Original Article

Initiating Therapy or Switching to Biphasic Insulin Aspart Improves Glycaemic Control in Type 2 Diabetes: An Indian Experience from the A_1chieve® Study

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Abstract

Biphasic insulin aspart 30 (BIAsp 30) has been used in patients for almost a decade; There is a wealth of knowledge from clinical trials to document its efficacy and safety and suggest that BIAsp 30 is an option for initiation and intensification of insulin therapy in patients with type 2 diabetes mellitus (T2DM). The A_1chieve® was a non-interventional study that explored the safety and effectiveness of initiating or switching to insulin analogues in routine clinical practice in more than 60,000 patients from 28 different countries. In this manuscript, we discuss the findings from the subgroup of the Indian cohort who were treated with BIAsp 30. In a cohort of 15287 who were on BIAsp 30, 12645 (83%) were insulin naïve and 2642 (17%) had been on insulin therapy earlier. Glycaemic parameters were high at baseline. Mean (SD) HbA1c was 9.2% (1.3) in the these and was comparable in the insulin naïve and insulin experienced groups. After 24 weeks of therapy with BIAsp 30, there were reductions in HbA1c in both the insulin naïve group, [-1.8 (1.3)] and insulin experienced group [-1.6 (1.3)]. Fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels were also reduced significantly from baseline [-3.4 (2.7) and -4.8 (3.8) mmol/L, respectively, $p < 0.05$). Overall, hypoglycaemia decreased from 1.33 events/ patient years at baseline to 0.19 events/ patient years at 24 weeks. There was also an increase in quality of life score as evaluated by EQ-5D questionnaire. Initiating insulin therapy with or switching to BIAsp 30 in patients with poor glycaemic control leads to an improvement in glycaemic profile with no major hypoglycaemia or clinically significant weight gain. Therapy with BIAsp 30 also improves the quality of life in patients with type 2 diabetes.

Introduction

The hallmark of type 2 diabetes mellitus (T2DM) is progressive deterioration of β-cell function associated with a steady decline in glucose control. While the evidence suggests that HbA_{1c} should remain the focus, there is increasing awareness of the significance of glucose excursions, particularly PPG excursions, and their contribution to the overall glycaemic burden.[1,2,3] There is sustained evidence that PPG control is important to avoid long-term and, more importantly, cardiovascular complications.[2] The recently released IDF guidelines on management of postmeal glucose also support the view that control of fasting hyperglycaemia is necessary but usually insufficient for achieving HbA_{1c} goals <7.0%.[4] Furthermore, control of postmeal hyperglycaemia is an important consideration for achieving recommended HbA1c goals.[5] The efficacy of different approaches to insulin therapy in achieving HbA_{1c} target (with or without targeting hyperglycaemia) has also recently been evaluated in two meta-analyses.[6,7] The overall conclusions were that a greater HbA1c reduction may be obtained in type 2 diabetes using biphasic or prandial insulin rather than a basal regimen.[6,7] Biphasic insulin aspart (BIAsp 30, NovoMix™ 30, Novo Nordisk A/S, Denmark) comprises a mixture of 30% soluble rapid-acting insulin aspart (IAsp) along with an intermediate acting 70% protaminated IAsp to provide coverage of prandial and basal insulin in a single injection. BIAsp 30 was launched in the international market in 2002, and over the past 10 years it has been used by a large number of patients to treat type 2 diabetes.

