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ORIGINAL RESEARCH

Adherence to Subcutaneous Interferon Beta-1a in Multiple Sclerosis Patients Receiving Periodic Feedback on Drug Use by Discussion of Readouts of Their Rebismart® Injector: Results of the Prospective Cohort Study REBIFLECT

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ABSTRACT

Introduction: Consistent treatment adherence is an important determinant of durable response in multiple sclerosis (MS). Published data indicate that adherence to > 80% of prescribed doses may be considered optimal. Feedback of electronic application monitoring data to patients has been considered a promising means to support high adherence.

Methods: The 2-year prospective non-interventional study REBIFLECT conducted at outpatient neurological centers (731 patients at 134 study sites in Germany) investigated whether treatment adherence to subcutaneous (sc) interferon beta-1 injection during a 1-year period is enhanced by regular physician-patient talks reflecting dosing data recorded by the application device in the context of clinical data or disease parameters. Qualitative adherence was defined as number of weeks with properly distributed injections per total number of weeks with prescribed injections. Quantitative adherence was defined as number of administered injections per prescribed injections.

Results: Overall median qualitative adherence was 90.5%. Approximately 70% of patients with adherence data available in the respective periods had a qualitative treatment adherence of 80–100%. With a mean of 97.9% quantitative adherence was very high and remained stable in the 2-year observation period. The stability of this effect is demonstrated by the subgroup with just one reflection talk (≥ 100%) and only a slight decrease in the subgroup with more than five reflection talks (97.9%).

Conclusion: Treatment adherence with the Rebismart® device was generally very high, consistent with other non-interventional

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studies. The first reflection talk supported by RebiSmart® induces excellent adherence, stabilized by repetition. Reflection to patients of subcutaneous interferon beta-1a treatment monitored by RebiSmart® is recommended to ensure prolonged strong treatment adherence.

Keywords: Adherence; Feedback; Injector; Interferon beta-1a sc; REBIFLECT; Reflection; Rebif®; Rebismart®

Key Summary Points

Why carry out this study?

Feedback of electronic application monitoring data to patients has been considered a promising means to support high adherence in patients with multiple sclerosis (MS). This study explored this approach in MS patients using interferon beta-1a sc (subcutaneous) in Germany.

What did the study ask?

Do physician-patient talks reflecting application data recorded by the injection device affect patient adherence?

What were the study conclusions?

Regularly reflecting treatment adherence and clinical status to patients on treatment with interferon beta-1a sc is associated with high treatment adherence over prolonged periods of therapy.

What has been learned from the study?

The results of this study may be extrapolated to support consistent adherence in MS populations of similar age and gender distribution who are using the RebiSmart® device for injecting interferon beta-1a sc.

INTRODUCTION

Therapy of chronic diseases is generally riddled by poor long-term adherence to the prescribed treatment regimens. Data accrued by the World Health Organization (WHO) indicate that only half of patients suffering from chronic diseases adhere to treatment recommendations [1].Particularly in multiple sclerosis (MS), consistent adherence is an essential determinant of durable treatment response [2, 3]. While adherence levels have not been sufficiently defined, published data indicated that an adherence of > 80% prescribed doses may be considered optimal as this level is significantly associated with reduced risk of hospitalization, acute visits and total costs of disease management in MS patients [4–6].

Studies consistently show that nonadherence is particularly prevalent in the early phases of therapy [7, 8]. Poor adherence is an unfavorable prognostic factor due to a potential of suboptimal suppression of disease activity [9]. MS patients with poor treatment adherence or persistence may experience higher relapse rates and lower quality of life [10, 11]. This, in turn, may have detrimental effects on health-economic and socio-economic aspects as well [12]. Long-term self-injection therapies in particular may pose significant challenges for sustained adherence [13, 14].

Rebif® [interferon beta-1a sc (subcutaneous)] is an established disease-modifying drug licensed for use in patients with relapsing multiple sclerosis (RMS) and people with a single demyelinating event (CIS) at a high risk of developing clinically confirmed MS [15–17]. The licensed dosage regimen requires three weekly subcutaneous injections of 22 µg or 44 µg interferon beta-1a.

