Herpes Zoster in rheumatoid arthritis patients receiving tofacitinib, a single center experience from Taiwan

Yen-Ju Chen, MDa,b,c, Yi-Ming Chen, MD, PhDab,c,d,e,f, Wen-Nan Huang, MD, PhDab,d, Hsin-Hua Chen, MD, PhDab,d,e,f,g, Tsai-Ling Liao, PhDab,f, Jun-Peng Chen, MSb, Tsu-Yi Hsieh, MD, BScb,h, Yi-Hsing Chen, MD, PhDab,d, Der-Yuan Chen, MD, PhDj,i,∗

Abstract

In clinical trials of tofacitinib for rheumatoid arthritis (RA), Japanese and Korean patients had higher incidence of herpes zoster (HZ) than subjects from elsewhere; however, post-market data from Asia are lacking. Hence, we investigated the incidence of HZ and its risk factors in Taiwanese RA patients receiving tofacitinib. At a medical center in Taichung, Taiwan, we enrolled patients with active RA treated with tofacitinib between January 4, 2015 and December 9, 2017, following unsuccessful methotrexate therapy and no tofacitinib exposure RA patients as a control group. Demographic characteristics, interferon-gamma levels, and lymphocyte counts were compared. Among 125 tofacitinib-treated RA patients, 7 developed HZ, an incidence rate of 3.6/100 person-years. Patients with HZ had shorter disease duration than those without, but higher frequency of prior HZ. Baseline interferon-gamma levels and HLA-DR* activated T cell counts were positively correlated and significantly lower in patients with HZ than without. Strikingly, 5/7 HZ cases occurred within 4 months of starting tofacitinib therapy. Incidence of HZ in tofacitinib-treated Taiwanese RA patients is lower than rates in Japan or Korea, and commensurate with the global average. HZ may occur soon after commencing tofacitinib therapy. The role of interferon-gamma and activated T cells in tofacitinib-related HZ deserves further investigation.

Abbreviations: DAS28 = 28-joint disease activity score, ELISA = enzyme-linked immunosorbent assay, HZ = herpes zoster, IFN-γ = interferon-gamma, IL-17RB = IL-17 receptor B, JAK = Janus kinase, RA = rheumatoid arthritis, SNP = single nucleotide polymorphism, VZV = varicella zoster virus.

Keywords: herpes zoster, rheumatoid arthritis, tofacitinib

1. Introduction

Herpes zoster (HZ) is a prevalent and potentially debilitating illness caused by varicella zoster virus (VZV) reactivation; its common complications include post-herpetic neuralgia, ophthalmic involvement, and neurological sequelae. Patients with rheumatoid arthritis (RA) have increased risk for HZ,[2,3] and iatrogenic risk factors include glucocorticoids, methotrexate, and biologic agents used to treat RA.[6] Weakened host cell-mediated immunity is an important etiologic factor for varicella zoster reactivation.[7]

Tofacitinib is a small molecule Janus kinase inhibitor, approved for treating RA since 2012. It has efficacy similar to other biologics, but has been associated with significantly increased incidence of HZ in clinical trials and long-term extension studies.[10] Moreover, the incidence of HZ among tofacitinib-treated RA patients in clinical trials was higher in...
Japan (8.0 per 100 person-years) and Korea (8.4 per 100 person-years), than that in Taiwan/China (3.0 per 100 person-years), Thailand/Malaysia/Philippines (4.0 per 100 person-years), or the global rate (4.0 per 100 person-years); the reason for differential susceptibility remains obscure.

Analysis of United States health plan data showed that tofacitinib-treated RA patients had comparable incidence of HZ to that reported in clinical trials (3.9 per 100 person-years). To the best of our knowledge, there are no corresponding post-market data from Asian patients with RA using tofacitinib; such data are needed to establish whether the incidence of HZ varies between Asian countries. Hence, this study investigated the incidence of HZ and its risk factors in Taiwanese patients with RA who received tofacitinib therapy.

2. Methods

2.1. Study population

From April 1, 2015 until September 12, 2017, at a medical center in Taichung, Taiwan, we consecutively recruited patients aged ≥18 years who had active RA according to American College of Rheumatology/European League against Rheumatism criteria[11] and were treated with tofacitinib, due to responding inadequately to methotrexate. Subjects were excluded if tofacitinib exposures were <6 months to avoid underestimating the incidence of HZ. RA patients without prior tofacitinib exposure were also enrolled as a control group. Disease activity was assessed using the 28-joint disease activity score (DAS28).[12] Taichung Veterans General Hospital Ethics Committee approved the study (CE14149B), and waived requirement for informed consent because patient data were anonymized prior to analysis.

