して承認されている経口薬剤であるが、上記のような病態を示す難治性SLEに対する応用が期待される。難治性 SLE に対するボルテゾミブ療法の有効性・安全性検証試験の可及的速やかな実施が期待される。

E．結論

SLE患者の末梢血では、B細胞はTfh細胞からの刺激を受容し、CXCR5 の減弱と CXCR3 の増強を介してリンパ組織から標的臓器へ遊出して、エフェクター機能を発揮するとともに、形質細胞への分化が亢進している可能性が示された。これらの結果より、形質細胞を主要な標的としたボルテゾミブの難治性 SLE に対する検証試験の速やかな実施が期待される。

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G. 知的財産権の出願・登録状況
（予定を含む）

1. 特許取得
該当無し

2. 実用新案登録
該当無し

3. その他
該当無し

厚生労働科学研究費補助金（医療技術実用化総合事業）
分担研究報告書

難治性SLEに対するボルテゾミブ療法の有効性・安全性検証試験

SLEにおけるP糖蛋白質発現リンパ球の治療抵抗性および組織病態への関与に関する研究

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研究要旨：SLEに対する薬物療法に於いて、薬剤抵抗性は重要な問題点である。これまで、SLE患者リンパ球に於ける多剤抵抗性遺伝子産物P-糖蛋白質の発現と薬剤抵抗性との関連性を検討し、P糖蛋白質は，活動期SLEの疾患活動性上昇に伴ってリンパ球上に発現することを明らかにしてきた．今回、P糖蛋白発現細胞の組織での病態形成への関与およびBリンパ球を標的とした治療の抵抗性解除への有用性を検討した。P-gp^{+}CD69^{+}CD4^{+}cellは疾患活動性に従って増加し，ステロイド(CS)不応例，増殖性腎炎，NPSLE合併例で増加を認めた．難治性増殖性腎炎症例では腎間質へのP-gp^{+}CD4^{+}cell集簇を認めた．ステロイドに免疫抑制剤併用を行っても多臓器病変が進行し，リンパ球上P糖蛋白質発現量が1000molecules/cell以上かつP糖蛋白質高発現する症例にRituximab投与（500mg/bodyを1週間間隔で反復4回点滴静注）を行い，Rituximab投与開始後，尿蛋白は速やかに消失して疾患活動性は低下しはじめ，末梢血中B cellが消失したのみならず，CD4^{+} T cellにおけるP糖蛋白質高発現サブグループは消失した．以上から、SLE患者におけるB細胞標的療法は多剤治療抵抗性の側面からも有用であると考えられた。SLEにおいては形質細胞への分化が亢進している可能性が示されており、形質細胞を主要な標的としたボルテゾミブも難治性SLEにおける治療抵抗性の解除をもた

A. 研究目的

SLEに対する薬物療法に於いて、薬剤抵抗性は重要な問題点である。薬剤抵抗性は、長期間の薬剤投与による薬剤耐性（二次無効）、疾患活動性が高いために薬剤に反応しない薬剤不応性に大別される。これまで、SLE患者リンパ球に於ける多剤抵抗性遺伝子産物 P-糖蛋白質の発現と薬剤抵抗性との関連性を検討した。薬剤の細胞外排出によって治療抵抗性を齎す P 糖蛋白質(P-gp)は，活動期SLE の疾患活動性上昇に伴ってリンパ球上に発現する。しかし、Bリンパ球を標的とした治療の抵抗性解除への有用性およびP糖蛋白発現細胞の組織での病態形成への関与は不明である。 今回、リツキシマブによる治療抵抗性の克服および P-gp 発現細胞の組織における役割を検討した。

B. 研究方法

SLE 患者末梢血リンパ球上の P 糖蛋白、細胞機能分子の発現はフローサイトメーターで、残りのリンパ球でそのステロイド排泄能を指標とした薬剤排出能を評価した。（リンパ球に in vitro で dexamethasone を添加して細胞内外に均一に拡散する 14C label Butanol をバックグラウンドとして細胞内に残留する 3H label dexamethasone の medium に対する比を算出した.）また、組織浸潤リンパ球は免疫組織染色で評価した。