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Given the fact that BIAsp 30 has been used in patients for almost a decade, there is a wealth of knowledge available to document its efficacy and safety. BIAsp 30 is an optimal choice for initiation of insulin therapy and an effective option for intensification of the same. The ADA/ EASD position statement on management of hyperglycaemia in type 2 diabetes states that in general, when compared with basal insulin alone, pre-mixed regimens tend to lower HbA_{1c} to a larger degree, but often at the expense of slightly more hypoglycaemia and weight gain.[8] The American Association of Clinical Endocrinologists (AACE) clinical practice guidelines also suggest that premixed insulin analogue therapy is suitable option for patients in whom adherence to a drug regimen is an issue.[9] The Indian insulin guideline also concludes that premix insulins are reasonable options which are effective in all the stages of diabetes offering advantages of simplicity and convenience.[10] Besides, the limited number of injections also premixed insulin analogues less intrusive in the life of a patient with diabetes. Furthermore, it is becoming more evident that ethnicity plays a role in determining the contribution of PPG to HbA_{1c}.[11] Also, racial and ethnic differences in insulin resistance, dietary pattern, glucose metabolism, genetic variation have been postulated to affect response to insulin therapy.[12,13] An ethnopharmaceutic approach that takes into consideration certain ethnic characteristics of populations may be more apt to decide the best form of insulin therapy in a particular population rather than following a "blanket" guideline.[13] The rationale for using premixed insulins as the preferred regimen in the Indian population has been discussed elsewhere in this supplement.

The A_1chieve® was a non-interventional study that explored the safety and effectiveness of initiating or switching to insulin analogues in routine clinical practice in more than 60,000 patients from 28 different countries.[14] In this manuscript, we discuss

Table 1 : HbA1c, blood glucose and lipids at baseline and 24 weeks for patients treated with biphasic insulin aspart (Novomix) ± OADs, by prior insulin usage

Variable	Visit/Change	Statistic	All	Insulin naïve	Insulin experienced
		Total number of patients	15287	12645	2642
HbA1c, %		N	11625	9661	1964
	Baseline	Mean (SD)	9.2 (1.3)	9.2 (1.3)	9.2 (1.4)
	Week 24	Mean (SD)	7.4 (0.8)	7.4 (0.8)	7.5 (1.0)
	Change from Baseline	Mean (SD)	-1.8 (1.3)	-1.8 (1.3)	-1.6 (1.3)
		p-value from paired t-test	<0.001	<0.001	<0.001
FPG, mmol/L (before breakfast)		N	11580	9719	1861
	Baseline	Mean (SD)	10.8 (3.0)	10.8 (3.0)	10.3 (3.0)
	Week 24	Mean (SD)	7.3 (1.9)	7.3 (1.9)	7.2 (2.0)
	Change from Baseline	Mean (SD)	-3.4 (2.7)	-3.5 (2.6)	-3.1 (2.9)
		p-value from paired t-test	<0.001	<0.001	<0.001
PPG, mmol/L (after breakfast)		N	8259	6966	1293
	Baseline	Mean (SD)	15.8 (3.6)	15.8 (3.5)	15.4 (4.0)
	Week 24	Mean (SD)	10.9 (3.2)	10.8 (3.1)	11.6 (3.5)
	Change from Baseline	Mean (SD)	-4.8 (3.8)	-5.0 (3.8)	-3.8 (4.2)
		p-value from paired t-test	<0.001	<0.001	<0.001
HDL-C, mmol/L		N	1644	1011	633
	Baseline	Mean (SD)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)
	Week 24	Mean (SD)	1.0 (0.3)	1.0 (0.3)	1.0 (0.3)
	Change from Baseline	Mean (SD)	-0.0 (0.2)	0.0 (0.3)	-0.0 (0.2)
		p-value from paired t-test	0.836	0.053	0.002
LDL-C, mmol/L		N	1631	1005	626
	Baseline	Mean (SD)	3.1 (0.9)	3.2 (0.9)	3.0 (0.9)
	Week 24	Mean (SD)	2.8 (0.7)	2.9 (0.8)	2.7 (0.7)
	Change from Baseline	Mean (SD)	-0.3 (0.6)	-0.3 (0.6)	-0.3 (0.6)
		p-value from paired t-test	<0.001	<0.001	<0.001
TG, mmol/L		N	1585	959	626
	Baseline	Mean (SD)	2.1 (0.7)	2.1 (0.7)	2.1 (0.7)
	Week 24	Mean (SD)	1.8 (0.6)	1.8 (0.5)	1.8 (0.6)
	Change from Baseline	Mean (SD)	-0.2 (0.5)	-0.3 (0.5)	-0.2 (0.5)
		p-value from paired t-test	<0.001	<0.001	<0.001
Total cholesterol, mmol/L		N	898	526	372
	Baseline	Mean (SD)	5.2 (0.8)	5.2 (0.8)	5.2 (0.8)
	Week 24	Mean (SD)	4.8 (0.8)	4.8 (0.8)	4.8 (0.7)
	Change from Baseline	Mean (SD)	-0.4 (0.5)	-0.4 (0.6)	-0.4 (0.4)
		p-value from paired t-test	<0.001	<0.001	<0.001
HbA1c, %	Baseline	N	14098	11605	2493
		HbA1c <7.0%, n (%)	213 (1.5)	146 (1.3)	67 (2.7)
		HbA1c ≤6.5%, n (%)	86 (0.6)	60 (0.5)	26 (1.0)
	Week 24	N	12462	10411	2051
		HbA1c <7.0%, n (%)	2885 (23.2)	2404 (23.1)	481 (23.5)
		HbA1c ≤6.5%, n (%)	1322 (10.6)	1141 (11.0)	181 (8.8)

