Trial to Reduce IDDM in the Genetically at Risk

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TRIGR Family News

Editor's Corner

Dear Study Families!

The TRIGR pilot study is now completed and the results have been published in a high level scientific journal. Our Principal Investigator Mikael Knip wrote a summary of the article and the promising results support even more our confidence in the TRIGR study hypotheses.
The road is sometimes long and winding. That we experienced on our return trip back home after the TRIGR meeting held in Budapest, Hungary in April. Finnish Study Doctor Kristiina Luopajärvi wrote about her experiences on OGTT tests in Helsinki and Jacki Catteau from Australia tells us how far the TRIGR study visits can reach.

Matti Koski
Chief Editor

Encouraging results from the TRIGR pilot after observation up to the age of 10 years

Mikael Knip, Principal Investigator for TRIGR
Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland

The final results from the TRIGR pilot study were published in the November 11, 2010 issue of the New England Journal of Medicine. The report was based on the observation of 230 Finnish children with a family member affected by type 1 diabetes and HLA-conferred disease susceptibility from birth up to the age of 10 years. Initially the pilot study included in addition to the 230 Finnish children eight Estonian and four Swedish subjects, and the observation was planned up to the age of 2 years. In Finland we obtained ethical approval for continued observation up to the age of 10, and accordingly the 10-year report was based on the Finnish children. Actually 208 children had provided at last one blood sample for the analyses of diabetes-associated autoantibodies. Those children comprised the study population for the study of beta-cell autoimmunity, while we obtained data on possible progression to clinical diabetes from all 230 participants based on our national diabetes register.
One hundred thirteen infants were randomized to be weaned to the hydrolyzed study formula (Nutramigen) while 117 were randomized to be weaned to the cow's milk based study formula. Ninety-nine participants in the hydrolyzed formula group and 109 in the control formula group provided at least one blood sample for the analyses of diabetes-associated autoantibodies. Of some reason the study formula was introduced earlier in the control group (median age 1.1 months) than in the hydrolysate group (median age 2.6 months). The intervention was completed at the median age of 7.4 months in the hydrolysate group and at the median age of 6.4 months in the control group. The median duration of study-formula feeding was 3.3 months in the hydrolysate group and 4.9 months in the control group. The results were adjusted for the differences mentioned above but the results did not change after any of these adjustments.
Fifty participants (24%) developed at least one autoantibody by the age of 10 years; 17 (17%) in the hydrolysate group and 33 (30%) in the control group. This observation indicates that the early dietary intervention applied reduced the frequency of at least one autoantibody by 46%. At least two autoantibodies were observed in 25 children (12%); eight (8%) in the hydrolysate group and 17 (16%) in the control group reflecting a reduction of 48% in the frequency of two or more autoantibodies in the hydrolysate group. Sixteen out of the 230 participants presented with clinical diabetes by

the age of 10 years. Seven (6%) were in the group randomized to the hydrolyzed formula and nine (8%) in the group randomized to the control formula. This difference was not conspicuous. However, three out of the seven who developed diabetes in the group randomized to receive hydrolyzed formula dropped out from the study before the first follow-up visit at the age of 3 months and were never exposed to any study formula. When the comparison was adjusted according to the actual treatment received, four (4%) in the hydrolysate group and nine (8%) in the control group developed clinical diabetes suggesting that the hydrolysate intervention reduced the frequency of overt diabetes by 60%. This reduction remained statistically non-significant, as the number of children presenting with diabetes was low from a statistical point of view.

The full-scale TRIGR study with nine times more participants than the pilot study has enough power to provide a reliable answer to the question whether weaning to a highly hydrolyzed formula is capable of reducing the frequency of diabetes. It is, however, essential that more than 80% of the randomized children remain in the study up to the age of 10 years. Therefore I do hope that you all participating families realize the importance of staying in the study till the end. We investigators and all TRIGR staff do appreciate the contribution that you participating families, are bringing to the trial, and we are committed to make the continued participation as convenient and rewarding as possible. Let's work together to reach our common goal.

As a matter of fact the highest rate of diabetes was seen among those children who dropped out from the pilot study, as three of 22 (14%) presented with diabetes. This may suggest that it is worthwhile to remain in the study till its completion.

