Science AMA Series: We are a team of scientists, including diabetes specialist and dermatologists, trialling a new treatment for type 1 diabetes.

**ABSTRACT**

This is a pilot study to begin examining whether ustekinumab, a drug typically used for psoriasis, has the potential to reduce or eliminate the need for insulin injections in people with recently diagnosed Type 1 diabetes.

“As one of the first clinical trials to target the immune cells that cause Type 1 diabetes, we are hopeful that this treatment will be a step towards finding a way to stop or slow the destruction of the body’s own insulin-producing cells.” Dr. Jan Dutz, Principal Investigator

We are here to answer questions about diabetes, what this drug could mean for people with Type 1 diabetes, why we are looking at repurposing what seems like an unrelated medication, and anything else you’d like to ask us.

http://www.bcdiabetes.ca/type1study/

Dr. Tom Elliott: Since 1992, Dr. Elliott has been a faculty member at UBC, where his current rank is Clinical Associate Professor. He was Co-Director of Undergraduate Medical Education for the UBC Division of Endocrinology from 1992 to 2012, and chaired the Endocrinology & Metabolism Society of BC, the professional body representing all BC endocrinologists and diabetes specialists, from 2008 to 2012.

Also since 1992, Dr. Elliott has been on the active medical staff at Vancouver General Hospital, as well as conducting a busy private office practice in Endocrinology & Diabetology. Dr. Elliott is Director of Clinical Trials at BC Diabetes. He has authored more than 50 scientific papers and is actively engaged in 15 ongoing research projects.

Dr. Ashish Marwaha Dr. Ashish Marwaha is a clinical pediatric academic who was appointed as a Radcliffe Travelling Fellow of University College, Oxford to pursue a PhD, in which he identified a novel subset of highly inflammatory immune cells (Th17) were present in children with new-onset type 1 diabetes (T1D) (Cutting Edge: Journal of Immunology, 2010). He has taken an active role in obtaining funding, designing, setting-up and running the current clinical trial of ustekinumab that will block the Th17 pathway in T1D.

**Correspondence:**

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What preclinical work is there to support the hypothesis that your drug, ustekinumab - an IL12 and IL23 inhibitor - is appropriate for type I diabetes. To my knowledge the IL23 pathway has not generally been associated with T1D.

**SirT6**

My impression is that ustekinumab is appropriate for psoriasis because of the unique convergence of IL12 and IL23 in this disease (notably these cytokines are elevated in affected tissue of psoriasis patients). Im not convinced ustekinumab is a cure all for autoimmune disorders; for example it failed to demonstrate efficacy in a phase II multiple sclerosis trial.

Thanks for this important question! We believe there is a strong basic science rationale for targeting the IL-23/IL-12 access in T1D. This is based on the knowledge that inhibiting these two cytokines
diabetes specialist and dermatologists, trialling a new treatment for type 1 diabetes., The Winnower 2:e144439.91844, 2015, DOI: 10.15200/winn.144439.91844 © et al. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and redistribution in any medium, provided that the original author and source are credited.

Why do you think this drug will help type one diabetes patients? Did you notice an unexpected improvement in insulin management for patients taking the drug for psoriasis? How does the drug work to regulate insulin production?

_firedrops_
This is Dr Ashish Marwaha:

This was not an observation made on insulin regulation in psoriasis patients who take the drug. Unfortunately in those trials there has been no one included who had new onset T1D and had psoriasis (we checked!). The rationale is based on an indication that the same immune pathways (Th1/17) may be involved in both disease processes. With psoriasis effecting the skin and diabetes effecting the pancreas. So the idea is to prevent the autoimmune attack that happens at the beginning of the disease process and allow the insulin producing beta cells in the pancreas enough time to hopefully recover and regenerate if we get in there early enough. The drug itself doesn’t effect insulin production but that’s one of the ideas for how people think we might move forward. I.e. we should combine an immune blocking drug like ours with another that promotes beta cell function. We are actively looking into combination therapy as an arm in our next phase of the study.

