2. Distinguished Improvement of Survival Times of the Patients with Diffuse Panbronchiolitis (DPB) Treated with 14-Membered-Ring Macrolide (14-MM)

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Over the past 10 years diffuse panbronchiolitis (DPB) has changed from a fatal disease to one with a positive outcome due to the advent of erythromycin therapy. I would like to discuss today; 1. the introduction of this therapy, 2. the results of a large study concerning the survival rate of DPB patients using this therapy, and 3. the potential mechanism of action of erythromycin in DPB patients.

This is a typical view of DPB. Chest x-ray showed ill-defined small nodal shadow in the low field of the lung. Central lobule granule shadows were seen in the CT scanning. Pathological features showed broncheolitis and peribroncheolitis with the infiltration of lymphocytes and plasma cells, and the closing obstruction of small airways through the formation of lymph follicles and gradual scarring.

This is a well-known diagnostic criteria. The very important point is that there is a large amount of sputum, prurental sputum and radiographic findings as shown previously. Obstructive lung function with hypoxemia was seen, but the $DLCO_2$ was maintained in the normal range, and hemagluttin titer was elevated. The most important point is a past history of coexistence of chronic pansinusitis. The pathological features are very important for strengthening the diagnosis, but are not always necessary.

The effectiveness of erythromycins in the treatment of DPB was first observed in 1982 when Professor Kudoh treated a patient with 6 mg daily for more than 2 years. This patient showed a marked improvement in disease, something previously unheard of. Clinical trials in 1984 of erythromycin effectiveness indicated that low doses had; 1. a high degree of clinical efficacy, with 2. no significant changes in lung sputum bacterial species, and that 3. a certain degree of clinical effectiveness was even noted in cases of *Pseudomonas aeruginosa* infection.

This is a prospective double-blinded study using 600 mg of erythromycin in comparison with inactive placebo. In this study we evaluated the clinical effect according to a scoring system of six items. The improvement rate of the better and moderately improved were significantly different, and also the latent aggravation rate was significantly different. We can say that this controlled trial established the clinical effect of erythromycin on DPB in Japan.

Now I will show the clinical change of the patient with DPB which we reported in the HALCCM now in press. We compared the survival rates of patients with DPB treated with erythromycin to untreated individuals. A total of 498 patients were divided into three groups based on the time of diagnosis. Group A, registered in 1970～1979, were identified prior to erythromycin therapy. Group B, registered in 1980～1984, were identified before general use of erythromycin and Group C, registered after 1984, were identified when erythromycin therapy was routinely used. Five year survival ratios of the pre-erythromycin groups were 62.9% and 72.4% for groups A and B respectively. In contrast, the five year survival rate for the erythromycin treated group (C) was 91.4%. This increase, between Groups A/B and Group C was found to be statistically significant ($p < 0.0001$). There was, however, no statistical difference between groups A and B.

The efficacy of erythromycin was marked in all the treated patients, particularly in older patients where the untreated individuals showed a rapid decline in survival rate, unlike the treated individuals.

Another specific characteristic of this disease is a high correlation with HLA-Bw54 in patients in East

Asia, and Dr Keicho will show you the data regarding this antigen in DPB later.

The efficacy of erythromycin raises the issue of what is the mechanism of action of the drug at the inflammatory site. Erythromycin is believed to inhibit hypersecretion by inhibiting both mucus and water secretion from epithelial cells. In addition, it is believed to inhibit neutrophil accumulation due to decreased attachment of the cells to the capillary walls and also through decreased production of IL8 by epithelial cells. Thus there would be less neutrophil-derived tissue destructive substances present in the lung, such as elastases and superoxide, following treatment. However more work needs to be done to clarify these actions of neutrophils on airway inflammation.

I would like to discuss the relationship between airway infection and the anti-inflammatory actin of erythromycin. It is believed that erythromycin is important in breaking the vicious cycle of chronic airway infection. Chronic airway infection is accompanied by an inflammatory response that is deleterious and so it is likely that an antibacterial treatment will be limited in effectiveness, whereas an anti-inflammatory agent, such as erythromycin, would be much more beneficial and therefore be more useful as a basic treatment.

Recently it has been published that erythromycin is able to inhibit bromonea induced acute lung injury. We found that erythromycin inhibited neutrophil accumulation in the lung and neutrophil-derived elastase in the lung, which prevented acute lung injury induced by bromophene. These data were published in the March issue of Thorax this year.

The effectiveness of erythromycin therapy in Japan has gone beyond our initial expectations and we believe that the use of this and other 14-MM macrolides may be useful in a variety of diseases in the future.

3. Apoptosis induced by Diesel Exhaust Particles in Human Airway Epithelial Cells *in vitro*

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I am going to talk about apoptosis induced by diesel exhaust particles in human airway epithelial cells in vitro. Our research background is as follows. Several lines of evidence have shown that diesel exhaust particles (DEP) may cause lung cancer, bronchial asthma, and lung fibrosis. The mechanisms of pathogenesis in these diseases remains unknown. We postulated that DEP might induce apoptosis in human airway epithelial cells (AEC). As a first step to investigate the effects of DEP on the human respiratory system, we investigated the effects of DEP on AEC in vitro.

First let me describe the diesel engine we used. The 2369-cc diesel engine manufactured by Hino Motor Company of Japan was operated at a speed of 1050 rpm and the concentration of DEP was in the range of 3 mg/m^3. This is the basic scheme showing the diesel engine system. We connected a small silicon tube to the dilution tunnel B. This small tube was introduced into the cell culture system containing the 5% CO_2 incubator.

This picture shows this culture system. We placed our microcell culture plates and cell chambers into the small container and the container was exposed for different intervals to DEP. Bet-1A, a kind of