D. 考察

ムコ多糖症Ⅰ型(Hurler 病)においては造血細胞移植の効果が確認されているが、Ⅱ型(Hunter 病)における治療効果について統一した見解がえられていなかった。MPSⅡ型は日本などアジア人に多い病型であることから、わが国では造血細胞移植の実施例が多く、重症例で早期に移植を行えば中枢神経系を含めて一定の効果が期待できることが本研究班などの調査により判明しつつある。

一方、2000 年代後半から臨床応用が開始された酵素補充療法は中枢神経系以外の臓器に対しては効果が認められるものの、定期的な外来受診と点滴ルートの確保など生涯にわたる治療の継続が必要なため、造血細胞移植は今後も必要とする専門家が多い。

今後2つの治療法の評価を前方視的に行うことにより、科学的に正確な比較が可能になると思われる。現在酵素補充療法の治験期間中と市販後調査で用いられている評価方法と評価時期を造血細胞移植にも適用することにより両者を同一基準で比較できると考えている。

E. 結論

昨年度から継続しているムコ多糖症Ⅱ型における造血細胞移植の効果に関する後方視的研究の結果、今後前方視的に評価すべき項目と評価頻度に関するガイドラインを試作した。

F. 健康危険情報

本研究は後ろ向きの疫学調査であるため、本研究による健康被害はなかった。

G. 研究発表

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H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

厚生労働科学研究費補助金（医療技術実用化総合研究事業）
分担研究報告書

酵素補充療法を受けたポンペ病患者のフォローアップの研究
「ポンペ病酵素補充療法の有効性評価の検討」

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研究要旨

ポンペ病の酵素補充療法が本邦で行われるようになって 2 年半ほどたった。その間に有効性が示されている症状とそうでない症状などが徐々に見えつつあり、また患者ごとにも効果が異なるなど、多彩な状態が判明してきた。それらのポンペ病患者を全身的にとらえていくために、我々は QOL 評価である FIM（Functional Independence Measure）スコアを用いて、日本人における有効性、安全性を集計した。投与短期間での評価で亜はあるが、これにより発症年齢が早期な症例ほどスコアの上昇率が良いことが判明し、早期治療の重要性が高まる結果となった。

研究協力者

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A. 研究目的

ポンペ病は、酵素製剤アルグルコシダーゼアルファが 2007 年に本邦でも承認されたことにより、多くの患者に点滴治療が施されている。多くの患者はおおよそ 2 年半の投与を継続しているが、その間に有効性についていろいろなことが判明してきた。有効性が示されている症状とそうでない症状などが徐々に見えつつあり、また患者ごとにも効果が異なるなど、多彩な状態が判明してきた。そのため、それらのポンペ病患者を全身的にとらえていくために、我々は QOL 評価である FIM（Functional Independence Measure）スコアを用いて、12 名の日本人における有効性を評価、集計した。

B. 研究方法

ADL を評価する FIM 質問紙を用いたアンケート調査を施行した。FIM（Functional Independence Measure）とは機能的自立度評価表（質問紙）を用いた ADL 評価法であり、介助者が客観的に患者の可能な日常生活動作を記載するものである。評価する項目は食事、整容、入浴、更衣上半身、更衣下半身、トイレ動作、排尿コントロール、排便コントロール、移乗、トイレ移乗、浴槽移乗、移動、階段、理解、表出、社会的交流、問題解決、記憶の全 18 項目であり、各項目 7 点満点で、全 126 点となる。

この FIM 質問紙アンケート調査を、酵素補充療法を行っているポンペ病患者に郵送し、患者本人の了承のもとで、介助者に回答してもらい返送してもらうこととした。

C. 研究結果

12 名のポンペ病患者より回答があった。病型は成人型が 4 名、小児型が 8 名である。FIM スコア合計を検討した結果、スコア上昇が 8 例（A：74 点→83 点、B：39 点→57 点、C：66 点→68 点、D：68 点→72 点、E：63 点→75 点、F：121 点→122 点、G：113 点→124 点、H：93 点→102 点、）、不変 3 例（I：73 点→73 点、J：112 点→112 点、K：97 点→97 点）、低下 1 例（L：123 点→121 点）であった。

その中で、10 歳以下で発症した症例は全例がスコア上昇（B：39 点→57 点、D：68 点→72 点、E：63 点→75 点、F：121 点→122 点、G：113 点→124 点、H：93 点→102 点）となっており、10 歳以上で発症した症例は スコア上昇、低下、不変（A：74 点→83 点、C：66 点→68 点、I：73 点→73 点、L：123 点→121 点、J：112 点→112 点、K：97 点→97 点）を示した。平均スコア上昇は 10 歳以下で発症した症例は+9.2 点、10 歳以上で発症した症例は+1.5 点である。また、各項目におけるスコア上昇は、

排尿コントロールと移動が 4 名、排便コントロールと移乗がそれぞれ3名、食事と更衣下半身がそれぞれ2名、整容、更衣上半身、トイレ移乗、階段、理解、問題解決がそれぞれ 1 点であった。スコア低下項目は移乗、トイレ移乗、階段の 3 項目であった。

D. 考察

ポンペ病に対する酵素補充療法について、乳児型においては生存期間の延長など著明な効果が報告されている。しかし、小児型、成人型についての有効性については不明な点が多い。そのため、成人型ポンペ病について、日本人での安全性評価を確認していくとともに、有効性を観察してくことは重要な意義がある。

今回我々は、酵素補充療法を受けている 12 名のポンペ病患者に対して、全身的な改善の程度を把握するための一つのツールとして、QOL を評価するための FIM スコア:機能的自立度評価を用いた。臨床検査では評価が現れにくい短期の評価指標として、臨床症状の改善を表す FIM スコアは有用な指標になると考えられる。

ポンペ病患者 12 人のFIMスコアからみると、10 歳以下で発症した症例では全例スコアが上昇し、短期的には有効性がよく示されている結果となった。10 歳以上で発症した症例に関しては、今後スコアが徐々に上向いてくるのか長期的に検討する必要があるものの、蓄積期間が長いほど改善も遅いもしくは困難であると考えられることが示された。そのため、酵素補充療法を行うに当たっては早期診断・治療が重要であると考えられ、今後治療評価指標の検討と並行して早期診断のための新生児スクリーニングの体制の構築を検討していく必要があると考えられた。