Hello there.

I'm a 5th year medstudent at the National Hospital of Iceland. My partner has had DM1 for 20 years next year so this topic is very close to me. I'm 25, she is 24.

Am I correct that this treatment is only for people with a recent diagnosed DM1?

Is there a possibility that this could be used for patients with a long history of DM1?

What is the future in DM1 research? I've decided not to specialize in endocrinology; I don't want to be my wife's doctor, but I want to know what to expect in our future.

Thank you for doing this AMA and good luck with your future research.

_indi90_
This is Dr Ashish Marwaha

Hi, if you are a medical student I would definitely recommend entering endocrinology and diabetes
research it is an exciting time to take part. I personally think we will have a curative treatment regimen within the next 10-20 years of research but I really want to see that happen.

This current trial is for adults with T1D that have been diagnosed within 100 days.

My personal opinion is that the 100 day window could be extended if we show this drug works as some people have a more slower decline in their beta cell function over time (especially adults who get disease). We decided on the 100 day cut off to match up with all the other major type 1 diabetes trials that have been done so far and so that our study can be compared.

In the future, I think there is a possibility that drugs will work beyond the 100 day cut off in some people that have residual pancreatic beta cell function. The issue is that we need some function there to rescue and so we can’t use an immune blocker too late in the process.

Infact there has been one study with ATG and GCSF that used this therapy in long term T1D patients and showed a benefit more so in the adults. So there is hope out there for patients beyond the 100 day window especially with this regime.

A link to this study is below: https://clinicaltrials.gov/ct2/show/NCT01106157?term=ATG+and+GCSF+in+diabetes&rank=1

Thanks for doing the AMA, T1D is something I’ve often worried about, since its symptoms appear so rapidly. Not knowing much about the field: do you think it will it be possible to screen for markers that perhaps predetermine development of Diabetes I?

If so, could it effectively be stopped before it starts by using ustekinumab? Or is this something that can be used just to treat symptoms after they manifest, rather than a preventative or a cure?

Cheers!

StonedPhysicist

This is Dr Ashish Marwaha we answered this question in part elsewhere:

So the TrialNet initiative are currently screening relatives of people with T1D for development of diabetes. It is thought if you have 3 or more autoantibodies to proteins in the pancreas (antigens) you have a virtually 100% chance of getting T1D within 5-10 years. They use this rationale to give some therapies before onset of disease and have trials that are actively recruiting. Relatives of people with T1D can also just enter the study to be monitored and there are sites all over the world. See link below:

https://www.diabetestrialnet.org/patientinfo/index.htm

We hope that if ustekinumab works in new-onset we could try it in children we know before they actually get the disease officially as TrialNet are doing with some of their therapies.

Diabetes is actually now thought to be a slow process that is predictable. Although it seems to happen rapidly that is just the cut off at which you start requiring insulin being met. We think now looking at pancreases from cadaveric specimens that there is a lot of heterogeneity and even perhaps a process whereby the lobes of the pancreas are taken out eventually. There is huge research efforts by JDRF and others to identify new biomarkers to try and predict disease so we can give treatment earlier.

T1D here. When you say “Has the potential to reduce or eliminate the need for insulin injections in people with recently diagnosed Type 1 diabetes” just how recent are we talking here?

Pairomedics

Dr. Tom Elliott replying: Type 1 diabetes diagnosed within the last 100 days.
T1D here. When you say “Has the potential to reduce or eliminate the need for insulin injections in people with recently diagnosed Type 1 diabetes” just how recent are we talking here?

**Pairomedics**

Dr Marwaha replying: HI our current study is for within 100 days of diagnosis. We have to stick to this protocol unfortunately to give us the best chance of rescuing some beta cell function before it is completely lost.

There are studies out there recruiting for long term T1D patients. I would recommend you search clinicaltrials.gov to look if you are interested.

There is lot’s of great work being done on stem cells and artificial pancreas research too so there may be more opportunities to enter studies in the future.

