it was reported that interferon-$\alpha$ (IFN-$\alpha$) was effective for ITP.

In Japan, traditional Chinese medicine is sometimes used for ITP, which is well known for the use of Sho-saiko-to (Tsumura & Co. Japan) or Kami-kihi-to (Tsumura & Co. Japan). These medications were used in cases 1 and 2, for a duration of six months to two years. Only Kami-kihi-to was slightly effective.

As Hochu-ekki-to resembles Kami-kihi-to in its chemical structure (Table I), it was thought that this medicine might have a similar or better effect.

After the use of this medicine, the platelet counts in the four cases increased significantly and had no adverse reactions.

## Subjects and Methods

*Patients* : Case 1 was a fourteen-year-old female. Her body weight was 53 kg. At the age of ten, she had purpura in her lower legs. Her platelet count was $0.8\times10^4/\mu l$. In bone marrow examination, the megakaryocyte count increased slightly and no morphological abnormality was

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Table I The traditional Chinese medicine (kampo).

| Bu-Zhong-Yi-Qi-Tang (TSUMURA) | | Jia-Wei-Gui-Pi-Tang (TSUMURA) | |
|---|---|---|---|
| Astragari Radix | 4.0 g | Astragari Radix | 4.0 g |
| Atractylodis Lanceae Rhizoma | 4.0 g | Atractylodis Lanceae Rhizoma | 3.0 g |
| Ginseng Radix | 4.0 g | Ginseng Radix | 3.0 g |
| Angelicae Radix | 3.0 g | Angelicae Radix | 2.0 g |
| Bupleuri Radix | 2.0 g | Bupleuri Radix | 3.0 g |
| Zizyphi Fructus | 2.0 g | Zizyphi Fructus | 2.0 g |
| Aurantii Nobilis | 2.0 g | Hoelen | 3.0 g |
| Cimicifuge Rhizoma | 1.0 g | Glycyrrhizae Radix | 1.0 g |
| Zingiberis Rhizoma | 0.5 g | Polygalae Radix | 2.0 g |
| | | Zingiberis Rhizoma | 1.0 g |
| | | Gardeniae Fructus | 2.0 g |
| | | Saussureae Radix | 1.0 g |
| | | Zizyphi Spinosi Semen | 3.0 g |
| | | Longanae Arillus | 3.0 g |

Each 7.5 g of the kampo in formula comprises 5.0 g of dry extract of crude drugs mixed in the proportions described above.

recognized. She was diagnosed as having acute ITP and since then was administered prednisolone or $\gamma$-globuline infusions, but neither treatment was significantly effective. Because of the long-term prednisolone treatment, she developed a moon-face, obesity and osteoporosis. Prednisolone treatment was discontinued and changed to traditional Chinese medicines, Sho-saiko-to or Kami-kihi-to. Only Kami-kihi-to was partially effective. Her treatment was changed to Hochu-ekki-to and her platelet count increased to $23.2 \times 10^4/\mu l$. When administration was stopped, her platelet count decreased to $10.7 \times 10^4/\mu l$ in the first week, and $6.1 \times 10^4/\mu l$ in the second week. Then administration was resumed but her platelet count dropped to $2.5 \times 10^4/\mu l$ after one week. After three weeks of administration, her platelet count recovered to $6.9 \times 10^4/\mu l$. Details are shown in Fig. 1.

Case 2 was a six-year-old female. Her body weight was 23 kg. At the age of one, she had suggillation in her lower legs and was diagnosed as having acute ITP by bone marrow examination. At the age of three, she was treated similarly to case 1, with prednisolone or $\gamma$-globuline, but it was not effective. After the treatment of Hochu-ekki-to, her platelet count increased significantly (Fig. 2).

Case 3 was a five-year-old male. His body weight was 12.5 kg and he suffered from endocardial cushion defect due to Down's syndrome. At the age of two, after acute pharyngitis, his platelet count was $2.2 \times 10^4/\mu l$, and he was dignosed as having acute ITP by bone marrow examination. He received no treatment as his mother refused prednisolone treatment. The course of treatment is shown in Fig. 3.

Case 4 was a thirty-two-year-old female. Her body weight was 74 kg. When she was twenty-four years old, she was diagnosed with acute ITP and was treated with many immunosuppressants including prednisolone, vincristine and azathioprine. These treatments were unsuccessful in addition to having side effects, so the treatment for her was discontinued. She hoped to be treated with traditional Chinese medicine. Details are shown in Fig. 4.