Besides prefilled pens and syringes, interferon beta-1a sc can be administered by means of the autoinjector RebiSmart®. This device carries an electronic unit recording date, time, and dosage of each injection. Thus, it retains a detailed record of the injection history. These data can be downloaded and used for documentation and discussions with the patient.

Several European studies investigated the adherence of MS patients to interferon beta-1a sc applied by RebiSmart® when managed without feedback of adherence data recorded by the device [18, 23–26]. Feedback of electronic medication monitoring to patients on chronic

medication has been considered a promising means to increase adherence in various therapeutic areas [19, 20].

Here, we report the final results of REBIFLECT (REbif® adherence data from the readout function of ReBISmart® reFLEcted baCk to the paTients), a prospective, long-term study assessing the treatment adherence of patients who used the RebiSmart® autoinjector and had regular physician-initiated discussions reflecting the injection data recorded by the device in context of information on their current clinical and/or radiographic disease status.

METHODS

Study Objectives

This noninterventional study primarily investigated whether treatment adherence to subcutaneously injected interferon beta-1 sc might be enhanced during a 1-year period by regular physician-patient discussions reflecting dosing data recorded by the device in the context of clinical data and disease parameters.

The primary study objective was the extent of treatment adherence in patients who had experienced a clinically isolated syndrome (CIS) or had been diagnosed with relapsing multiple sclerosis (RMS) and who received treatment with interferon beta-1 sc administered by RebiSmart® with recording of actual injections if information on treatment adherence and clinical data had been provided to the patient regularly by the treating physician during "reflection talks" comprising an interview on adherence and talks on the clinical status and MRI results according to routine clinical practice.

Secondary study objectives included the evaluation of quality of life aspects, health economic measures, and MS disease parameters including the Expanded Disability Status Scale (EDSS) score and the annualized relapse rate while on "reflected" treatment.

Study Design

REBIFLECT was conducted at neurology practices and hospital outpatient clinics representative of the institutions treating the great majority of MS patients in Germany from September 2013 to August 2017.

The invited centers were located at sites throughout the country to ensure a representative sample.

Patients eligible for inclusion were adults with previous CIS who were at high risk of developing clinically definitive MS and patients diagnosed with RMS (RRMS or SPMS) according to revised McDonald criteria 2010. They were to have received treatment with interferon beta-1 sc administered by RebiSmart® for at least 3 months immediately before study inclusion.

The participating patients were observed for a period of 24 months. During the study, quantitative and qualitative data on injection adherence recorded by RebiSmart® were documented at 3-month intervals via the readout function of the device. Patients were supposed to inject interferon beta-1 sc in accordance with the approved indications and the recommendations stipulated by the summary of product characteristics (SPC) [15]. Any treatment decisions made before and during the study were solely at the discretion of treating physician and patient.

Guidance was provided for the transfer of RebiSmart®readout data and the number of expected injections to the eCRF. Safety data were recorded and assessed according to reporting of adverse drug reactions as per good clinical practice (GCP) [21].

Endpoints included the quantitative and qualitative adherence, i.e., percentage of administered (recorded by RebiSmart®) per prescribed injections and the percentage of injections applied in correct injection intervals, respectively. These endpoints were calculated for the first year, second year and full 2-year study period. Exploratory analyses studied the effects of factors known or suspected to affect treatment adherence. In addition, treatment adherence was categorically assessed by physicians on a three-step scale (high, medium, low). Guidance was provided for the transfer of

REBISMART readout data and the expected number of injections into the eCRF. Patient adherence was self-reported with the Morisky Scale (score range 0–4) and a visual analog scale (VAS, range 0–100) [22].

These endpoints were calculated the first year, second year and the complete study. Data were recorded using an electronic case report form (eCRF). Processing, summarization, and analyses were performed using the statistical software package SAS® version 9.1.3 or higher.

Data analysis was based on the safety population, i.e., on all patients enrolled in the study who received ≥ 1 injection of interferon beta-1 sc after enrollment. All collected data were analyzed with descriptive statistics. Nonparametric methods were used to analyze changes from baseline and for comparing patient groups. The association between quantitative treatment adherence and factors related to disease or treatment was assessed with Spearman's correlation analysis. Statistical tests were exploratory at the 5% significance level. Adjustment for multiple testing was not performed.