Hi. What’s your opinion on possibility of screening for T1D in children? Another question is are there any link fond between T1D and other autoimmune diseases?

**flandre-kun**

Dr Ashish Marwaha answering here. I'm answering the first bit and Tom will handle the tricky second question!

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We hope that if ustekinumab works in new-onset we could try in in children we know before they actually get the disease officially as TrialNet are doing with some of their therapies.

There are multiple links between T1D and other autoimmune diseases. We think there is a set of genes that predisposes you to getting autoimmune diseases and the site in which it happens dictate what disease process occurs (psoriasis is skin, crohn's is bowel, diabetes is pancreas). In particular there is a strong link with coeliac disease. In kids we recommend that they be screened for this as it is easy. Also there is a trial in canada seeing if gluten free diets make a difference to those children with T1D and coeliac.

I've been hearing "this new drug/treatment will be the next cure/treatment for diabetes and will be on the market soon" for years now and I've given up holding my breath

**novohash0905**

Dr Ashish Marwaha here:

one of the issues in T1D research is that the NOD mouse model of diabetes was used for a long time as a standard and many many things work to 'cure' those mice of diabetes. Hence, everything was labelled a cure by the press.

now we are getting to the stage of human clinical trials when they report there is a lot more scrutiny. I still have faith that a cure for T1D is attainable, I guess as a clinician scientist working in the field you should have that attitude. If not our approach I think eventually we will hit on a combination therapy that
will help provide a cure and a biomarker set that will help predict disease. Though it might take 10-20 more years of research to happen. At least now we are finally moving away from mice and into human research.

I'm a T1D myself, diagnosed at age 5, if I'm reading this correctly, and I may not be, this seems like a solution for a fairly young T1D to prevent the loss of insulin producing cells. Does this have any application to T1Ds who have had diabetes for an extended period of time?

Beaun

Dr. Tom Elliott replying: yes, you are right - this is a treatment for very early Type 1 diabetes: hence the study protocol calling for volunteers diagnosed within the previous 100 days. Ustekinumab as a potential treatment for Type 1 diabetes will only be effective if functional beta cells (insulin-secreting cell) still exist. In long-standing Type 1 diabetes (beyond 5 years) it is unlikely any beta cells remain.

What are your thoughts on the newly revised and unchanged Dietary guidelines...

here's a clip...

...Instead the committee has abandoned standard methodology, leaving us with the same dietary advice as before - low fat, high carbs.

Growing evidence suggests that this advice is driving rather than solving the current epidemics of obesity and type 2 diabetes.


Gallionella

Dr. Tom Elliott replying: I hear you re some of the guidelines! There is epidemiologic (cross-sectional population) evidence in Europe and the USA that high sugar diets and big sugary drinks increase the prevalence of Type 2 diabetes which is independent of obesity. This has yet to be supported with Grade A evidence, a randomized controlled trial, the "gold-standard" in clinical science.

As a practicing diabetologist I suggest to my patients no foods are forbidden and invite them to discover, with the help of my excellent team of diabetes case managers (see bcdiabetes.ca) how to achieve good pre & post-prandial sugars through a combination of diet, exercise (and other lifestyle measures being tested such as meditation) and medication. In Type 1 diabetes that means insulin, prandial & basal. But newer agents like the SGLT2 inhibitors are being trialled and look promising.

what is the best diet for controlling bloodsugars in a type 1, and what do you think about mortality for type-1 compared to type-2? The latter die on average 10 years before non-diabetics.

Also is there a cure for type 2 diabetes? If you look at the american association for diabetes, it says that type 2 is uncurable and that you can only control it, but recent research by Roy Taylor http://www.ncl.ac.uk/magres/research/diabetes/reversal.htm at Newcastle university show that as long as you lose enough dangerous visceral fat, you bloodsugar response can become just like that of a non-diabetic. Any thoughts on this apparent mismatch on type-2 diabetes and its ethiology?