the findings from the subgroup of the Indian cohort who were treated with BIAsp 30.

Methods

Study design

The A_1chieve® was a 24-week, international, prospective, multicentre, non-interventional, observational study of people with T2DM who were initiated on or switched to insulin analogues including BIAsp 30, alone or in combination with oral glucose lowering drugs (OGLD). The study design has been described earlier in this supplement and also been published earlier and here we confine our discussions to the patients treated with BIAsp 30 in Indian cohort of the A_1chieve® study.[14]

Participants

In a cohort of 20,554 participants from India, 15287 (74.4%) received therapy with BIAsp 30. They were on therapy with OGLD and/ or insulins. Patients may have received BIAsp 30 for no longer than 4 weeks prior to recruitment. The study excluded women who were pregnant or had an intention of getting pregnant during the study period. The protocol, clinical report forms (CRF) and informed consent documents (ICD) were approved by ethics committee. Patients could withdraw at any time and use of the study insulins could be terminated at any time at the discretion of the physician, following clinical evaluation; patients who withdrew from the study were not replaced.

All patients were enrolled and treated at the discretion of their

Table 2 : Body weight and hypoglycaemia at baseline and 24 weeks for patients treated with biphasic insulin aspart (Novomix) ± OADs, by prior insulin usage

Variable	Visit/Change	Statistic	All	Insulin naïve	Insulin experienced
		Total number of patients	15287	12645	2642
Body weight, kg		N	11290	9368	1922
	Baseline	Mean (SD)	68.4 (9.5)	68.2 (9.2)	69.1 (10.9)
	Week 24	Mean (SD)	68.5 (9.1)	68.4 (8.7)	69.1 (10.4)
	Change	Mean (SD)	0.1 (3.2)	0.1 (3.3)	-0.1 (2.9)
		p-value from paired t-test	<0.001	<0.001	0.419
Hypoglycaemia	Baseline	Number of patients	15287	12645	2642
Overall hypoglycaemia		Patients, n (%); events, n (events/patient year)	878 (5.7) 1567 (1.33)	510 (4.0) 731 (0.75)	368 (13.9) 836 (4.11)
Nocturnal hypoglycaemia		Patients, n (%); events, n (events/patient year)	355 (2.3) 457 (0.39)	177 (1.4) 207 (0.21)	178 (6.7) 250 (1.23)
Major hypoglycaemia		Patients, n (%); events, n (events/patient year)	133 (0.9) 171 (0.15)	48 (0.4) 52 (0.05)	85 (3.2) 119 (0.59)
Minor hypoglycaemia		Patients, n (%); events, n (events/patient year)	828 (5.4) 1396 (1.19)	480 (3.8) 679 (0.70)	348 (13.2) 717 (3.53)
	Week 24	Number of patients	12922	10808	2114
Overall hypoglycaemia		Patients, n (%); events, n (events/patient year)	149 (1.2) 192 (0.19)	94 (0.9) 113 (0.14)	55 (2.6) 79 (0.49)
Nocturnal hypoglycaemia		Patients, n (%); events, n (events/patient year)	22 (0.2) 27 (0.03)	12 (0.1) 12 (0.01)	10 (0.5) 15 (0.09)
Major hypoglycaemia		Patients, n (%); events, n (events/patient year)	0 (0.00) 0 (0.000)	0 (0.00) 0 (0.000)	0 (0.00) 0 (0.000)
Minor hypoglycaemia		Patients, n (%); events, n (events/patient year)	149 (1.2) 192 (0.19)	94 (0.9) 113 (0.14)	55 (2.6) 79 (0.49)