All cases did not get any disease of producing IFN-$\alpha$.

*Methods*: The oral administration dose of Hochu-ekki-to in these four cases was from 7.5 g to 20,0 g per day (0.27 g − 0.65 g / kg / day). Patients took this medicine three times a day before their meals.

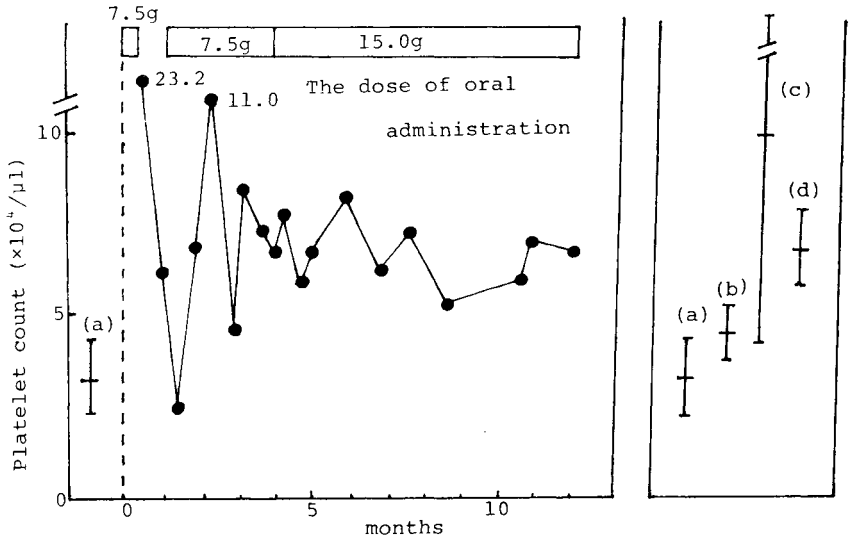


Fig 1. Details on case 1.
(a) ; Mean±ISD of platelet counts in Xiao-Chai-Hu-Tang administration. ($3.2\pm1.1\times10^4/\mu l$ ; n=46) (b) ; Mean±ISD of platelet counts in Jia-Wei-Gui-Pi-Tang administration. ($4.4\pm0.8\times10^4/\mu l$ ; n=10) (c) ; Mean±ISD of platelet counts in Bu-Zhong-Yi-Qi-Tang administration (7.5g). ($9.7\pm5.6\times10^4/\mu l$ ; n=7) (d) ; Mean±ISD of platelet counts in Bu-Zhong-Yi-Qi-Tang administration (15.0g) ($6.7\pm1.1\times10^4/\mu l$ ; n=10) (a)−(d) : $p<0.001$. (b)−(d) : $p<0.001$. (a)−(b) : $p<0.01$.

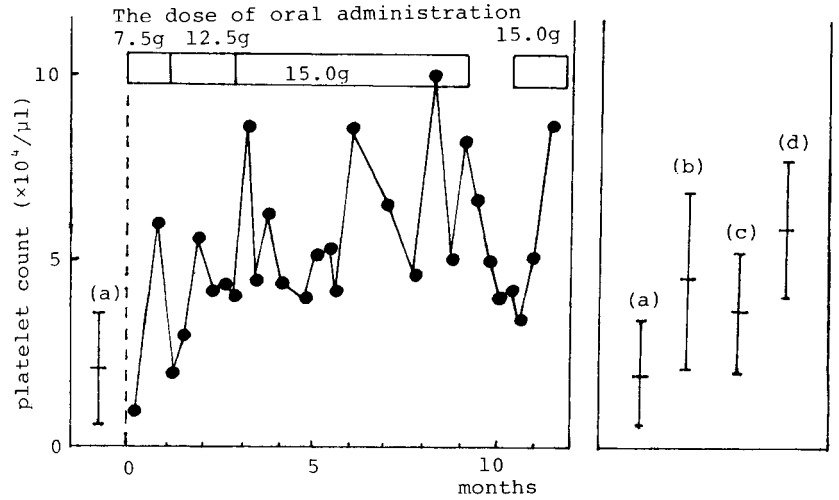


Fig 2. Details on case 2.
(a) ; Mean±ISD of platelet counts in Xiao-Chai-Hu-Tang administration. ($2.1\pm1.5\times10^4$/ul ; n=51) (b) ; Mean±ISD of platelet counts in Jia-Wei-Gui-Pi-Tang administration. ($4.5\pm2.4\times10^4/\mu l$;n=9) (c) ; Mean±ISD of platelet counts in Bu-Zhong-Yi-Qi-Tang administration (7.5−12.5g). ($3.7\pm1.6\times10^4/\mu l$ ; n=8) (d) ; Mean±ISD of platelet counts in Bu-Zhong-Yi-Qi-Tang administration (15.0g). ($5.9\pm1.9\times10^4/\mu l$ ; n=18) (a)−(d) : $p<0.001$. (a)−(c) : $p<0.01$.