（倫理面への配慮）

臨床検体を使用する場合には、所属機関の倫理委員会、或は、IRBで承認を得た研究に限定し、患者からインフォームドコンセントを得た上で、倫理委員会の規約を遵守し、所属機関の現有設備を用いて行う。患者の個人情報が所属機関外に漏洩せぬよう、試料や解析データは万全の安全システムをもって厳重に管理し、人権擁護に努めると共に、患者は、経済的負担を始め如何なる不利益や危険性も被らない事を明確にする。

C. 研究結果

健常人に比して SLE では P-gp, CD69 は有意に発現増強した。 P-gp は CD69+CD4+cell に有意に高発現した。P-gp+CD69+CD4+cell は疾患活動性に従って増加し, ステロイド(CS)不応例、増殖性腎炎、NPSLE 合併例で増加を認めた。難治性増殖性腎炎症例では腎間質への P-gp+CD4+cell 集簇を認めた.ステロイドに免疫抑制剤併用を行っても多臓器病変が進行し、リンパ球上 P 糖蛋白質発現量が 1000molecules/cell 以上かつ P 糖蛋白質高発現する症例に Rituximab 投与(500mg/body を 1 週間間隔で反復 4 回点滴静注）を行い、P 糖蛋白質発現に及ぼす効果を評価した。ステロイド増量と IVCY を併用したが、疾患活動性改善乏しく、1.0 g / 日を超える高度な蛋白尿持続、BILAG A1 /B2 項目 (15 points)と多臓器病変合併、B cell 上 P 糖蛋白質発現量は低下しても依然 1000 molecules/cell を超えたままで、かつ、P 糖蛋白質高発現リンパ球が消失せず、リンパ球からのステロイド排出は亢進して細胞内残留ステロイド濃度は低下していた。

Rituximab 投与開始後, 尿蛋白は速やかに消失して疾患活動性は低下しはじめ、末梢血中 B cell が消失したのみならず、CD4+ T cell における P 糖蛋白質高発現サブグループは消失した。

D. 考察

P-gp+CD69+CD4+cell は薬剤抵抗性かつ臓器侵襲を齎しうるサブセットと考えられ、その制御が治療抵抗性克服に重要である。末梢血リンパ球上 P-gp 発現は治療抵抗性とリンパ球の臓器浸潤を反映し、治療選択において有用な指標となり得る。

また、多剤抵抗性症例に Rituximab 投与が奏効する場合、B 細胞の消失に伴い T 細胞活性化も抑制され、かつ治療抵抗性がﾘｾｯﾄされる可能性が示唆された。

Rituximab は難治性病態の改善のみならず、治療反応性の回復を齎し、長期寛解維持を可能としうる。

E．結論

以上から、SLE 患者における B 細胞標的療法は多剤治療抵抗性の側面からも有用であると考えられた。SLE においては形質細胞への分化が亢進している可能性が示されており、形質細胞を主要な標的としたボルテゾミブも難治性 SLE における治療抵抗性の解除をもたらす可能性が示唆される。

F. 研究発表

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   2013 年 12 月 千葉

G. 知的財産権の出願・登録状況
（予定を含む）

1. 特許取得
   該当無し

2. 実用新案登録
   該当無し

3. その他
   該当無し

厚生労働科学研究費補助金（医療技術実用化総合事業）
分担研究報告書

難治性SLEに対するボルテゾミブ療法の有効性・安全性検証試験

ループス腎炎のpodocyteにおけるCD86分子を介した蛋白尿発現メカニズムに関する研究

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研究協力者　一瀬邦弘　長崎大学大学院医歯薬学総合研究科展開医療科学講座（第一内科）　助教

研究要旨：ループス腎炎におけるポドサイトはバリア機能を有し、蛋白尿発現との関連が示唆されている。以前、プロテアーゼ阻害薬であるボルテゾミブのループス腎炎抑制効果が報告された(Nature Medicine 14, 748 - 755 (2008))が、形質細胞制御が主なメカニズムであり、腎の構成細胞への影響については明らかにされていない。そこで今回、我々は健常人およびループス腎炎患者から分離したIgGを用いて、ヒトのポドサイトと免疫担当細胞の関与について検討した。健常人およびループス腎炎IgGをインキュベートし、RNAを抽出した。Microarrayによる Gene Ontology 解析で CD86, CD80, PTPN22, PDE5A, CD47 や MALT1 などの免疫細胞の活性化、ポドサイト障害に関わる分子の発現亢進がループス腎炎 IgG でみられた。ポドサイトにも抗原提示細胞と同様に co-stimulatory pathway を介した免疫活性を有し、ボルテゾミブが形質細胞だけではなく、ポドサイトに直接、機能変化をもたらす可能性が示唆された。

