polymorphism patients, the amount of RANTES in the serum was significantly increased after 4-week 1(OH) vitamin D3-treatment. The amounts of IL4, IFN-γ, IP-10, MCP-1 in the serum were significantly decreased after 4-week 1(OH) vitamin D3-treatment. The administration of 1 (OH) vitamin D3 could reduce the high IP-10 status that is reported to be difficult-to-treat. Then, we compared the amounts of 10 cytokines between 1(OH) vitamin D3/Peg-IFN/RBV group and Peg-IFN/RBV group at 0 week and 12 weeks after the Peg-IFN/RBV treatment. The amounts of cytokines in the patients treated with 1(OH) vitamin D3/Peg-IFN/RBV at 0 week were affected by 4 weeks 1(OH) vitamin D3 pre-treatment. The amounts of IP-10 in the patients treated with 4 weeks-1(OH) vitamin D3 were significantly lower than those in the group treated without 1(OH) vitamin D3. However, the amounts of IFN-gamma and RANTES in the *IL28B* TT patients treated with 1(OH) vitamin D3/Peg-IFN/RBV were significantly higher than those in the *IL28B* TT patients treated with Peg-IFN/RBV without 1(OH) vitamin D3 at 12 weeks after the start of Peg-IFN/RBV treatment (Fig. 4B). In addition to the absolute amounts of several cytokines, the changes in the amounts after the 12 weeks Peg-IFN/RBV treatment were analyzed (Fig. 4B and Fig. S2). Changes in the amounts of IL4, IL-12, IFN-gamma and RANTES during the 12 weeks-treatment of Peg-IFN/RBV were significantly different between the 1(OH) vitamin D3/Peg-IFN/RBV group and Peg-IFN/RBV group ($p<0.05$) (Fig. 4B and Fig. S2).

The Biological Effects of 1(OH)vitamin D3 and 1,25(OH)$_2$ Vitamin D3 on the Production of Cytokines from PBMCs

Then, we examined whether the administration of 1(OH) vitamin D3 could affect the production of various kinds of cytokines from PBMCs. We used trans-well systems to analyze the effects of hepatocytes with various kinds of enzymes that affect the metabolism of 1(OH) vitamin D3 (Fig. 4C). We used a ng/ml order of calcitriol(1,25(OH)$_2$ vitamin D3) as the active form of vitamin D3 and a μg/ml order of 1(OH) vitamin D3 as the pre-active form of vitamin D3 with or without IFN-α (0.025 ng/ml). The amounts of IL4, IL6, IFN-γ, IP-10 and TNF-α were significantly decreased by the active and pre-active form of vitamin D3 without IFN-α (Fig. 4D). Among them, the amount of IP-10 was dose-dependently decreased by 1(OH)vitamin D3 and 1,25(OH)$_2$vitamin D3 without IFN-α. On the other hand, the amount of RANTES was dose-dependently increased by 1(OH)-vitamin D3 and 1,25 (OH)$_2$ vitamin D3 with or without IFN-α. The amounts of IL10 and IFN-γ were significantly increased by 1(OH)vitamin D3 and 1,25(OH)$_2$vitamin D3 with IFN-α (Fig. 4D). These data indicated that 1(OH)vitamin D3 and 1,25(OH)$_2$vitamin D3 could modulate the immunological status of PBMCs, especially the down-regulation of IP-10 production.

Comparison of the Frequency of Th1 and Tregs between 1(OH) Vitamin D3/Peg-IFN/RBV and Peg-IFN/RBV

Sequential analyses of $CD3^+CD4^+CXCR3^+CCR5^+$(Th1 cells) and $CD3^+CD4^+CD25^+CD127^-$ (Tregs) were carried out during 1(OH) vitamin D3/Peg-IFN/RBV or Peg-IFN/RBV treatment. Representative dot plots indicating Th1 and Tregs are shown (Fig. 5A). The subsets of these cells could be clearly recognized by flow cytometry. Four-week treatment of 1(OH) vitamin D3 could significantly decrease the frequency of Th1 cells but not Tregs ($p<0.05$) (Fig. 5B). However, the frequency of Th1 cells was rapidly increased after the start of Peg-IFN/RBV therapy, especially in the *IL28B* T/T subjects treated with 1(OH) vitamin D3/Peg-IFN/RBV therapy (Fig. 5B and C). The frequency of Th1 cells in the subjects treated with 1(OH) vitamin D3 was significantly higher than in those treated with Peg-IFN/RBV at 12 weeks after the Peg-IFN/RBV therapy, especially in the *IL28B* T/T patients (Fig. 5C). Moreover, the expression of IFN-γ and T-bet mRNA in the isolated $CD4^+$ cells of subjects treated with 1(OH) vitamin D3/Peg-IFN/RBV therapy was significantly higher than in those treated with Peg-IFN/RBV therapy at 4 weeks and 12 weeks after Peg-IFN/RBV therapy (Fig. 5D).