In subgroups defined by age, subcutaneous interferon beta-1 dose, use of Rebif starter pack, and number of reflection talks (i.e., discussions on adherence and/or clinical and radiographic status), quantitative treatment adherence in the first and second year and the full study period was compared with the Wilcoxon rank sum test or Kruskal-Wallis test.

Percent quantitative adherence was defined as 100 × (number of administered injections per prescribed injections during the respective observation time). Percent qualitative adherence was defined as 100 × (ratio of the number of weeks with properly distributed injections [intervals of 2 × 1 day and 1 × 2 days] to total number of weeks with prescribed injections). Adverse drug reactions were reported as per good clinical practice.

Ethics approval was received from Ethik-Kommission der Medizinischen Fakultät der FAU Erlangen-Nuernberg, Erlangen, Germany (ref. no. 153_13 B; July 17, 2013). In accordance with the legal provisions in Germany (§ 67 subsection 6 of the German Medicinal Products Act), the competent authority, i.e., the German Federal Institute for Drugs and Medical Devices, confirmed that this approval covered all study centers. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All subjects provided informed consent (part of the ethics approval) to participate in the study. The study centers were remunerated for their time spent per included patient; patients did not receive any compensation.

RESULTS

REBIFLECT was performed at 134 study centers; 746 patients were enrolled; 15 patients were excluded from the analysis because of missing adherence data. The analysis population thus included 731 patients who were predominantly female (73.9%), at a median age of 43 years. One hundred eighty-five patients (24.8%) discontinued the study prematurely, the most frequent reason being change of treatment strategy (n = 97).

Most participating patients (87.3%) suffered from relapsing–remitting MS (RRMS); 8.2% had CIS (Table 1). The mean EDSS score at baseline was 2.1. Prior treatment with other disease-modifying drugs was reported for 119 patients (16.3%). Glatiramer acetate was the most common prior drug (n = 36). Interferon beta1a sc had been administered for > 6 months in 82.6% of patients.

The median number of reflection talks per patient was 3 during both the first and second year of study (Table 2). Over the full study period (month 1–24) the median number of talks per patient was 4 (range 0–9). Readout data recorded by RebiSmart were available for > 86% of the patients at all time points.

Treatment Adherence

Mean quantitative treatment adherence during the first 12 months, based on the RebiSmart® readout data of 642 patients, was 98.8% (median: 100.2%). Quantitative adherence of 85% through 105% was documented in 88.5% of 642 patients (n = 568). Adherence rates < 85% were

Table 1 Patient disposition and characteristics

Patient disposition		
Patients included in the safety population, *n* (%)	746	(100%)
Patients with premature discontinuation of study, *n* (%)	185	(24.8%)
Due to "change of treatment strategy"	97	13.0%
Baseline patient characteristics		
Gender, female, *n* (%)	731	73.9%
Age, median, years (range)	43	(18–77)
Type of MS, *n* (%)		
RRMS	638	(87.3%)
CIS	60	(8.2%)
SPMS	31	(4.2%)
EDSS score, mean (± SD) [*n* = 594]	2.1	± 1.6
Previous MS therapy, *n* (%)	119	(16.3%)
Glatiramer acetate	36	(4.9%)
Interferon beta-1a IM	35	(4.8%)
Interferon beta-1b SC	26	(3.6%)
Duration of interferon beta-1a SC treatment at baseline		
> 6 months, *n* (%) [*n* = 731]	604	(82.6%)
Mean (± SD)	46.6	(± 44.9)

reported in 9.3% ($n = 60$). Adherence rates > 105% were seen in 14 patients (2.2%).

During the second 12-month period, mean quantitative treatment adherence was 96.8% (median: 100.2%, $n = 482$). Quantitative adherence of 85% through 105% was documented in 86.5% of patients. Adherence rates < 85% were seen in 9.8%; 3.7% had an adherence rate > 105%.

Mean quantitative treatment adherence over the full study period (month 1–24) was 97.9 ± 30.2% (SD) (median: 99.9%, $n = 644$), with 87.4% patients showing quantitative adherence of 85% through 105%, 10.7% had an adherence of < 85%, and 1.9% were over-adherent with > 105% of prescribed doses.

