Mastering cholesterol to optimise CVD prevention webinar series

Driving LDL-C to target: Novel lipid therapies (01 June 2023)

Q&A with Phil Jennings (PJ) and Mohamed Elnaggar (ME)

Question 1

Is there any situation where Bempedoic acid should be used as a monotherapy?

ME: Yes, absolutely! Do we not see patients who have intolerance to ezetimibe as well? We do. Phil, what do you think?

PJ: Yes, absolutely!

ME: The thing we should do with statin intolerance is challenge statin intolerance. Statin intolerance is over-reported and there has been a recent study that shows that 92% of patients who have been labelled as statin intolerance where retried on statin and took it, and 80% of these took a higher dose of statin than what they were labelled intolerant to. In a similar way if people are intolerant to statins as a nocebo effect, they will be intolerant to ezetimibe as a nocebo effect as well and therefore this is why bempedoic acid on its own exists.

Question 2

Our local guidance which is Pan Mersey states we should not use bempedoic acid alongside a statin. But we have seen some recommendations trickling through for triple therapy – statin, ezetimibe and bempedoic acid. Is this a combination that you think should only be initiated by a specialist?

ME: So, I will read both questions together [Innovation Agency insertion for context: two questions were posted about bempedoic acid during this part of the Q&A] because the answer is one answer. So, the second question is *''NICE TA694 recommends bempedoic acid in conjunction with ezetimibe and only in patients who are intolerant to statins''.* That is not true. There is the second point to NICE TA694 which says "with ezetimibe, if LDL level are not reached". So that answers that one.
In relation to your local guidance in Pan Mersey, I don't know why it says you should not use bempedoic acid alongside a statin. Patients who do not reach their targets with statins and ezetimibe can get bempedoic acid on top. I have a large percentage of my patients who do not want injectable medications and so the next step to elevating their lipid lowering therapy while they are already on statins and ezetimibe will be the addition of bempedoic acid. *Should it be initiated by only specialist*? I don't see why. There is no specific monitoring that needs to be done in secondary care. They don't have/share the same side effect profiles. It's not something like when you start fibrates with statins where you really need to look at TK levels and you need to be really careful with myopathy. This is not the case. So, I don't see why the local guidance in your area states that to be honest because they can be used and there shouldn't be a problem.

Question 3

Would you recommend going straight to inclisiran with max [tolerated] or without statin (if intolerant) as the data shows a higher LDL-C lowering percentage? I am just thinking of the tablet burden and reviewing patients by following NICE current step two, which is bempedoic acid?

PJ: Again, I think the guideline is meant to be a shared decision really, when we need to make that decision. So, I can see that for some patients the reduced tablet burden would be a plus. Certainly, a lot of the patients we see who would qualify as we have seen in the case studies, have got hypertension and diabetes etc. Given that we are seeing a move to dual therapy in a lot of cardiovascular diseases, you can quickly see why these patients might be already on 10-12 medicines. So, for some patients, yes, and I think they would probably prefer that. The only caution I would say is that it's an injectable and as we saw through COVID-19 that injections don't sit well with everybody in our populations. So, I do think you have to have that discussion with patients and there would be a cohort of patients who don't want an injection for one reason or another. I do think that it's a shared decision that you should be having at that stage, taking into account your particular patient.

ME: It's a very nice question in terms of what you say; "a higher LDL-lowering percentage". Let's say a real life patient here who has LDL of, let's say 4.0, and is statin intolerant, you know that if you give ezetimibe you are not going to get any where near the target. So, this is where, yes, you can jump straight to injectable therapies. But this is a patient-shared decision – you need to make sure the patient understands what the percentage of lowering is, what the risk percentage is, what it's likely to be in terms of side effect profile, that they have to attend their GP service every six months or every three months [initially] for injections, so yes, it is definitely a conversation to be had.

Question 4

Are you aware of any resources that succinctly list doses, side effects, interactions, contraindications, dose reductions in renal impairment etc, for all of the lipid lowering medicines?

ME: I don't think there is one resource that shares them all. You could do a search of the BNF and print them out and have them on your desk, but I don't think that there is one resource.

PJ: I have not seen anything that you can put up on the wall if that is what you are looking for there.

ME: But to be honest, ezetimibe, bempedoic acid, inclisiran and PCSK9 have no problems with renal impairment. So, it is only statins as far as I am concerned.

Question 5

Can we challenge statin intolerance as pharmacists in primary care? Usually our patients are referred to secondary care, but time and access is an issue, therefore patients do not always follow through.

PJ: There is a difference between genuine statin intolerance – 8% or 9% in the trials – versus what we see in practice which is more like double that. We know that there is a big nocebo effect with statins; they get a lot of bad press and I think there is a lot of suggestion that goes on out there. I do think it is important to try to get to the bottom of whether this is genuine intolerance or this nocebo effect. I don't see why that can't be challenged by the pharmacists in primary care or any member of the primary care team.

ME: I think you are absolutely right. It needs to be challenged. As someone in secondary care, if we see every single patient who states that they're statin intolerance, we would not be able to see the patients that really need genetic testing, that really need to be on PCSK9s; we'll be delaying a lot of

patients that we really need to prioritise. Especially the type of conversation that I am having with them should be no different than what a primary care physician or primary care pharmacist should be having with them. It is only convincing patients of the importance, the benefit, the risk and the fact that stats show 8% to 9% only are genuinely statin intolerant. Other than that, it's a lot of hearsay. So, it has to be challenged in primary care.

IA addendum: AAC/NHS Statin Intolerance Pathway: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/08/Statin-intolerance-pathway-January-2022.pdf

Question 6
What can we offer to patients with established CVD on maximum tolerated oral therapy whose non-HDL remains over target at 2.5 or triglycerides over 1.7, but the LDL is 2.5; higher than the target 1.8, as they do not qualify for vazkepa or inclisiran or PCSK9?