physician in accordance with local, routine clinical practice. For the participants who had withdrawn from the study, data was collected till their last visit. The participating investigators were trained on the protocol, safety reporting and CRF completion for the study.

Assessment and outcome measures

The primary objective of this study was to evaluate the clinical safety of the insulin analogues by the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic events, considered related to the study insulin between baseline and final visit. Secondary safety assessments were the change in number of hypoglycaemic events in the last 4 weeks before interim and final visits, compared with the last 4 weeks before baseline visit, the change in number of nocturnal hypoglycaemic events during these periods and the number of adverse drug reactions (ADRs) from baseline to final visit. The insulin dose(s) at the baseline and end of 24 weeks were also quantified. Efficacy assessments were change in HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPPG) and body weight between baseline and final visits, and change in systolic blood pressure (SBP) and lipid profile at final visit.

Statistics

Analysis of all variables, including safety and efficacy outcomes, was performed using any participant entered into the study who had the data relevant to that analysis. A detailed note on the statistics used in analysis of results has been published earlier and also described earlier in the supplement.[14]

Results

Participants

In a cohort of 15287 who were on BIAsp 30, 12645 were insulin naïve and 2642 had been on insulin therapy earlier. Baseline demographics were comparable between the overall population and the insulin-naïve patients and the insulin experienced patients. The reasons for initiating therapy with or switching over to BIAsp 30 were to improve glycaemic control, reduce the risk of hypoglycaemia and reduce plasma glucose variability among others.

Glycaemic control

Glycaemic parameters were high at baseline. Mean HbA1c was 9.2 (1.3) in the study cohort and was comparable in the insulin naïve and insulin user groups. After 24 weeks of therapy with BIAsp 30, there were significant reductions in HbA1c in both the insulin naïve group, [-1.8 (1.3), p<0.05] and insulin experienced group [-1.6 (1.3) , p<0.05].

At baseline, 1.5% of patients had an HbA_{1c} level of <7.0% with the percentage being slightly higher in those who had been treated with insulin earlier (2.7%). After 24 weeks, more than 23% of the patients achieved an HbA_{1c} target of <7.0% in both the insulin-naïve patients and insulin experienced groups. Forced titration algorithm was not used in the study.

Fasting plasma glucose and postprandial plasma glucose levels were also reduced from baseline in all the patients' groups receiving therapy with BIAsp 30 (Table 1).

Hypoglycaemia and body weight

The rates of hypoglycaemia (overall, nocturnal and minor) were reduced compared to the baseline values in all the groups. At 24 weeks of therapy with BIAsp 30, patients in both insulin naïve and insulin experienced groups had low rates of minor hypoglycaemia and no major hypoglycaemia in patients treated with BIAsp 30 (Table 2).

SADRs and serious adverse events

A total of seven serious adverse events were reported. No SADRs were reported. There was one withdrawal due to adverse events..

