Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

The A_1chieve study: a 60 000-person, global, prospective, observational study of basal, meal-time, and biphasic insulin analogs in daily clinical practice

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ARTICLE INFO

Keywords:
Type 2 diabetes
Observational study
A_1chieve
Insulin

ABSTRACT

While evidenced-based guidelines promote glycated hemoglobin (HbA_{1c}) targets <7.0% in order to reduce the long-term risk of diabetic complications, many individuals with type 2 diabetes do not achieve these targets. Fear of hypoglycemia provides a major barrier to improving blood glucose control as a result of delayed insulin initiation and failure to appropriately titrate insulin following initiation. Modern insulin analogs were designed to achieve improved blood glucose control with similar hypoglycemic risk compared with non-analog insulins (or similar blood glucose control with reduced hypoglycemic risk). While this has been demonstrated in randomized controlled trials, there is a need to confirm these findings in an everyday clinical setting. The A_1chieve study will evaluate adverse events and effectiveness of premix (biphasic insulin aspart 30 [NovoMix 30]), basal (insulin detemir [Levemir]), and meal-time (insulin aspart [NovoRapid]) insulin analogs in people with type 2 diabetes in near-routine clinical practice. A_1chieve is an international, prospective, multi-center, open-label, non-interventional, 24-week study of people with type 2 diabetes using an insulin analog. The study will recruit 60 000 people from 30 countries across four continents (Asia, Africa, South America, and Europe). The primary aim of the study is to assess the adverse event profile of the study insulins in routine clinical practice, including rates of hypoglycemia. In addition, effectiveness (HbA_{1c}, fasting plasma glucose, and postprandial plasma glucose) and patient quality of life outcomes will be measured. Comprehensive epidemiological data will be collected at baseline, including recent plasma glucose results and hypoglycemic episodes, prevalence of diabetes-related complications, and measures of current standards of care. Thus, A_1chieve should provide important information about how insulin analogs perform in daily clinical practice.

1. Introduction

Central to the effective management of diabetes mellitus is the need to sustain glycemic control for many years. The often-cited UK prospective diabetes study (UKPDS), for ex-

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0168-8227/$ – see front matter

ample, demonstrated that every 1.0% reduction in glycated hemoglobin (HbA_{1c}) is associated with a 43% reduction in the risk of amputation or death from peripheral vascular disease, a 37% reduction in microvascular disease, and a 16% reduction in heart failure [1]. Following these reports, the UKPDS group has continued to generate data supporting timely intervention to maintain glycemic control. Most recently, reports of the 10-year follow-up study (median 14.5 years in all from randomization) have shown that people with type 2 diabetes who maintain better blood glucose control can experience benefits many years later, consistent with similar data from the DCCT study in type 1 diabetes [2]. Significantly, these benefits occurred despite limited maintenance of lower HbA_{1c}, while they included in particular lower rates of myocardial infarction and diabetes-related death [2]. Two meta-analyses including the UKPDS and other studies published recently support these conclusions [3,4].

While, historically, type 2 diabetes was termed 'non-insulin dependent', it has long been acknowledged that, even with significant lifestyle changes and consistent use of multiple oral glucose-lowering therapies (OGLDs), the natural progression of underlying loss of islet B-cell function usually necessitates insulin use with time. Current evidence-based guidelines from the IDF reflect this need, and suggest that insulin should be introduced when blood glucose levels fail to be controlled to an HbA_{1c} of $\leq$7.5% by lifestyle means and two to three OGLDs [5]. An insulin-based regimen can then be intensified as needed to achieve appropriate glucose targets [5].

Despite wide dissemination of such views, in practice and in many countries, most people with type 2 diabetes still experience significant periods where their HbA_{1c} levels are >7.0 or even 8.0%, thus rendering them vulnerable to diabetes-related complications later in life [6,7]. In part a reported reluctance to introduce insulin therapy, and then failure to titrate doses adequately, can be attributed to concerns regarding tolerability of insulin, and specifically the risks of hypoglycemic episodes and gain in body weight [8–10].