Although the pilot study results did not provide a definite answer to the research question whether weaning to a highly hydrolyzed formula reduces the rate of diabetes in children with at least one family member affected by type 1 diabetes and with HLA-conferred disease susceptibility, they represent a milestone in the efforts aimed at primary prevention of type 1 diabetes. The results show for the first time that it is possible to decrease the initiation of the disease process leading to clinical diabetes with a safe and relatively simple measure. This outcome is highly encouraging from the perspective of the full-scale TRIGR study. We have, however, to be patient and continue our efforts to complete the TRIGR trial giving us the final answer in 2017.

Source:
Knip M, Virtanen SM, Ilonen J, Savilahti E, Vaarala O, Reunanen A, Teramo K, Hämäläinen AM, Paronen J, Dosch HM, Hakulinen T, Åkerblom HK, the Finnish TRIGR Study Group: Dietary intervention in infancy and later signs of beta-cell autoimmunity. N Engl J Med 2010;363:1900-1908.

TRIGR in ashes

Most TRIGR investigators started their trip to the TRIGR European Steering Committee Meeting in Budapest Hungary on April 15, 2010. The morning flights were pleasant and we started our meeting on schedule at 1.00 PM. We got the first alarming news in the afternoon. The volcano eruption near the Eyjafjallajökull glacier in Island had started. We started to worry how to get back home after the meeting. These are our stories.

Brenda Bradley, Canada, National Coordinator

We started to set the wheels in motion to come up with imaginative ways to return home for most of the European contingency however, heading back to North America was a different story. With the closure of many larger European airports having the Budapest airport remain open was futile as flights to connecting airports such as Paris, London and Frankfurt were cancelled. This left us stranded in Budapest! Endless attempts were made to find alternate flights home. Luckily I had a patient husband at home willing to spend hours on hold with airlines and travel agencies to re-book several flights. The new plan was via Munich on Tuesday April 20th which seemed to be a good solution until ……the ash migrated eastward and closed the Budapest airport. At this point, a raft down the Danube River looked like the only viable solution! Another flight scheduled for Saturday April 24th! After much patience, many emails, phone calls and frustrations…..my husband managed to find an earlier flight on Swiss Air to Zürich then on to Toronto and finally Ottawa. Eventually after 24 hours of travelling I arrived home late in the evening of April 22nd. This may not have been the most economical "two day meeting" but I must say, the city was beautiful, the hotel and airlines sympathetic, the company GREAT and the experience PRICELESS! There was just enough time to regroup before heading to the North American Steering Committee meeting in Tampa, Florida in May… in the hub of the Gulf of Mexico oil crisis! ☺

Pavla Mendlova, Czech Republic, National Coordinator

In the afternoon, there was some slightly bothering news about a volcano in Iceland and some Finnish

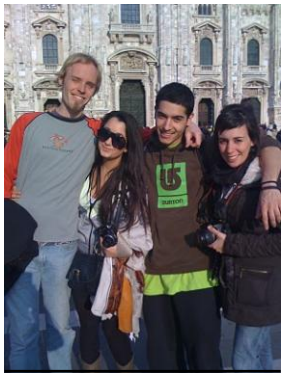
and Swedish participants started to worry, but all and around, no big issue yet. When a Swedish coordinator asked me at the dinner, how we Czech were going to get home, I told her it was a nice joke, the cloud was far from our country, so we were going by plane as planned. I badly needed to be back in time to breastfeed my baby, as there was only a certain amount of frozen breast milk ready at home. However, I slept well, no nightmares about the journey home. In the morning, when I realized that the Frankfurt airport was closed already, it dawned on me that we were in real trouble. As many of the participants were already leaving, the Professor Vavrinec decided it was time to find us a way home too. Blessed by the Internet, as soon as the second lecture of that day finished, we knew the plan and were out to follow it. Fortunately, Budapest is not so far from Prague and it took us only about 7 hours to get home by train. Taking the advantage of being among the first ones "trapped" to want to travel by train, there was enough place there and as we left earlier, I got home almost on time, no milk scandal emerged. Next year though we will double check the alternative routes when planning our travel to the meeting.

Teba Gonzalez, Study Center SPA01 Barakaldo, Spain Local Coordinator

I would like to tell you a story that now it is an anecdote but, when it happened, I was living a nightmare. My flight back was scheduled for Saturday via Munich. Never took that flight. The insight that I was not able to arrive in Spain was storming in my head. At four o'clock on Sunday my Dutch colleague helped me with my suitcase to jump in a taxi. Then I could not help myself, and I started crying when saying goodbye to her.