Quality of life

Quality of life was improved for patients in both the insulin-naïve and insulin experienced groups. At the start of the study, 62.5% of the insulin-naïve patients reported problems with walking but after 24 weeks, only 14.8% reported such difficulties. Overall, 69% of the patients reported an improvement in self care and 76% had no pain or discomfort. As compared to 37.9% at baseline, 80.5% of patients reported no anxiety and depressed.

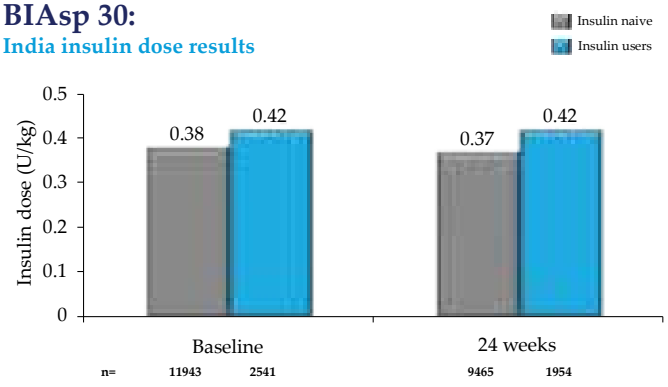

Fig. 1 : Dose of insulin in insulin users and insulin naïve patients at baseline and 24 weeks

The parameters assessed for quality of life have been described in Table 3.

Insulin dose

In the insulin-naive cohort, total daily insulin dose at 24 weeks had been titrated up to 0.37 ± 0.13 U/kg. In prior insulin users, pre-analogue insulin dose was 0.43 ± 0.19 U/kg, total starting insulin dose was 0.42 ± 0.17 U/kg and, at 24 weeks, was 0.42 ±0.17 U/kg (Figure 1).

Discussion

Key findings

This is the largest study patients in insulin therapy for type 2 diabetes and it is interesting to note that the results presented here are comparable to those from other similar studies.[15,16] Initiating insulin therapy with, or switching existing insulin therapy to, BIAsp 30 in routine practice resulted in improved glycaemic control (HbA_{1c}, FPG and PPG), reduced rates of major hypoglycaemia and greater patient treatment satisfaction. As obvious from the baseline data, HbA1c was high in all patients at baseline indicating poor glycaemic control. It also suggests clinical inertia leading to delayed initiation (and intensification) of insulin therapy in these patients. All patients experienced a reduction in HbA_{1c} by the end of the study period with 23%

Table 3 : Quality of life at baseline and 24 weeks for patients treated with biphasic insulin aspart (Novomix) ± OADs, by prior insulin usage

Variable	Visit/change	Statistic	All	Insulin naïve	Insulin experienced
		Total number of patients	**15287**	**12645**	**2642**
EQ-5D (weighted)		N	12240	10249	1991
	Baseline	Mean (SD)	0.498 (0.279)	0.489 (0.280)	0.546 (0.271)
	Week 24	Mean (SD)	0.805 (0.169)	0.803 (0.172)	0.816 (0.157)
	Change from Baseline	Mean (SD)	0.307 (0.297)	0.315 (0.297)	0.270 (0.297)
		p-value from paired t-test	<0.001	<0.001	<0.001
EQ-VAS		N	11397	9576	1821
	Baseline	Mean (SD)	55.9 (14.1)	56.0 (14.8)	55.5 (10.2)
	Week 24	Mean (SD)	75.6 (9.3)	76.2 (9.2)	72.5 (9.3)
	Change from Baseline	Mean (SD)	19.7 (15.9)	20.2 (16.4)	16.9 (13.0)
		p-value from paired t-test	<0.001	<0.001	<0.001
Mobility		N	12337	10329	2008
No problems in walking	Baseline	N (%)	4644 (37.6)	3878 (37.5)	766 (38.1)
	Week 24	N (%)	10532 (85.4)	8803 (85.2)	1729 (86.1)
		p-value for chi-square	<0.0001	<0.0001	<0.0001
Self-care		N	12320	10314	2006
No problems with self-care	Baseline	N (%)	4502 (36.5)	3682 (35.7)	820 (40.9)
	Week 24	N (%)	8501 (69.0)	7080 (68.6)	1421 (70.8)
		p-value for chi-square	<0.0001	<0.0001	<0.0001
Usual Activity		N	12342	10330	2012
No problems with performing my usual activities	Baseline	N (%)	4195 (34.0)	3420 (33.1)	775 (38.5)
	Week 24	N (%)	8956 (72.6)	7436 (72.0)	1520 (75.5)
		p-value for chi-square	<0.0001	<0.0001	<0.0001
Pain/discomfort		N	12335	10322	2013
No pain or discomfort	Baseline	N (%)	4156 (33.7)	3341 (32.4)	815 (40.5)
	Week 24	N (%)	9359 (75.9)	7789 (75.5)	1570 (78.0)
		p-value for chi-square	<0.0001	<0.0001	<0.0001
Anxiety/Depression		N	12298	10298	2000
Anxiety/Depression - not anxious or depressed	Baseline	N (%)	4655 (37.9)	3763 (36.5)	892 (44.6)
	Week 24	N (%)	9897 (80.5)	8244 (80.1)	1653 (82.7)
		p-value for chi-square	<0.0001	<0.0001	<0.0001