A. 研究目的

SLE患者の中で、腎障害は症例の約40～75%に認められ、重要な予後規定因子である。しかし、これまでのところループス腎炎における蛋白尿発現のメカニズムについては明らかにされていない。ループス腎炎におけるポドサイトはバリア機能を有し、蛋白尿発現との関連が示唆されている。

B.　研究方法

今回、我々は健常人およびループス腎炎患者から分離したIgGを用いて、ヒトのポドサイトの cell line (AB8/13)における影響について検討した。健常人およびループス腎炎患者の血清からIgG purification kitを用いてIgGを分離し、IgGをポドサイト とともに24時間インキュベートして、Microarray による網羅的遺伝子解析を行った。

（倫理面への配慮）

本研究では「全身性エリテマトーデスの病態を多角的に解析する臨床研究」というテーマで長崎大学病院倫理委員会に申請・承認を得て、十分にインフォームドコンセントを行い検体採取している。匿名化された検体を用い、情報管理を厳重に行っているため倫理面での問題はない。

C. 研究結果

Microarray による Gene Ontology 解析では CD86, CD80, PTPN22, PDE5A, CD47 や MALT1 などの免疫細胞の活性化、ポドサイト障害に関わる分子の発現亢進がみられた。

D. 考察

ループス腎炎におけるポドサイトでは抗原提示細胞と同様に co-stimulatory pathway を介した免疫活性を有し、ボルテゾミブが形質細胞だけではなく、ポドサイトにも直接、機能変化をもたらす可能性が示唆された。

E. 結論

ボルテゾミブの SLE、ループス腎炎の病態制御には多彩な免疫学的機序を介した抑制効果が期待される。

F. 研究発表

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G.　知的財産権の出願・登録状況
（予定を含む）

1. 特許取得
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2. 実用新案登録
該当なし

3. その他
該当なし

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌【欧文】

発表者氏名	論文タイトル名	発表誌名	巻号, ページ	出版年
Tanaka Y, Hirata S.	Is it possible to withdraw biologics from therapy in rheumatoid arthritis?	Clinical Therapeutics	In press.	
Tanaka Y, Hirata S, Sawamura F, Saito K. et al.	Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthiritis: 1-year outcome of the HONOR study.	Annals of the Rheumatic Diseases	In press.	
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ORIGINAL ARTICLE

Improvement of plasma endothelin-1 and nitric oxide in patients with systemic sclerosis by bosentan therapy

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Abstract The aim of this study was to evaluate the effects of bosentan on plasma endothelin-1 (ET-1) and nitric oxide (NO) as pulmonary hypertension (PH)-associated biochemical markers in patients with systemic sclerosis (SSc). Twenty-four SSc patients receiving bosentan for 24 weeks were registered in this prospective observational study. Ten patients were complicated with clinically suspected PH. Plasma levels of ET-1 and NO were assessed at baseline and after 24 weeks of treatment in SSc patients and in 15 healthy controls. Plasma levels of ET-1 and NO at baseline were significantly higher in SSc patients than in healthy controls ($p < 0.000$), and they were also significantly higher in SSc patients with PH than in those without PH ($p < 0.01$). Plasma ET-1 levels were significantly decreased after 24 weeks of bosentan therapy ($p < 0.0001$), and ET-1 levels of SSc patients with PH decreased to a level comparable to that in patients without PH. In the 10 SSc patients with PH, changes in plasma ET-1 levels during the 24 weeks of the study were significantly larger in the 5 patients whose functional class (FC) improved than in the 5 patients whose FC was unchanged ($p < 0.05$). Plasma NO levels were also slightly decreased in SSc patients after 24 weeks of bosentan therapy. Plasma ET-1 levels could reflect the presence and severity of PH in SSc patients. Additionally, changes in plasma ET-1 levels may indicate the response to bosentan therapy in SSc patients with PH.