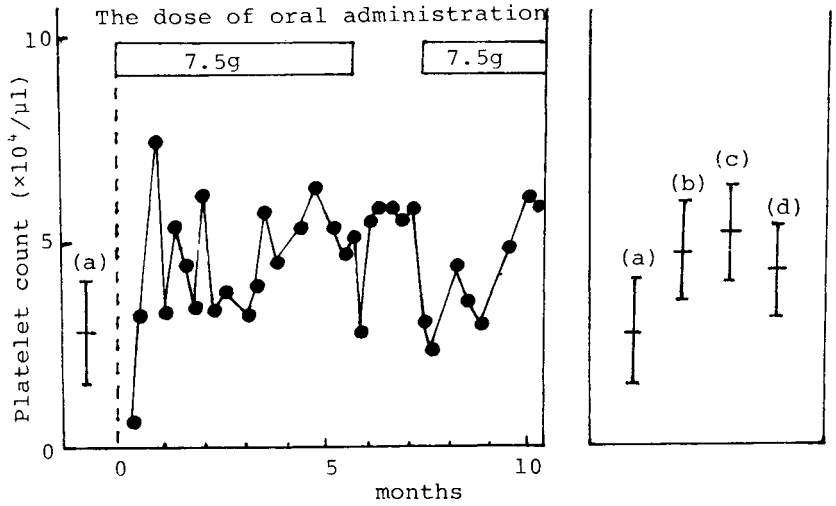


Fig 3. Details on case 3.
(a) ; Mean±ISD of platelet counts in no treatment. ($2.8\pm1.3\times10^4/\mu l$ ; n=27) (b) ; Mean± ISD of platelet counts in Bu-Zhong-Yi-Qi-Tang administration before stop. ($4.7\pm1.2\times10^4/\mu l$ ; n =18) (c) ; Mean±ISD of platelet counts in the discontinued term. ($5.1\pm1.2\times10^4/\mu l$ ; n =5) (d) ; Mean±ISD of platelet counts after readministration. ($4.2\pm1.2\times10^4/\mu l$ ; n =10) (a)−(b) : $p<0.001$. (a)−(c) : $p<0.001$.

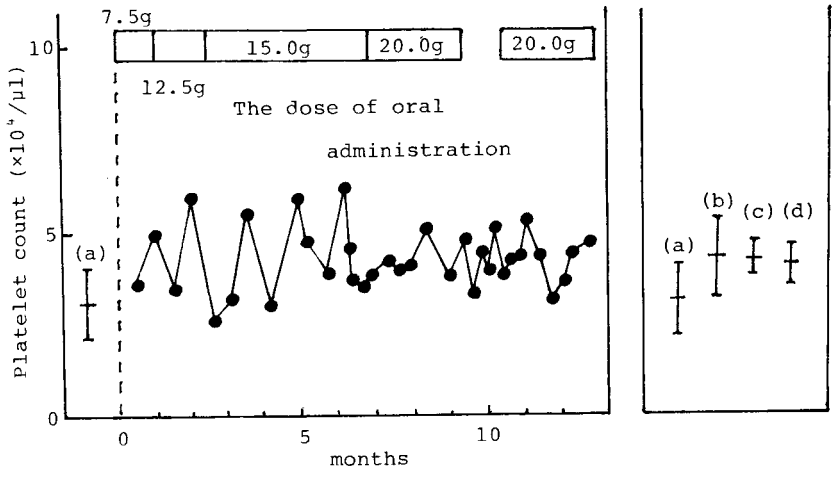


Fig 4. Details on case 4.
(a) ; Mean±ISD of platelet counts in no treatment. ($3.1\pm1.0\times10^4/\mu l$ ; n=56) (b) ; Mean± ISD of platelet counts in Bu-Zhong-Yi-Qi-Tang administration (7.5 g−15.0 g), ($4.2\pm1.1\times10^4/\mu l$ ; n=16) (c) ; Mean±ISD of platelet counts in Bu-Zhong-Yi-Qi-Tang administration (20.0g). ($4.2\pm0.6\times10^4/\mu l$ ; n =14) (d) ; Mean±ISD of platelet counts in the discontinued term. ($4.0\pm0.6\times10^4/\mu l$ ; n =5) (a)−(b) : $p<0.001$. (a)−(c) : $p<0.001$.