The travel to Venice in the night train was absolutely unforgettable; 14 hours, four borders to cross (Hungarian, Croatian, Slovenian and, Italian) with respective national passport controls. We were all trying to get some sleep but it was almost impossible. Five times we had to show our passports. I arrived in Venice at 7:05 AM. In Venice I got a ticket to Milan. In Milan the central station was quite chaotic. People all over were trying to get home. No tickets to Spain were available. My emotional status was down because of the uncertainty and the lack of sleep. So, I left the station behind and, looked for a solution.

By chance I met a group of students (in the picture above) and asked them if they knew about any cheap hostel or bed and breakfast. They were Spanish. Nice coincidence. But, their hostel was fully booked and I needed to find another place. "Well, it's not that bad!" I told myself but when I was leaving they called me back and said that they could share their room with me if the hostel would allow it. So, that's what we did and I stayed for 3 days with them in Milan, visiting the city and trying to relax.



My boyfriend Toni and another friend of mine sent me many messages to check how I felt and "where I was" and, it helped me a lot.

On Tuesday the Milan airport was opened. On Wednesday, at last, I got a taxi to Linate airport. There were extremely few people at the airport. I checked myself in without problems and I took a deep breath when I entered into the plane to take off to Madrid. After that I arrived in Bilbao eventually!

The Finnish TRIGR group

We thought of many possibilities how to get back to Finland. Flights were out and the train option was quite unsure and complicated. The best way we could think of was to hire a car and drive to Tallinn, Estonia and go to Helsinki by ship. The biggest problem was the car because Budapest was emptied out of rental cars. Thanks to our host Professor László Madácsy arranging a rental car for us and the first group of us could start the trip to Helsinki on Friday afternoon, April the 16th.

Our Hungarian driver did have a GPS device and he programmed the way from Budapest to Tallinn and as you can see something happened in Slovakia. After midnight we were driving in the Carpathian Mountains up and down and it was really dark. At last we reached the border but what a surprise; it was not the border of Poland which was our target but it was the border of Ukraine. Well, back partly along the same road to the Polish border. We drove altogether for 27 hours with two one hour breaks. We reached the Tallinn harbour just in time to catch the last ship that evening thanks to our excellent driver. The boat trip took about 2 hours more. Two other cars took two other TRIGR groups (Estonians and Finns) using the same way without visiting at the Ukrainian border.

OGTT-tests in Helsinki

In Helsinki, we like to congratulate the TRIGR families. Seventy OGTT tests have been successfully performed at the follow-up visits at the age of 6 years in the study in Helsinki, Finland. For the families the OGTT test has many advantages:

1) Nowadays the OGTT together with the test results for diabetes-associated autoantibodies are the only way to provide information on the progression of beta-cell autoimmunity in type 1 diabetes.

2) We have seen that a normal result of the OGTT test (reflecting normal glucose tolerance) is a relief for the family.

3) Few children in the TRIGR study will develop signs of autoimmunity. The duration of the prediabetic period can range from a few months to decades. In such individuals, type 1 diabetes can be diagnosed and detected in the early phase through an OGTT test (usually in asymptomatic children).

4) If diabetes have been detected early, the management of hyperglycemia and starting insulin treatment is easier. Early insulin treatment benefits the preservation of residual beta-cell secretion.

Thank you for taking part in the study.

Kristiina Luopajärvi, Finnish Local Investigator

TRIGR in Australia

TRIGR in Australia is spread far and wide; our participants live as close as 3.6 kilometres from each other to as far away as 5,674 kilometres. Getting to visit each and everyone is a challenge but definitely a work in progress. The red dots indicate just how far spread out our families are.

Matilda and her brother Jordan at home in Albany with their pet wallaby

Last year I visited Albany. Albany is situated on the southern coast of Western Australia, and is a 4 hour 45 minute drive from Perth to see Matilda for her 5 year visit. Albany is home to a range of spectacular natural wonders, including: The Torndirrup National Park, a dramatic convict history, set against a backdrop of rugged granite coastline, green seas and a wild beauty. There are convict jails, old taverns, whaling ships and settlers' cottages and Grand National Trust homes to explore.

Albany's dramatic coastline

The children that had their oral glucose tolerance tests this year filled in time with the glorious pictures that adorn the 2011 calendar. This coming year we have many more oral glucose tolerance tests to do and I am looking forward to the abundance of high grade art to decorate the 2012 calendar. A big thank you to the families that put in extra time in travel and patience needed for the oral glucose tolerance testing.

Jacki Catteau, Australia, National Coordinator