Modern insulin analogs were designed to achieve better levels of blood glucose control with similar hypoglycemic risk, or similar control with less hypoglycemia, or a mixture of the two [11–13]. While this has been so reported in the many clinical studies, there is a need to replicate findings in an everyday setting. In particular, more vulnerable people such as the elderly and/or those with comorbidities are often excluded from randomized controlled trials (RCTs), yet these groups in particular may derive the greatest benefits from the improved tolerability offered by modern insulins. Observational studies are, as discussed in the sister papers in this supplement [14], an effective way of assessing the effectiveness and safety of drugs under routine clinical conditions in a wide variety of clinical environments. Although there have been some observational studies of insulin analogs, no large-scale observational study has yet been carried out involving basal, bolus and premix insulin analogs.

The A_1chieve study will evaluate the clinical safety and effectiveness of premix (biphasic insulin aspart 30 [NovoMix 30]), basal (insulin detemir [Levemir]) and meal-time (insulin aspart [NovoRapid]) insulin analogs in people with type 2 diabetes in near-routine clinical practice.

2. The A_1chieve study

2.1. Study design

The A_1chieve study has been designed as an international, prospective, multi-center, open-label, non-interventional, 24-week study of people with type 2 diabetes using an insulin analog. The study will be carried out in 30 countries across four continents (Asia, Africa, South America, and Europe): Algeria, Argentina, Bahrain, Bangladesh, Brazil, China, Egypt, India, Indonesia, Iran, Jordan, Kuwait, Lebanon, Libya, Malaysia, Mexico, Morocco, Oman, Pakistan, Philippines, Qatar, Russia, Saudi Arabia, Singapore, South Korea, Taiwan, Tunisia, Turkey, United Arab Emirates, and Yemen, but not Western Europe or North America. The study will explore the post-authorization use of the three insulins named above in people with type 2 diabetes who have not previously taken, but who have recently begun, these medications. A_1chieve is recruiting from January 2009 to June 2010, and baseline data should be available in the first quarter of 2011, with final study results by the end of the same year.

A_1chieve is recruiting a large (60 000 participants) and diverse cohort that will reflect the highly heterogeneous population naturally affected by diabetes. Inclusion and exclusion criteria are minimal in order to better reflect real-life clinical practice. All individuals with type 2 diabetes who have not used one of the study insulins previously, and who have been started on one of the insulins in the 4 weeks prior to the study start, are eligible for participation. People with hypersensitivity to the study insulins or excipients are excluded, as are women who are pregnant, breast feeding, or who intend to become pregnant within 6 months of the study. Individuals cannot be enrolled into the study more than once (ie, after a withdrawal).

The prior choice of insulin (before the study) in any individual is at the discretion of their advising physician, who will also determine all subsequent treatment decisions according to his or her usual practice. Participants are free to withdraw from the study at any time. Demographic and baseline data are taken at visit 1, with an interim visit 12 weeks after baseline and a final visit following 24 weeks of participation in the study. Information will be gathered from the physician's usual clinical notes, and the participants' recall and self-monitoring glucose diary at each visit as available. This information is transferred to a standard case report form (CRF). During the study follow-up period study monitors visit the investigators on a regular basis to check data quality and to reinforce the importance of complete and consistent adverse event reporting, including reminding investigators to proactively enquire about such events at all study visits.

2.2. Data analysis

For data analysis participants are being allocated into four treatment groups according to the insulin types used but independent of use of concomitant oral agents as follows: 1. biphasic insulin aspart; 2. insulin detemir only; 3. insulins detemir + aspart; 4. other insulin combinations. Within these four groups, consideration of outcomes based on the imme-

diately prior glucose-lowering treatment regimen (for example insulin-naïve, particular OGLD combinations, switching from another insulin) and demographic factors (for example age and duration of diabetes) will be undertaken at the time of analysis under the guidance of expert epidemiological and statistical advice using a pre-defined statistical analysis plan. Post-hoc analyses will be separately identified.

2.3. *Good clinical research practice*

Participants are enrolled into the study at the judgement of their treating clinician, and according to their particular interests and needs. All participants give written, informed consent, and each study center will fulfil the national requirements for their health authority and ethics committee. The study will be conducted in accordance with the Declaration of Helsinki [15]. During the planning of the study it became apparent that there are large variations between countries regarding regulations and requirements for observational studies, in contrast to greater consistency for randomized controlled trials. However, in a global observational trial it is desirable to have a consistent approach despite differences in local regulations. Therefore, for this study, the sponsor, Novo Nordisk, developed a standard operating procedure that ensured ethics committee approval and written informed consent for all participants entering in the study (unless otherwise directed by the local ethics committee). In addition, all the investigators taking part in the study underwent specific training either at an investigator meeting or from a study monitor. This training was focused on the study protocol, CRF completion, informed consent, and safety reporting procedures.

