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Comparative Efficacy of iBGStar™ Glucose Meter vs. A Traditional Glucose Meter in Type 1 Diabetes

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Abstract

Background: Optimal metabolic control and compliance to self-monitoring of blood glucose (SMBG) are poor in adolescents and young adults with type 1 diabetes mellitus (T1DM), and may require innovative management strategies. These may include the use of telemedicine and smartphone-linked blood glucose self-monitoring systems. To this purpose, a specific glucose meter (iBGStar™) and a dedicated Diabetes Manager Application (DMApp) have been developed. Aim of the study is to demonstrate the superiority of a smartphone-linked versus a traditional self-monitoring system in reducing HbA1c levels and improving compliance to SMBG.

Methods/Design: The "i-NewTrend" study is an open-label, randomized (1:1) trial involving 21 diabetes outpatient clinics in Italy. Overall, 178 subjects aged 14–24 years with type 1 diabetes, with any diabetes duration, HbA1c ≥8%, treated with basal-bolus insulin regimen, and with poor compliance with SMBG will be randomized to two different SMBG strategies: Group A will use iBGStar™+ DMApp and Group B (control group) will use a traditional meter for SMBG during a 6-month follow-up (experimental phase). Between-group differences on metabolic control, compliance to SMBG, insulin doses, quality of life, risk of hypoglicaemic episodes and number and type of contacts with diabetes clinics will be evaluated. During a 6 month post-trial observational phase, all randomized patients in group A and B will use iBGStar™ + DMApp to evaluate the impact of the system on all the outcomes when the system is used under routine clinical practice conditions.

Discussion: Results of the trial iNew Trend will assess whether and to what extent this new strategy of SMBG based on the use of iBGStar™ + DMApp will improve the management of type 1 diabetes in adolescents and young adults poorly controlled and poorly compliant, both in experimental and usual care settings.

Keywords: Type 1 diabetes; Self-monitoring blood glucose; Telemedicine; Compliance

Abbreviations:

CRF: Case Report Form; SMBG: Self-Monitoring Blood Glucose

Background

Many patients, especially during adolescence, do not fully adhere to the diabetes treatment and, as a result, suffer from adverse health consequences [1,2]. A tight metabolic control is a key point, as it has been shown to prevent or at least delay diabetes complications [3]. Adolescents have particular difficulty in achieving glucose control, as they usually attain higher average glycated haemoglobin levels than adults, despite similar treatments [4]. This is in part due to increasing insulin resistance during puberty [5] and in part to a lack of adherence to the multifaceted treatment regimen [6]. The deterioration in adherence behavior associated with the transition to adolescence is well documented among children with type 1 diabetes [7]. In particular, the literature documents decreased self-monitoring of blood glucose (SMBG) frequency [8] and deterioration in hemoglobin A1c (HbA1c) levels [9,10], with a few adolescents achieving optimal HbA1c values (<7.5%) [11]. The link between frequency of SMBG and glycemic control has also been documented in several studies [12].

In Italy, data from the AMD Annals, relative to 1871 individuals with T1DM in the age range of 16-24 years, show that 25.2% of patients have HbA1c levels between 8.1 and 9.0%, while 26.9% have a value over 9.0%. The specific needs of young people with T1DM necessitate innovative management strategies [13]. One approach for improving glycemic control is the use of telemedicine (TM) [14]. Several recent studies do support the effectiveness of telemedicine in improving metabolic control and quality of life. Furthermore, communication by web sites, e-mail, social networks, or text messages via mobile phone is becoming a natural component of the daily management of patients and is considered the best way to reduce the number of face-to-face visits and clinical inertia [15]. At the same time, the iPhone's popularity among adolescents is increasing and the Apple® applications have become one of the reasons why the iPhone attracts teenagers. In this context, the innovative iBGStar™ glucose meter to be installed on the iPod touch or iPhone. It is associated to the iBGStar™ Diabetes Manager App which works as a digital logbook and diabetes management tool; it allows patients to view and analyze

accurate, reliable information in 'real time' and share the data (blood glucose readings, notes, logbook and statistics) with healthcare professionals via e-mail. The system iBGStar™ with iBGStar™ Diabetes Manager App is expected: to improve the level of knowledge of patient about the relationship between glycemic values and risk of hyperglycemia or hypoglycaemia;to increase adherence to SMBG; to ensure an easier communication with healthcare professionals and greater flexibility in managing diabetes. At last, the system should increase the likelihood to achieve and maintain the desired metabolic goal in uncontrolled patients poorly compliant with the care.