patients achieving the ADA recommendation of HbA1c<7.0%. Hypoglycaemic events were low in insulin-naïve and insulin experienced patients and most events were minor with no major hypoglycaemia. Change in body weight after 24 weeks of therapy with BIAsp 30 was very modest for all pre-study subgroups, so possibly clinically irrelevant.

Comparison with other studies

Results from this study are similar to those from the PRESENT observational study, which also investigated safety and effectiveness of BIAsp 30 therapy in patients with type 2 diabetes.[15] Both the trend and the size of the HbA_{1c} reductions are comparable as are the results for major and minor hypoglycaemia (in the PRESENT Study, HbA1c decreased approximately 2.2%-points, FPG decreased 4.5 mmol/L and PPG decreased approximately 6.8 mmol/L).[15] The findings are also similar to the IMPROVE™ study which reported initiating insulin with, or switching insulin therapy to, BIAsp 30 in routine care resulted in improved glycaemic control, reduced major hypoglycaemia and greater treatment satisfaction compared with previous therapies. In the IMPROVE™ study, in a population of patients with type 2 diabetes,HbA1c, fasting and postprandial blood glucose were reduced from baseline in all subgroups (no pharmaceutical therapy: -3.1%, -5.9 and -9.0 mmol/l, respectively; OADs-only: -2.1%, -4.1 and -6.1 mmol/l; insulin +/- OADs: -2.0%, -3.3 and -5.1 mmol/l).[16]

A decade-long clinical evaluation indicates that BIAsp 30, irrespective of prior therapy status (insulin naive, BHI or basal), offers better glycemic control and is associated with reduced rates of hypoglycemia (compared to biphasic human insulins).[17,18] Administered once or twice daily, BIAsp 30 is a useful option for individuals initiating insulin. Guidelines from AACE 2011 recommended the use of premixed analogues over human insulins, considering its more physiological profile and improved adherence. The IDF guidelines propose that "*Biphasic insulin analogues are associated with advantages compared with biphasic human insulin preparations in controlling postmeal glucose.*"[4]

This was an observational study and hence the data extracted at baseline relied on patient recall and may be subject to recall bias. Inclusion into the study may also have introduced bias by increasing the patients' awareness in avoiding hypoglycaemic episodes or increasing their awareness of episodes. Variations in clinical practice may influence treatment outcome in addition to the treatment regimen itself which is again an inherent limitation of observational studies.

In summary, initiating insulin therapy with or switching to BIAsp 30 in patients with poor glycaemic control leads to an improvement in glycaemic control with no major hypoglycaemia. These improvements in glycaemic control do not require higher doses of BIAsp 30 and are not associated with clinically significant weight gain. Besides, therapy with BIAsp 30 also leads to an increase in quality of life.

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