Dataset Integrity Check for Low-Dose Anti-Thymocyte Globulin (ATG) Preserves β-Cell Function and Improves HbA_{1c} in New-Onset Type 1 Diabetes

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April 9, 2019

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1 Standard Disclaimer

The intent of this DSIC is to provide confidence that the data distributed by the NIDDK repository is a true copy of the study data. Our intent is not to assess the integrity of the statistical analyses reported by study investigators. As with all statistical analyses of complex datasets, complete replication of a set of statistical results should not be expected in secondary analysis. This occurs for a number of reasons including differences in the handling of missing data, restrictions on cases included in samples for a particular analysis, software coding used to define complex variables, etc. Experience suggests that most discrepancies can ordinarily be resolved by consultation with the study data coordinating center (DCC), however this process is labor-intensive for both DCC and Repository staff. It is thus not our policy to resolve every discrepancy that is observed in an integrity check. Specifically, we do not attempt to resolve minor or inconsequential discrepancies with published results or discrepancies that involve complex analyses, unless NIDDK Repository staff suspect that the observed discrepancy suggests that the dataset may have been corrupted in storage, transmission, or processing by repository staff. We do, however, document in footnotes to the integrity check those instances in which our secondary analyses produced results that were not fully consistent with those reported in the target publication.

2 Study Background

This study is a three-arm, 1:1:1 randomized, placebo controlled, double- blinded trial in which at least 28 subjects will receive active Anti-Thymocyte Globulin and Granulocyte colony-stimulating factor (ATG-GCSF), at least 28 subjects will receive ATG alone and at least 28 subjects will receive placebo alone within 100 days from diagnosis of Type 1 Diabetes (T1D). TrialNet researchers are testing whether ATG used alone or in combination with GCSF will help people continue to make some of their own insulin.

3 Archived Datasets

All the SAS data files, as provided by the Data Coordinating Center (DCC), are located in the TrialNet_19/private_orig_data/Data.Extraction.19.Version190118PW/19/sasv9/ folder in the data package. For this replication, variables were taken from the “mastable.sas7bdat”, “autoab.sas7bdat”, “bmi.sas7bdat”, “hba1c.sas7bdat”, and “insulin.sas7bdat” datasets.

4 Statistical Methods

Analyses were performed to duplicate results for the data published by Haller et al [1] in the journal Diabetes Care in 2018. To verify the integrity of the dataset, descriptive statistics were computed.

5 Results

For Table 1 in the publication [1], Baseline characteristics, Table A lists the variables that were used in the replication and Table B compares the results calculated from the archived data files to the results published in Table 1.

6 Conclusions

The NIDDK repository is confident that the TrialNet_19 data files to be distributed are a true copy of the study data.

7 References

[1] Michael J. Haller, Desmond A. Schatz, Jay S. Skyler, Jeffrey P. Krischer, Brian N. Bundy, Jessica L. Miller, Mark A. Atkinson, Dorothy J. Becker, David Baidal, Linda A. DiMeglio, Stephen E. Gitelman, Robin Goland, Peter A. Gottlieb, Kevan C. Herold, Jennifer B. Marks, Antoinette Moran, Henry Rodriguez, William Russell, Darrell M. Wilson, Carla J. Greenbaum, and the Type 1 Diabetes TrialNet ATG-GCSF Study Group. "Low-Dose Anti-Thymocyte Globulin (ATG) Preserves β-Cell Function and Improves HbA_{1c} in New-Onset Type 1 Diabetes". Diabetes Care (2018) 41(9): 1917-1

Table A: Variables used to replicate Table 1**:** Baseline characteristics

Table Variable	**dataset.variable**
Treatment description	mastable.rxdesc
Age	mastable.age
Male sex	mastable.sex
Race	mastable.race
Ethnicity not Hispanic or Latino	mastable.ethnicity
GAD65H autoantibody positive	autoab.gad65h
IA2H autoantibody positive	autoab.ia2h
ICA autoantibody positive	autoab.ica
ZNT8 autoantibody positive	autoab.znt8
No. of autoantibodies positive	
No. of days from diagnosis to randomization	mastable.treatmentdate mastable.dtdx
Weight	bmi.weightkg
BMI	bmi.weightkg bmi.heightcm
AUC mean for C-peptide	
HbA_{1c}	hba1c.hba1c
Total daily insulin dose at baseline	insulin.totinsulin

Table B: Comparison of values computed in integrity check to reference article Table 1 values