Given these premises, this randomized controlled trial aims to compare the system iBGStar™ and iBGStar™ Diabetes Manager App with a traditional glucose meter in terms of glycemic control and compliance towards SMBG in a cohort of adolescents/young adults with type 1 diabetes. The impact of the system on risk of hypoglycemia, management of insulin therapy, quality of life and communication between patients and diabetes clinics will be investigated.

An additional post-trial observational phase lasting 6 month will be carried out to assess the long-term impact of the device on all the outcomes, when the device is used under routine clinical practice conditions.

Methods/Design

The experimental device: iBGStar™ glucose meter and iBGStar™ Diabetes Manager App

The iBGStar™ glucose meter works with the iBGStar™ Diabetes Manager Application (App) installed on the iPod touch or iPhone OS version 3.0 or higher.

When iBGStar™ is connected to the iPhone with the iBGStar™ Diabetes Manager App launched, the new blood glucose readings will be downloaded from the meter to the Application.

The free iBGStar™ Diabetes Manager App is a state-of-the-art digital diabetes management tool accessed from Apple® iPhone featuring: intuitive user interface; automated download of meter results; interactive diabetes management reports featuring log books, trend charts, statistical analyses and more. It allows patients to view and analyze accurate and reliable information in 'real time'. The iBGStar™ Diabetes Manager App allows patients to input, for each test result, specific notes like amount of carbohydrate in the diet, type and dose of insulin or pre-defined or custom notes. It allows personalizing information to help patients and their healthcare professional analyze patterns and variations to make better-informed diabetes-related decisions. Another important tool which differentiates iBGStar™ from traditional glucose meters is the Share tab. It allows the sharing of data (blood glucose readings, notes, logbook and statistics) by mail to healthcare professional while on-the-go, allowing greater flexibility in managing diabetes.

For the study, the supply to the patients of the iBGStar™ and iBGStar™ Diabetes Manager App installed on iPhone instead of an iPod touch has been chosen because:

- To share the data, iPod touch has to have access to a wireless network and in Italy the Wi-Fi network is still not widespread.
- iPhone allows patients to contact the health care professionals and share their data with them by mails and by phone contacts. A rechargeable SIM card, automatically reloaded each month, will allow patients calling their health care professionals and sending them the glycemic data by e-mail.

Primary objective

The primary end-point of this study is to demonstrate the superiority of iBGstar™ + DMApp as a component of the diabetes management vs. traditional blood glucose self-monitoring system in reducing HbA1c levels after 6 months of follow-up.

The co-primary study end-point is to demonstrate the superiority of iBGstar™ as a component of the diabetes management vs. usual blood glucose self-monitoring system in improving the compliance to SMBG. Patient is considered as compliant if performing at least 30% of the recommended SMBG tests/week.

Secondary objectives

As secondary objectives, the randomized phase of the study will allow the evaluation of the following efficacy parameters after 6 months:

- Percentage of patients with HbA1c ≤7.5%;
- Variation in the average number of SMBG daily, weekly and monthly;
- Mean fasting blood glucose and post prandial blood glucose levels and glycemic variability;
- Variation in the average insulin dose and number of insulin dose adjustments;
- Quality of life and patient satisfaction;
- Number and type of overall contacts between centers and patients

The following safety end-points will be investigated:

- Adverse events and serious adverse events
- Incidence of hypoglycemia

Hypoglicemic episodes will be registered and classified as Grade 1 or Grade 2. Grade 1 is defined as symptoms of hypoglycemia (adrenergic symptoms - e.g., tachycardia, palpitations, shakiness - cholinergic symptoms - e.g. sweating - , or neurologic symptoms - e.g. inability to concentrate, dizziness, hunger, blurred vision, obvious impairment of motor function, confusion or inappropriate behavior) associated with an SMBG confirmed blood glucose value < 60 and the patient is still alert enough to seek self-treatment. Grade 2 is any episode resulting in coma, seizure, or significant neurologic impairment so that the subject is unable to initiate self-treatment or requires the assistance of another person.

The observational post-trial phase of the study will allow the evaluation of the same parameters after 12 months from randomization, measured under routine clinical practice conditions.

Study design

A multicenter, national, randomized (1:1), open-label, parallel group design will be adopted.

Randomization will be performed using closed envelopes. Random lists will be stratified by centre. To ensure equal allocation rates within centers, permuted blocks randomization will be used.