Changes in ISG mRNA Expression in Liver with 1(OH) Vitamin D3 Treatment

The administration of 1(OH) vitamin D3 could reduce various kinds of cytokines in the serum. Therefore, we carried out quantification of ISG mRNA in samples from liver biopsies (Fig. 6A). We selected the Mx, IFI44, IFIT1 genes among the various kinds of ISGs, since another group previously reported that these ISGs could clearly recognize patients as difficult-to treat or easy-to-treat with IFN-based therapy [30]. The expression level of ISGs in the *IL28B* TT polymorphism was significantly lower than in the *IL28B* TG or GG polymorphism. Moreover, the expression levels of liver ISGs in the CH-C patients receiving 4 week-administration of 1(OH) vitamin D3 were significantly lower than those in the CHC patients without administration of 1(OH) vitamin D3.

Direct Effect of Vitamin D on the Expression of ISGs in Hepatocyte without Immune Cells

We used Huh-7 cells with a JFH-1 system that mimicks the acute phase of ISG induction in HCV infection, since we wanted to determine whether 1 (OH) vitamin D3 and 1, 25 (OH)2 vitamin D3 could affect the ISG expression directly. Three representative ISGs (MxA, IFI44 and IFIT1) were analyzed by real-time PCR. JFH-1 replication could induce these ISGs in Huh-7 cells (Fig.6 B). We used 1(OH) vitamin D3 and 1,25(OH)$_2$ vitamin D3 to analyze the ISG expression after JFH-1 inoculation. These ISGs were not affected by 1(OH) vitamin D3, and 1, 25(OH)$_2$ vitamin D3 in vitro.

Discussion

Recently, it has been reported that supplementation of vitamin D3, a potent immunomodulator, could improve the HCV response to antiviral therapy [2,3,31]. We used 1(OH) vitamin D3, since hepatocytes have various kinds of enzymes to convert 1(OH) vitamin D3 to the active metabolite 1,25(OH)$_2$ vitamin D3. Therefore, we speculated that the administration of 1(OH) vitamin D3 could affect the liver adaptive immune cells since the local concentration of 1,25(OH)$_2$ vitamin D3 might be higher than the systemic concentration of this active metabolite. Another group reported that 25(OH) vitamin D3, but not vitamin D3 or 1,25(OH)$_2$ vitamin D3, could have direct-antiviral activity at the level of infectious virus assembly [7]. However, the antiviral activity of 25(OH) vitamin D3 is not so remarkable. Moreover, the system of HCV replication in that study did not include the immune cells that are important for the control of HCV replication [32–35].

In this study, we first reported that administration of 1(OH) vitamin D3 could affect the cytokine production from PBMCs and suppress the ISGs mRNA expression in the liver samples. Among the various kinds of cytokines, IP-10, which was reported to be an important biomarker for the treatment response, could be significantly decreased after 1(OH) vitamin D3 treatment in vivo [36,37]. It has been reported that a high amount of IP-10 is a promising biomarker for difficult-to-treat patients regardless of the *IL28B* polymorphism [36,37]. IP-10 can be produced from various kinds of immune cells including monocytes. In this study, we found