E. 結論

ポンペ病に対する酵素補充療法の有効性評価に関して、FIM スコアが短期的には鋭敏に評価可能であることが示唆された。発症年齢が若年であるほど、FIMスコアの上昇は酵素補充開始初期には顕著である。今後これらのデータの長期的な変化を確認していくとともに、さらに早期に治療を開始した症例についても検討していくことが必要である。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

なし

2. 学会発表

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H. 知的財産権の出願・登録状況

該当なし

厚生労働科学研究費補助金（医療技術実用化総合研究事業）
分担研究報告書

ライソゾーム病の新生児スクリーニング導入の倫理的課題について

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研究要旨

わが国にライソゾーム病の新生児マススクリーニング（NBS）を導入する際の倫理的諸問題について、すでに一部で導入が計画されている米国での議論を参照しながら提言を行う。現段階での結論としては、ライソゾーム病のNBS は、公衆衛生事業として位置付けるよりも個別医療の範疇で実施すべきと考え、そのための検査前のインフォームド・コンセントや検査陽性者への遺伝相談を含めたカウンセリング体制の整備が不可欠と考える。

研究協力者

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A. 研究目的

ライソゾーム病の治療法である酵素補充療法は、早期あるいは発症前から治療を開始することが効果的である。そのため、酵素補充療法による治療が可能なライソゾーム病については、新生児マススクリーニングで早期に発見し、早期に治療を開始することにより酵素補充療法の効果を最大限に引き出すことが可能であると考えられる。

しかし、疾患によっては、酵素補充療法の効果は限定的であり、生後早期の無症状時から治療を開始しても、知的障害等の進行を抑制できないものもある。これは、新生児マススクリーニングの国際的クライテリアであるWilson-Jungner スクリーニング・クライテリア（WHO, 1968）（表 1）に厳密な意味においては合致しないことを意味している。

一方、米国においては、既に二つの州でライソゾーム病の新生児マススクリーニングが開始されようとしている。

本研究では、これらの背景を考慮し、米国での議論等を参照、検討することにより、わが国においてライソゾーム病の新生児マススクリーニングを導入することの是非、ならびに導入に際して考慮すべき倫理的諸課題についての検討を行うことを目的とする。

B. 研究方法

2008 年に米国大統領生命倫理委員会が作成した白書“The Changing Moral Focus of Newborn Screening. An Ethical Analysis by the President's Council on Bioethics”の検討、および当該委員会の座長であったEdmund D. Pellegrino 先生へのインタビュー調査、ならびに新生児マススクリーニングの専門家である Ethan Hausman 先生、ならびに米国の新生児科医であるArthur Kopelman 先生へのインタビュー調等を通じて、わが国におけるライソゾーム病の新生児マススクリーニングの是非ならびに実施する場合の体制整備等に関する検討を行った。

C. 研究結果

検討の結果、わが国におけるライソゾーム病新生児マススクリーニング導入の是非を検討する際に参考となる米国大統領生命倫理委員会白書の見解の一部を示す。

(1) Wilson-Jungner スクリーニング・クライテリアの本質的な重要性と継続的な適切性を再確認する。

(2) 明らかに典型的なクライテリアに合致している疾患に対してのみ義務的な新生児スクリーニングが州において推奨されることを主張する。

上記の見解に基づくと、本来的には、新生児マススクリーニング対象疾患は、原則的に Wilson-Jungner スクリーニング・クライテリアに基づく必要があり、ライソゾーム病はこの新生児マススクリーニングの対象として適切ではないと解釈できる。

表1. The ten Wilson-Jungner criteria for including a condition in a screening program

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

一方、見解の(3)では、

(3) 典型的なクライテリアに合致しないその他の疾患のスクリーニングが、州によって自主的な研究のパラダイムのもとで両親へ依頼されて構わないとする見解を支持する。

とされており、これに基づけば、ライソゾーム病のようなこの基準に厳密には合致しない疾患については、それぞれの州が独自の基準のもとでパイロット研究として実施していくことは許容できることとなる。

D. 考察

わが国の現行の新生児マススクリーニングの対象疾患は6疾患で、いずれも新生児早期に発見し治療を開始することにより、ほぼ正常に近い成長や発達が期待できる疾患に限られている。すなわち、Wilson-Jungner スクリーニング・クライテリアと合致しているのである。一方、ライソゾーム病の場合は、一部疾患を除き、発症前に治療を開始した場合であっても、完全に病態の進行を抑えることはできない。しかしながら、疾患の進行を遅らせ、患者ならびに家族のQOLを高めることは期待できることから、新生児マススクリーニングの導入により、一定の効果が期待される。

新生児マススクリーニングには、公衆衛生の考え方に基づく「義務的なスクリーニング」と、個別医療の考え方に基づく「任意のスクリーニング」がある。前者については、公衆衛生事業であることから、費用対効果の問題や費用負担の問題等も検討されなければならない。そのため、効果的な治療法が存在し、介入により確実な効果が認められる必要がある。

ライソゾーム病の治療については、酵素補充療法の開発によりかなり効果が期待できるようになったが、未だ完全に障害発生ならびに進行を抑制することは難しい状況である。このことから、現段階ではパイロット研究として任意のスクリーニングを実施するに留めることが適当であると考える。

E. 結論

ライソゾーム病の新生児マススクリーニングを導入するということは、従来から対象疾患選定に基準を踏み越えることを意味することから、のわが国における NBS のあり方を根本的に変革するものと考えられる。一般論として、一旦枠組みを越えてしまうと、スリッパリー・スロープ(slippery slope) を防ぐことは非常に難しくなることから、慎重な検討が必要であると考える。

また、パイロット研究として個別医療として実施する場合、検査前のインフォームド・コンセントを十分に行うこと、および検査陽性者とその家族に対する心理社会的な支援体制の整備、長期的なフォローアップ体制の整備等、新たな体制整備が導入に先立ち不可欠と考える。

F. 健康危険情報

特になし

G. 研究発表

なし

研究成果刊行に関する一覧表

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Japan Elaprase® Treatment (JET) study: Idursulfase enzyme replacement therapy in adult patients with attenuated Hunter syndrome (Mucopolysaccharidosis II, MPS II)