2.2. HZ diagnosis

HZ was diagnosed based on rheumatologists’ clinical assessment, use of anti-viral therapy, and medical records. The positive predictive value of this approach was reported to identify 97.5% of HZ cases based on large validation studies.[13] History of HZ before tofacitinib was excerpted from medical records.

2.3. Cytokines detection and lymphocyte subpopulations

Plasma interferon-gamma (IFN-γ) levels were measured using enzyme-linked immunosorbent assay (ELISA) method (Cellestis Ltd., Victoria, Australia) according to the manufacturer’s instructions. White blood cells (WBC), total neutrophils and lymphocytes were counted at baseline, after 4 weeks and 6 months of tofacitinib treatment. Lymphocyte subpopulations after the emergence of HZ during tofacitinib therapy, and in consecutive controls without HZ, were quantified by flow cytometry (Beckman Coulter Inc., CA), to investigate associations between lymphocyte subpopulations and HZ; subset markers analyzed included: CD3+ (total T cells), CD3+/CD4+ (T helper cells), CD3+/CD8+ (cytotoxic T cells), CD3+/HLA-DR+ (activated T cells), CD19+ (B cells), and CD16+/CD56+ (natural killer cells).

2.4. Statistical analysis

All data were analyzed using IBM SPSS version 22.0 (International Business Machines Corp, New York, USA). For data that were not normally distributed by Kolmogorov–Smirnov test, Chi-square, and Kruskal-Wallis tests were used to compare categorical and continuous variables. The association between IFN-γ levels and HLA-DR+ activated T cell counts in tofacitinib-treated RA patients was calculated by Spearman correlation. The crude incidence rate of HZ was calculated by dividing the number of cases that arose during tofacitinib exposure by total case person-years. P < 0.05 was considered statistically significant.

3. Results

Between April 1, 2015 and September 12, 2017, 125 patients received tofacitinib (median observation period: 1.7 years), with a total exposure of 195 patient-years; 7 developed HZ, a crude incidence rate of 3.6 (1.5–7.4) per 100 person-years. Twenty RA patients without tofacitinib were also included in the analysis as negative control group. Patients with versus without HZ had a shorter disease duration and higher frequency of previous HZ (Table 1). However, patients with zoster had lower baseline plasma IFN-γ levels compared with those without herpes zoster and no tofacitinib exposure group (pg/mL, 2.0, 1.5–2.5 vs 3.0, 2.0–4.0 vs 3.8, 2.5–5.4, P < 0.05, Table 2 and Fig. 1C). We also found a tendency of neutrophil counts increase at 4th week (7859, 4371–8269 vs 4819, 3566–6415, P = 0.082) and decrease at 6th month (5843, 4242–6974 vs 5052, 3477–6901, P = 0.57) after tofacitinib treatment in patients with zoster infection compared with no herpes zoster group.

To study whether zoster infection were related to lymphocyte subpopulation changes, flow cytometry analysis was performed in 7 patients when zoster infection occurred, 22 consecutive patients without herpes zoster during tofacitinib treatment and 20 patients without tofacitinib exposure (Table 2). Lymphocyte subpopulation in the non-zoster tofacitinib group was measured after longer period of tofacitinib treatment compared with the zoster group (months, 21.7, 14.2–25.2 vs 9.3, 0.7–15.0, P < 0.05). Flow cytometry analysis workflow of CD3-positive, HLA-DR-positive activated T cell counts was shown in Fig. 1A. The activated T cell counts were significantly lower in tofacitinib-treated RA patients with HZ than without tofacitinib exposure (30.2, 14.0–61.9 vs 102.4, 60.5–175.0, P < 0.05, Fig. 1B); moreover, plasma IFN-γ levels and HLA-DR+ activated T cell counts in tofacitinib-treated patients were positively correlated (r=0.427, P < 0.05). B cell counts in tofacitinib-treated RA patients without HZ were also significantly lower compared with the no tofacitinib exposure group (119.8, 52.2–175.2 vs 241.4, 174.9–374.0, P < 0.005). However, other lymphocyte subpopulations did not differ significantly between patients with or without HZ.

Table 3 shows the disease status and treatment of the 7 on-study HZ cases; all 7 were uncomplicated, single-dermatome HZ, and 5 (71.4%) developed <4 months after starting tofacitinib treatment. All were treated with valacyclovir with fair outcome. Tofacitinib was discontinued for 2 to 3 weeks during HZ infection and resumed afterwards without further complications.

