Global Bridges Amsterdam

25 countries. One disease.

The DBA Symposium, June 10-12.

June 2019

Martin Winter, DBA UK (with contributions from our Research ambassador, Dr. Noémi Roy)

This meeting was excellently organised. It was very well attended, by clinicians, scientists and patient representatives from circa 25 countries, including China, France and the U.S. The programme was high quality and varied. The role that DBA UK has played in individual researchers' projects, as well as in the organisation and funding of the conference itself was made clear numerous times over the few days, and there was genuine gratitude for DBA UK's role in promoting not only research projects, but a collaborative attitude in the DBA community. Progress on these international collaborations was clearly evident, with room for strengthening and extending of these ties.

The programme covered some basic science, reporting on registries, discussion of clinical pathways, and update in treatment of DBA.

Monday 10th June -

4pm – 6pm EuroDBA business meeting (closed)

4pm – 6pm Meeting of EuroDBA patient representatives chaired by Martin Winter (see final update)

Tuesday 11th June -

(1) Basic science

This was the most heavy-going aspect of the conference.

Nicholas Watkins (UK) spoke in detail about how ribosomes go wrong in DBA. The talk focused on the current model that was thought to explain the ribosome abnormalities, why Dr Watkins thought it was not correct, and what an alternative model could be. While we know which genes are abnormal in DBA, we don't yet understand in absolute detail how that leads to red blood cells dying in the bone marrow before they get the chance to mature and come out in the bloodstream. While this research is not going to lead to new treatments imminently, the more we understand step by step how ribosomes go wrong when the genes are abnormal, the greater the likelihood that we can find new treatments or ways of modifying the cells.

Marianna Penzo (Italy) showed her work on translation, meaning how the ribosomes are doing their job despite being abnormal. The reason why this is important is that it helps us understand in more detail what is happening inside the cell that has defective ribosomes- do all proteins get made abnormally? If not, why not? If only some are abnormally made, could we modify that so that even if we don't change the gene itself we can minimise its effect?

Christiane Zorbas (Belgium) then spoke on the structure of the nucleolus (the nugget inside the nucleus where all the ribosomal genes are working) and also highlighted that not all ribosomes are created equal (even in someone who doesn't have DBA). These ribosomes can get 'decorated' with other substances, meaning they might be slightly more specialised than others. Understanding this not only helps us understand DBA better, but also opens the door to some potential new diagnostic tools. These need to be validated, but it is exciting to think there might be a new test to determine if someone has DBA or not.

Rita Ferreira (Australia), who is studying nucleolar stress, presented more work on the nucleolus. This is very important because it is probably one of the ways in which DBA red cell precursors die in the bone marrow- because their protein making machinery (the ribosomes) goes awry and abnormal proteins build up, the cell senses something is not right (feels the nucleolar stress) and triggers cell death in a controlled fashion- this is the p53 response. The team is using an unbiased approach to identify how exactly this p53 nucleolar stress response is controlled. Will this lead to new treatments? Quite possibly at some point in the future, but we must remember that all of this basic science research is critical in ways we cannot predict so early on.

Devon Germain (Austria) showed a piece of work using iPS cells to try to understand what is happening in 'silent carriers'. iPS cells are 'reprogrammed' from human tissue- you can take a human skin cell and reverse engineer it back to a stem cell and then turn it into a blood cell. His work is in comparing the iPS cells of a DBA patient and that of his/her father/mother who has the same mutation but does not have anaemia. This work is extremely important- can we identify what in the 'silent carrier' is protecting the cells so they don't die? If we can find that, can we turn that on/off in the patient with the same mutation so that their red blood cells can survive in their marrow? The project is off to a good start, but it's early days.

Beren Karaosmanoglu (Turkey) talked about how bone stem cells behave when they are missing RPS19 (the most frequently mutated DBA gene). It is interesting to see how the rest of the bone behaves- this might explain the bony abnormalities in DBA, but also how the bone marrow environment itself might be abnormal and affect the development of red blood cells.