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ABSTRACT

This open-label clinical study enrolled 10 adults with attenuated Mucopolysaccharidosis II and advanced disease under the direction of the Japan Society for Research on Mucopolysaccharidosis Disorders prior to regulatory approval of idursulfase in Japan. Ten male patients, ages 21–53 years, received weekly intravenous infusions of 0.5 mg/kg idursulfase for 12 months. Significant reductions in lysosomal storage and several clinical improvements were observed during the study (mean changes below). Urinary glycosaminoglycan excretion decreased rapidly within the first three months of treatment and normalized in all patients by study completion (−79.9%). Liver and spleen volumes also showed rapid reductions that were maintained in all patients through study completion (−33.2% and −31.0%, respectively). Improvements were noted in the 6-Minute Walk Test (54.5 m), percent predicted forced vital capacity (3.8 percentage points), left ventricular mass index (−12.4%) and several joint range of motions (8.1–19.0 degrees). Ejection fraction and cardiac valve disease were stable. The sleep study oxygen desaturation index increased by 3.9 events/h, but was stable in 89% (8/9) of patients. Idursulfase was generally well-tolerated. Infusion-related reactions occurred in 50% of patients and were mostly mild with transient skin reactions that did not require medical intervention. Two infusion-related reactions were assessed as serious (urticaria and vasovagal syncope). One patient died of causes unrelated to idursulfase. Anti-idursulfase antibodies developed in 60% (6/10) of patients. In summary, idursulfase treatment appears to be safe and effective in adult Japanese patients with attenuated MPS II. These results are comparable to those of prior studies that enrolled predominantly pediatric, Caucasian, and less ill patients. No new safety risks were identified.

Introduction

Mucopolysaccharidosis type II (MPS II, Hunter syndrome, OMIM #309900) is an X-linked recessive, lysosomal storage disorder caused by a deficiency of iduronate-2-sulfatase (IDS, EC3.1.6.13). This lysosomal enzyme catalyzes the first step in the degradation of the glycosaminoglycans (GAG), dermatan sulfate and heparan sulfate [1]. Iduronate-2-sulfatase deficiency leads to the accumulation of GAG within the lysosomes of virtually every cell in the body and is excreted in excessive amounts in the urine. MPS II encompasses a wide phenotypic spectrum that includes severe and attenuated forms. The severe form has onset of symptoms by 2–4 years old, progression of somatic symptoms and severe cognitive impairment during childhood, and death by 10–15 years of age. The attenuated form has a later onset in childhood, slower and milder progression of somatic disease, little to no cognitive impairment, and survival into adulthood. (Fig. 1) Common clinical features include coarse faces, upper airway obstruction, cardiac valve regurgitation, restrictive lung disease, hepatosplenomegaly, hernias, joint contractures, poor endurance, and reduced quality of life [2,3]. *IDS* gene mutations are heterogeneous, but some show genotype–phenotype correlations: deletions and gross rearrangements of the *IDS* gene are associated with the severe form, whereas missense

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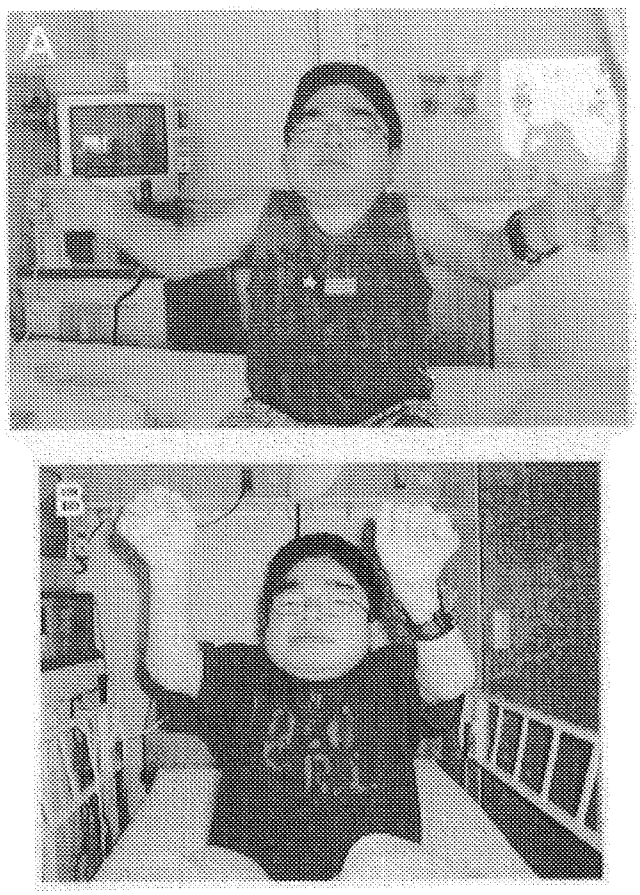

Fig. 1. A 23-year-old Japanese male study patient with MPS II. (A) Before treatment. (B) After 12 months of idursulfase treatment. Note the coarse facial features characteristic of MPS II. At baseline, the patient had severely limited shoulder range of motion (flexion and abduction), which improved following treatment.

mutations are more often associated with attenuated disease [4–10]. No racial or geographic differences have been observed. Females are only rarely affected, most often through skewed X-inactivation [1]. MPS II is the most prevalent MPS disorder in Asia, accounting for >50% of all MPS patients in Japan [10]. The annual incidence of all MPS disorders in Japan is estimated to be 1/50,000–1/60,000, and approximately half of the cases are due to MPS II. The estimated birth incidence of MPS II in Japan is, therefore, 1/90,000–1/100,000 [11], similar to the 1/92,000 to 1/162,000 incidences reported for predominantly Caucasian countries [12–15].

Until recently, treatment of MPS II was mainly palliative and focused on alleviating clinical symptoms through a variety of surgeries, medical devices, therapies, and medications. Several patients have undergone hematopoietic stem cell transplant (HSCT) as a source of iduronate-2-sulfatase, but unlike for MPS I, cognitive decline is not halted and the long-term effects on somatic disease are not well-documented [16,17]. Therefore, most centers consider the risk–benefit profile unfavorable and do not recommend HSCT for patients with MPS II.