Table II Platelet count and immunological data before and after administration of the medicine.

| | weeks | before | 4 | 7 | 9 | 11 | 12 | 15 | 18 | 20 | 23 | 26 | 30 | 45 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case 1 | platelet (×10⁴/μl) | 3.3 | 6.1 | 6.9 | 11.0 | 4.6 | 8.4 | 6.7 | 5.9 | 6.7 | 9.3 | 6.2 | 7.1 | 6.8 |
| | MPV (fl) | 10.8 | 11.2 | 9.5 | 9.4 | 10.3 | 9.8 | 10.0 | 9.9 | 10.1 | 9.9 | 11.4 | 10.1 | 10.7 |
| | OKT 4 (%) | – | 41.7 | 33.7 | 32.5 | – | 42.5 | 35.0 | 34.5 | 39.2 | 36.8 | 36.4 | 30.4 | 37.7 |
| | OKT 8 (%) | – | 29.8 | 23.6 | 25.5 | – | 30.4 | 68.6 | 24.4 | 31.6 | 26.8 | 28.3 | 24.6 | 26.8 |
| | OKT 4/8 | – | 1.40 | 1.43 | 1.27 | – | 1.40 | 1.22 | 1.41 | 1.24 | 1.37 | 1.28 | 1.24 | 1.41 |
| | IgG (mg/dl) | 1560 | – | 1780 | 1660 | – | – | – | 1660 | 1510 | – | 1510 | 1670 | 1540 |
| | PA-IgG (ng/10⁷plt) | – | – | – | 28.6 | 133.2 | 31.5 | 44.9 | 24.0 | 82.6 | 21.0 | – | 71.0 | 67.1 |
| | weeks | before | 7 | 11 | 18 | 19 | 21 | 25 | 28 | 30 | 34 | 38 | 42 | 45 |
| Case 2 | platelet (×10⁴/μl) | 2.2 | 5.7 | 8.6 | 5.2 | 5.3 | 8.6 | 6.5 | 4.5 | 9.9 | 8.2 | 4.2 | 5.1 | 8.5 |
| | MPV (fl) | 10.2 | 9.4 | 9.2 | 11.2 | 9.7 | 9.6 | 10.2 | 11.1 | 9.7 | 10.1 | 10.2 | 9.8 | 8.9 |
| | OKT 4 (%) | 39.1 | – | 41.8 | 47.7 | 41.2 | 49.3 | 44.4 | 45.0 | 47.3 | 40.8 | 44.9 | 53.7 | 49.4 |
| | OKT 8 (%) | 29.5 | – | 27.7 | 23.8 | 22.4 | 24.0 | 23.4 | 26.3 | 26.7 | 24.3 | 24.5 | 22.4 | 25.4 |
| | OKT 4/8 | 1.33 | – | 1.51 | 2.00 | 1.84 | 2.06 | 1.90 | 1.71 | 1.77 | 1.68 | 1.83 | 2.40 | 1.94 |
| | IgG (mg/dl) | 928 | – | – | 843 | 910 | 898 | 948 | 1070 | 1080 | 1050 | 874 | 873 | 1060 |
| | PA-IgG (ng/10⁷plt) | – | 18.6 | 19.6 | 30.0 | 30.8 | 14.9 | 76.3 | 43.2 | 45.9 | 46.9 | 60.2 | 71.9 | 31.0 |
| | weeks | before | 2 | 3 | 5 | 7 | 8 | 14 | 16 | 18 | 22 | 25 | 31 | 35 |
| Case 3 | platelet (×10⁴/μl) | 1.4 | 3.1 | 7.5 | 5.4 | 3.4 | 6.2 | 5.7 | 5.1 | 6.2 | 5.1 | 5.5 | 3.5 | 4.8 |
| | MPV (fl) | 7.4 | 7.8 | 11.7 | 12.9 | 8.9 | 12.1 | 8.8 | 8.7 | 8.0 | 12.6 | 11.0 | 8.2 | 10.7 |
| | OKT 4 (%) | 36.6 | 38.3 | 35.6 | 35.1 | 34.5 | 38.2 | 35.3 | 39.3 | 33.7 | 34.5 | 38.3 | 30.1 | 38.3 |
| | OKT 8 (%) | 46.8 | 36.5 | 34.8 | 45.3 | 42.2 | 39.2 | 46.3 | 38.0 | 45.5 | 40.6 | 38.1 | 47.8 | 40.6 |
| | OKT 4/8 | 0.78 | 1.05 | 1.02 | 0.77 | 0.82 | 0.97 | 0.76 | 1.04 | 0.74 | 0.85 | 1.01 | 0.63 | 0.94 |
| | IgG (mg/dl) | – | 1290 | 1310 | 1240 | 1210 | 1340 | 1380 | 1410 | 1420 | 1300 | 1270 | 1390 | 1590 |
| | PA-IgG (ng/10⁷plt) | 241.9 | 177.9 | 76.4 | 124.9 | 123.9 | 115.4 | 82.8 | 139.6 | 128.7 | 214.8 | 129.4 | 76.1 | 141.8 |
| | weeks | before | 2 | 5 | 6 | 9 | 16 | 19 | 24 | 26 | 28 | 32 | 36 | 39 |
| Case 4 | platelet (×10⁴/μl) | 2.1 | 3.5 | 3.3 | 5.8 | 5.5 | 4.6 | 6.2 | 4.2 | 4.0 | 4.9 | 4.7 | 5.0 | 4.3 |
| | MPV (fl) | 12.5 | 11.3 | 11.0 | 12.1 | 11.1 | 10.7 | 11.7 | 11.8 | 12.6 | 11.5 | 11.5 | 10.6 | 10.4 |
| | OKT 4 (%) | 31.3 | – | 34.2 | 33.7 | – | 32.8 | 38.1 | 37.7 | 34.4 | 40.2 | 30.6 | 37.9 | 35.7 |
| | OKT 8 (%) | 43.5 | – | 43.4 | 50.4 | – | 43.3 | 30.3 | 43.0 | 43.4 | 42.0 | 42.6 | 42.3 | 44.0 |
| | OKT 4/8 | 0.72 | – | 0.79 | 0.67 | – | 0.76 | 0.97 | 0.88 | 0.79 | 0.96 | 0.74 | 0.90 | 0.81 |
| | IgG (mg/dl) | 1480 | – | – | – | 1510 | – | 1560 | 1440 | 1690 | 1690 | 2050 | 1680 | 1620 |
| | PA-IgG (ng/10⁷plt) | – | 121.7 | 101.2 | 51.7 | 88.5 | 124.2 | 95.9 | 138.8 | 141.8 | 146.3 | 246.9 | 115.4 | 231.1 |