Alyson MacInnes (Netherlands) presented some fascinating cases of DBA due to a new gene – *(to be published)*. She explained how she and other researchers were barking up the wrong tree until a chance connection with another clinician led them all to this discovery.

Alan Warren (UK) gave a very clear and well-illustrated talk on the details of how ribosomes are kept 'inactive' until they are ready to start processing RNA and turning it into protein. While the condition he works on is not DBA but Schwachman-Diamond syndrome, the more we understand about ribosomes in minute details, the more we can hopefully manipulate them. He also showed beautifully why it's so important to study rare diseases- they give us insight into basic human biology that underpins the very survival of all of our cells.

Lydie Da Costa (France) focused on the role of free iron in what causes DBA cells to die in the marrow before they can become mature. Not only does this help explain why iron is so toxic, but she was able to manipulate a chaperone protein inside red blood cells to mop up the excess iron and allow the red cells to survive and mature. This was all done in petri dishes however, so further progress is needed to see whether any of this could be done in bone marrow of patients.

Pierre Gleizes (France) spoke about a reliable technique to study what is called the 'ribosome profile' of cells studied. This is important for 3 reasons- it can confirm if a mutation is found that might be causing DBA but has no proof that it does, it can diagnose

DBA in patients in whom no mutation is found, and finally it might help us detect 'silent carriers'. More validation is needed (extensive validation is needed for all new techniques to ensure that the test is of high quality enough to cause more good than harm).

Yannick Thueringer (Austria) spoke about using a genetic screening technique to find other proteins which can affect how severe or mild DBA is. While this might sound like a blind fishing experiment, this would allow some targets to emerge- targets which might, in fact, already have drugs that work against them. This might allow a quick find of an unexpected drug that we already know is safe in humans.

Birgit van Dooijeweert (Netherlands) presented some very promising findings on metabolomics (all the proteins and 'stuff' in a sample- a real soup, but one which can give lots of clues about what is going wrong in the body) carried out on tiny dried blood spots. She called to everyone to contact her with more samples- the more samples she runs, the more patterns she will be able to detect. Will it allow us to diagnose DBA in a new way? Predict who is likely to respond to steroids? Time will tell, but let's work with her!

(2) Registries

<u>Wednesday June 12th</u>

It was wonderful to hear about Registries from all over the world- **Poland (Kasia Albrecht), South Africa (Colin Noel), Italy (Irma Dianzani), Russia (Galina Ovsyannikova), and North America (Jeffrey Lipton)**. What came through loud and clear though, is the importance of joining these Registries together. We saw how linking cases can lead to finding new genes (see **Alyson MacInnes** above). Euro DBA is a wonderful initiative to ensure everyone is working together.

(3) Clinical consequences and pathways

Kim de Keersmaecker (Belgium) presented an interesting insight into how DBA blood precursors can go from being absent to dividing too quickly and causing leukaemia or pre-leukaemia. It's all to do with the careful balance of different proteins in the cells, and an important area of study to help us stop the development of leukaemia in its tracks.

Eduard J van Beers (Netherlands) also spoke iron overload in DBA, highlighting why it's important not to rely on blood ferritin levels, but making sure to get MRI scans regularly to assess how much iron is in the liver and the heart. Clinicians who are not used to looking after DBA might assume that the iron overload is like in other haematological conditions, but in DBA iron overload occurs differently and vigilance is paramount.

Lionel Blanc (USA) gave a fascinating talk on the bony abnormalities in DBA, and in particular the risk of development of bone cancer. These are mouse studies, but are providing crucial clues that will inform on complications in humans.

Finally, **Dagmar Pospisilova (Czech Republic)** gave a sobering talk on the frequency of cancer development in DBA (~12%, occurring at a young age: 27-56). This was based on the Czech Registry, and although numbers were too small for convincing statistics to emerge, the importance of taking the development of cancer seriously was crystal clear.