4. Discussion

Our study demonstrated that Taiwanese patients receiving tofacitinib to treat RA had incidence of HZ (3.6 per 100 person-years) lower than Japanese or Korean counterparts, and commensurate with the global average. Varicella zoster reactivation in RA patients treated with tofacitinib was associated with shorter RA duration, history of HZ, lower baseline IFN-γ levels,
Table 1
Demographic and laboratory data of tofacitinib-treated RA patients with versus without herpes zoster, and no tofacitinib exposure patients.

| Data show median (interquartile range) or n (%) | No tofacitinib exposure (n = 20) | With tofacitinib and no herpes zoster (n = 118) | With tofacitinib and herpes zoster (n = 7) | P-value* |
|------------------------------------------------|-------------------------------|-----------------------------------------------|---------------------------------|----------|
| Age, yr                                         | 63.0 (52.5–67.5)              | 58.5 (46.0–66.0)                             | 55.0 (49.0–66.0)                | .416     |
| Sex (male)                                      | 17 (85.0)                     | 21 (17.8)                                    | 1 (14.3)                        | <.001*** |
| RA duration, yr                                 | 12.0 (10.0–15.0)              | 12.0 (7.0–13.0)                              | 6.0 (2.0–8.0)                   | <.001*** |
| 28-joint disease activity score                 | 3.7 (2.4–5.1)                 | 6.0 (4.6–6.5)                                | 5.7 (3.8–6.5)                   | <.001*** |
| Rheumatoid factor positive                      | 16 (80.0)                     | 94 (81.7)                                    | 4 (51.7)                        | .283     |
| Anti-citrullinated protein antibody positive     | 14 (73.7)                     | 59 (70.2)                                    | 4 (66.7)                        | .934     |
| History of herpes zoster                        | -                             | 17 (14.4)                                    | 7 (100)                         | <.001    |
| Diabetes mellitus                               | 3 (15.0)                      | 16 (15.3)                                    | 3 (42.9)                        | .158     |
| Chronic obstructive pulmonary disease           | 0 (0)                         | 3 (2.5)                                      | 0 (0.0)                         | .764     |
| Cancer                                          | 0 (0)                         | 9 (7.6)                                      | 2 (28.6)                        | .116     |
| Number of previous biologics                    | 0                             | 50 (42.4)                                    | 4 (57.1)                        | <.005    |
| 0                                              | 0                             | 15 (75.0)                                    | 47 (39.8)                       | 1 (14.3) |
| 1                                              | 5                             | 25 (20.0)                                    | 21 (17.8)                       | 2 (28.6) |
| Erythrocyte sedimentation rate (mm/hr)          | 21.0 (12.5–25.0)              | 39.0 (29.0–59.0)                             | 34.0 (20.0–43.0)                | <.001*** |
| C-reactive protein (mg/dl)                      | 0.5 (0.2–1.7)                 | 1.3 (0.6–2.3)                                | 0.9 (0.0–4.0)                   | .086     |
| White blood cell count                          | 7215 (5775–9860)              | 7815 (6150–9680)                             | 8960 (7570–11970)               | .321     |
| After 4 weeks tofacitinib therapy              | 7550 (5500–9160)              | 7200 (5783–8820)                             | 8820 (7500–11400)               | .120     |
| After 6 months of tofacitinib therapy           | 8175 (5490–9225)              | 7340 (5740–9590)                             | 8610 (6000–9280)                | .910     |
| Lymphocyte count                                | 2302 (1489–2532)              | 1444 (1017–1913)                             | 1696 (876–2422)                 | <.001*** |
| After 4 weeks tofacitinib therapy              | 2075 (1456–2755)              | 1747 (1175–2208)                             | 1253 (780–2763)                 | .183     |
| After 6 months of tofacitinib therapy           | 2058 (1206–2867)              | 1619 (1146–2129)                             | 1767 (1383–1973)                | .324     |
| Neutrophil count                                | 4833 (3299–6553)              | 5613 (4008–7296)                             | 6003 (4572–9395)                | .215     |
| After 4 weeks tofacitinib therapy              | 4868 (3302–5833)              | 4819 (3386–6410)                             | 7839 (4371–9269)                | .082     |
| After 6 months of tofacitinib therapy           | 5069 (3407–6138)              | 5052 (3477–6901)                             | 5843 (4234–6794)                | .557     |
| Glucocorticoids (mg/day)                        | 5.0 (0.2–10.0)                | 5.0 (5.0–10.0)                               | 10 (5.0–10.0)                   | .531     |
| Methotrexate                                    | 5.0 (0.2–10.0)                | 76 (84.4)                                    | 5 (71.4)                        | .378     |
| Hydroxychloroquine                              | 16 (80.0)                     | 79 (86.9)                                    | 4 (57.1)                        | .532     |
| Leflunomide                                     | 11 (55.0)                     | 27 (22.9)                                    | 1 (14.3)                        | .053     |
| Sulfasalazine                                   | 0 (0)                         | 51 (43.2)                                    | 3 (42.9)                        | .306     |
| Cyclosporine                                    | 5 (25.0)                      | 12 (10.2)                                    | 1 (14.3)                        | .940     |