Idursulfase (Elaprase®, Shire Human Genetic Therapies, Inc., Cambridge, MA, USA) is a recombinant human form of iduronate-2-sulfatase that is produced in a human cell line. Preclinical studies carried out in an MPS II knockout-mouse model [18] and in a Phase 1/2 dose-ranging study of MPS II patients [19] indicated that idursulfase was effective at reducing lysosomal GAG. The safety and efficacy of idursulfase was confirmed in a Phase 2/3 double-blind, placebo-controlled clinical study that randomized 96 MPS II patients to one of three treatment arms for 52 weeks: 0.5 mg/kg idursulfase weekly, 0.5 mg/kg idursulfase alternating with placebo every other week, or placebo weekly [20]. The primary efficacy endpoint was a composite of changes in percent predicted forced vital capacity (FVC) and the 6-Minute Walk Test (6MWT). Patients who received weekly idursulfase showed a greater difference in the composite endpoint compared to placebo ($p = 0.005$) than did the every other week idursulfase group ($p = 0.042$). The weekly idursulfase arm showed a mean 44.3 m increase in 6MWT distance (37 m difference from placebo, $p = 0.013$) and a mean 3.45 percentage point increase in percent predicted FVC (2.7 percentage point difference from placebo, $p = 0.065$). These clinical changes were associated with significant reductions versus placebo in urinary GAG level (−52.5%, $p < 0.0001$), liver volume (−25.3%, $p < 0.0001$), and spleen volume (−25.1%, $p < 0.0001$). Idursulfase was well-tolerated, with infusion-related reactions being the most common drug-related related adverse events, occurring in 69% (22/32) of patients in the weekly idursulfase arm.

Idursulfase was approved for the treatment of MPS II by the United States Food and Drug Administration (FDA) in July 2006 and by the European Medicines Agency (EMEA) in January 2007. Due to the life-threatening nature of the disease and the small number of patients, the Japanese Ministry of Health, Labour, and Welfare (MHLW) Committee for the Use of Unapproved Drugs recommended that idursulfase be approved based on ethical grounds and the results of overseas clinical trials, which included four Japanese patients. The committee also requested that idursulfase be made available to the most seriously ill MPS II patients prior to approval, which occurred in October 2007. Consequently, the Japan Elaprase Treatment (JET) study was initiated under the direction of the Japan Society for Research on MPS Disorders. Here, we present the results of this study.

Materials and methods

Patients

To be eligible for the study, patients had to meet all of the following inclusion criteria: (1) Documented deficiency of iduronate-2-sulfatase enzyme activity of <10% of the lower limit of normal with a normal enzyme activity level of one other sulfatase. (2) Male and above 20 years of age. (3) Clinically advanced disease status with <80% predicted FVC and New York Heart Association Class II–IV. (4) Capable of showing improved quality of life. (5) Able to complete study assessments.

Patient exclusion criteria included: (1) Previous bone marrow or cord blood transplant. (2) Known hypersensitivity to one of the components of idursulfase. (3) Previous treatment with idursulfase. (4) Unable to receive weekly infusions of idursulfase at the patient's local hospital. All patients provided signed informed consent prior to enrollment.

Study design

This was a multi-center, open-label study that enrolled 10 adult males with MPS II at 5 clinical sites in Japan. The study adhered to the guidelines set forth in the Declaration of Helsinki. Idursulfase was manufactured by Shire Human Genetic Therapies, Inc. and distributed by Genzyme Corporation (Cambridge, MA, USA). Genzyme Corporation performed all statistical analyses, and Genzyme Japan KK (Tokyo, Japan) provided data management support.

Idursulfase

Patients were administered 0.5 mg/kg idursulfase diluted in saline to a final volume of 100 cc intravenously over 3 h on a weekly

basis (±3 days) for up to 12 months. Infusions rates were ramped up over the first hour as described in the Phase 2/3 study [20]. Patients were monitored during each infusion and were discharged 1 h after completing the infusion, if clinically stable.

Efficacy assessments

Urinary GAG level was determined as the concentration of uronic acid normalized for creatinine (mg/g creatinine) and was measured using the carbazole reaction at a central laboratory (SRL Medisearch, Tokyo, Japan) or at Osaka City University Hospital. Liver and spleen volumes were quantitated by computerized tomography (CT), with the upper limits of normal being 2.5% and 0.2% of body weight, respectively. Percent predicted FVC and the 6MWT were performed according to American Thoracic Society guidelines [21,22]. Cardiac structure and function were evaluated by echocardiography (two-dimensional and M-mode). Left ventricular mass index (LVMI) was calculated as the left ventricular mass normalized for body surface area, with normal values defined as <131 g/m^2. Active joint range of motion was measured by goniometry, and included the shoulder (flexion, extension, and abduction), elbow (flexion and extension), hip (flexion and extension), and knee (flexion and extension). Left and right joint ranges of motion for each were averaged for each patient. The sleep study oxygen desaturation index (ODI) was assessed by pulse oximetry and defined as the number of desaturations (<89% oxygen saturation or ⩾4% decrease in oxygen saturation from baseline lasting ⩾10 s) per hour of sleep. A normal ODI was considered to be <5 events/h [23].

Safety assessments

Safety evaluation included continuous monitoring of adverse events and periodic clinical laboratory and physical examination evaluations. Adverse events were reported by severity (mild, moderate, severe, life-threatening) and by relatedness to idursulfase. An infusion-related reaction was defined as any adverse event occurring during or following an infusion (i.e., within 24 h of infusion initiation) that was reported by the investigator as related to idursulfase. Antibodies to idursulfase were measured by an enzyme-linked immunosorbant assay (ELISA; Shire Human Genetic Therapies).

Statistics

Efficacy results are reported as the mean ± standard error of the mean (SEM). For missing data at 12 months, the last observation carried forward method was used for values obtained at 6 months or later. The number of evaluable patients was at least nine for each endpoint, except for LVMI ($n = 6$, primarily due to missing baseline data) and the 6MWT ($n = 7$, primarily due to the inability to perform the test). The Wilcoxon signed rank test was used to evaluate changes in efficacy endpoint from baseline to 12 months, and p-values <0.05 were considered statistically significant. Percent change was tested for pharmacodynamic parameters (i.e., urinary GAG level and liver and spleen volumes), whereas absolute change was tested for clinical endpoints.

Results

Patient disposition

Ten adult Japanese males with attenuated MPS II were enrolled in the study and received idursulfase treatment. Nine patients completed the 12-month study; one patient died of causes unrelated to idursulfase after receiving 41 of 44 scheduled infusions (see Safety Section). Compliance with treatment was excellent, with all 10 patients receiving >93% of scheduled infusions; 80% (8/10) of patients did not miss a single scheduled infusion.

Patients

The mean patient age was 30.1 years (range 21.1–53.9). All patients had been diagnosed during mid-childhood or adolescence with MPS II (mean age 7.9 years), and all had advanced disease burden at the time of enrollment into the study. All patients had short stature (height <3rd percentile for Japanese adult males). Past medical history was significant for the following MPS II-related features (n = number of patients): valvular heart disease consisting mainly of aortic and/or mitral valve insufficiency (10), joint contractures (7), hepatomegaly (7), deafness (6), retinal degeneration (5), sleep apnea (5), otitis media

Table 1
Summary of efficacy changes after 12 months of treatment with idursulfase.