Keywords Bosentan · Systemic sclerosis · Pulmonary hypertension · Endothelin-1 · Nitric oxide

Abbreviations

cGMP	Cyclic guanosine monophosphate
ELISA	Enzyme-linked immunosorbent assay
ET	Endothelin
FC	Functional class
NO	Nitric oxide
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PH	Pulmonary hypertension
SSc	Systemic sclerosis
WHO	World Health Organization
6MWD	6-minute walk distance

Introduction

Pulmonary hypertension (PH) is a critical complication in patients with systemic sclerosis (SSc) [1]. The primary classifications of SSc-associated PH are pulmonary arterial hypertension (PAH), PH due to lung disease and/or hypoxia, and PH due to left heart disease. PAH affects approximately 10–15 % of patients with SSc [2] and is associated with a worse prognosis than Ssc with idiopathic PAH [3]. The three pathways to PAH treatment are the endothelin (ET) pathway, the nitric oxide (NO) pathway, and the prostacyclin pathway [4]. Treatment via the ET

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pathway uses an ET-receptor antagonist. Bosentan is a non-peptide antagonist that blocks both endothelin A (ET_A) and B (ET_B) receptors. The strength of recommendation of bosentan therapy is "A," which is a strong recommendation, in World Health Organization (WHO) functional class (FC) II and III patients in the PAH evidence-based treatment algorithm [5, 6]. Bosentan is also effective in patients with SSc-associated PAH [7–10].

Endothelin-1 has been shown to play a significant pathogenic role in PAH [11]. Endothelin-1 is a strong vasoconstrictor. Furthermore, it can stimulate the proliferation of pulmonary smooth muscle cells, fibroblast collagen production, and the contraction of fibroblast-populated collagen lattices [12]. In contrast, NO is a potent, endogenous, endothelium-derived vasodilator that directly relaxes vascular smooth muscle through the stimulation of soluble guanylate cyclase and increased production of intracellular cyclic guanosine monophosphate (cGMP) [13]. PAH is associated with a defect in the production of NO and therefore with decreased NO-induced vasodilatation [13].

In patients with SSc, ET-1 is a key pathogenic mediator that influences vasoconstriction, fibrosis, vascular hypertrophy, and inflammation [12]. In this study, we evaluated the effects of bosentan on plasma ET-1 and NO as PH-associated biochemical markers in SSc patients with or without PH.

Materials and methods

Patients and controls

Twenty-four SSc patients suspected by physicians of having PH were consecutively enrolled in the present study at the Center for Rheumatic Disease of Sasebo Chuo Hospital from June to December 2007. All patients provided their informed consent to participate in the present protocol, which was approved by the Institutional Review Board of Sasebo Chuo Hospital. All patients fulfilled the American College of Rheumatology preliminary classification for SSc [14]. The present study was a prospective observational study lasting 24 weeks. In this study, PH was defined as (1) a resting systolic pulmonary artery pressure (PAP) of >30 mmHg on echocardiogram, (2) mild to moderate dyspnea on exertion, (3) WHO FC II/III, and (4) symptoms not attributable to lung disease or hypoxia [15]. Since the present study was conducted before the establishment of guidelines for the diagnosis and treatment of PH [16], the diagnostic criteria of PH used here and mentioned above are different from those described in the guidelines. Systolic PAP was assessed by maximal tricuspid regurgitation jet velocity, which was measured as the peak regurgitate velocity in a continuous-wave Doppler flow profile obtained from the cardiac apex. No patient had undergone right-heart catheterization. In all patients, left ventricular function was normal on echocardiogram. Patients received a starting dose of bosentan of 62.5 mg twice daily, and the dose was increased to and then maintained at 125 mg twice daily after 4 weeks. Plasma samples were collected at baseline and at 24 weeks and were stored at −80 °C until assay. We also collected plasma samples from 15 healthy controls whose mean ± SD of age was 42 ± 10 years and whose sex ratio (men–women) was 7:8.

