11

Differences in Erythrocyte Index and Hyporesponsiveness to Erythropoiesis in Hemodialysis Patients Treated with Different Erythropoiesis-Stimulating Agents

Osamu Saito[1], Yoichi Furusawa[2],
Kousuke Okuda[2] and Eiji Kusano[1]
[1]*Division of Nephrology, Jichi Medical University,*
[2]*Okuda Clinic*
Japan

1. Introduction

The majority of patients undergoing hemodialysis have anemia due to decreased production of erythropoietin. This condition is referred to as renal anemia, and is a type of normocytic and normochromic anemia. Renal anemia contributes to a worsening of quality of life (QOL) and has a poor prognosis for survival.

Clinical use of erythropoiesis-stimulating agents (ESAs) has markedly improved the QOL and prognosis for survival of hemodialysis patients. ESA is commonly used for treatment of renal anemia, but some hemodialysis patients subsequently develop macrocytic and hypochromic anemia that is not responsive to vitamin B12 and folic acids (Ogura et al., 2007). Macrocytic and hypochromic anemia after ESA treatment is also common in elderly hemodialysis patients (Murata, 1998). However, the mechanism underlying ESA induction of these changes in erythropoiesis is unknown.

The correlation between renal anemia and ischemic heart disease, which is referred to as cardiorenal anemia syndrome (CARS) (Silverberg, 2003), suggests that treatment of anemia may also suppress cardiovascular events. However, the results of the Correction of Hemoglobin and Outcome in Renal Insufficiency (CHOIR) study showed that patients with a high hemoglobin level in stage III-IV chronic kidney disease (CKD) after use of large doses of ESA have a poor prognosis for cardiovascular complications (Singh et al., 2006). Also, in a meta-analysis, Phrommintikul et al. reported an increased incidence of cerebrovascular disease in patients treated with ESAs at a high dose, with the incidence not related to the hemoglobin value (Phrommintikul et al., 2007). Recently, the results of a randomized control study (Trial to Reduce cardiovascular Events with Aranesp Therapy: TREAT) in diabetic CKD patients showed that darbepoetin did not have an inhibitory effect on the progression of renal dysfunction and the new onset of cardiovascular events (Pfeffer et al., 2009). Based on the results of the TREAT trial, it was concluded that the cause of the poor prognosis in patients receiving large doses of ESA is an increased incidence of cerebrovascular disorders. However, analyses in the CHOIR and TREAT trials were based on ESA treatment with

different intervals of administration, and there has not been sufficient investigation of the effects of different types of ESA on prognosis. Therefore, it remains unclear whether treatment of anemia leads to suppression of cardiovascular events.

2. Effects of erythropoiesis stimulating agents on hematopoietic response and cerebrovascular disorders

The mechanism through which large doses of ESA promote the onset of cerebrovascular disorders has not been fully elucidated, and it is unclear whether there is a direct causal relationship. Therefore, in this study, we evaluated the effects of different types of ESA on erythropoiesis, investigated the factors responsible for determining the poor response to ESAs, and determined the incidence of cerebrovascular disorders with different types of ESA.

2.1 Effects of different types of ESA on hematopoietic response

The subjects were 78 maintenance hemodialysis patients with ESRD (40 men and 38 women; age 63.9 ± 9.8 (mean ± SD) years old, range: 32-82 years old) who were treated at our clinic (HD duration 13.4 ± 9.8 years, range: 2-35 years). Inclusion in the study required that patients were taking epoetin for treatment of renal anemia and had no active inflammatory disease. The causes of ESRD were diabetes mellitus (n=20), chronic glomerulonephritis (n=42), renal sclerosis (n=5), IgA nephropathy (n=2), and unknown/uncertain (n=9). Patients were being treated twice or thrice weekly with standard bicarbonate dialysis with semisynthetic membranes (dialysis filter surface area 1.3-2.4 m^2). The mean weekly HD duration was 10.3 ± 1.5 h. Dry weight was targeted in each case to achieve a normotensive edema-free state. The study protocol complied with the ethical guidelines of our institution and informed consent was obtained from each patient.