Vaclavzyzz

Dr. Elliott replying (this paragraph posted to another question) As a practicing diabetologist I suggest to my patients no foods are forbidden and invite them to discover, with the help of my excellent team of diabetes case managers (see bcdiabetes.ca) how to achieve good pre & post-prandial sugars through a combination of diet, exercise (and other lifestyle measures being tested such as meditation) and
medication. In Type 1 diabetes that means insulin, prandial & basal. But newer agents like the SGLT2 inhibitors are being trialled and look promising.

With respect to the best diet I say to my patients: "whatever works for you" providing the following conditions are met: a decent A1c, an absence of severe hypoglycemia, a sense of being in control and an acceptable quality of life. In terms of a decent A1c I consider 6.5-7.5% a good target providing there are no severe lows and no significant long-term complications like retinopathy, neuropathy or nephropathy).

In terms of the science around diet I promote carb counting with all my patients who have the wherewithal, and add to it the concept of glycemic load [https://en.wikipedia.org/wiki/Glycemic_load]. Ultimately the amount of rapid insulin required for any meal will be determined by the glycemic load of the meal and the insulin-to-carb ratio. I ask my patients to target 2 hour post-prandial sugars in the 6.0-10.0 mmol/L range (108-180 mg/dl) using carb counting (with glycemic load preferably over grams of carbs/starch) and corrections if their pre-meal sugar is above a certain level, say 8 mmol/L.

With respect to visceral fat and Type 2: it is true that visceral fat correlates with insulin resistance thus the less the better however the primary cause of type 2 diabetes is natular aging - as we age our cells exhibit apoptosis or natural cell death - thus our beta cells die off too making us insulin deficient (independent of insulin resistance), ultimately leading to Type 2 diabetes - almost universal above age 110.

My son who is 7 has had type 1 since 4. We also have stem cells stored from his birth cord. Could the stem cells be used to generate new islets of langerhans that this drug could then protect?

Fairfacts
Dr Ashish Marwaha here:

There is lots of exciting work coming out of Harvard and actually Tim Kieffer's group here in Vancouver trying to use stem cells as a treatment for T1D. This is definitely an area that is being actively researched and would offer hope for those who have more long-term loss of function of their pancreas. Look out for trials involving this soon. I actually think its very sensible to save stem cells at birth as long as it is done in a sterile way by experts and they are stored appropriately.

I should have added this to my last post. Why cannot some of the u damaged islet cells be harvested immediately on diagnosis and cryogenic frozen. This would at least store template cells if we get the technology to copy them eg from stem cells in the future. In theory this would give a low rejection rate but if you can solve the body attacking these cells, having stored material gives the best hope for regeneration? This would allow the therapy you are testing to be applied later in the disease cycle

Fairfacts
Dr Ashish Marwaha replying:

HI fairfacts. The issue is to go in and take out islet cells from a pancreas is a very invasive process that would require surgery and actually probably reduce pancreatic function to nothing and maybe speed up complications. At the moment T1D patients have to take insulin injections every day which is not ideal but keeps them stable. I think any therapy has to be less invasive than that. Our therapy is an injection that is taken the same way as insulin every 3 months. You might have a hard job convincing someone with T1D to go through invasive surgery until we can prove that this would cure them and take them off insulin forever. We tried this with pancreatic islet cell transplants but the problem is that they don't last long enough so many endocrinologist don't think its worth doing this until there are multiple complications and severe disease.
Can advances in research on type 1 diabetes lead to corresponding advances in type 2 diabetes as well?

mambugalbon
Dr. Elliott replying: Type 1 diabetes is a condition of absolute insulin deficiency while Type 2 one of relative insulin deficiency. If sufficient beta cells can be made available via techniques such as beta cell transplantation (= islet cell transplantation currently) it is conceivable that sufficient beta cells can be present to adequately treat insulin-resistant diabetes. That is a long way off however.