3. Baseline data: comparative epidemiology

3.1. *Baseline data analyses*

While the primary objective is around the adverse event profile and efficacy of insulin analogs when started in people with type 2 diabetes, the inclusion of a large number of individuals from a wide range of countries is intended to provide answers or information about comparative aspects of diabetes care. A_1chieve will gather baseline information about diabetes complications including cardiovascular (CV) disease, renal disease, retinopathy and other eye disorders, and foot ulcers and neuropathy. Given the numbers of people enrolled and their geographic diversity, this information will provide important insights into the natural history of diabetes and the quality of diabetes care around the world. Further insight into comparative diabetes care will be provided by examining the information on patient management revealed by A_1chieve, including use of primary or secondary preventative treatments for CV disease and foot ulcers. The availability of specialist foot ulcer care, and the provision of screening programs for eye and renal disease will be assessed.

Epidemiological surveys such as the US National Health and Nutrition Examination Statement (NHANES) report suggest that many people with type 2 diabetes have poor glycemic control [7]. This disjunction between evidence-based recommendations and practice is in need of further investigation. It should be possible to define whether there are situations in which physicians deem it inappropriate to assist in dose titration of insulin to an HbA_{1c} target of <7.0%. Attitudes to management of more elderly people should become apparent, if treatments are, for example, more conservative. Associations will be sought for relationships between different treatment decisions and significant comorbidities. Where starting insulin is delayed to higher HbA_{1c} levels, the difference in motivation from earlier intervention will be determined from the systematic collection of the reasons for beginning insulin.

Lipid profiles (total-, LDL-, and HDL-cholesterol and triglycerides) and serum creatinine will be measured at baseline, providing additional valuable information on the CV risk profile of individuals with diabetes in diverse clinical environments, and possibly enabling identification of differences in regional approaches to CV risk management.

The rationale for choosing a particular study insulin will be recorded; physicians may select a particular study insulin (long-acting, biphasic or rapid-acting) with specific patient needs in mind (eg, to improve glycemic control, reduce hypoglycemic episodes, or minimize weight gain), or they may be more influenced by local or national practices and guidelines for insulin use. A_1chieve will enable review of the demographic characteristics of people transferred to analog insulin regimens across many countries. Physicians transferring people from a variety of different OGLD regimens, and switching people from one insulin to a study insulin, will need to determine starter doses, and whether to continue OGLD treatment or not, and other decisions not covered by national or international guidelines. Retrospective analysis of these decisions may reveal which strategies appear to work best for a given group or circumstance, thus contributing to the development of best diabetes practice.

3.2. *Health and economic modeling*

The data collected by the A_1chieve study, such as the presence of CV, renal, and other diabetes-related complications, current standards of diabetes care, lipid measures, and glycemic control will provide useful baseline measures for populating health economic and outcome modeling. However, the local economic components of the model (such as costs of professional time and medications) are outside the scope of this study.

4. Objectives, endpoints, and their clinical relevance

Narrowly defined, the primary objective of the A_1chieve study is to assess the adverse event profile of the three study insulin analogs; the primary endpoint will, therefore, be the number of serious adverse drug reactions (SADRs) including major hypoglycemic events recorded from baseline to final visit. All serious adverse events (SAEs) and adverse drug reactions (ADRs) will be recorded. An ADR was defined as an adverse event for which the reporting or reviewing physician

suspected a possible or probable relationship to a study drug. One of the advantages that observational studies have over RCTs is the size of the subject population involved. A_1chieve will recruit 60 000 people, enabling rarer serious adverse reactions to be detected. A_1chieve will also provide important information on the comparative rates of adverse events in people who switch to biphasic insulin aspart 30, insulin detemir, or insulin aspart, alone or in combination. This should become a useful resource for clinicians considering a choice of insulin.