Patients will be assigned to one of the following arms:

- Group A: SMBG will be managed with iBGStar™ and iBGStar™ Diabetes Manager App uploaded on iPhone during the 6-month experimental phase.
- Group B: SMBG will be managed with a traditional glucose meter (Accu-Chek Aviva™) according to usual care during the 6-month experimental phase.

In the post-trial observational phase, all patients in the two arms will use iBGStar™ and iBGStar™ Diabetes Manager App to manage SMBG during additional 6-months (Figure 1).

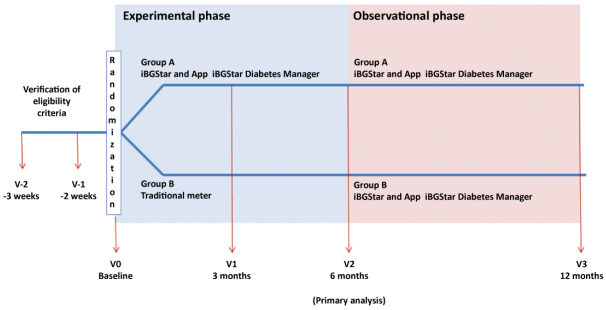

Figure 1: Study design

Study population

Male and female subjects aged 14-24 years are eligible for the study if they meet the following inclusion criteria:

Inclusion criteria

- Type 1 diabetes
- Written informed consent obtained from the patient or his/her legal representative (for patients aged <18 years)
- Any diabetes duration
- Cared for by the diabetes center for at least 1 year
- HbA1c ≥8.0%
- Basal:bolus insulin regimen (any insulin)
- Poor compliance with SMBG (less than 30% of the recommended BG measurements recorded in the glucose meter in the two weeks preceding the randomization).

Exclusion criteria

- Refusal or inability to give informed consent to participate in the study;
- Patients with short life expectancy;
- Patients with conditions/concomitant diseases making them non evaluable for the primary efficacy endpoint according to physician's judgment;
- Requirement for concomitant treatment that could bias primary evaluation (i.e. corticosteroid treatment);
- Patients with high likelihood of being unavailable for 6 and/or 12 months visits;
- Subject is the investigator, sub-investigator, research assistant, pharmacist, study coordinator, other study site staff or relative of study site staff thus considered directly involved in the conduct of the study;
- Current addition/abuse of alcohol or drugs;
- Severe visual or dexterity impairment;
- Patients with any mental condition rendering them unable to understand the nature, scope, and possible consequences of the study;
- Pregnant or breast-feeding women;
- Treatment with insulin regimens other than basal bolus;
- Subjects unlikely or unable to comply with the Protocol requirements (e.g. illiterate, inability to use mobile phone; uncooperative, unable to return for follow-up visit, unlikely to complete the study).

Participating centres

The study will be conducted by diabetes specialists in 21 centers in Italy.

Data collection

The following baseline information will be collected on the Clinical Record Forms (CRFs): birthdate, gender, height and weight, school level, occupational status, living status, date of diabetes diagnosis, insulin treatment (insulin type, dose, and number of injections), previous education to carbohydrate counting, number of HbA1c measurements collected during the last 12 months, severe hypoglycaemic episodes in the last 12 months, episodes of ketoacidosis in the last 12 months, presence and severity of diabetes complications, comorbidities, concomitant treatments. Clinical data collected at each study visit are showed in table 1.

HbA1c will be centrally measured.

SMBG data will be downloaded by the glucose meters on the physician's computer during the office visit and recorded on the Clinical Record Forms.

Hypoglicemic episodes will be assessed by reviewing patient diaries and reported in CRF.

Patients will be asked to fill in the questionnaire including the following instruments:

- Audit of diabetes-dependent quality of life (ADDQoL): this tool produces a diabetes impact rating weighted by importance for 18 potentially applicable domains of life [16]. The average weighted impact is a composite score of all applicable domains indicating individualized impact of diabetes on quality of life. Scores for single domains and average weighted impact can range from −9 (maximum negative impact of diabetes) to +9 (maximum positive impact of diabetes). The questionnaire also includes a single item measuring "present quality of life," with scores ranging from −3 (extremely bad) to +3 (excellent). It will be used in patients aged between 18-24 years.
- Diabetes Quality of Life for Youth (DQOLY): this tool consists of 52 items, divided into 4 sections, with one single separated item, i.e.: impact of diabetes (23 items); worries about diabetes (11 items); satisfaction with treatment (10 items); and satisfaction with life (7 items); plus one single item on health perception. Questions are scored using a 5-point Likert scale, with the exception of health perception, which is measured using a 4-point Likert scale. Lower scores indicate poorer quality of life. For ease of comparisons across subscales, items on all subscales are scored in the same

directions. It will be used in adolescents aged between 14-17 years [17].