normal range ; MPV : 6.8−10.2
OKT : 25−56
OKT8 : 17−44
OKT 4/8 : 0.6−2.9
PA-IgG : 9.0−25.0

All cases were administered medicine from the same manufacturing lot in order to assure consistent quality.

Platelet count and mean platelet volume (MPV) were measured with a COULTER counter (COULTER ELECTRONICS, INC. USA).

PA - IgG was measured using the micro ELISA method and T-cell subset was measured with direct immunofluoroscopy using monoclonal antibody for the OKT series.

Serum IFN-$\alpha$ and IFN-$\gamma$ were measued with highly sensitive monoclonal-antibody-based immunoradiometric assays (Sucrosep, Boots-Celltech Ltd. Slough, UK). IFN-$\beta$ was measured by the EIA method using monoclonal-antibody. Serum samples were collected under non-infectious symptoms and stored at -20°C.

## Results

In all cases, platelet counts increased significantly with the administration of Hochu-ekki-to ($p<0.001$) (Figs. 1, 2, 3 and 4).

The dose dependency of this medicine did not correlate with platelet count. When platelet count increased in all cases, PA-IgG tended to decrease but there was not a direct correlation between PA-IgG and platelet count.

In the course of taking this medicine, the data of serum IgG, OKT 4, OKT 8, OKT 4/8 and MPV did not change significantly (Table II) and other data from examinations for RBC, WBC, GOT, GPT, BUN and creatinine were within normal limits as well as the physical condition.

Serum IFN-$\alpha$ was raised in all cases after administration but it could not be detected before administration. Serum IFN-$\beta$ and IFN-$\gamma$ did not change before or after administration (Fig. 5).

Lag time existed in the decrease or the recovery of the platelet counts when administration of this medicine was stopped.