	N	Baseline	12 months	Change	% Change	p-Value
Urinary GAG (mg/g creatinine)	9	106.4 ± 7.8	21.2 ± 2.9	−85.2 ± 7.1	−79.9 ± 2.2	0.004†
Liver volume (cc)	10	1491.2 ± 92.9	993.2 ± 75.0	−498.0 ± 70.2	−33.2 ± 4.0	0.002†
Spleen volume (cc)	10	210.2 ± 22.5	138.1 ± 12.5	−72.1 ± 15.7	−31.0 ± 5.5	0.002†
6-Minute Walk Test (m)	7	286.0 ± 53.4	340.5 ± 49.6	54.5 ± 27.0	37.4 ± 18.1	0.109
Forced vital capacity (% predicted)	9	39.9 ± 6.6	43.7 ± 6.0	3.8 ± 2.8	15.0 ± 8.0	0.250
Forced vital capacity (L)	9	1.4 ± 0.3	1.5 ± 0.2	0.1 ± 0.1	16.3 ± 8.0	0.250
Left ventricular mass index (g/m^2)	6	139.9 ± 25.1	133.2 ± 38.9	−6.7 ± 15.5	−12.4 ± 11.1	0.563
Left ventricular ejection fraction (%)	10	67.0 ± 5.2	64.3 ± 6.0	−2.8 ± 2.5	−6.1 ± 5.7	0.244
Joint range of motion (degrees)					NA	
Shoulder flexion	10	93.8 ± 4.9	109.8 ± 7.1	15.0 ± 7.3		0.066
Shoulder extension	10	44.1 ± 4.1	43.8 ± 3.8	−0.3 ± 4.1		0.945
Shoulder abduction	10	76.3 ± 3.9	95.3 ± 8.1	19.0 ± 8.8		0.125
Knee flexion	9	103.7 ± 8.5	114.4 ± 5.2	10.7 ± 10.3		0.461
Knee extension	9	−11.1 ± 4.5	−10.3 ± 5.0	0.8 ± 2.5		0.875
Hip flexion	9	89.2 ± 8.1	103.3 ± 7.6	14.2 ± 5.1		0.031
Hip extension	9	3.1 ± 5.0	1.9 ± 6.7	−1.3 ± 1.8		0.750
Elbow flexion	10	120.9 ± 4.0	121.8 ± 3.7	0.9 ± 2.5		0.828
Elbow extension	10	−43.1 ± 4.2	−35.0 ± 4.2	8.1 ± 3.4		0.063
Oxygen desaturation index (events/h)	9	18.5 ± 6.1	22.3 ± 7.4	3.9 ± 3.5	NA	0.426

The last observation carried forward (LOCF) method was used to replace a missing value at the 12-month timepoint.
All values are the observed means ± SEM. All p-values are based on the Wilcoxon signed rank test for change from baseline to the 12-month timepoint.
NA, not applicable. Some patients had values of 0 at baseline that precluded calculation of percent change.
† The p-value is based on the Wilcoxon signed rank test for % change from baseline to the 12-month timepoint.

(4), macroglossia (3), umbilical hernia (2), carpal tunnel syndrome (2), heart failure (2), and left ventricular hypertrophy (1).

Urinary glycosaminoglycan (GAG)

All nine evaluable patients had elevated urinary GAG levels at baseline (mean 106.4 mg/g creatinine, approximately 8 times the upper limit of normal); one patient lacked an appropriate baseline value (Table 1). Following idursulfase treatment, urinary GAG levels decreased rapidly within the first three months of treatment and remained low for the remainder of the study (Fig. 2A). There was a statistically significant mean decrease in the urinary GAG level of −79.9 ± 2.2% from baseline to 12 months ($p = 0.004$). All nine evaluable patients showed a >70% decrease in urinary GAG levels and had normal values by the end of the study.

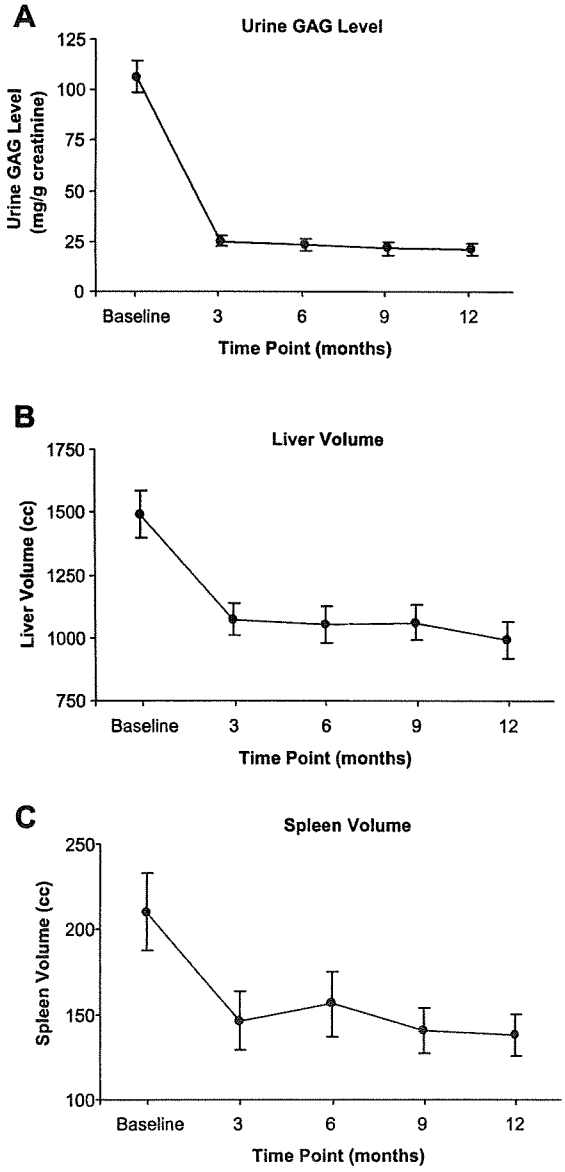

Fig. 2. The effects of idursulfase treatment on lysosomal storage over 12 months. (A) Urinary GAG level. (B) Liver volume. (C) Spleen volume. All changes are reported as mean ± SEM.