Secondary endpoints include the change in the number of minor, major, and nocturnal hypoglycemic events between baseline and the last 4 weeks before the interim visit and the final visit. Major hypoglycaemia is defined as an event with severe central nervous system symptoms consistent with hypoglycemia in which the affected individual is unable to treat himself/herself and has one of the following characteristics: (1) plasma glucose <3.1 mmol/L or 56 mg/dL (<2.8 mmol/L or 50 mg/dL blood glucose) or (2) reversal of symptoms after either food intake or glucagon or intravenous glucose administration. All other hypoglycemic events defined as above in which the affected individual was able to treat himself/herself were classified as minor. Hypoglycemia will be classed as 'nocturnal' if the events occur between bedtime and before getting up in the morning. Events will be recorded through participant recollection in the 4 weeks prior to the baseline visit, the interim visit, and the final visit.

Secondary efficacy endpoints will include:

1. measures of glycemic control: change in HbA_{1c}, fasting plasma glucose (FPG), and post-prandial glucose at interim visit and final visit compared with baseline;
2. measures of other CV risk factors: body weight, blood pressure, and serum lipids at final visit compared with baseline;
3. Quality of Life (QoL) measured with the EQ-5D questionnaire [16].

Type 2 diabetes is frequently associated with a series of concurrent CV risk factors, specifically obesity, high blood pressure, high levels of LDL cholesterol, and low levels of HDL cholesterol (or high triglycerides). Increasingly, these factors are thought to be interrelated in the pathogenesis of the complications of type 2 diabetes and so, in addition to conventional measures of glycemic control, an integral part of the management of the condition [5], A_1chieve will also monitor these CV risk factors. The information will be used to consider not only how management of a participant's blood glucose control relates to management of other CV risk factors, but also whether the different insulin regimens themselves have an impact on them.

5. Statistical analysis of the data

Statistical analysis of the data will be performed using two-sided alternatives and a 5% significance level to assess the degree of change from baseline to end of study for each endpoint. Participants will be grouped by treatment as described previously, but, as these groups are not randomized, between-treatment comparisons will not be made. However, summary statistics for each treatment group will be used to report data such that qualitative observations can be made and possible areas for future clinical research identified. Continuous variables will be summarized using descriptive statistics, and discrete variables will be summarized using frequency tables. Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for the reporting of data will be followed in all publications [17].

Within-treatment tests will be used to compare the study insulin with previous treatments (OGLDs and/or conventional insulin regimens). Continuous variables will be compared using paired *t*-tests and discrete variables will be compared using McNemar's test of paired proportions. Analysis of covariance will be applied for continuous variables, where appropriate. Logistic models will be applied for discrete variables (where appropriate) and relevant baseline characteristics will be included as covariates in the models. Treatment-by-factor interaction effect will also be evaluated for key baseline characteristics, where the interaction effect will be removed if it proves to be not statistically significant. Finally, summary statistics and statistical analysis (where appropriate) will be provided for various subgroups defined on baseline characteristics.

The primary endpoint (SADRs including major hypoglycemic events) and other similar endpoints will be summarized as number of events and number (percentage) of participants with an event. In addition, summary tables will be presented for SADRs, non-serious adverse drug reactions, and other serious adverse events in relation to study insulin.

6. Limitations

A key feature of observational studies, and arguably their principle value, lies in their ability to record and reflect drug use under routine clinical conditions. Inherent in this element of study design is the fact that participants may, within the same study, receive very different levels of care, and that this might itself influence treatment outcomes more significantly than the study insulins. Inevitably, we cannot eliminate variation in clinical practice, and indeed if the study is able to adequately capture differences in treatment approach it may be possible to quantify and understand best practice. However, it should be noted that potential confounding factors arising from the heterogeneity of global healthcare systems and practices is likely to influence all aspects of treatment management, and so may undermine the validity of some of the findings.

Since observational studies do not have tightly controlled populations or control groups, conclusions drawn from the data are limited. Outcomes cannot be ascribed to the treatment intervention with the same confidence as for a clinical trial due to potential confounding elements. Lack of randomization also means that between-treatment comparisons are not possible. However, inferences from summary statistics can be used to identify potential areas of research interest that might be explored further under randomized, controlled conditions. Since some of our analyses will rely on participant recall, including for hypoglycemia, there is also a possibility that recall bias may affect some results.