The 78 patients were randomly divided into two groups in December 2008: those (N=30) who continued to take epoetin (epoetin group), and those (N=48) who switched to darbepoetin instead of epoetin (darbepoetin group). The dose of darbepoetin was determined using a ratio of 1:200 relative to the epoetin dose. In addition to a general physical examination and routine blood tests, the erythrocyte index, iron metabolism markers, normalized protein catabolic rate (nPCR) as a nutrition factor, and Kt/V as a dialysis efficacy factor were measured before dialysis every month for 1 year. Comparisons between the two groups were made using average values over 1 year. The doses of ESA and venous iron were modulated with the goal of maintaining hemoglobin (Hb) at 10-11 g/dL and ferritin at 100–200 ng/mL.

The general characteristics of the study population are summarized in Table 1. There were no significant differences in baseline values between the epoetin and darbepoetin groups.

Changes of parameters in the epoetin group are shown in Table 2. Ferritin, transferrin saturation (TSAT) and iron dose all decreased after one year, compared to the respective baseline values. There were no significant differences in the mean corpuscular volume (MCV) and the mean corpuscular hemoglobin concentration (MCHC) (Fig. 1).

Changes of parameters in the darbepoetin group are shown in Table 3. The Ht value increased significantly and MCHC decreased significantly after one year, compared to the respective baseline values. The change from epoetin to darbepoetin resulted in a significant decrease in MCHC (Fig. 2).

Parameter	Epoetin (N=30)	Darbepoetin (N=48)	P-value
Age (year)	62.3±10.9 (32-82)	65.0±9.8 (36-80)	n. s.
HD duration (year)	14.0±10.6 (2-35)	12.9±9.0 (2-34)	n. s.
Male / Female	12/ 18	28 / 20	n. s.
Cause of CKD			
Chronic glomerulonephritis	17	25	
Diabetic nephropathy	7	13	
Renal sclerosis	2	3	
IgA nephropathy	1	1	
Unknown	3	6	
Pre Hb (g/dl)	10.25±0.41	10.28±0.53	n. s.
Pre Ht (%)	31.13±1.12	31.42±1.60	n. s.
Pre MCV (fl)	98.01±5.23	96.90±3.09	n. s.
Pre MCH (pg)	32.28±1.86	31.70±1.24	n. s.
Pre MCHC (%)	32.93±0.51	32.71±0.45	n. s.
Pre Ferritin (ng/ml)	151.4±91.3	152.6±35.3	n. s.
Pre TSAT (%)	30.2±8.4	30.2±7.2	n. s.
Pre Iron dose (mg/week)	10.8±10.0	15.5±6.2	n. s.
Pre rHuEPO dose (IU/week)	4318±2219	3591±1792	n. s.

Table 1. General characteristics of the 78 hemodialysis patients.

Parameter	Baseline	After one year	P-value
Hb (g/dl)	10.28±0.53	10.21±0.35	n. s.
Ht (%)	31.42±1.60	31.17±0.99	n. s.
MCV (fl)	96.90±3.09	97.39±3.82	n. s.
MCH (pg)	31.70±1.24	31.90±1.43	n. s.
MCHC (%)	32.71±0.45	32.74±0.40	n. s.
Ferritin (ng/ml)	152.6±35.3	128.3±40.6	p<0.05
TSAT (%)	30.2±7.2	26.0±7.4	p<0.05
Iron dose (mg/week)	15.5±6.2	8.1±6.1	p<0.01
rHuEPO dose (IU/week)	3591±1792	3766±1942	n. s.

Table 2. Changes of parameters in the epoetin group.

Parameter	Baseline	After one year	P-value
Hb (g/dl)	10.25±0.41	10.23±0.49	n. s.
Ht (%)	31.13±1.12	31.77±1.34	p<0.05
MCV (fl)	98.01±5.23	98.60±5.92	n. s.
MCH (pg)	32.28±1.86	31.75±2.13	n. s.
MCHC (%)	32.93±0.51	32.18±0.59	p<0.001
Ferritin (ng/ml)	151.4±91.3	136.0±63.4	n. s.
TSAT (%)	30.2±8.4	28.3±9.2	n. s.
Iron dose (mg/week)	10.8±10.0	12.8±7.9	n. s.
rHuEPO dose (IU/week)	4318±2219	4131±3145	n. s.

Table 3. Changes of parameters in the darbepoetin group (DA dose: 20.7±15.7 μg/week).