that calcitriol could reduce the production of IP-10 from PBMCs dose-dependently *in vitro*. In addition to the production of IP-10, the expression of ISG mRNA in the liver biopsy samples with 1(OH) vitamin D3 treatment was significantly lower than in those without 1(OH) vitamin D3 treatment regardless of the *IL28B* polymorphism. The excessive expression of ISG mRNA before the Peg-IFN/RBV therapy might induce a poor response to IFN administration [38,39]. In addition to these results, we confirmed that the amounts of IFN-gamma and RANTES induced by 12-weeks 1 (OH) vitamin D3/Peg-IFN/RBV treatment was significantly higher than those induced by 12 weeks Peg-IFN/RBV treatment without 1 (OH) vitamin D3. 1 (OH) vitamin D3 could suppress the basal levels of the immune response in the CH-C patients. However, the subsequent response of the adaptive immune system after the start of Peg-IFN/RBV treatment could have been augmented by 1(OH) vitamin D3. These data indicated that calcitriol might be able to stabilize the adaptive immune systems that were out of control in CH-C patients instead of inducing their activation. In this study, we could not detect a significantly higher rate of SVR in the 1(OH) vitamin D3/Peg-IFN/RBV group in comparison with those in the Peg-IFN/RBV group. However, the addition of 1(OH) vitamin D3 could improve the adaptive immune response. Therefore, the SVR rate in the 1(OH) vitamin D3/Peg-IFN/RBV group might have been significantly higher than in the Peg-IFN/RBV group, if the sample size had been large enough to analyze the SVR.

In addition to previous reports, our data indicated that calcitriol could affect the production of cytokines from PBMCs [25,40]. However, we could not exclude the possibility of affecting cytokines other than the 10 cytokines we analyzed in this study. Moreover, other groups reported that vitamin D3 might modulate the expression of TLRs and/or their signaling, which are important in the immunopathogenesis of hepatitis C virus persistent infection [6,14,41]. This study was not a randomized control trial and did not have a large number of patients, since it focused on the effect of 1,25 $(OH)_2$ Vitamin D3 on the immune cells. For this purpose, the number of included patients was sufficient for the analysis. Moreover, we are conducting a randomized control trial that includes a large number of chronic hepatitis C patients with sever fibrosis and low vitamin D3 concentrations (ongoing study) (UMIN000007400).

In conclusion, the active metabolite of vitamin D3, calcitriol, could improve the response to Peg-IFN/RBV therapy. Supplementation of 1(OH) vitamin D3 or 1,25$(OH)_2$ vitamin D3 should be reasonable for the conditioning of IFN-based treatment including Direct Acting Antiviral (DAA)/Peg-IFN/RBV, DAA/Peg-IFN, Peg-IFN/RBV and Peg-IFN monotherapy.

Supporting Information

Figure S1 Cytokine profiles in the ex vivo treated with 1(OH) vitamin D3/Peg-IFN/RBV. Sequential data of quantification of 7 cytokines (IL4, IL6, IL10, IL12, IL17, MCP-1 and TNF-α) during 1(OH) vitamin D3 pre-treatment (pre vs 0w), 1(OH) vitamin D3/Peg-IFN/RBV therapy are shown. Dotted lines indicate the data of each subject. Black lines indicate the averaged data. Error bars indicate standard deviation. The data from IL28B (T/T) subjects or IL28B (T/G or G/G) subjects are shown in the separate graphs.
(TIFF)

Figure S2 Comparison of the cytokine profiles between 1(OH) vitamin D3 plus SOC and SOC. Comparisons in the amounts of 7 cytokines (IL4, IL6, IL10, IL12, IL17, MCP-1 and TNF-α) between 1(OH) Vitamin D3/PEG-IFN/RBV group (VitD3+standard of care (SOC)) and Peg-IFN/RBV group (SOC) at 0 weeks and 12 weeks after the start of Peg-IFN/RBV treatment are shown. Analysis of the changes in the amounts of 7 cytokines (IL4, IL6, IL10, IL12, IL17, MCP-1 and TNF-α) during 12 weeks treatment of Peg-IFN/RBV is shown.
(TIFF)

Author Contributions

Conceived and designed the experiments: YK T. Kato OK TI MN EK MM TA YM T. Kobayashi MI NK KS HN TI NO YU TM TS. Performed the experiments: YK T. Kato OK TI MN EK MM TA YM T. Kobayashi MI NK KS HN TI NO YU TM TS. Analyzed the data: YK T. Kato OK TI MN EK MM TA YM T. Kobayashi MI NK KS HN TI NO YU TM TS. Wrote the paper: YK T. Kato OK TI MN EK MM TA YM T. Kobayashi MI NK KS HN TI NO YU TM TS. Immunological analysis: YK OK MM TA. Virological analysis: YK T. Kato MN EK.