Comparison of quantitative treatment adherence between the first and second year in patients with RebiSmart® injection data available for the complete duration of 24 months ($n = 251$) showed a mean difference of 1.8% ($p = 0.0025$). Mean adherence rates were high during both periods (first year: 98.9%; second year: 97.1%) and with an identical median of 100.2% in both years.

Significant differences ($p = 0.025$) in quantitative adherence were observed between men and women in the second year: 96.4% in females vs. 98.1% in males and a somewhat higher proportion of men vs. women with an adherence of 85% through 105% (90.4% vs. 85.2%).

Median values of quantitative adherence were highly similar between genders (100.4% vs. 100.2%). During the full 2-year observation period, the differences between men and women were not significant, with identical proportions of patients being in the 85–105% adherence category (87.4% each).

Statistically significant differences ($p \leq 0.005$) were seen between the dropout vs. persistent subgroups during all three periods, with considerably lower mean adherence rates in the dropout subgroup compared to the persistent subgroup: 74.1% vs. 99.3% during the first year, 79.7% vs. 97.7%) during the second year, and 82.2% vs. 99.0% during the full study period. Thus, in all three observation periods the share of patients with 85–105% adherence was considerably lower among the dropouts than in the persistent subgroup (< 58% vs. > 88% of patients).

No statistically significant differences between the subgroups defined by disease duration or prior MS treatment were seen in any of the observation periods. Mean quantitative adherence during the second year among the subgroups defined by pre-baseline relapse frequency was numerically lowest in the subgroup with > 1 relapse.

Adherence frequency categories could not be compared between dose groups because of the high percentage (33.7%) of patients with

Table 2 Reflection and adherence results

Reflection of treatment data		
Reflection talks, *n*, median (range)	4	(0–9)
During first year	3	(0–5)
During second year	3	(0–4)
Reflection of quantitative and qualitative treatment adherence data based on RebiSmart readouts during the last quarter, *n* (%) of patients		
Baseline [*n* = 731]	593	(81.1%)
Month 12 [*n* = 488]	392	(80.3%)
Month 24 [*n* = 375]	281	(74.9%)
Quantitative treatment adherence		
During first year [*n* = 642], mean percentage of prescribed doses [PD], (95% CI)	98.8%	(96.4–101.1%)
85–105% of PD, *n* (% of patients)	586	(88.5%)
< 85% of PD, *n* (% of patients)	60	(9.3%)
> 105% of PD, *n* (% of patients)	14	(2.2%)
During second year [*n* = 482], mean percentage of prescribed doses [PD], (95% CI)	96.8%	(95.6–98.0%)
85–105% of PD, *n* (% of patients)	417	(86.5%)
< 85% of PD, *n* (% of patients)	47	(9.8%)
> 105% of PD, *n* (% of patients)	18	(3.7%)
During full study period [*n* = 644], mean percentage of prescribed doses [PD], (95% CI)	97.9%	(95.5–100.2%)
85–105% of PD, *n* (% of patients)	563	(87.4%)
< 85% of PD, % *n* (% of patients)	69	(10.7%)
> 105% of PD, *n* (% of patients)	12	(1.9%)
Qualitative treatment adherence, % of weeks [PD], mean (± SD)		
During first year [*n* = 642]	81.6%	(± 22.1%)
During second year [*n* = 482]	81.9%	(± 21.5%)
During full study period [*n* = 644]	81.9%	(± 22.0%)
Adherence scale		
Morisky Scale, total score, mean (± SD)		
Baseline [*n* = 721]	3.6	(± 0.7)
Month 12 [*n* = 430]	3.8	(± 0.7)
Month 24 [*n* = 301]	3.8	(± 0.6)

missing quantitative adherence rates in the 22-μg subgroup.

Mean qualitative adherence was approximately 82% in all three study periods, with medians of 90.4% through 90.6%. Approximately 70% of the patients with adherence data available in the respective periods had a qualitative treatment adherence of 80–100%. Low qualitative adherence (< 50%) to the prescribed regimen was observed in < 10% of the patients in each period.