Marcin Wlodarski (USA) spoke on the long-awaited International Consensus Guidelines for diagnosing and treating DBA. These guidelines are not yet ready to publish, and Marcin was clear that we cannot at this stage discuss the specifics of what he presented, but we are hoping it is not long before these are in print (prior to the next ICC Atlanta meeting). DBA UK will play a critical role in ensuring that lay language/pictorial explanations are derived from these for the benefits of patients. One important discussion which was had about clinical consequences and pathways, was the role of screening for cancer. It was suggested that screening for bowel cancer, for example, should start 5 years before the usual age at which cancer presents. For this to become and actual recommendation, however, we need to have the data that strongly (and statistically) shows when that is, and how screening would be beneficial (usually this is in terms of finance- if we spend X amount screening X number of people for X number of years, we would prevent X number of cancers and save the NHS X amount of money). At the moment the stats don't add up because the numbers are too small. The answer? Put all the patients into one Registry, you will have enough to be able to do those calculations.

(4) Update on treatment

a- Stem Cell Transplantation

Felicia Loewecke (Germany) presented the results from the German and French bone marrow registries for patients who have had a transplant. What is now clear is that transplant gives the best results if carried out before the age of 10. It should be considered in patients with transfusion dependence or steroid dependence or intolerance. And finally, outcomes are just as good for sibling or matched unrelated donors.

b- Searching for novel compounds that could work in DBA- very early lab data

Aimee George (Australia) spoke about an approach where they are testing compounds that improve the nucleolar stress response (see above), with some early interesting candidates having been identified. From a patient perspective, it was also interesting to see some of the robotic machinery that is used for this purpose; further details can be found here:

https://m.youtube.com/watch?v=fbCrozGHC8Q&feature=youtu.be

Johan Flygare (Sweden) is specifically focusing on drugs that target a protein called CDK8. This protein seems to hold the DBA cells in a state that prevents them from turning into mature red blood cells. Taking CDK8 out of action seems to release the cells from their inactive state and allows them to carry on maturing normally. Johan will present his work at the next DBA UK family weekend (2020) following our grant award. Further details of "SEL120" (published) can be found here:

https://www.b3cnewswire.com/201811211856/selvita-announces-presentations-on-cdk8-inhibitor-sel120-at-the-60th-american-society-of-hematology-annual-meeting.html

c- Current clinical trials

Jeffrey Lipton (USA) spoke on behalf of Adriana Vlachos who unfortunately couldn't come, about ongoing clinical trials in DBA. The L-leucine trial shows promising results and the next steps are to increase the dose. The sotatercept trial is also in its early days with only 8 patients recruited so far, but it is interesting that it is being tried in patients on steroids and other patients off steroids. Luspatercept hasn't started yet, but could be an alternative drug, and possibly has fewer side effects on bone strength. We also heard about a completely new drug in the DBA field- TFP. This is a drug that's been used in the past for some forms of mental health disorders. In zebrafish it works to reverse some of the DBA

aspects, so it is being tried in very low doses in patients- the drug company has pledged that if it looks like it will work, they will work on the drug some more to make sure it doesn't cross into the brain so that it can be safely used in DBA patients. We have to remember, none of these are cures, and some of these may not even get everyone off steroids or transfusions. But if they can reduce the amount of steroids needed or reduce the number of transfusions needed, we are already winning- fewer side effects, fewer complications.

Ugo Ramenghi (Italy) presented a case of a girl with DBA who became transfusion independent after she was started on eltrombopag. This is a drug used in people with low platelets and there are several reports that it can also improve anaemia. This is extremely exciting, although it is a single case (there were 2 or 3 others mentioned by members of the audience). However…. Eltrobopag is what we call a "growth factor". It affects stem cells in the bone marrow. The worry is that it could potentially increase the risk of leukaemia in the long term. The DBA community needs to think very carefully about where to go next with this, but perhaps clinical trials will occur in the future.

d- Gene Therapy – fixing the cells directly in the bone marrow

Min-Joon Han (USA) spoke on exploring techniques for gene correction. We all know gene therapy and genome editing will come into our treatment options in the future. But between now and then, there are multiple studies that need to be done, in all sorts of different laboratory experiments, mouse experiments, bone marrow studies, and human clinical trials. This current work in iPS cells provides a laboratory platform in which new drugs can be tested, disease mechanisms studied, and allows gene therapy techniques to be refined.