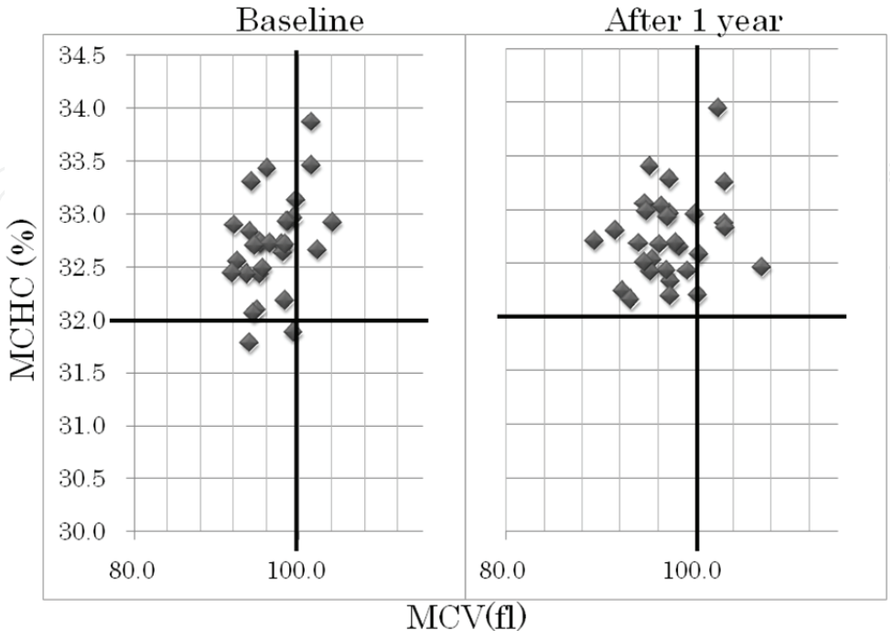


Fig. 1. Changes of annual mean values of MCV and MCHC in the epoetin group.

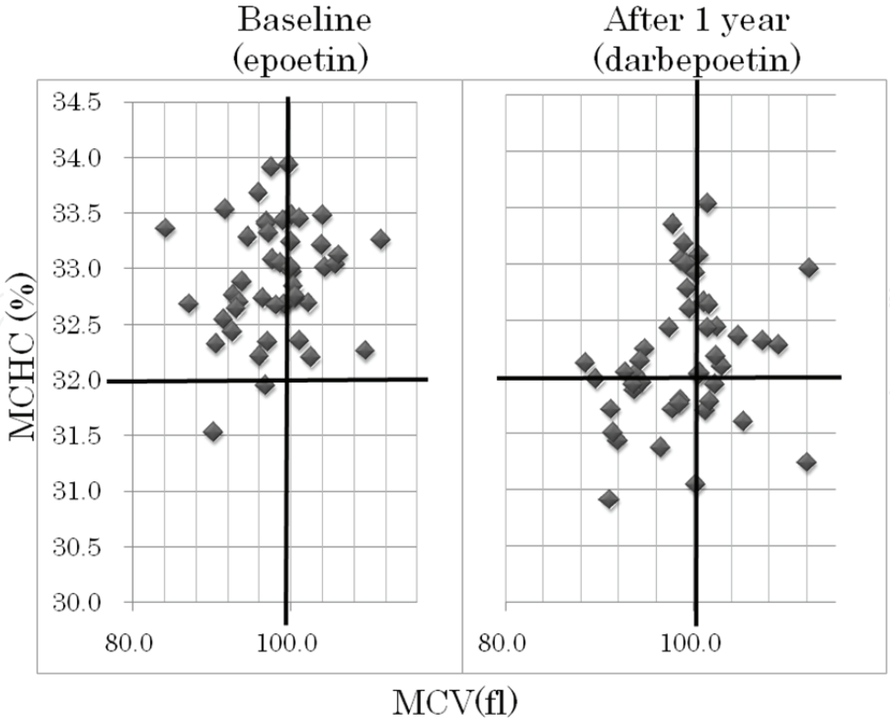


Fig. 2. Changes of annual mean values of MCV and MCHC in the darbepoetin group.