Clinical and laboratory assessment

Clinical response to the therapy was evaluated based on the WHO FC and 6-min walk distance (6MWD) in SSc patients with PAH. Exercise capacity was evaluated by 6MWD in accordance with the American Thoracic Society guidelines [17]. ET-1 and NO were assessed at baseline and after 24 weeks of treatment. Plasma levels of ET-1 were measured by enzyme-linked immunosorbent assay (ELISA; RIA2 method, BML, Tokyo, Japan). Plasma levels of NO were measured by chemiluminescence, using a highly sensitive NO measurement system (FES-450; Scholar-Tec Co., Ltd., Osaka, Japan) [18].

Statistical analyses

Within-group comparisons were made using the Mann–Whitney U test; changes from baseline were compared using the Wilcoxon's signed-rank test. Correlations were assessed with Spearman's correlation coefficient test. The overall significance level for statistical analysis was 5 % (two sided). p values of <0.05 were considered statistically significant.

Results

Baseline characteristics of the 24 SSc patients

The demographic data of the present 24 SSc patients at baseline are described in Table 1. In these patients, the mean ± SD of age was 60 ± 13 years and that of disease durations was 13 ± 6 years. Ten patients were complicated with PH; these patients were 62.4 ± 13 years old and all female. Five were WHO FC II, and the other 5 were FC III. The median (range) of 6MWD was 568 (600–440) m in these 10 patients.

Clinical efficacy of bosentan therapy in the 10 SSc-PH patients

The clinical efficacy of bosentan therapy was evaluated in the 10 SSc patients with PH. The WHO FC improved from

Table 1 Demographic and clinical characteristics at baseline of 24 SSc patients

	$N = 24$
Age (years[a])	60 ± 13
Gender: male/female (*N*)	4/20
Disease durations (years[a])	13 ± 6
Cutaneous type: limited/diffuse (*N*)	10/14
Complications (*N*)	
Interstitial lung disease	13
Digital ulcers	4
Pulmonary hypertension	10

[a] Mean ± SD

II to I in 3 patients and from III to II in 2 patients, though no statistically significant change was observed (Table 2). No patient showed an exacerbated FC. We observed significant increases in 6MWD at 12 and 24 weeks ($p < 0.01$, Table 2). The median changes (range) in 6MWD were 40 (28–70) m at 12 weeks and 60 (40–92) m at 24 weeks.

Plasma ET-1 and NO at baseline in the 24 SSc patients

Plasma levels of ET-1 and NO at baseline were significantly higher in the 24 SSc patients than in the 15 healthy controls ($p < 0.0001$). The median (range) of plasma ET-1 levels was 2.4 (1.8–4.5) pg/ml in the SSc patients and 0.4 (0.2–1.0) pg/ml in healthy controls. The median (range) of plasma NO levels was 60.9 (47.0–85.0) μM in SSc patients and 36.0 (29.5–45.6) μM in healthy controls. There was a positive correlation between plasma ET-1 and NO levels at baseline in SSc patients ($r = 0.59, p < 0.01$). Plasma ET-1 and NO levels at baseline were significantly higher in SSc patients with PH than in those without PH, and the values of plasma ET-1 and NO levels were relatively clearly dividable between SSc patients with and without PH (Fig. 1; Table 2).

In the 10 SSc patients with PH, plasma ET-1 and NO levels at baseline were significantly higher in FC III patients than in FC II patients ($p < 0.05$). The median (range) of plasma ET-1 levels was 3.4 (2.1–3.7) pg/ml in FC II patients and 4.0 (3.8–4.5) pg/ml in FC III patients. The median (range) of plasma NO levels was 77.3 (75.0–81.5) μM in FC II patients and 82.3 (77.6–85.0) μM in FC III patients.

Changes in plasma ET-1 and NO in 24 SSc patients treated with bosentan

Plasma ET-1 levels were significantly decreased after 24 weeks of bosentan therapy in SSc patients both with and without PH (Table 2). In the patients with PH, plasma ET-1 levels decreased to a level comparable to that in patients without PH (Table 2). Plasma NO levels were also significantly decreased after 24 weeks of bosentan therapy in patients both with and without PH, but changes in plasma NO levels during the 24 weeks of treatment were very slight (Table 2). Among the 10 SSc patients with PH, changes in plasma ET-1 levels during the 24 weeks of treatment (⊿ET-1) were significantly larger in the 5 patients whose FC improved than in the 5 patients whose FC remained unchanged; the median (range) of ⊿ET-1 was −1.6 (−2.2 to −1.1) versus −0.7 (−1.9 to −0.3) pg/ml, respectively ($p < 0.05$). However, changes in plasma NO levels during the 24 weeks of treatment (⊿NO) were not different between the improved patients and the unchanged patients; the median (range) of ⊿NO was −1.7 (−2.1 to −1.2) versus −1.7 (−1.9 to −1.2) μM, respectively.