- Visual analogue scale (VAS): patient satisfaction with glucose meter will be assessed through a visual analogue scale.

Visit Number	V-2 Pre-screening -3 weeks	V-1 Qualification -2weeks	V0 Randomization Baseline	V1 3 months	V2 6 months	V3 12 months Follow up
Eligibility criteria	x	x				
Demographic data			x			
Informed consent	x					
Medical History			x			
Current therapies	x		x	x	x	x
Body weight			x	x	x	x
Height			x			
StandardizeHbA1c*	x			x	x	x
Blood glucose values and notes stored in glucose meters	x		x	x	x	x
Type and insulin dose adjustments			x	x	x	x
Quality of life questionnaires			x		x	x
Patient satisfaction			x		x	x
Episodes of hypoglycemia			x	x	x	x
Adverse Events			x	x	x	x

Table 1: Flow Chart

Study procedures

The study consists of 6 scheduled visits:

Prescreening visit (2 weeks before randomization, V-2): On the occasion of the prescreening visit, eligibility criteria will be verified.

To check the patient's SMBG compliance, SMBG data recorded on the glucose meter during the 2 weeks preceding the visit will be verified by the physician. Eligible patients will be proposed to participate in the study and sign the informed consent form. For patients below 18 years of age, the informed consent form will also be signed by the patient's parent(s) or by the subject's legal representative. Subsequently, to confirm the eligibility in terms of HbA1c levels, a blood sample will be collected and sent to the centralized laboratory.

Qualification visit (1 weeks before randomization, V-1): Within 1 week from visit -2 (visit -1), patients with confirmed centralized HbA1c levels ≥8.0% will receive a traditional glucose meter to collect SMBG data during the following two weeks. Blood glucose values collected during this period will represent the baseline values to be compared with measurements performed during the follow-up.

Randomization visit (V0): After two weeks (visit 0), socio-demographic and clinical information will be collected. SMBG values stored in the glucose meter will be evaluated. All patients will be requested to perform a daily number of glucose measurements, according to guideline recommendations and patient's characteristics. Patients will be randomized to continue with the traditional meter (group B) or to use the iBGStar™ with iBGStar™ Diabetes Manager App installed on iPhone (group A, experimental arm). During visit 0, patients allocated to group A will receive a specific training on the use of iBGStar™. Patients in group A will be requested to share data (blood glucose readings, notes, logbook and statistics) by mail with healthcare professional, using the Share tab in the iBGStar™ Diabetes manager App, every 2 weeks in the first 3 months (until V1). Patients in both groups will be requested to fill in the quality of life questionnaire and satisfaction with the glucose meter.

First visit (3 months after randomization, experimental phase, V1): Clinical data collection will be repeated. All glucose data recorded in the meters will be collected and reported in both groups. In the group A, additional notes recorded on iBGStar™ Diabetes Manager App will be collected in the database. In the group B, additional notes will be recorded on the diary. Patients in group A will be requested to share data (blood glucose readings, notes, logbook and statistics) by e-mail to healthcare professional, using the Share tab in the iBGStar™. Diabetes Manager App, monthly during the following 3 months (until V2). A refresh training on the SMBG's importance will be performed in all patients in both groups, and health care professionals will check if patients in the group A are using all functionalities of iBGStar™ Diabetes Manager App. Number and type (face-to-face visits, e-mail, telephone calls, SMSs) of contacts between patients of both groups and diabetes clinics will be registered on a hoc form.

Second visit (6 months after randomization, experimental phase, V2): The same procedures of data collection applied in the V1 will be repeated at visit 2. Additionally, patients will be requested to fill in the

quality of life questionnaire and satisfaction with the glucose meter. Subjects in group B will switch from the traditional glucose meter to the iBGStar™ with iBGStar™ Diabetes Manager App installed on the iPhone. They will be adequately trained about the use of the iBGStar™ and iBGStar™ Diabetes manager App. All patients in Group A and Group B will continue to be followed under routine clinical practice conditions.

Third post-trial visit (12 months after randomization, observational phase, V3): The same procedures of data collection applied in the V1 and V2 will be repeated at visit 3, as well as the download of data recorded in the glucose meter. Patients will be requested to fill in the quality of life questionnaire and satisfaction. Number and type (face-to-face visits, e-mail, telephone calls, SMSs) of contacts between patients of both groups and diabetes clinics will be registered on a hoc form.