Liver and spleen volumes

At baseline, 9 (90%) patients had hepatomegaly (mean 1.3 MN, multiples of normal) and all 10 (100%) patients had splenomegaly (mean 2.4 MN) by CT. After 12 months of treatment, mean liver volume decreased by −33.2 ± 4.0% and mean spleen volume decreased by −31.0 ± 5.5% (Fig. 2B and C; Table 1), and both changes were statistically significant ($p = 0.002$). Most of the reductions occurred within the first three months of treatment. By the end of the study, all patients had liver volumes within the normal range and spleen volumes that were <2 MN, demonstrating efficient reduction of lysosomal GAG storage.

6-Minute Walk Test (6MWT)

At baseline, the mean 6MWT distance was 286.0 m for the seven patients who could perform the test (Table 1). All but one patient walked <399 m, the lower limit of normal for healthy adult men in the United States [24]. Three patients could not perform the 6MWT: one patient broke his leg just prior to the start of the study; one patient was wheelchair-bound secondary to shortness of breath and muscle weakness; and one patient was obese and could only walk a few steps with assistance. By the end of the study, the mean 6MWT distance had increased by 54.5 ± 27.0 m (Fig. 3A). This change represents a relative increase of 37.4%, and included one patient whose 6MWT distance increased by 131%. Four patients (57%) showed a clinically meaningful improvement of ⩾54 m [25], while the one patient with a normal 6MWT at baseline showed a decline (−71 m).

Percent predicted forced vital capacity (FVC)

Nine patients underwent spirometry at baseline and all showed a restrictive lung disease pattern: three were classified as having a severe defect (<50% predicted FVC) and five had a very severe defect (<34% predicted FVC) [26]. At baseline, mean percent predicted FVC was 39.9% (Table 1), and after 12 months it increased by 3.8 ± 2.8 percentage points (Fig. 3B). This improvement corresponds to a relative increase of 15.0% over baseline, which is considered clinically meaningful (⩾15% relative change) [25] and was achieved by four (44%) patients. Similarly, mean FVC increased by 16.3% over the baseline of 1.4 L. The mean forced expiratory volume in 1 s (FEV_1):FVC ratio remained unchanged at 0.70 during the study.

Cardiac

All patients had valve disease that remained stable during the study. The mean ejection fraction (EF) was normal at baseline and showed little change over 12 months (67.0–64.3%, change of −2.8 ± 2.5%) (Table 1). One patient with pre-existing cardiac failure showed gradual worsening during the study (EF 27–14%). At baseline, mean LVMI was slightly elevated at 139.9 g/m^2 (normal <131 g/m^2), and 50% (3/6) of evaluable patients had an elevated LVMI. After 12 months, mean LVMI decreased by −12.4%, with four patients showing a clinically meaningful improvement of >10% [27]. The patient with the largest LMVI at baseline showed a further increase (254.1–312.9 g/m^2).

Joint range of motion

Fig. 4 and Table 1 show the changes in joint range of motion observed during the study. At baseline, patients had significant joint contractures involving the shoulder (flexion, extension, and abduction), knee (flexion and extension), hip flexion and extension), and elbow (flexion and extension). Following 12 months of treatment, several joints showed increased range of motion, including mean

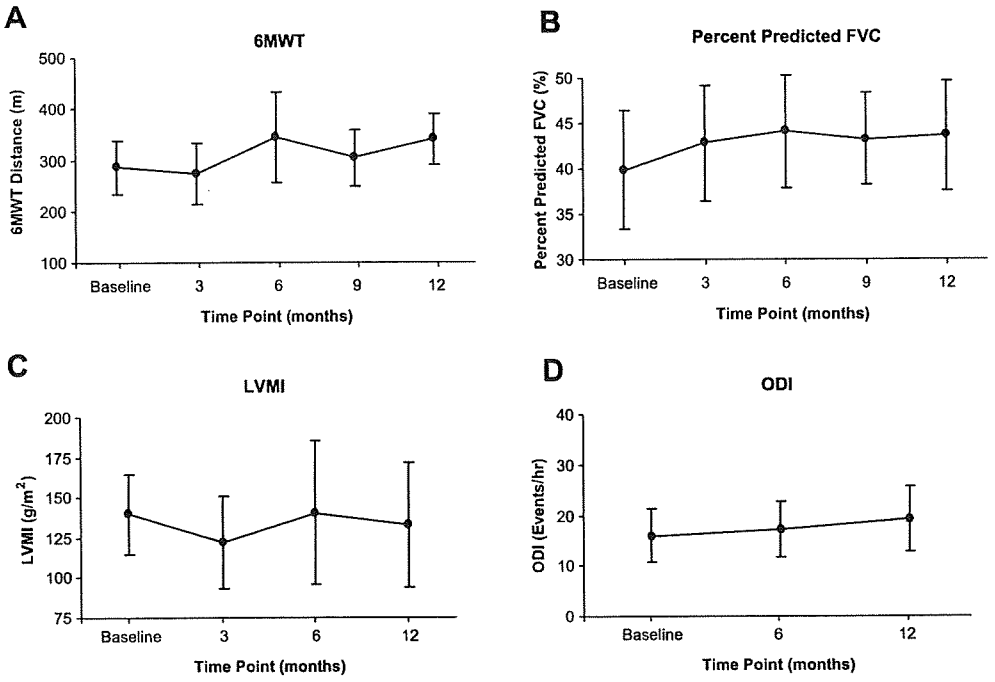

Fig. 3. The effects of idursulfase treatment on clinical endpoints over 12 months. (A) 6-Minute Walk Test. (B) % Predicted forced Vital Capacity. (C) Left Ventricular Mass Index. (D) Oxygen Desaturation Index. All changes are reported as mean ± SEM.