RA=rheumatoid arthritis.

*Comparisons between groups using Chi-square test (binary variables) or Kruskal-Wallis test (continuous variables).

P-post-hoc test with Dunn-Bonferroni method.

Table 2
Interferon-γ levels and lymphocyte counts in tofacitinib-treated rheumatoid arthritis patients with versus without herpes zoster, and no tofacitinib exposure patients.

| Data show median (interquartile range) or n (%) | No tofacitinib exposure (n = 20) | With tofacitinib and no herpes zoster (n = 22) | With tofacitinib and herpes zoster (n = 7) | P-value* |
|------------------------------------------------|-------------------------------|-----------------------------------------------|---------------------------------|----------|
| Age                                            | 63.0 (52.5–67.5)              | 61.5 (49.3–65.3)                              | 55.0 (49.0–66.0)                | .574     |
| Gender                                         | 17 (85.0)                     | 4 (18.2)                                      | 1 (14.3)                        | <.001    |
| Baseline IFN-γ, pg/mL                          | 3.8 (2.5–5.4)                 | 3.0 (2.0–4.0)                                 | 2.0 (1.5–2.5)                   | <.05     |
| Activated T cells (CD3+/HLA-DR*)               | 102.4 (60.5–175.0)            | 73.6 (65.3–129.8)                             | 30.2 (14.0–61.9)                | <.005*   |
| T cells (CD3⁺)                                 | 1664 (1030–1825)              | 1008 (612–1667)                               | 1027 (600–1509)                 | <.05     |
| T helper cells (CD3⁺/CD4⁺)                     | 935 (605–1162)                | 636 (371–974)                                 | 579 (416–966)                   | .103     |
| Cytotoxic T cells (CD3⁺/CD8⁺)                  | 475 (339–651)                 | 301 (237–534)                                 | 286 (148–721)                   | .303     |
| T helper+cytotoxic T cell ratio                | 2.4 (1.2–3.0)                 | 1.5 (1.2–2.2)                                 | 2.1 (1.7–3.7)                   | .449     |
| B cells (CD21⁺)                                | 251 (148–438)                 | 260 (96–512)                                  | 313 (75–830)                    | .920     |
| Natural killer cells (CD16⁺/CD56⁺)             | –                             | 21.7 (14.2–25.2)                              | 9.3 (0.7–15.0)                  | <.005    |

IFN-γ=interferon-gamma.

*Kruskal-Wallis test.

Tofacitinib treatment period when lymphocyte subpopulation was measured.

P-post-hoc test with Dunn-Bonferroni method.

P<.05 in no tofacitinib exposure group versus with tofacitinib and herpes zoster group.
and lower activated T cell counts. Strikingly, >70% of HZ cases occurred during the first 4 months of tofacitinib therapy; rheumatologists and patients with RA should be aware of this heightened HZ risk shortly after starting tofacitinib.

Involvement of the Janus kinase/signal transducer and activator of transcription pathway in the anti-viral actions of IFN types 1 and 2,[14] may explain increased susceptibility to HZ associated with tofacitinib. Consistent with HZ risk observed in clinical trials of anti-IFN biologicals,[15] we have discovered that HZ infection during tofacitinib treatment is associated with lower baseline IFN-γ levels. This novel finding supports a rationale for HZ risk stratification before tofacitinib therapy.