Treatment description	Patient characteristic	Manuscript (n=89)	DSIC (n=89)	Diff. (n=0)
ATG and GSCF	Age, years – Mean ± SD	17.2 ± 5.0	17.2 ± 5.0	0.0 ± 0.0
	Age, years – Median	16.4	16.4	0.0
	Age, years – Range	12.0-32.8	12.0-32.8	0.0-0.0
	Male sex, no. of patients (%)	16 (55.2)	16 (55.2)	0 (0.0)
	Race, no. of patients (%) – White	28 (96.6)	28 (96.6)	0 (0.0)
	Race, no. of patients (%) – Black	1 (3.4)	1 (3.4)	0 (0.0)
	Ethnicity not Hispanic or Latino, no. of patients (%)	28 (96.6)	28 (96.6)	0 (0.0)
	Autoantibodies positive, no. of patients (%) – GAD65H	23 (79.3)		
	Autoantibodies positive, no. of patients (%) – IA2H	25 (86.2)		
	Autoantibodies positive, no. of patients (%) – ICA	26 (92.9)		
	Autoantibodies positive, no. of patients (%) – ZNT8	21 (72.4)		
	No. of autoantibodies positive, no. of patients (%) – 1	0 (0.0)		
	No. of autoantibodies positive, no. of patients (%) – 2	3 (10.3)		
	No. of autoantibodies positive, no. of patients (%) – 3	2 (6.9)		
	No. of autoantibodies positive, no. of patients (%) – 4	11 (37.9)		
	No. of autoantibodies positive, no. of patients (%) – 5	13 (44.8)		
	No. of days from diagnosis to randomization – Median	83	83	0
	No. of days from diagnosis to randomization – Range	49-97	49-97	0-0
	Weight, kg – Median	62.3	62.3	0.0
	Weight, kg – Range	39.8-89.1	37.3-89.1	2.5-0.0
	BMI, kg/m² - Median	21.4	21.1	0.3
	BMI, kg/m² - Range	16.6-27.7	16.3-27.7	0.3-0.0
	AUC Mean for C-peptide, nmol/L – Mean ± SD	0.793 ± 0.321		

Treatment description	Patient characteristic	Manuscript (n=89)	DSIC (n=89)	Diff. (n=0)
	AUC Mean for C-peptide, nmol/L – Median	0.701		
	AUC Mean for C-peptide, nmol/L – Range	0.33-1.78		
	HbA_{1c}, %/mmol/mol – Median	7.3/56	7.3	0.0
	HbA_{1c}, %/mmol/mol – Range	5.3-12.3/34-111	5.3-12.3	0.0-0.0
	Total daily insulin dose at baseline, units/kg – Median	0.339	0.339	0.000
	Total daily insulin dose at baseline, units/kg – Range	0-1.06	0-1.02	0-0.04
ATG only	Age, years – Mean ± SD	18.1 ± 6.9	18.1 ± 6.9	0.0 ± 0.0
	Age, years – Median	15.5	15.5	0.0
	Age, years – Range	12.4-42.5	12.4-42.5	0.0-0.0
	Male sex, no. of patients (%)	17 (58.6)	17 (58.6)	0 (0.0)
	Race, no. of patients (%) – White	29 (100.0)	29 (100.0)	0 (0.0)
	Race, no. of patients (%) – Black	0 (0.0)	0 (0.0)	0 (0.0)
	Ethnicity not Hispanic or Latino, no. of patients (%)	27 (93.1)	27 (93.1)	0 (0.0)
	Autoantibodies positive, no. of patients (%) – GAD65H	23 (79.3)		
	Autoantibodies positive, no. of patients (%) – IA2H	23 (79.3)		
	Autoantibodies positive, no. of patients (%) – ICA	25 (86.2)		
	Autoantibodies positive, no. of patients (%) – ZNT8	21 (72.4)		
	No. of autoantibodies positive, no. of patients (%) – 1	3 (10.3)		
	No. of autoantibodies positive, no. of patients (%) – 2	2 (6.9)		
	No. of autoantibodies positive, no. of patients (%) – 3	1 (3.4)		
	No. of autoantibodies positive, no. of patients (%) – 4	11 (37.9)		
	No. of autoantibodies positive, no. of patients (%) – 5	12 (41.4)		
	No. of days from diagnosis to randomization – Median	81	81	0
	No. of days from diagnosis to randomization – Range	47-100	47-100	0-0
	Weight, kg – Median	66.4	66.4	0.0
	Weight, kg – Range	39.6-92.4	39.6-92.4	0.0
	BMI, kg/m^2 - Median	22.6	22.3	0.3