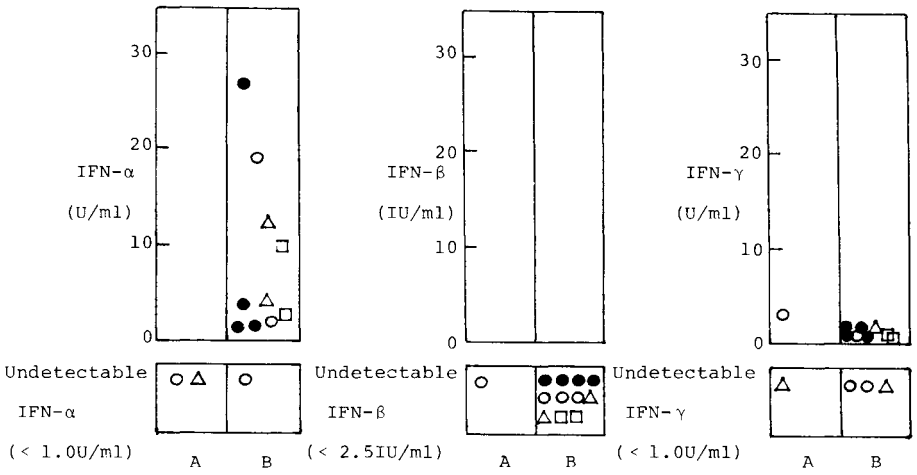


Fig 5. Serum IFN-$\alpha$, IFN-$\beta$ and IFN-$\gamma$ concentration in four cases with no infectious symptoms.
A=before the administration of Bu-Zhong-Yi-Qi-Tang. B=after the administration of Bu-Zhong-Yi-Qi-Tang. ● case 1. ○ case 2. △ case 3. □ case 4.

## Discussion

Hochu-ekki-to is an extract of a mixture of herbs, which is well known in traditional Chinese medicine. It is used usually for hemorrhoids, loss of appetite or maintaining physical ability.

This medicine was used in four cases with ITP and obtained successful results. In all cases, side effects were not exhibited at all during the trial period of this medicine.

Hochu-ekki-to contains four kinds of herbs (Astragali Radix, Angelicae Radix, Bupleuri Radix and Cimicifuge Rhizoma) that function as interferon inducer. Interferon which affects cell immunity, must suppress non-specifically extensive types of viral proliferation, on the other hand, its effect on macrophages or lymphocytes is related to immuno-regulation. Since ITP is considered to be caused by some antigen-antibody reaction, the role of interferon is important for the suppression of viral proliferation or for immuno-regulation. Now IFN-$\alpha$ is used in myeloproliferative disorders or hepatitis B infections. However, bone marrow suppression is exhibited as its side effect. A recent report has described that the treatment of IFN-$\alpha$ was effective in severe steroid-refractory ITP patients.[4] This study showed that serum IFN-$\alpha$ was increased in all cases after administration of this medicine. But the proportion of increased platelet counts was low compared with their result. It was speculated that this difference was from the injection of IFN-$\alpha$ or the production of it in the body.

It is difficult to understand that this medicine acts on the immunosuppression in the body for the data of serum IgG or OKT 4/8.

In bone marrow examination, the megakaryocyte form was matured slightly in all cases after administration of this medicine, but the number of megakaryocytes did not change. As PA-IgG was decreased and platelet count was increased, the speculation was made that this medicine decreased the antibodies for platelets or this medicine decreased the binding of anti-platelet antibodies for platelets. This treatment can be a new approach for the patients with ITP.

## 和文抄録

慢性特発性血小板減少性紫斑病 (ITP) は，抗血小板抗体による持続的な血小板減少症として理解されている。

多くの免疫抑制剤や摘脾が，難治性のITPに対し治療としてなされているが，著者らは4例のITP患者に対し，漢方製剤である補中益気湯を使用した。全例において補中益気湯使用後，1～3週間以内に有意の差 ($p<0.001$) をもって血小板数は増加した。それと共に，PA-IgGは血小板増加時には減少した。血清中のインターフェロン $\alpha$ は，補中益気湯使用前に比し，使用後は増加した。この薬剤は，内因性インターフェロンの産生により，血小板に対する抗体の減少作用，あるいは血小板への抗体付着の抑制作用を有するものと推測される。

本薬剤による副作用は認められず，ITP 患者に対し治療剤として有用であると考えられる。

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