In this study, the change from epoetin to darbepoetin resulted in a significant increase in Ht and a significant decrease in MCHC, while continuation of epoetin did not change the erythrocyte index (EI). Since there were no significant differences in ferritin, TSAT and iron dose between the two groups, the changes of Ht and MCHC may have originated from the effect of darbepoetin. The increase of Ht and decrease of MCHC indicate macrocytic and hypochromic changes of erythrocytes. The mechanism of these changes induced by darbepoetin remains unknown.

2.2 Factors responsible for determining a poor response to an ESA

Next, the responsiveness to darbepoetin was evaluated by dividing the 48 patients in the darbepoetin group into two subgroups. The high dose (n=14) and low dose (n=34) subgroups comprised patients who required a DA dose of ≥60 g/week and <60 g/week, respectively, during the follow-up period. The annual mean values of EI, iron metabolism markers, nPCR and Kt/V and the incidences of complications were compared between the two subgroups (Table 4). A higher rate of complication of hepatic cirrhosis was found in the high dose subgroup ($p<0.02$). There were no significant changes in Kt/V, nPCR and other parameters between the two subgroups. There was also no significant difference in the given dose of iron; however, the ferritin level was lower in the high dose subgroup.

Parameter	Low dose subgroup (DA＜60ug/week)	High dose subgroup (DA≧60ug/week)	P-value
N	34	14	
Age (year)	64.88±10.57	65.31±6.00	n. s.
HD duration (year)	13.03±9.37	15.00±9.53	n. s.
Sex (Male / Female)	19 / 15	11 / 3	n. s.
Diabetes (%)	38.2 (13/34)	35.7 (5/14)	n. s.
Complication of liver cirrhosis (%)	2.9 (1/34)	28.5 (4/14)	P<0.02
Dry weight (kg)	50.48±8.33	53.35±7.84	n. s.
HD time (hour)	4.02±0.23	4.44±0.46	n. s.
Kt/V	1.53±0.17	1.58±0.22	n. s.
nPCR (g/kg/day)	0.89±0.15	0.85±0.19	n. s.
Alb (g/dL)	3.92±0.21	3.95±0.17	n. s.
Hb (g/dL)	10.31±0.47	10.11±0.25	n. s.
Ht (%)	32.05±1.19	31.48±0.58	n. s.
MCH (pg)	31.57±1.90	32.63±1.29	n. s.
MCV (fL)	98.16±5.20	101.60±4.02	n. s.
MCHC (%)	32.16±0.66	32.12±0.37	n. s.
TSAT (%)	29.19±9.27	30.31±7.12	n. s.
Ferritin (ng/mL)	153.55±66.45	110.25±21.88	p<0.01
CRP (mg/dL)	0.32±0.52	0.33±0.31	n. s.
Iron dose (mg/week)	10.73±6.57	14.62±4.75	n.s.
Average DA dose (μg/week)	13.53±5.19	33.77±16.95	p<0.02

Table 4. Comparison of the high dose and low dose darbepoetin subgroups.

The required dose of darbepoetin was significantly higher for patients complicated with liver cirrhosis. Such patients were not excluded from the CHOIR or TREAT study, which suggests that this complication affects the prognosis of patients receiving a high dose of darbepoetin. In Japan, ESA hyporesponsiveness is defined as a failure of improvement of anemia with a darbepoetin dose of 60 g/week or an epoetin dose of 9000 IU/week without iron deficiency (Tsubakihara et al., 2010). Insufficient dialysis, malnutrition, unclean dialysate, and drug effects have been suggested as causes of ESA hyporesponsiveness (Ifudu et al., 1996). In this study, there were no significant differences in any parameters except ferritin between the low dose and high dose darbepoetin subgroups. Since there was no difference in the given iron dose, the patients in the high dose subgroup might be exhibiting hyporesponsiveness to iron.

2.3 Incidence of cerebrovascular events with different types of ESA

Finally, the incidence of cerebrovascular events was evaluated in follow-up of onset of cerebrovascular disorders for another year (a total observation period of 2 years) in patients in both groups. The Kaplan-Meier method was used to analyze the incidence of cerebrovascular disorders from the beginning of the observation period (Fig. 3). There was no significant difference in cerebrovascular event-free survival between the epoetin and darbepoetin groups. Although no difference in the incidence of cerebrovascular events was found following the change from epoetin to darbepoetin, the incidence of cerebrovascular events showed a tendency to increase in the high dose darbepoetin subgroup.