In tofacitinib clinical trials and long-term extension studies, Asian race was an independent risk factor for HZ.[9] Besides, real-world studies demonstrated that older age, women, higher glucocorticoid dosage, and greater prior hospitalization number were associated with higher zoster infection risks.[16] Ours are the first post-market single center data in ethnically Taiwanese RA

| Prior history of zoster | Tofacitinib duration | Glucocorticoids, mg/d | Methotrexate, mg/wk | Baseline DAS28 | IFN-γ, pg/mL | Activated T cells |
|-------------------------|----------------------|-----------------------|---------------------|----------------|--------------|------------------|
| 9                       | 0.25                 | 10.0                  | 7.5                 | 7.0            | None         | 3.0              |
| 7                       | 0.5                  | 10.0                  | 0.0                 | 2.6            | 5.0          | 37.5             |
| 15                      | 1.0                  | 5.0                   | 15.0                | 3.8            | Tocilizumab (0.8) | 2.0          |
| 32                      | 3.0                  | 10.0                  | 15.0                | 5.9            | Adalimumab (2.3), Tocilizumab (2.3) | 5.0          |
| 206                     | 4.0                  | 20.0                  | 15.0                | 5.7            | None         | 4.0              |
| 139                     | 10.0                 | 5.0                   | 15.0                | 5.4            | Abatacept (1.0), Rituximab (1.5) | 4.0          |
| 18                      | 20.0                 | 5.0                   | 0.0                 | 6.5            | None         | 4.0              |

DAS28 = 28-joint disease activity score; IFN-γ = interferon-gamma.

*All subjects were treated with valacyclovir.
patients, who have incidence of HZ commensurate with that of predominantly European populations, but lower than Japanese or Koreans. Iwamoto et al.\textsuperscript{(17)} reported 5 HZ cases in Japanese RA patients receiving tofacitinib, an incidence rate of 18.7 per 100 person-years, which is much higher than in our study or clinical trials.\textsuperscript{(9)} Human leukocyte antigen gene and IL-10 polymorphism were associated with susceptibility to HZ in Taiwan and Korean population.\textsuperscript{(18,19)} Genome-wide association data indicate that 2 polymorphisms near CD83 and IL-17 receptor B (IL-17RB) might partly explain increased susceptibility to HZ in Japanese patients.\textsuperscript{(17)} A single nucleotide polymorphism (SNP) near CD83 (and LINC01108) was associated with increased risk of HZ events after adjusting for age, lymphocyte counts, ethnicity, and concomitant methotrexate. The frequency of CD83 allele was rare in Japanese compared with other part of the world.\textsuperscript{(17)} As a marker of dendritic cell maturation and B cell activation marker, CD83 is down-regulated after zoster virus infection, indicating a plausible mechanism. Besides, another risk SNP near IL-17RB was associated with rapid zoster onset.\textsuperscript{(17)} This risk allele was common in Japan (~17% in the general Japanese population) but <0.2% in Caucasians.\textsuperscript{(17)} IL-17RB is highly expressed by invariant natural killer T cells and diminished IFN-γ production due to invariant natural killer T cell deficiency is also linked to disseminated varicella.\textsuperscript{(20)} Tofacitinib was also associated with diminished natural killer cell counts in psoriasis patients,\textsuperscript{(21)} while a smaller CD8+ T cell population predicts infectious adverse events in tofacitinib-treated RA patients.\textsuperscript{(22)}

All 7 HZ cases had an earlier occurrence prior to tofacitinib therapy. It was also striking and never reported by other studies that 100% zoster patients in our study had prior history of HZ infection (9–206 months before tofacitinib exposure) compared with only 14% in the non-zoster group. It is hypothesized that recurrence of herpes zoster is associated with decline of VZV-specific cellular immunity.\textsuperscript{(31)} Endogenous exposure to VZV due to reactivation may facilitate to maintain robust VZV-memory immunity. However, in tofacitinib-treated patients, the zoster-specific memory immunity from prior exposure might have been suppressed by Janus kinase (JAK) inhibition, leading to earlier recurrent zoster infection. Besides, we found that patients with HZ during tofacitinib therapy had numerically higher WBC and neutrophil counts than those without HZ at 4th week. Moreover, neutrophil counts seemed to decrease at 6th month following tofacitinib treatment. Post-viral reactive phenomenon may only partly contribute to the kinetic changes of neutrophil counts in those with zoster infection. Further investigation of larger sample size is needed.

Interestingly, we observed a trend of lower activated T cell counts in tofacitinib-treated patients with HZ compared with uninfected counterpart (30.2 vs 73.6), and the HLA-DR+ activated T cell counts correlated positively with IFN-γ levels. The significant lower activated T cell counts in patients with HZ compared with no tofacitinib exposure group can be attributable to JAK inhibition. Since HLA-DR expression by proliferating cytotoxic T cells correlates with hepatitis C virus clearance,\textsuperscript{(23)} we postulated that HZ infection might also link to the observed lower T cell activation in HZ group. Taken together, these results suggest that decreased activated T cell count and IFN-γ production might contribute to impaired cell-mediated immunity, which enables quiescent VZV to reactivate.