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東日本大震災後の避難所において発生した２つのインフルエンザＡ集団発生への対応

八田　益充[1)]，遠藤　史郎[1)]，徳田　浩一[1)]，國島　広之[2)]，北川　美穂[1)]，賀来　満夫[1)]

[1)]東北大学大学院医学系研究科　感染制御・検査診断学分野
[2)]東北大学大学院医学系研究科　感染症診療地域連携講座

Abstract

Background：Miyagi Prefecture was the area most severely devastated by the tsunami of 11 March 2011 in Japan, with extensive loss of lives and property. In the aftermath of the tsunami disaster, transmission of infectious diseases in evacuation centers was a concern, because of several factors including overcrowding, poor hand hygiene due to disrupted water supply. Here we report two outbreaks of influenza A at evacuation centers in Miyagi Prefecture after the disaster.

Patients and Methods：The first outbreak occurred at a large-scale evacuation center in Kesennuma in March, with 25 patients diagnosed as influenza. The second one occurred at a middle-scale center in Natori in April, with 20 patients. More than half of cases were diagnosed as influenza A by rapid antigen tests, however the rest of them were clinically diagnosed.

Results：Several measures to control the outbreaks were taken. Hand hygiene with hand sanitizers and cough etiquette were strongly promoted, using posters and stickers. Bottles of alcohol-based hand sanitizers were installed at common sites in the centers, and surgical masks were distributed to evacuees. Symptomatic patients were kept at isolation rooms in evacuation centers until 2 days after the resolution of fever. Individuals including the family members and those who were within 2 meters from the symptomatic patients were closely monitored whether they might develop symptoms later. Post-exposure chemoprophylaxis was performed for exposed persons. In the former evacuation center, a medical examination room for febrile patients was set up aside from a general medical office. As a result of control measures, both of outbreaks subsided without any complicated or fatal cases of influenza.

Conclusions：Outbreaks of influenza after a severe natural disaster present unique challenges, and our report highlights the need for prompt implementation of a systemic approach with a bundle of control measures in evacuation settings, as in hospital settings.

はじめに

2011 年 3 月 11 日に宮城県沖で発生した東日本大震災は，マグニチュード 9.0 という国内観測史上最大の地震であった[1,2)]．局地的な家屋の倒壊や火災だけでなく，地震直後に発生した広範囲の大津波による被害は甚大で，推定被害総額 16 兆 9,000 億円，死者・行方不明者約 2 万人という，かつてない規模の被害がもたらされた．また家屋の倒壊・流出によって，死者・行方不明者をはるかに上回る多数の避難者が避難所での長期生活を余儀なくされた．一般的に，大規模災害の発生後は避難所において各種感染症の流行リスクが高まることが知られているが[3,4)]，今回の震災においても，衛生面や設備面での問題から被災地の避難所における感染症の流行が震災直後から危惧されるような状況であった．

そのような中で，感染制御・検査診断学分野では，被災地支援の一環として，県庁や地元保健所と共同で県内全域における避難所の感染対策支援を継続的に行ってきた．本稿で紹介する２つの事例は，情報もなくガソリンも不足し道路が至る所で寸断されている状況の中，宮城県内の避難所を１つ１つ訪問していた際にまさに遭遇したインフルエンザ集団発生事例である[5)]．