A further complication of the randomized and observational studies is loss of data due to participant drop out. This can be particularly problematic for observational studies because follow-up and recording of individual participant's data is less stringent in, and dependent on, the clinical records practice of individual physicians. These missing data may adversely affect results if there is drop-out bias, leading to skewed findings, particularly as people doing less well on a particular insulin will probably be more likely to withdraw from the study. Finally, participants who do complete the study may not have data recorded for every single measurement as part of their routine care. In this case, inclusion in the efficacy analysis does not preclude missing data entries for individual endpoints, and this may, in turn, restrict the analytical model used. However, it is to be hoped that the potential confounding effects of missing data are ameliorated by the large sample size used.

7. Discussion

A_1chieve aims to evaluate the safety of a series of insulins in a diverse, heterogeneous population. However, the scale of the study provides scope for broader investigation into current practice and effective treatment strategies for better outcome in subjects with type 2 diabetes.

Observational studies with sufficiently large sample sizes provide, uniquely, the opportunity for exploratory subset analysis to identify novel relationships between measured variables. Thus, the PREDICTIVE study suggested an HbA_{1c}-corrected correlation between FPG variability and nocturnal hypoglycemia, suggesting that variation in the easily measured FPG could serve as an indicator for risk of this undesirable outcome in clinical practice [18]. This relationship is currently being further explored through clinical data.

Observational studies can also provide an insight into the quality of treatment that individuals receive in normal clinical practice. For example, the baseline HbA_{1c} levels of PREDICTIVE, IMPROVE, and PRESENT significantly exceeded recommended guideline interventional levels, suggesting a discrepancy between evidenced-based guidance and current practice [19–21]. Comprehensive epidemiological data including prevalence of diabetes-related complications and treatment management practice (current standard care) will allow analyses of the cohort prior to the introduction of modern insulin analogs and to model incidence of complications over different time periods and quality of adjusted life expectancy.

In terms of reflections on randomized clinical trial data, A_1chieve will revisit the findings of the Treating to Target in Type 2 Diabetes (4T) study [22], allowing us to expand our knowledge and understanding of insulin initiation in a real life setting. The 4T study was an open-label, controlled, multi-center trial involving 708 people who were previously managed on maximally tolerated dose of metformin and a sulfonylurea. It aimed to determine the efficacy of different insulin regimens when subjects were initiated on biphasic insulin aspart twice daily, prandial insulin aspart three times daily, or basal insulin detemir once daily (twice if required). After 1 year, the proportion of subjects with HbA_{1c} <6.5% did not differ significantly between the biphasic group (17.0%) and the prandial group (23.9%), but the proportion in the basal group was lower (8.1%) than that in the other groups ($p < 0.001$ for both). However, the biphasic and prandial groups also reported higher rates of hypoglycemia and weight gain [22]. A_1chieve will enable further consideration of the specific treatment groups in routine clinical practice to help define who might benefit the most from each regimen based on individual need.

Observational studies must provide a new angle and focus for scientific information if they are to be given any weight in the evidence hierarchy; the methodology of the A_1chieve study seeks to address the limitations found in conventional observational studies, and provides scope for wider scientific exploration of the management of type 2 diabetes in routine clinical practice.

Conflict of interest

All authors were members of the A_1chieve study advisory board and received support from Novo Nordisk to attend advisory board meetings. Dr. Siddharth N Shah reported no other conflicts of interest. Dr. León Litwak has participated in Advisory Boards for Eli Lilly and Sanofi-Aventis for which he received an honorarium. Dr. Jihad Haddad has acted as as consultant for Sanofi-Aventis, Eli Lilly, Takeda, MSD, Bristol-Myers Squibb, and GlaxoSmithKline for which he received honoraria. Dr. Praful N Chakkarwar is an employee of Novo Nordisk Region International Operations A/S. Dr. Issam Hajjaji reported no other conflicts of interest.

Authorship

All authors made substantial contributions to the conception and design of the study or the acquisition of data. All authors had the opportunity to critically review the manuscript during development and the final draft of the manuscript was approved by all authors prior to submission.

Acknowledgements

The authors take full responsibility for this paper but are grateful to Mike Lappin, PhD, of Watermeadow Medical (supported by Novo Nordisk A/S) for writing assistance.

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