Quantitative and qualitative adherence exhibited moderate but significant positive correlation in both the first and second year of study (Spearman rank coefficients: 0.48 and 0.44; $p < 0.001$). No correlations were observed between quantitative adherence and the following parameters: duration of prior interferon beta-1a sc treatment, change of EDSS from baseline, and EQ-5D-3L (total score and VAS).

Physician-assessed treatment adherence was "high" in > 80% of patients at all times. The median total Morisky Scale score was 4 at all times, indicating very strong patient-reported adherence. Patient adherence self-assessed by VAS was very strong as well, with mean VAS scores > 90 (median ≥ 98; on a scale of 0–100) at baseline and all follow-up times. Any changes from baseline were not statistically significant. Spearman rank correlation analysis revealed no or very weak positive correlations between changes from baseline in quantitative adherence vs. self-assessed adherence at months 12 and 24.

Mean quality of life (EQ-5D-3L total score) was high at baseline (mean: 0.79 of 1.00) and did not change substantially during the study. Similar results were seen with the EQ-5D-3L VAS score (data not shown).

The proportion of patients with MS-related visits to the neurologist in addition to the regular follow-up visits was 19.4% (142/731) during the year before baseline, 16.8% (33/488) in the first year, and 5.9% (22/375) in the second year of the study.

Quantitative treatment adherence in the first year, second year, and full observation period was compared with the Wilcoxon rank sum test or Kruskal-Wallis test in subgroups defined by age, subcutaneous interferon beta-1 dose, use of the Rebif starter pack, and the number of reflection talks.

Statistically significant differences ($p = 0.039$) were observed between patients who did or did not use the starter pack in the second year, with slightly lower mean adherence rates in patients who did not use the starter pack (97.6% vs. 95.3%) and a slightly higher share of patients in the 85% through 105% adherence category in the subgroup with the starter pack (87.1% of patients) vs. without (85.3% of patients). The median values between both groups were similar (100.4% vs. 100.1%).

The differences between the subgroups by number of reflection talks (0 through 5 and > 5 talks) were statistically significant ($p = 0.020$) for the entire study period. No trend toward higher quantitative adherence rates in patients with a larger number of reflection talks was seen. During the full trial period, mean quantitative adherence was strongest in the subgroup with 1 reflection talk (116.3%; including outliers) followed by the subgroup with > 5 reflection talks (97.9%) and weakest in the subgroup with 2 reflection talks (90.7%).

In line with this finding, the share of patients with 85% through 105% adherence was largest in the subgroup with > 5 talks (93.8%), which was also the largest subgroup, and smallest in the subgroup with 2 reflection talks (72.8%). There were no statistically significant differences in any of the three periods between the subgroups defined by age or subcutaneous interferon beta-1a dose.

Safety Findings

A total of 132 patients (18.1% of 731 patients) experienced 263 adverse events (AEs) during the study period. Thirty AEs in 20 patients (2.7%) were reported as serious: 5 of these events in 4 patients (0.5%) were considered medically significant. The pattern and frequencies of reported adverse events were consistent with the established safety profile of interferon beta-1a sc and primarily involved injection site reactions (5.5%), influenza-like illness (3.3%), injection site erythema (2.3%), and injection site pain (1.5%).

DISCUSSION

Poor adherence is an unfavorable prognostic factor in multiple sclerosis because of potential suboptimal suppression of disease activity. Patients missing injections early after treatment initiation are at risk of higher relapse rates [9].

The high level of quantitative treatment adherence (97.9%) observed in REBIFLECT was comparable to or exceeded the high adherence rates to interferon-beta-1a sc administered by RebiSmart® from previous European observational studies.

Unlike these studies, adherence in the REBIFLECT study was evaluated under the premise that treatment adherence and clinical data were regularly reflected back to the patients by their treating physicians.

The recent READOUTsmart [18] study found a mean quantitative adherence rate of 85.3% overall (2 years), 89.6% for the first year and 83.3% for the second year. In the SMART study, the mean cumulative quantitative adherence over 12 months (or until early discontinuation) in 791 patients was 97.1%. [23]. In a retrospective study in 258 patients in Spain, the overall adherence rate over a period of 36 months was 92.6% [24]. A retrospective study performed in the UK and Ireland in 225 patients revealed a mean adherence over 24 months of 95.0% [25]. A retrospective analysis of data from RebiSmart® devices used by 1682 MS patients in Germany and The Netherlands over a 5-year period indicated mean adherence rates of 90.7% and 82.9%, respectively [26].