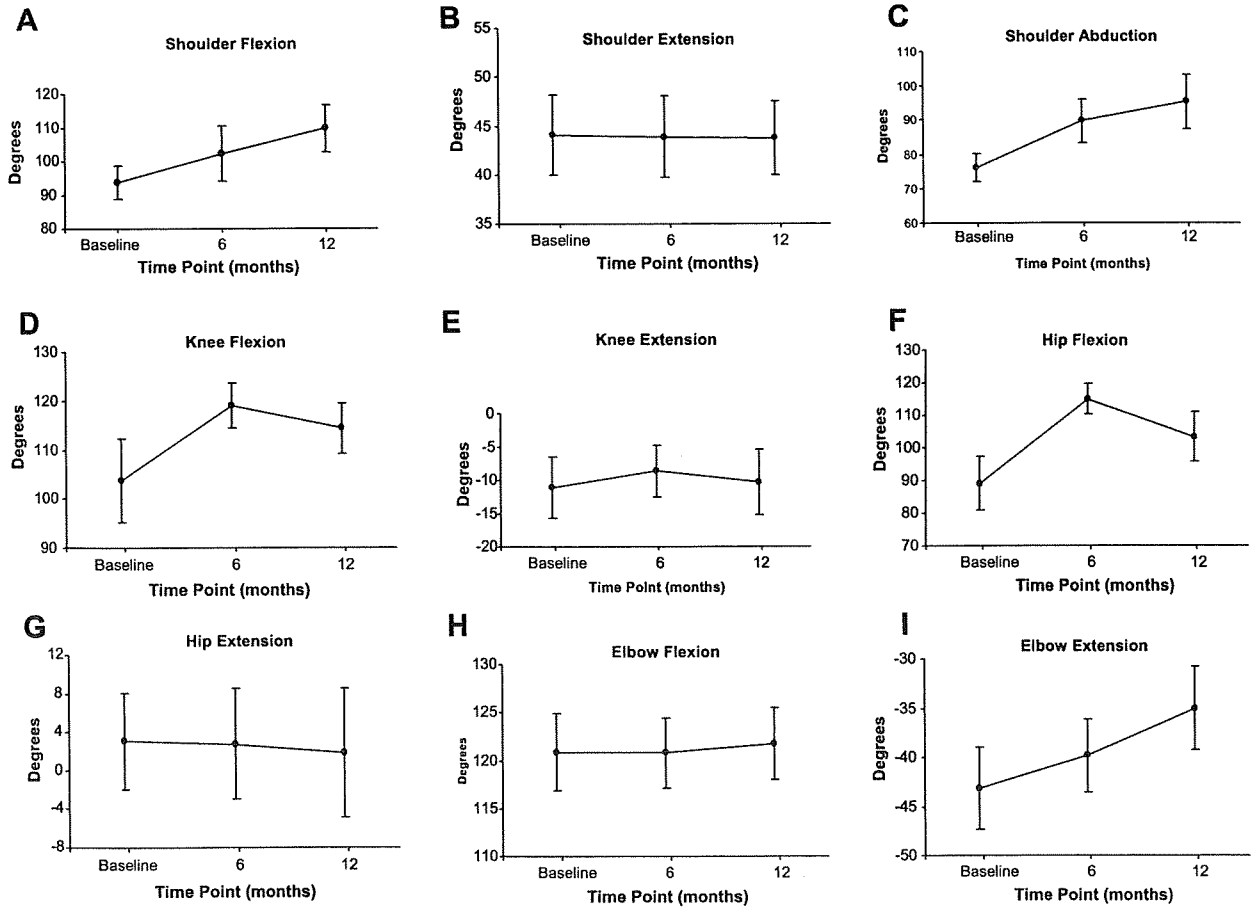

Fig. 4. The effects of idursulfase treatment on joint range of motion over 12 months. (A) Shoulder flexion. (B) Shoulder extension. (C) Shoulder abduction. (D) Knee flexion. (E) Knee extension. (F) Hip flexion. (G) Hip extension. (H) Elbow flexion. (I) Elbow extension. All changes are reported as mean ± SEM.

shoulder flexion (15.0 ± 7.3 degrees), shoulder abduction (19.0 ± 8.8 degrees), knee flexion (10.7 ± 10.3 degrees), hip flexion (14.2 ± 5.1 degrees; $p = 0.031$), and elbow extension (8.1 ± 3.4 degrees). However, most of the changes did not achieve statistical significance. Shoulder extension (−0.3 ± 4.1 degrees), elbow flexion (0.9 ± 2.5 degrees), knee extension (0.8 ± 2.5 degrees), and hip extension (−1.3 ± 1.8 degrees) showed little change during the study. Fig. 1 shows a 23 year-old study patient with severely limited shoulder range of motion (abduction and flexion), which improved following one year treatment with idursulfase.

Oxygen desaturation index (ODI)

At baseline, the mean oxygen desaturation index (ODI) was 18.5 events/h ($n = 9$), which is moderately abnormal [23]. Three patients had a normal ODI (<5 events/h), two had a mildly abnormal ODI (5–15 events/h), and four had a moderately to severely abnormal ODI (>15 events/h). During the study, the mean ODI increased by 3.9 ± 3.5 events/h, which was largely due to a single patient with an increase of 26.8 events/h. The other seven patients had stable ODI values (changes $\leqslant$ 10 events/h).

Safety

Idursulfase was well-tolerated over the course of the study. Adverse events were mainly mild, unrelated, and attributable to expected symptoms of MPS II disease. Fifty percent (5/10) of patients experienced a total of 11 drug-related adverse events. Urticaria was the most frequent event (five events in two patients), followed by erythema (two events in the same patient). Similarly, 50% (5/10) of patients experienced infusion-related reactions (i.e. adverse events assessed as drug-related and occurring within 24 h of the infusion). The highest patient incidence involved skin reactions, i.e. urticaria and erythema (three patients each), while dyspnea, abdominal pain, and vasovagal syncope also were observed in one patient each. Except for one patient who experienced several episodes of urticaria between 9 and 12 months, the other four patients had infusion-related reactions only once or twice during the first three months of treatment. Management of infusion-related reactions included antihistamine therapy and temporary interruption of the infusion, and all events were followed by a successful patient recovery. There were no clinical laboratory abnormalities reported as related to idursulfase.

Two patients experienced serious adverse events, including one death, in the study. A 26 year-old male experienced an infusion-related reaction involving diffuse urticaria, flushing, and numbness of the tongue 1 h after initiation of the fifth infusion. The patient was pre-medicated with antihistamines without further events. A 42 year-old male had an infusion-related reaction reported by the investigator as vasovagal syncope, which consisted of hypotension, vomiting, weak pulse, and decreased consciousness and occurred 30 min into the first infusion. Subsequent infusions were preceded by corticosteroid pre-medication administration without further infusion-related reactions. The patient had a history of cardiac valve incompetence and cardiac failure requiring medications, including furosemide. Later in the study, he experienced an increase in leg edema secondary to worsening congestive heart failure. He was depressed and attempted suicide by drug overdose (not idursulfase). Upon arrival at the hospital, the patient went into cardiac arrest. Subsequent resuscitation measures were unsuccessful, and he died due to hypoxic encephalopathy, pneumonia and renal failure.