Jonathan Schwartz (USA, pharmaceutical company) showed some very nice data on gene therapy in Fanconi Anaemia. While this is quite different from DBA, the way they have developed it and are able to give it to patients without giving a lot of chemotherapy is of great interest to the DBA community. Fanconi anaemia patients, like DBA, are at increased risk of cancer. Giving chemotherapy increases that risk. Being able to do gene therapy without/using minimal chemotherapy will be very important for DBA patients. As with all gene therapy trials, long term safety profiles will need to be carefully studied as time passes.

Yang Liu (Sweden) presented her data on gene therapy approaches being studied in mice.

Susana Navarro (Spain), of the same group that has been working on gene therapy for Fanconi Anaemia, showed wonderful progress in showing they can design a gene therapy strategy for DBA. They have shown it works in a cell line (cells grown in the lab), but they have also managed to reverse the anaemia in DBA patient cells that were taken from a patient and grown in the lab. Most excitingly, when they took those 'corrected' human cells and put them in a mouse (I know, science is bonkers, isn't it?), the cells survived in the mouse's bone marrow and made beautiful red blood cells. Very promising indeed. But before we get too excited, for humans to receive these corrected cells, they would need to have chemotherapy first to 'clear out' the bone marrow (the mouse had chemo too, to be

honest). And we do worry that giving chemo to DBA patients = increased risk of cancer long term.

Martin Winter (UK) presented the patient perspective. For clinicians and scientists, it was evident that the DBA community is active, thoughtful, appreciative of the work that is going on yet demands high standards and collaboration and cooperation. "There is no room for egos", Martin said, and although much progress has been made and was evident at the conference, there is room for more pooling of data, more sharing of results.
During the patient representative meeting, we discussed 3 primary questions:

What can patients do to enhance the quality of life for patients with DBA?

Answer (Consensus view):
Promote care pathway
Promote and encourage patients to sign up to the country register (pooling of data/sharing of results)
Undertake patient led initiatives such as the Global DBA map.

How can we better support our researchers and medics?

Answer (Consensus view):

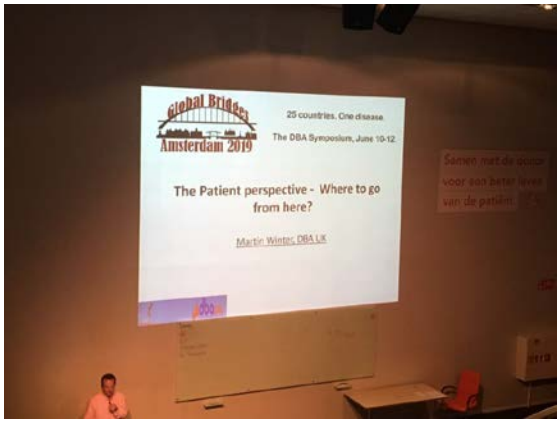
Continuous dialogue between medics and patients regarding challenges of DBA. This may lead to certain patterns being established for specific gene mutations and ultimately improve long term care.

Fundraise for future research, Together? (Further work needs to be undertaken to establish certain patient groups as charities/foundations etc)

What do we want from our researchers and medics?

Answer (Consensus view):

A cure!
Continuation of a collaborative approach between medics, researchers and pharmaceutical companies
Endorsement of a revised care pathway
A better understanding of the research community's plans in view of recent patient-focused research prioritisation and strategy (James Lind Alliance Priority Setting Partnership in Rare Inherited Anaemias)



Going forward, DBA UK would recommend a provision of the talks in lay language for the patient reps. It would be simple to ask each presenter to finish their talk with one slide in lay language summarising what the research was about, why it's important, what it has shown, and what the next steps are. Another recommendation would be to have a question and answer session with a panel of experts (medics/researchers) to facilitate additional discussion.

All in all, it was wonderful to see so much progress, so many new things in the pipeline, so much goodwill and enthusiasm to make the lives of DBA patients better, and all work together towards finding a cure.