Sample size estimates

Assuming a standard deviation of HbA1c of 0.9% and considering as clinically relevant a minimum between-group difference in HbA1c levels of 0.4%, the number of patients to be enrolled to ensure a power of 80% (alpha=0.05) is 81 patients per arm. Assuming a drop-out rate of 10%, 178 patients are needed.

The same sample size will ensure a statistical power of over 90% to detect a difference of 25% in the proportion of patients compliant with SMBG schedule (i.e. >30% of recommended measurements).

Statistical Analysis

Baseline characteristics will be summarized as mean and standard deviation (continuous, normally distributed variables), median and interquartile range (continuous, not normally distributed variables and ordinal variables) or frequency (categorical variables). Patient characteristics will be compared between study arms using the unpaired t-test, the Mann-Whitney U test or the χ^2 test, as appropriate.

In case of any between-group imbalance in one or more characteristics, multivariate analyses will be used to take this imbalance into consideration.

The co-primary endpoints will be evaluated as the difference between arms at 6 months vs. baseline. Generalized hierarchical linear regression models for repeated measures will be applied to assess trends over time between the groups. An unstructured correlation type will be used to take into account incomplete follow-up (i.e. drop-outs) [18].

The same method will be applied to assess the difference between and within arms at 6 and 12 months vs. baseline. Incidence of grade 1, grade 2, and overall (grade 1 and grade 2) hypoglycemic episodes, and number (and type) of overall contacts between centers and patients, after 6 months will be compared through Poisson regression models.

Analyses relative to efficacy parameters will be performed on all randomized patients (Intention-to-treat analysis). Per-protocol analysis will be also performed as secondary analysis.

Safety analyses will be performed on all randomized patients with at least one follow-up visit.

Timing

The planned study duration will be of 20 months (5 quarters).

The estimated duration of the screening/enrollment will be of 7 months, followed by 2-3 weeks of qualification phase, the 6-months experimental phase plus the 6-months follow-up in the post-trial observational phase.

The end of the study will coincide with the last patient last visit at 12 months from the randomization.

Overall, the study will last from June 2012 to August 2014.

Ethical aspects

The protocol was approved by all the Ethics Committee of the participating centers in accordance with the local legal requirements.

The study will be conducted in accordance with the EC guidelines for Good Clinical Practice and performed according to the revised Declaration of Helsinki.

The trial was registered at ClinicalTrials.gov (registration number NCT02073188).

Patient information

A patient will be enrolled in the study only after a full discussion of all the aspects related to study design, implications for the patient, expected benefits and possible side effects, in line with the content of the patient information sheet, to be read and retained by the patient. The patient will be given time to consider fully the information given and will be encouraged to ask questions. If then he/she is willing to participate in the trial, he/she will be asked to sign a consent form.

Withdrawal from the study

Patients will be not excluded from the study for permanent or temporary discontinuation of use of SMBG, since compliance with SMBG represents a study end-point.

Pregnancy or initiation of continuous subcutaneous insulin infusion will lead to early study cessation. The subjects may withdraw from the study at any time and irrespective of the reason, or this may be the Investigator's decision. Subjects who have been withdrawn from the study cannot be re-included in the study and their subject number will not be re-used.

All withdrawn or non-qualified subjects will be recorded by the Investigator in the case report form as per instructions provided.

Publication of the trial results

The trial results will be published by the members of the Steering Committee and approved by the Sponsor.

The Sponsor has the right at any time to publish the results of the study.

Discussion

SMBG represents a key strategy in diabetes management. However, SMBG is performed with different levels of complexity according to patient needs and skills. Therefore, one single glucose meter is unlikely to meet the requirements for all the people with diabetes and specific

features can help obtaining the best benefits in specific patients. Attaining adequate metabolic targets in adolescents and young adults is a major challenge, and traditional self-management strategies are generally not adopted by most young patients. The study will allow to evaluate whether a new strategy of SMBG based on a technologically advanced telemedicine system can improve diabetes management in a complex population of poorly controlled and poorly adherent young people. The observational phase will provide additional important information regarding the cost-effectiveness of the telemedicine system under routine clinical practice conditions.

If proven to be effective, this new strategy could represent an important advancement in the management of type 1 diabetes.

Competing Interests

AN received research grant from Sanofi SpA. MCR, FP, PDB, DI, VC no conflict of interests.

Authors' Contributions

All authors contributed to the design of the study, PB, DI, and VC are responsible for the recruitment and the follow-up of the patients enrolled, AN, MCR, and FP are responsible for methodological and statistical aspects of the study, MCR and AN wrote the manuscript.

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