On the other hand treatments for Type 2 diabetes are being used investigationally in Type 1 diabetes - witness the SGLT2 inhibitors. at BCDiabetes we are involved in trials with dapagliflozin and sotagliflozin. I can report that canagliflozin & dapagliflozin are being prescribed off-label in Type 1 diabetes by many of my colleagues.

There are a whole lot of recently diagnosed T1D patients (and parents) who are acutely aware of the ticking-clock that dangles from their last few surviving pancreatic beta cells and want to do everything in their power to properly manage care in order to maximize the duration of their "honeymoon" window... so that they WILL qualify for these kinds of treatments.

What advice would you give to people in this position? For example, how might one get involved in these kind of studies? Are there therapies/treatments that benefit recently diagnosed T1D patients (prolong beta-cell function) which have not yet percolated through the medical community that patients/doctors SHOULD know about?

drpeterfoster
Dr Ashish Marwaha answering here:

One of the issues is that we don't have enough confidence or knowledge being disseminated about trials such as ours. One of the reasons we are doing the AMA is in the hope that someone in North America hears about our study and phones us up to enter as we need to recruit the last few patients. We attempted to get the word out in various ways but we found the best way was when patients saw our advertising for the trial direct.

My experience in the paediatric diabetes world is that some doctors don't quite have the immunological knowledge to realize that we are at a stage where immunotherapy trials and treatment for T1D should be being recommended to all patients coming through. There is a growing effort to ramp up these trials from TrialNet and ITN in the United states, the JDRF -CCTN (canadian clinical trials network) in Canada and the UK diabetes clinical trial consortium too. We need to spread the word to physicians and patients that they need to go to clinicaltrials.gov and look for current options for immunotherapy as there are lots of trials coming out.

hopefully outreach like this will help. I'm hoping to do some more work in the U.K. writing an article perhaps addressing the paediatric endocrinology community and highlighting the need for clinicians to be engaging with clinical trials and referrals for their new-onset T1D subjects.

My experience of the few patients in our study was that they were extremely grateful to be offered something rather than just insulin. Many flew in from other provinces to take part and are really keen to just have an opportunity to enter a trial.

How do we get in contact with you if we are interested in participating in this study?

The Tea Is Green
Dr Ashish Marwaha replying here:
We are still looking for patients to enroll in the trial. We have 7 more to recruit and we are keen to get this done as soon as possible. Please contact minducil@bcdiabetes.ca

we have had people fly in for the study so distance is not a factor if you are willing to travel. Please pass this on to anyone you know who might be newly diagnosed

We can only take patients who are 18+ and within 100 days of diagnosis but if that is you then please contact us:

How far along are we on developing technology for a pancreatic transplant? Or have we just given up on that concept completely?

Josh_Cola

Hi Josh_Cola it's Dr Ashish Marwaha replying here:

I think there was a lot of promise held for islet cell transplants in type 1 diabetes previously. In fact a lot of that research was done in Canada with the Edmonton protocol becoming famous. The issue was that these transplants were eventually rejected and patients had to go onto immunosuppression. It's hard to justify an invasive treatment which involves leaving you susceptible to infection unless you are suffering from severe complications. People have not given up trying to research why the transplants are rejected. Dr Bruce Verschere in our group in Vancouver does a lot of interesting work with amyloid in these islet cell transplant deposits and genetic engineering of islets to help protect them. People are also hoping for stem cell transplant technology. So the field of transplant is not dead but the immunologic therapies at the moment seem to have less side effects and be showing some promise for new-onset patients so the focus has shifted a bit.

Is there any work being done on a vaccine that could be widely deployed that would prevent type 1 diabetes? I read about this some time ago.

The concept is that some unknown pathogen enters the body. Part of the pathogen happens to mimic pancreatic beta cells. If the body’s immune response focuses on that part, the beta cells will be wiped out along with the pathogen. If a vaccine could be developed to that pathogen, the vaccine could direct the body’s immune system away from the part that is mimicking beta cells and towards another part. Thus, the pathogen would be wiped out and not the beta cells.

ron_leflore

Dr Ashish Marwaha replying:

in order for us to develop a vaccine we need to know the pathogen that is trigger T1D if there is one. A lot of people have theories as to various viruses and other pathogens that might act as an environmental trigger to develop T1D. If we could identify the pathogen this is an approach that would be worth trying! In Vancouver we have a PI called Mark Horwitz at UBC who does a lot of work with coxsackie virus and T1D.