Discussion

Endothelin-1 is a highly potent vasoconstrictor produced by endothelial cells that is a key pathogenic mediator of

Table 2 Change in clinical findings and plasma ET-1/NO concentrations during bosentan treatment

	SSc with PH ($N = 10$)			SSc without PH ($N = 14$)		
	Baseline	24 weeks	*p*	Baseline	24 weeks	*p*
WHO FC (*N*)	I, 0; II, 5; III, 5; IV, 0	I, 3; II, 4; III, 3; IV, 0	0.22	–	–	–
6MWD (m[a])	568 (600–440)	620 (532–650)	<0.01	–	–	–
Plasma ET-1 (pg/ml[a])	3.05 (2.1–4.5)[#]	2.05 (1.4–3.4)	<0.01	2.25 (1.8–3.1)	2.00 (1.7–2.4)	<0.01
Plasma NO (μM[a])	80.1 (75.0–85.0)[#]	78.5 (73.4–83.2)	<0.01	56.8 (47.0–61.4)	56.5 (44.1–62.9)	<0.05

Changes in WHO FC, 6MWD, and plasma concentrations of ET-1 and NO were examined during bosentan treatment as described in the text

The changes from baseline were compared using Wilcoxon's signed-rank test

ET endothelin, *FC* functional class, *NO* nitric oxide, *PH* pulmonary hypertension, *SSc* systemic sclerosis, *WHO* World Health Organization, *6MWD* 6-minute walk distance

[#] $p < 0.01$; The difference in baseline plasma ET-1 or NO concentrations between SSc patients with PH and those without SSc using Mann–Whitney's *U* test

[a] Median (range)

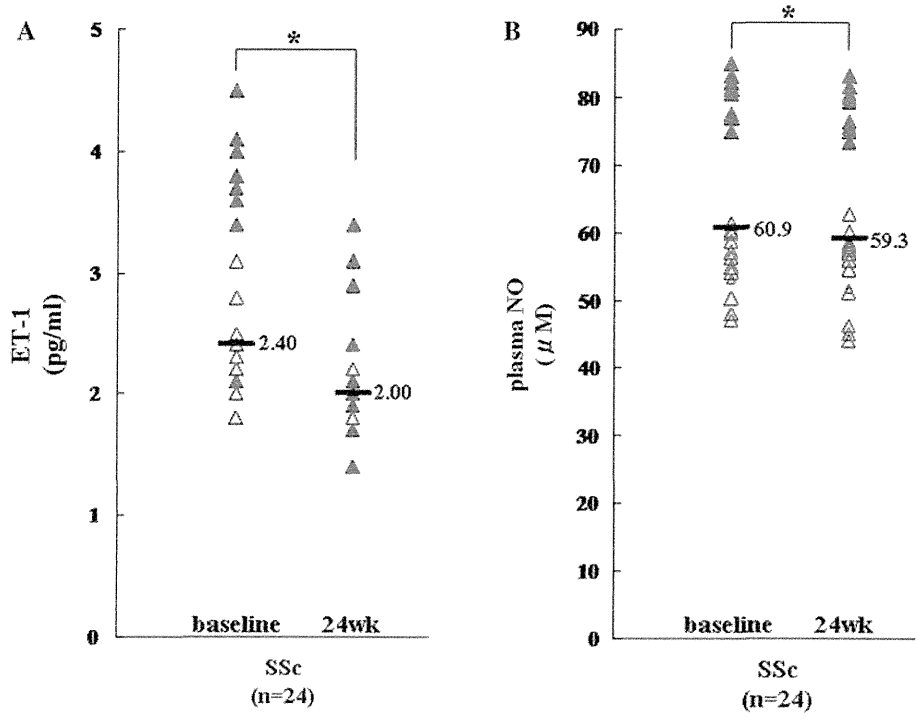

Fig. 1 Changes in plasma concentrations of ET-1 and NO during 24 weeks of bosentan therapy in 24 SSc patients. Closed triangles: SSc patients with PH; open triangles: SSc patients without PH; crossbar: median of plasma ET-1 levels. *$p < 0.0001$; changes from baseline were compared using the Wilcoxon's signed-rank test