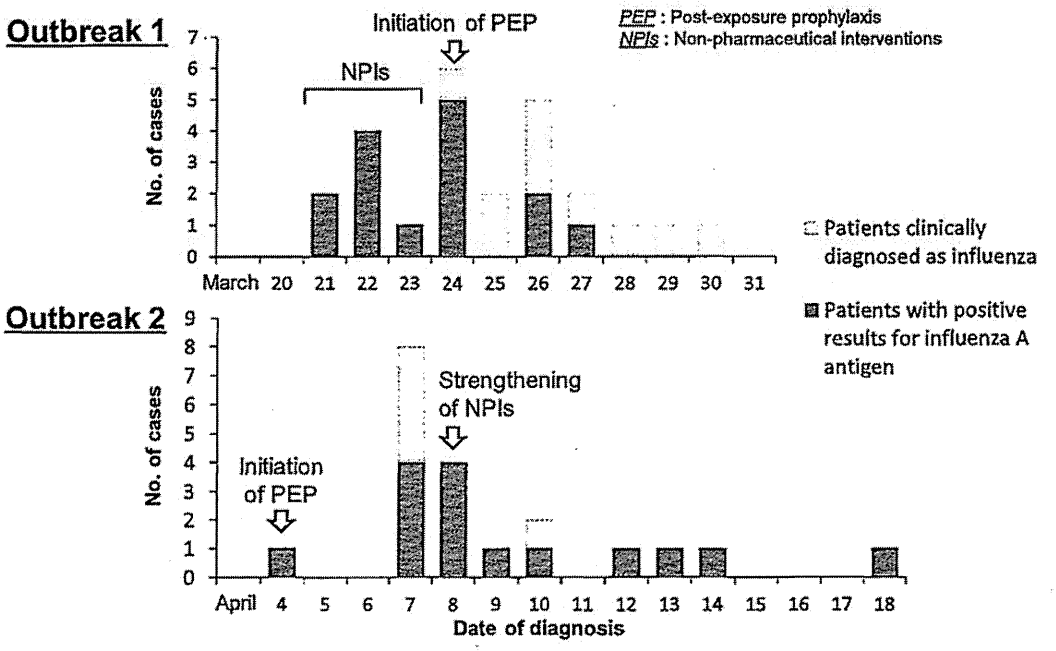

図1.

患者および方法

1例目の集団発生事例は，1,360名の避難者を収容していた気仙沼市内の大規模避難所において，2011年3月下旬にかけて発生した．2例目の事例は，収容者数約200人の名取市内の中規模避難所において4月上旬に発生した．

インフルエンザの診断は鼻腔検体を用いたインフルエンザ迅速抗原検出キット（イムノクロマト法）を原則としたが，抗原検査が陰性または未施行でも臨床的にインフルエンザが疑わしい場合にはインフルエンザと診断した．いくつかの抗原検査陽性検体に対して，リアルタイムPCRにてインフルエンザウイルスのサブタイプ同定も行った．

インフルエンザと診断された場合，オセルタミビル75 mg 1日2回内服にて治療を行った．また有症状者から半径2 m以内にいた濃厚接触者や基礎疾患を有するハイリスク患者に対して，原則的にオセルタミビル75 mg 1日1回内服にて曝露後予防投与を行った．

結　果

1例目の集団発生事例では，計25名（平均年齢50.2歳，男女比1：1.5）がインフルエンザAと診断され，attack rateは1.8%であった．2例目の事例でのインフルエンザA患者数は計20名（平均年齢47.2歳，男女比1：1.2）であり，attack rateは10%であった．また，2例目の集団発生事例の患者検体からは，リアルタイムPCRにてインフルエンザAウイルス香港型（H3N2）が検出・同定された．

これらの集団発生に対する感染対策として，アルコール手指消毒薬を用いた手指衛生と咳エチケットの強化，マスクの配布，ポスター掲示，有症者の個室収容，濃厚接触者へのオセルタミビルの予防投与などが行われ，重篤な合併症や死亡者を出すことなく2事例とも終息した（図1）．最終的に1例目では50名，2例目では34名に対してオセルタミビルによる予防投与が行われた．

考　察

この2つの避難所に共通した感染対策上の問題点として，① 密集した生活環境のため個人・家族間の距離が近かったこと，② 身内や知人，ボランティアなど施設外からの人の出入りが多かったこと，③ 手洗いなどの水道が使えず，換気が不十分であり衛生環境が良くなかったこと，④ 避難者には多数の高齢者が含まれていた，といった点が挙げられた．特に施設外から出入りする人に対しては，健康状態のチェックするシステムがない一方で，ボランティアを含めた訪問者から避難所に何らかの感染症が持ち込まれる可能性があり，今後は災害時の避難所における訪問者などへの何らかの健康管理体制の構築が必要である．

今回の2つの集団発生事例において，患者の約半数

以上がインフルエンザ迅速抗原検出キットにてインフルエンザAと診断された．その迅速性，簡便性，高い特異性（90-95%）は速やかな診断および対処を可能とし，今回の集団発生事例においても抗原検査の結果をもとに迅速に感染対策を実施できた点で極めて有用であった．

病院など医療機関での感染対策においては，有効な感染対策をいくつか組み合わせて実施する，ケアバンドルと称される複合的な感染対策の実施が近年求められている．今回の事例では，避難所で医療リソースがある程度限られるという特殊状況にありながら，迅速に複合的な感染対策を実施することで集団発生の終息につながった．災害時の避難所においても医療機関と同様な総合的な感染対策の重要性が示唆された．

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