Antibodies

Anti-idursulfase IgG antibodies were detected in 60% (6/10) of patients, two of who became seronegative later in the study. No IgE antibodies were detected in patients who underwent testing for infusion-related reactions. The mean reductions in urinary GAG levels did not differ between patients who were seropositive at any time (−80.9% ± 3.8%; $n = 5$) and those who remained seronegative throughout the study (−78.6% ± 1.8%; $n = 4$). Although hypersensitive reactions or infusion-related adverse reactions tended to occur in the antibody-positive patients (four antibody-positive patients versus one antibody-negative patient), there was no correlation between the presence of antibodies and other adverse events. Furthermore, the frequency of hypersensitivity reactions did not correlate with antibody titer.

Discussion

The most remarkable difference between this and previous clinical studies of idursulfase [19,20] relates to the patient demographics and characteristics. The purpose of the JET study was to provide access to treatment for the most seriously ill MPS II patients while awaiting regulatory approval of idursulfase in Japan, which occurred in October 2007. Patients in the JET study had a mean age of 30.1 years, all were Japanese, and all were seriously ill (mean percent predicted FVC 39.9% and mean 6MWT distance 286.0 m). By comparison, MPS II patients in the Phase 1/2 and Phase 2/3 studies of idursulfase were younger (mean ages 13.9 years and 14.2 years), predominantly Caucasian (100% and 83%, respectively), and less severely affected (mean percent predicted FVC 55.1% and 55.4%; mean 6MWT distance 397 m and 395 m) [19,20]. Despite these patient differences, the JET study has shown that idursulfase is a safe and effective (Table 1) treatment for Japanese patients with MPS II and its risk–benefit profile is similar to that reported in previous studies.

In this study, idursulfase efficiently reduced GAG storage, as evidenced by the statistically significant reductions in urinary GAG levels ($p = 0.004$) and hepatosplenomegaly ($p = 0.002$) (Fig. 2; Table 1). These pharmacodynamic changes appeared to translate into clinical benefit, as evidenced by trends towards improvement in functional capacity (mean 54.5 m increase in 6MWT), respiratory function (mean 15.0% relative increase in percent predicted FVC), joint range of motion (mean increases ranging from 8.1–19.0 degrees for several joints), and LVMI (mean −12.4% decrease). Cardiac EF and valve disease remained mostly stable, although one patient with severe congestive heart failure showed progressive worsening and one patient with a greatly elevated LVMI showed a further increase. The mean ODI increased slightly by 3.9 events/h, but importantly 89% (8/9) of patients showed no clinically significant changes.

The safety profile of idursulfase in the JET study was similar to that of previous studies with no new or unexpected adverse events despite the older and more seriously ill patient population. Most adverse events were considered by investigators to be disease-related and unrelated to idursulfase. The most common drug-related adverse events were infusion-related reactions, occurring in 50% of patients. The most common infusion-related reactions were skin reactions consisting of urticaria and erythema. There were two related serious adverse events that occurred during the infusions—one involving urticaria, flushing, and numbness of the tongue, and the other involving vasovagal syncope. The one patient death was attributed to suicide from a drug overdose and was not related to idursulfase.

MPS II is a progressive and debilitating multisystem disease that is associated with a shortened lifespan, primarily from cardiorespiratory compromise [28]. Therefore, it is noteworthy that in this one-year study, cardiac and respiratory functions were improved or stable in most patients. Decreasing lung volumes are known to be associated with increased morbidity and mortality [26];

given the low percent predicted FVC values at baseline in study patients (mean 39.9%), a relative increase of 15% is of particular importance. The American Thoracic Society defines a >15% relative change in FVC occurring over a one-year period as being clinically meaningful [26]. Similarly, the 54.5 m mean increase in 6MWT distance also is considered to be a clinically meaningful improvement, based on a study of adult men with chronic obstructive pulmonary disease [25]. The 6MWT is a sub-maximal exercise test that is a composite assessment of cardiac, respiratory, and musculoskeletal function. Because all three of these organ systems are involved in the MPS disorders, walking tests have been widely used as primary efficacy endpoints in clinical trials of enzyme replacement therapy for other MPS disorders, including MPS I [29,30] and MPS VI [31].

We observed no evidence for an effect of race on immunogenicity or safety. IgG antibodies were detected in 60% (6/10) of patients treated with idursulfase, which is similar to the 49.6% rate seen in the Phase 2/3 study that enrolled predominantly Caucasian and other non-Asian patients [20]. In addition, the adverse event profile was similar in all respects; infusion-related reactions occurred in 50% of patients in the current study compared to 69% of patients receiving weekly idursulfase in the Phase 2/3 study [20].

Limitations of this study include its open-label treatment, lack of control group, and small sample size. Other aspects of the study design, however, including the treatment dose and regimen, study duration, and efficacy and safety assessments were identical or very similar to those used in the Phase 2/3 study [20]. A placebo effect in this study cannot be excluded, especially for effort-dependent assessments such as the 6MWT and active joint range of motion. Nevertheless, the magnitude of change in the 6MWT distance was similar to those observed in previous studies of idursulfase [19,20]. Determination of FVC by spirometry is less susceptible to a placebo effect given the requirement for test–retest reproducibility at each assessment [21]. This study enrolled only 10 patients, which may not have had sufficient power to detect a statistically significant clinical response even if clinical improvements were present. On the other hand, the biomarkers of lysosomal GAG clearance, i.e. liver and spleen volumes and urinary GAG level, did have sufficiently large effect sizes (change/standard deviation of change) to show statistically significant differences. Finally, the study involved only adult males, all of whom had a substantial pre-existing disease burden. This study shows that many disease features of seriously ill patients, including diminished cardiorespiratory function, restricted joint range of motion, and hepatosplenomegaly can improve with idursulfase treatment. An even better response is expected in young children prior to final organ maturation and the development of chronic tissue damage. In this regard, a study in MPS II patients ≤5 years of age is underway.

Conclusions

Idursulfase was generally well-tolerated and produced clinical improvements in adult Japanese patients with attenuated MPS II treated with the labeled dose, 0.5 mg/kg administered intravenously once weekly. Treatment with idursulfase also resulted in substantial reductions in hepatosplenomegaly and urinary GAG excretion, indicating efficient clearance of lysosomal GAG. The safety profile and immunogenicity of idursulfase appear to be similar between Japanese and previously studied Caucasian patients.

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