Treatment description	Patient characteristic	Manuscript (n=89)	DSIC (n=89)	Diff. (n=0)
	BMI, kg/m² - Range	15.2-32.8	15.2-32.8	0.0-0.0
	AUC Mean for C-peptide, nmol/L – Mean ± SD	0.878 ± 0.474		
	AUC Mean for C-peptide, nmol/L – Median	0.757		
	AUC Mean for C-peptide, nmol/L – Range	0.211-2.15		
	HbA_{1c}, %/mmol/mol – Median	7.4/57	7.4	0.0
	HbA_{1c}, %/mmol/mol – Range	4.7-9.0/28-75	4.3-9.0	0.4-0.0
	Total daily insulin dose at baseline, units/kg – Median	0.315	0.334	0.019
	Total daily insulin dose at baseline, units/kg – Range	0-0.963	0-0.963	0-0.000
Placebo	Age, years – Mean ± SD	16.9 ± 4.6	16.8 ± 4.6	0.1 ± 4.6
	Age, years – Median	15.0	15.0	0.0
	Age, years – Range	12.2-29.3	12.2-29.3	0.0-0.0
	Male sex, no. of patients (%)	17 (54.8)	17 (54.8)	0 (0.0)
	Race, no. of patients (%) – White	29 (93.5)	29 (93.5)	0 (0.0)
	Race, no. of patients (%) – Black	2 (6.5)	2 (6.5)	0 (0.0)
	Ethnicity not Hispanic or Latino, no. of patients (%)	30 (96.8)	30 (96.8)	0 (0.0)
	Autoantibodies positive, no. of patients (%) – GAD65H	23 (74.2)		
	Autoantibodies positive, no. of patients (%) – IA2H	25 (80.6)		
	Autoantibodies positive, no. of patients (%) – ICA	22 (71.0)		
	Autoantibodies positive, no. of patients (%) – ZNT8	22 (71.0)		
	No. of autoantibodies positive, no. of patients (%) – 1	1 (3.2)		
	No. of autoantibodies positive, no. of patients (%) – 2	3 (9.7)		
	No. of autoantibodies positive, no. of patients (%) – 3	5 (16.1)		
	No. of autoantibodies positive, no. of patients (%) – 4	13 (41.9)		
	No. of autoantibodies positive, no. of patients (%) – 5	9 (29.0)		
	No. of days from diagnosis to randomization – Median	84	84	0
	No. of days from diagnosis to randomization – Range	52-99	52-99	0-0
	Weight, kg – Median	62.0	62.0	0.0

Treatment description	Patient characteristic	Manuscript (n=89)	DSIC (n=89)	Diff. (n=0)
	Weight, kg – Range	33.8-118	33.8-118	0.0-0
	BMI, kg/m² - Median	21.8	21.8	0.0
	BMI, kg/m² - Range	14.3-34.3	14.3-34.3	0.0-0.0
	AUC Mean for C-peptide, nmol/L – Mean ± SD	0.966 ± 0.503		
	AUC Mean for C-peptide, nmol/L – Median	0.932		
	AUC Mean for C-peptide, nmol/L – Range	0.144-2.08		
	HbA_{1c}, %/mmol/mol – Median	7.2/55	7.2	0.0
	HbA_{1c}, %/mmol/mol – Range	5.5-11.2/35-99	5.1-11.2	0.4-0.0
	Total daily insulin dose at baseline, units/kg – Median	0.306	0.314	0.008
	Total daily insulin dose at baseline, units/kg – Range	0-0.921	0-0.921	0-0.000

Attachment A: SAS Code

```
/*************************************************************************************************
TrialNet_07 DSIC
Saved As:  /prj/niddk/ims_analysis/TrialNet_19/prog_initial_analysis/check.table1.sas
Programmer:  Anne Taylor
Date Written:  21Mar2019
Purpose:  To check Table 1 of Low-Dose Anti-Thymocyte Globulin (ATG) Preserves
          B-Cell Function and Improves HbA1c in New-Onset Type 1 Diabetes.
*************************************************************************************************/

options validvarname=upcase mprint;

title 'TrialNet_07 DSIC';
title2 "Program Saved As:  %sysfunc(getoption(sysin))";

libname created '/prj/niddk/ims_analysis/TrialNet_19/private_created_data';
libname orig '/prj/niddk/ims_analysis/TrialNet_19/private_orig_data/Data.Extraction.19.Version190118PW/19/sasv9';

data mastable;
   set created.mastable;
   days_dxrand=treatmentdate-dtdx;
   label days_dxrand='No. of days from diagnosis to randomization';

proc sort data=orig.bmi out=bmi;
   by maskid dateofweight;

data bmi;
   set bmi;
   by maskid rxdesc;
   if last.rxdesc and not last.maskid then abort;
   if first.maskid;
   bmi=weightkg/((heightcm/100)**2);

proc sort data=orig.hba1c out=hba1c;
   by maskid dateofdraw;

data hba1c;
   set hba1c;
   by maskid rxdesc;
   if last.rxdesc and not last.maskid then abort;
   if first.maskid;

proc sort data=orig.insulin out=insulin;
   by maskid dtinsulin1;
```

```
data insulin;
   set insulin;
   by maskid rxdesc;
   if last.rxdesc and not last.maskid then abort;
   if first.maskid;

%macro medrnge(dsn,charact);
   proc tabulate data=&dsn missing f=12.3;
      class rxdesc;
      var &charact;
      table &charact*(mean stddev median min max),rxdesc;
      title4 'Table 1 - Baseline characteristics';
   run;
%mend medrnge;

%macro npct(dsn,charact,desc);
   proc tabulate data=&dsn missing;
      class rxdesc;
      class &charact/&desc;
      table &charact,rxdesc*(n*f=12. colpctn*f=12.1);
   run;
%mend npct;

%medrnge(mastable,age);

%npct(mastable,sex,descending);
%npct(mastable,race,descending);
%npct(mastable,ethnicity,descending);

%medrnge(mastable,days_dxrand);
%medrnge(bmi,weightkg);
%medrnge(bmi,bmi);
%medrnge(hba1c,hba1c);
%medrnge(insulin,totinsulin);
```