Nice to see UBC in these threads on a post about diabetes.

I was wondering what makes ustekinumab (IL-12, IL-23 inhibitor) different from another “broad spectrum immunomodulator” like cyclosporin. I understand that the antibody will selectively target these two cytokines, but shutting down a Th1 response system wide seems to be fairly broad in its mechanism of action. This would be acceptable in the short term, but this seems like something patients will have to take for the rest of their lives, increasing risk for things like infections and cancers.
Dr Ashish Marwaha:

What's interesting is that there seems to be a lot of redundancy in the pro-inflammatory pathways. As we began giving biologics that specifically targeted cytokines pathways (eg IL-12/IL-23), we saw that there were many immune side effects. In fact, the safety at a for our drug in psoriasis is great and the most common side effect is a slightly increased common cold incidence. This has been replicated in our experience of the drug in T1D patients in our trial. They are tolerating it very well and are not heavily immunosuppressed.

We are doing extensive immune analysis to see the generic effects if the drug on the patients immune system. At least on a numbers scale you don't lose overall numbers of your immune cells but seem to target a particular subset of T cells (central memory T cells) and we think this is the fraction in which the autoimmune pathogenic cells lie.

A big benefit if using a drug well tested and licensed in another disease is that we can safely recommend it to our patients and in the future to children and reassure them that they won't get these immunosuppressive side effects.

On a final note I think fear of immunosuppression is a key reason more endocrinologists in the paediatric world don't think immunotherapy is a good method when we already have insulin. We hope to try to help persuade them with the science that this is not the case and they should be recommending immunotherapy to their patients (we now have several drugs that are showing long-term efficacy in preserving c-peptide/pancreatic function).

How would children/adults be screened for T1DM to determine who is eligible for treatment with ustekinumab? Since T1DM has an acute onset and diagnosis is typically made following complete/near complete loss of beta cell function, how would clinicians determine who is eligible for the biologic?

Dr Ashish Marwaha replying here:

It is now thought that you can pick up pre-diabetes in type 1 by measuring how many autoantibodies you get positive as it seems that if you have three or more then you have a virtually 100% chance if developing T1D within 5-10 years. This strategy is used by the Trialnet consortium to monitor relatives of T1D and give immunotherapy before the onset of disease. At the moment there is a big drive by JDRF and others to identify other biomarkers. One of our collaborators at ubc Megan levings has developed a nano string gene identification assay that seems to identify different Treg gene signatures in Tregs in T1D. So there is hope that we will be able to find more specific biomarkers to predict disease beyond the autoantibodies that we currently use.

In terms of targeting ustekinumab we have a huge immunological assay plan to look at all the effects if the drug on aspects of the immune system. We also hope to do some genetic analysis to look at gene signatures that might predict a response or non-response to treatment. In previous trials it has been clear there are responders and non-responders to therapy and subanalysis has shown efficacy in certain groups (eg younger cohorts vs older). There is likely to be slightly different immune processes in different patients and so picking out genetically or immunologically the responders or non-responders to your therapy will be the next step!

People with severe diabetes often have problems with their feet such as Charcot foot... Do you think this treatment could help to alleviate these problems?

Dr Ashish Marwaha replying here:

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Dr. Tom Elliott replying: "Charcot foot" is otherwise known as "neuropathic foot" is an advanced complication of diabetes caused by many years of high blood sugar. It can occur in Type 1 or Type 2 diabetes, the common denominator is high blood sugar for years. So any treatment that improves control or prevents progression of diabetes (such as ustekinumab potentially) could help alleviate Charcot foot complication.