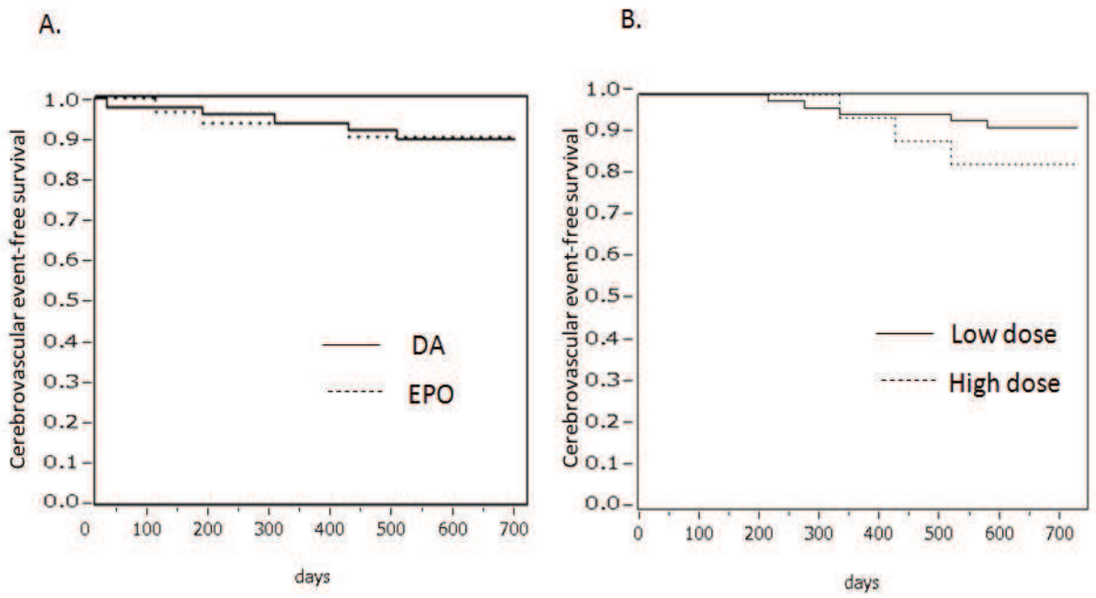


Fig. 3. A. Cerebrovascular event-free survival in the epoetin (EPO) and darbepoetin (DA) groups. B. Cerebrovascular event-free survival in the high dose and low dose darbepoetin subgroups.

A random prospective study showed poor mortality and a high incidence of cardiovascular events in hemodialysis patients with high Hb compared to those with normal hematocrit (Besarab et al., 1998). Moreover, the results of secondary analysis in the CHOIR study

showed that patients in whom anemia did not improve with administration of large doses of ESA had a worsened prognosis compared to patients in whom anemia did improve with a low dose of ESA (Szczech et al., 2008). Thus, it is currently thought that a lower response to ESA (ESA hyporesponsiveness) results in a poor prognosis. In the current study, we found no significant difference in the incidence of cerebrovascular events over a two-year observation period between patients treated with epoetin and darbepoetin. However, a higher, although not significantly higher, incidence of cerebrovascular events was found in patients who received a high dose of darbepoetin. Collectively, these data suggest that particular care is needed in treatment of patients with ESA hyporesponsiveness.

3. Conclusion

The ESA dose was significantly higher for patients complicated with liver cirrhosis, who were not excluded from either the CHOIR or TREAT study. This suggests that this complication affects the prognosis of patients receiving a high dose of an ESA. We found no significant difference in the incidence of cerebrovascular events with epoetin and darbepoetin during a two-year observation period; however, epoetin and darbepoetin might have different effects on the hematopoietic response.

4. Acknowledgment

This study was supported by a grant from The Kidney Foundation, Japan (No. JKFB10-23).