Importantly, the time to HZ after tofacitinib exposure was surprisingly short. In an earlier study, we showed that RA patients receiving anti-tumor necrosis factor agents and other biologic classes had significantly shorter time to HZ occurrence than those receiving non-biologics (1.7 and 2.3 vs 4.6 years).\textsuperscript{(6)} However, the time to HZ after tofacitinib therapy in this study was even shorter (median: 3 months). Prior reports of HZ events in tofacitinib phase I, II, III and long-term extension studies showed the median time to first HZ event was 1.6 years.\textsuperscript{(9)} Although the incidence of HZ did not increase with longer tofacitinib exposure (<8.5 years),\textsuperscript{(4)} our data suggest a need for heightened vigilance during the first 4 months. No subjects in this study had been immunized against HZ because this is not covered by Taiwan national health insurance. However, HZ immunization has been shown to be safe if administered 2 to 3 weeks before initiating tofacitinib therapy.\textsuperscript{(24)}

Our study has several limitations. First, the patient sample size is smaller than clinical trial cohorts. Besides, median tofacitinib exposure was only 1.7 years. Second, no HZ specificity was tested in our study. IFN-γ production in response to varicella zoster antigen and flow cytometric intracellular staining for IFN-γ producing HLA-DR-positive activated T cells were not performed. We cannot assure that zoster-specific memory immunity was suppressed by JAK inhibition. The mechanism responsible for differences in baseline IFN-γ levels remains unknown. We could not exclude the potential effects of previous biological treatment, concomitant glucocorticoids, and disease-modifying anti-rheumatic drugs to lower baseline IFN-γ levels since 3 of 7 zoster patients had previous biologics exposure. However, the distribution of concomitant medication and prior biologics were balanced in 2 groups. Further phenotyping of HLA-DR-positive T cells would be useful. Third, lymphocyte subpopulations were only measured during tofacitinib therapy and the population dynamics of activated T cells remain obscure. Notwithstanding these limitations, our study has shown that Taiwanese Chinese patients with RA have incidence of HZ during tofacitinib therapy commensurate with the global average. Last, we excluded subjects with tofacitinib exposure <6 months. In total, there were 4 cases of RA patients receiving tofacitinib <6 months. None of them developed herpes zoster infection. Before the study was conducted, we chose to exclude subjects receiving tofacitinib <6 months because the limited observation period of tofacitinib exposure might underestimate the risk of zoster. However, after investigation, we found that zoster may occur soon after commencing tofacitinib therapy. Prior real-world study also used tofacitinib start dates as the index date, which may include HZ events that developed rapidly following tofacitinib therapy.\textsuperscript{(25)} Therefore, exclusion of subjects with <6 months of tofacitinib treatment may bias zoster incidence toward overestimation.

In conclusion, our study suggested that lower baseline IFN-γ levels and activated T cell counts may be related to HZ infection in RA patients with JAK inhibition. More studies with HZ specificity are needed to clarify our findings of reduced IFN-γ levels and activated T cell counts in tofacitinib-treated RA patients.

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Author contributions

Conceptualization: Yen-Ju Chen, Yi-Ming Chen, Der-Yuan Chen.

Data curation: Yen-Ju Chen, Yi-Ming Chen.

Formal analysis: Yi-Ming Chen.

Investigation: Yen-Ju Chen, Yi-Ming Chen, Wen-Nan Huang, Hsin-Hua Chen, Tsai-Ling Liao, Jun-Peng Chen, Tsu-Yi Hsieh, Yi-Hsing Chen, MD, Der-Yuan Chen.

Methodology: Yen-Ju Chen, Yi-Ming Chen, Der-Yuan Chen.

Project administration: Yi-Ming Chen, Der-Yuan Chen.

Resources: Yi-Ming Chen, Der-Yuan Chen.

Supervision: Der-Yuan Chen.

Visualization: Yi-Ming Chen, Der-Yuan Chen.

Writing – original draft: Yen-Ju Chen, Yi-Ming Chen.

Writing – review & editing: Yi-Ming Chen, Wen-Nan Huang, Hsin-Hua Chen, Tsai-Ling Liao, Jun-Peng Chen, Tsu-Yi Hsieh, Yi-Hsing Chen, MD, Der-Yuan Chen.

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