vasculopathy, including PAH [11, 12]. Endothelin-1 represents an important molecular target for therapeutic intervention in the vascular disease manifestations of SSc [12, 19]. Plasma ET-1 levels were elevated in patients with PAH [20] and correlated with the severity of PAH [12, 21]. Raised plasma ET-1 levels have been described in SSc patients [17, 22, 23]. In the present study, plasma ET-1 levels were higher in SSc patients with PH than in those without PH, and they were highest in patients with severe PH. These data may reinforce the pathologic role of ET-1 in SSc patients, especially in those complicated with PH.

Although the criteria of PH in the present study were relatively loose compared with the recent established PH guidelines [16], bosentan therapy in SSc patients with PH was found to be as effective as that reported in previous studies [7–10]. Vizza et al. [24] report that plasma levels of ET-1 tend to decrease after bosentan therapy in a subset of patients with PAH (idiopathic and collagen tissue disease), with the baseline ET-1 being high; they also showed that baseline ET-1 levels were not associated with clinical efficacy. In the present study, plasma levels of ET-1 were also decreased after bosentan therapy in SSc patients with PH to a level comparable to that of SSc patients without PH. Moreover, the levels were further decreased in patients with improved function. These observations are consistent with the results reported by Vizza et al. [24], though the changes in ET-1 levels in the present study are larger This difference may arise from differences in the study populations such as ethnic differences. Vizza et al. [24] hypothesize that, during long-term bosentan therapy, a new ET_B receptor may be expressed at the cellular level or that ET-1 production could decrease due to an improvement in hemodynamic conditions and in neurohormonal activation. The latter hypothesis might explain the present results since the decrement in ET-1 levels appeared to be more significant in SSc patients with PH than in SSc patients without PH. Thus, the decrement in circulating ET-1 by bosentan therapy suggests an improvement in the clinical condition of SSc patients with PH. Bosentan may improve the pathologic niche of pulmonary microvasculature in SSc patients with PH, which is reflected as a decrement in plasma ET-1. ET-1 levels were also decreased by bosentan therapy in patients without PH. ET has been implicated in vasoconstrictor and profibrotic activity and in the increased extracellular matrix substances seen in the dermis and internal organs of patients with SSc. In the early stage of SSc, bosentan therapy could prevent the onset of organ lesions, including PAH and skin ulcers. Plasma NO levels were similarly high in SSc patients with PH, but decreased slightly after bosentan therapy. NO is known to be a vasodilator [24], and its production may increase to counteract the action of ET-1 since plasma NO levels were high in SSc patients with PH as compared to SSc patients without PH. Increments in plasma NO at baseline may counteract ET-1, while bosentan itself does not directly act on the NO pathway. Therefore, the NO decrement brought about by bosentan was not so obvious. Alternatively, a combination therapy of bosentan with phosphodiesterase inhibitors may be warranted in patients with SSc, especially in those complicated with PAH.

In conclusion, plasma ET-1 levels could reflect the presence and severity of PH in SSc patients. Moreover, changes in plasma ET-1 levels might show the therapeutic response to bosentan in SSc patients with PH. Although a decrement in plasma ET-1 was induced by bosentan in the present study, plasma ET-1 levels remained high when compared with those of healthy controls. The present study includes the limitation that PH was defined only by echocardiogram with a systolic PAP cutoff value of >30 mmHg in the absence of right-heart catheterization; the present study was carried out before the establishment of guidelines for the diagnosis and treatment of PH [16] and the cutoff value may not be sufficient to exclude SSc patients not complicated with PAH since the recent guidelines suggest that systolic PAP assumed by echocardiography is likely to have a PH value of >50 mmHg [16]. In addition, the present study included SSc patients classified as not having PH, though these patients were clinically suspected of having PH based on physician judgement. Therefore, the present observations should be confirmed through further examinations, including studies with larger numbers of patients and with a longer observation period.