5. References

Besarab, A. Bolton, W.K. Browne, J.K. Egrie, J.C. Nissenson, A.R. Okamoto, D.M. Schwab, S. J. & Goodkin, D.A. (1998). The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *New England Journal of Medicine,* Vol. 339, No. 9, (August 1998), pp. 584-590

Ifudu, O. Feldman, J. & Friedman, E.A. The intensity of hemodialysis and the response to erythropoietin in patients with end-stage renal disease. (1996). *New England Journal of Medicine,* Vol. 334, No. 7, (February 1996), pp. 420-425

Murata, M. (1998). The macrocytic anemia in hemodialysis patients, *Journal of Japanese Society for Dialysis Therapy*, Vol. 31, No. Suppl. 1, (April 1998), pp. 724, ISSN 1340-3451

Ogura, M. Ando, Y. Kusano, E. & Yagisawa, T. (2007). The macrocytic and hypochromic anemia seen in patients with chronic renal failure. *Journal of the Japanese Society of Internal Medicine*, Vol. 96, No. Suppl, (February 2007), pp. 214, ISSN 0021-5384

Pfeffer, M.A. Burdmann, E.A. Chen, C.Y. Cooper, M.E. de Zeeuw, D. Eckardt, K.U. Feyzi, J.M. Ivanovich, P. Kewalramani, R. Levey, A.S. Lewis E.F. McGill, J.B. McMurray, J.J. Parfrey, P. Parving, H.H. Remuzzi, G. Singh, A.K. Solomon, S.D. Toto, R. &TREAT Investigator. (2009). A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *New England Journal of Medicine,* Vol. 361, No. 21, (November 2009), pp. 2019-2032

Phrommintikul, A. Haas, S.J. Elsik, M. & Krum, H. (2007). Mortality and target hemoglobin concentration in anaemic patients with chronic kidney disease treated with

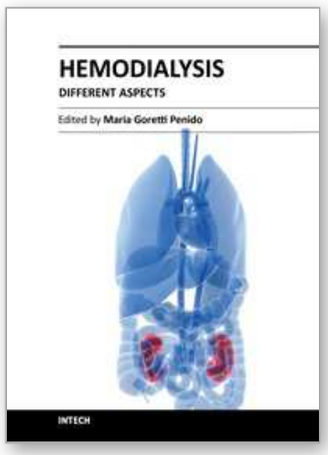
erythropoietin: a meta-analysis. *Lancet,* Vol. 369, No. 9559, (February 2007), pp. 381-388

Silverberg, D. (2003). Outcomes of anemia management in renal insufficiency and cardiac disease. *Nephrology Dialysis Transplantation,* Vol. 18, No. Suppl 2, (June 2003), pp. ii7-12,

Singh, A.K. Szczech, L. Tang, K.L. Barnhart, H. Sapp, S. Wolfson, M. Reddan, D. & CHOIR Investigators. (2006). Correction of anemia with epoetin alfa in chronic kidney disease. *New England Journal of Medicine,* Vol. 355, No. 20, (November 2006), pp. 2085-2098,

Szczech, L.A. Barnhart, H.X. Inrig, J.K. Reddan, D.N. Sappa, S. Califf, R.M. Patel, U.D. & Singh, A.K. (2008). Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney International*, Vol. 74, No. 6, (September 2008), pp. 791-798

Tsubakihara, Y. Nishi, S. Akiba, T. Hirakata, H. Iseki, K. Kubota, M. Kuriyama, S. Komatsu, Y. Suzuki, M. Nakai, S. Hattori, M. Babazono, T. Hiramatsu, M. Yamamoto, H. Bessho, M. & Akizawa, T. (2010). 2008 Japanese Society for Dialysis Therapy: guidelines for renal anemia in chronic kidney disease. *Therapeutic Apheresis and Dialysis*, Vol. 14, No. 3, (June 2010), pp. 240-275



Hemodialysis - Different Aspects

Edited by Prof. Maria Goretti Penido

ISBN 978-953-307-315-6

Hard cover, 321 pages

Publisher InTech

Published online 14, November, 2011

Published in print edition November, 2011

The book provides practical and accessible information on all aspects of hemodialysis, with emphasis on day-to-day management of patients. It is quite comprehensive as it covers almost all the aspects of hemodialysis. In short it is a valuable book and an essential aid in the dialysis room.

InTech Europe

University Campus STeP Ri

Slavka Krautzeka 83/A

51000 Rijeka, Croatia

Phone: +385 (51) 770 447

Fax: +385 (51) 686 166

www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai

No.65, Yan An Road (West), Shanghai, 200040, China

中国上海市延安西路65号上海国际贵都大饭店办公楼405单元

Phone: +86-21-62489820

Fax: +86-21-62489821

IntechOpen