Unlike the present study, it is unknown if or to what extent the patients of the other studies were informed about their adherence level during therapy by their physicians. However, some manner of treatment-directed support, counseling, or assistance is usually provided to patients on disease-modifying drugs, which may include informal feedback on treatment adherence. The patients in the study conducted in the UK and Ireland were offered patient support services [25]. In the prospective REBISTART study of patients participating in the RebiSTAR Nursing Service, the quantitative adherence rate was 95.8% ($n = 269$) over a 12-month period.

It remains unknown whether any patients observed in REBIFLECT participated in additional undocumented motivational programs or counseling prior to or during their participation in this study.

The rather high quantitative treatment adherence rates, objectively measured by automatically recorded injection data, were reflected in the very high VAS scores of patient self-reported treatment adherence assessment. Moreover, the physicians' global assessment of therapy adherence at baseline, year 1, and year 2 also supported the finding of strong adherence in this study.

Analysis of subgroups defined by factors with potential impact on treatment adherence did not yield meaningful differences regarding quantitative adherence between any of the explored covariates (age, sex, duration of MS, pretreatment, relapse rate prior to baseline, interferon beta-1a sc dose, receipt of starter pack).

The stepwise comparison of quantitative adherence between subgroups with 0 to > 5 reflection talks did not reveal any consistent trend toward stronger quantitative adherence in patients with a larger number of such talks.

Statistically significant and numerically obvious differences for all periods were only seen between the dropout vs. persistent subgroups. However, the outcome of this comparison may be unreliable as sample sizes were unbalanced between subgroups. No new safety signals were registered in treatment management during the study [27, 28].

The use of injection devices and participation in programs fostering adherence can cause between-treatment differentiation. Supporting treatment adherence may enhance clinical efficacy and tolerability of treatments [29].

The results of this study may be extrapolated to other MS populations of similar age and gender distribution who are using RebiSmart® to inject interferon beta-1a sc and receive regular feedback on their treatment adherence and clinical status.

The study had several limitations. The design included a schedule of follow-up visits every 3

months. As this was a noninterventional study, visits were performed according to routine practice. Therefore, the actual visit dates often did not accurately match the time points scheduled in the protocol.

In accordance with the observational study design, there was no control group (i.e., a group without reflection of injection data or clinical status) to measure the potential influence the reflection talks may have had on treatment adherence.

Non-interventional studies often have the problem of missing data and high dropout rates, which may generate biases. With the exception of the comparison of quantitative adherence between the first and second year, which included the same set of patients for both periods, results over time should be interpreted with caution because of a potential bias introduced by premature discontinuations. The rates of missing data in this study were low and remained in an acceptable range for observational studies.

Self-reporting instruments used to measure quality of life and self-assessed adherence are inherently subjective. Their accuracy relies on the honesty and introspective ability of the reporting patients. Moreover, the scales may be interpreted differently among patients.

CONCLUSIONS

In the 2-year prospective observational REBIFLECT study, quantitative treatment adherence to a prescribed regimen of three injections per week was very high and stable over 2 years of study: a mean percentage of 97.9% of prescribed doses was injected over 2 years. Regularly reflecting treatment adherence and clinical status to patients on interferon beta-1a sc therapy appears to be associated with highly favorable treatment adherence over prolonged periods of time.

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Compliance with Ethics Guidelines. Ethics approval was received from Ethik-Kommission der Medizinischen Fakultät der FAU Erlangen-Nuernberg, Erlangen, Germany, ref. no. 153_13 B (July 17, 2013). In accordance with the legal provisions in Germany (§ 67 subsection 6 of the German Medicinal Products Act), the competent authority, i.e., the German Federal Institute for Drugs and Medical Devices, confirmed that this approval covered all study centers. The German Association of Statutory Health Insurance Physicians and the German Federal Associations of Health Insurance Funds were notified. The provided information included the places, time, monitoring plan, and aim of the non-interventional study, the names of the participating physicians, again covering all study sites. This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All subjects provided informed consent (part of the ethic approval) to participate in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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