Conflict of interest None.

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SUPPLEMENT

Next stage of RA treatment: is TNF inhibitor-free remission a possible treatment goal?

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ABSTRACT

Biological agents targeting tumour necrosis factor (TNF) have revolutionised the treatment of rheumatoid arthritis (RA) and clinical remission has become a realistic treatment goal. Discontinuing anti-TNF therapy after sustained remission has emerged as an important area of investigation in rheumatology from the risk-benefit point of view, including health economic considerations. However, there is little information as to whether 'biologic-free remission' is possible after sustained remission following intensive treatment with TNF inhibitors in RA. European studies such as BeSt and OPTIMA in patients with early RA and Japanese studies such as remission induction by remicade in patients with RA and HONOR in patients with long-standing RA encountered during routine clinical practice have shown that, after a reduction in disease activity to clinical remission or low disease activity by infliximab or adalimumab in combination with methotrexate, patients can successfully remain in clinical remission without TNF inhibitors with no radiological and functional damage progression of articular destruction. Experimental findings in TNF-deficient mouse models suggest that TNF inhibitors may change the disease process of RA and bring about the potential of immunological remission, raising the possibility of a 'treatment holiday' of TNF inhibitors after intensive treatment.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes significant morbidity and mortality.[1–4] It is recommended that the treatment of RA is initiated with monotherapy or a combination of disease-modifying antirheumatic drugs (DMARDs).[5–8] Patients with active RA, however, are often resistant to DMARD therapy, especially in the context of structural progression. Thus, biological agents targeting proinflammatory cytokines such as tumour necrosis factor (TNF), which plays a pivotal role in the pathological processes of RA leading to joint destruction, have been developed. The combined use of biological agents targeting TNF and methotrexate (MTX) has revolutionised the treatment of RA, producing significant improvements in clinical, structural and functional outcomes that were not previously observed. Accordingly, the concept of treating RA to target by employing a composite measure of disease activity is generally being accepted worldwide.[5] Clinical remission is perceived as an appropriate and realistic primary goal in many patients while, in those with long-standing RA, low disease activity is the aim.

After the induction of clinical remission by combination therapy with TNF inhibitors and MTX, it has to be maintained as described in No. 8 of the 'Treat-to-Target', which leads to structural remission and functional remission.[5] Caution is needed when deciding to reduce or discontinue treatment with synthetic DMARDs because stopping DMARDs in remission was followed by twice as many flare-ups, difficulties in reintroducing remission and a halt in damage, whereas similar studies are not available for the biological agents.[5] However, because of the economic burden associated with expensive biological products and the long-term safety by inhibiting a particular cytokine, the possibility of discontinuation of biological products after the maintenance of remission needs to considered. Thus, treatment strategies with TNF inhibitors targeting induction and/or maintenance of clinical remission can potentially lead to subsequent discontinuation of the TNF inhibitors. However, there is no well-established firm evidence that remission can be sustained even if a biological agent is discontinued (ie, 'biologic-free remission'). In this paper we discuss whether the discontinuation of TNF inhibitors such as adalimumab and infliximab is possible in patients with RA after achieving low disease activity or clinical remission during a certain period with TNF inhibitors.

IS DISCONTINUATION OF ADALIMUMAB POSSIBLE AFTER SUSTAINED REMISSION?

Clinical remission has recently become an achievable goal by the combination therapy of TNF inhibitors and MTX in many patients, and appropriate induction of remission is a prerequisite to halt joint damage and functional disabilities, which revealed improved outcomes with strategic therapeutic approaches.[4–8] If a patient is in persistent remission after tapering of glucocorticoids, one can consider tapering TNF inhibitors, especially if this treatment is combined with DMARDs. However, there is little information about the characteristics of patients with long-standing RA in whom adalimumab can be successfully discontinued.

We have carried out a study (Humira discontinuation without functional and radiographic damage progressiON follOwing sustained Remission, HONOR) to investigate whether adalimumab-free remission is maintained after discontinuation of adalimumab in Japanese patients with established RA in sustained remission obtained with adalimumab plus MTX.[9] In this study, sustained remission