ME: Quite complicated numbers there, but I will make it easier; so someone who has an LDL less than 2.6. So they don't qualify for PCSK9 which have an LDL of 3.5-4.0, they don't qualify for inclisiran with a 2.6, and their triglycerides are less than 1.7, so they don't qualify for vazkepa… The answer is; nothing.

These are the five medications we have so far. If the patient is still at high risk – e.g. you said that the patient has established cardiovascular disease – the first thing I need to do is make sure they are on their current medications. So if they are already on maximum dose statin, maximum dose ezetimibe and bempedoic acid, and they are still not at target, then make sure 100% that they are taking these medications properly. Another thing to think of is that these medications, if they are being taken properly, they should lower LDL a lot. Where was baseline? What was their original LDL? Does these patient probably have FH? Was their LDL level probably very high to begin with? Because if that's the case and they do turn out to have FH, then we could think of injectables.

Remember that 'guidelines' are guidelines. And there is a lot of clinical judgement that needs to go into place. If you really think this patient of yours has had multiples episodes, this is their problem, they are on top of all of their other risk factors – so they're not still smoking, or they're not hypertensive, or very obese, and this is the one thing that you need to control, then I think that regardless of the numbers, you can start them. But then this is again very much a clinical judgement. If I were you, I will seek the opinion of your specialist in the area.

Question 7
When will outcome data be available for inclisiran?

PJ: The ORION-4 trial, which was always planned to be the big outcome data trial (that is a standardised multinational-multicentre randomized control trial looking at major cardiovascular endpoints). It was due to report next year, but it's been delayed because of problems with recruitment because of COVID-19, so we're now expecting that in 2026. And there is another one coming shortly after that called Victorian 2, which is due to publish in 2027.

I'm not aware of anything else before that. The only other thing I would just say is that it's not an unusual position with lipid lowering medicines. In terms of NICE approvals and indications for treatment, this is the position that we are normally in – we tend to start the treatments in our

patients before we necessarily see the full outcome data. We did that with statins, with ezetemibe, and PCSK9. All of them, in fact, have gone through this cycle. Inclisiran is the farthest behind in that regard, but no MACE data for a couple of years at least.

Question 8
How do we monitor these new therapies and do any of them requires particular blood tests etc?

ME: There is no specific monitoring except for bempedoic acid. I usually monitor uric acid levels. It's not a recommendation, but I do, just to make sure what's going on in terms of the side effect profile; just to keep an eye on my patients if they develop something else. But generally speaking, PCSK9s, inclisiran and vazkepa do not need any monitoring.

Question 9
Are both inclisiran and bempedoic acid for primary hypercholesterolemia only?

PJ: NICE TA and commercial agreement [for inclisiran] is very specific about the secondary prevention population who are included within that. There are broadly indications, but in terms of the NICE TA, that is for that secondary prevention population. You need to have that 2.6 or above to qualify for it.

ME: [This answer is given on the basis that the question may relate to 'familial' hypercholesterolemia, rather than primary prevention] The answer is no. All these medications can be given in patients with non-familial polygenic hyperlipidemia and mixed dyslipidaemia. What Phil was talking about was in secondary prevention, then the injectables and vazkepa are only in secondary prevention and bempedoic acid can be used for primary prevention.

Question 10
I notice that the NICE guidance for inclisiran is for secondary prevention but doesn't mention TIA. Do you think we should use inclisiran if there is a history of TIA?

PJ: Again, this goes back to guidelines being pragmatic; particularly in primary care. I think if you've got a patient who has had a TIA, bearing in mind that it's a diagnosis that is thrown about a lot and it's sometimes not particularly sound, I think that if you've got someone who clinically has had a previous obvious TIA, then they are high risk, in my book, and therefore I personally would have no problem in including them in an eligible population for inclisiran or other injectable therapies. I appreciate that is not completely aligned to/slightly at odds with NICE, but again, if you ever get involved in writing a guideline, it is almost impossible to cover every possible clinical scenario that you will encounter. So you do still have to use a modicum of common sense and clinical acumen along with all of this.

ME: I 100% agree with you. Think about this; you are a relative of a patient who has high cholesterol, intolerance to statins and they've had multiple TIAs, and they have the option of inclisiran, but you have not given that option and then they have a stroke… What do you have to say? So, yes, clinical judgement I think is very important in these cases.

Question 11
It is important to monitor FBC of patients on bempedoic acid. Have you had any experience with patients developing anaemia?

ME: Interestingly enough, when you look at the CLEAR Harmony trials, anaemia appeared only with bempedoic acid on its own, but when Nustendi was used – bempedoic acid with ezetimibe – it wasn't there anymore, which is interesting. However, it happened in about 4% of patients. I do do a full blood count for my patients when I see them in the clinic. I have more than a 100+ patients on bempedoic acid already and I have not seen one case of anaemia so far (I am expecting four, but I haven't seen one so far).

Question 12
I am not sure that GPs should be prescribing novel therapies and I wonder whether this should be prescribed only by a specialist. What do you think?

PJ: It's a conversation that we need to have as a profession. You'll be fully versed now with the move to population health as the new mantra in the NHS. I think that if we are going to get serious about treating some of the big modifiable risk factors, e.g. chronic disease that we all recognise, be that diabetes, heart failure, lipids or hypertension, then primary care has got to play a role in that. There's definitely been some controversy regarding inclisiran. You'll have probably seen the College position in the BMA letters that came out at the start of the programme. Some of that probably was missed opportunity not to engage more fully beforehand. But nevertheless, I maintain that these patients are our patients by and large, and most of the patients that are eligible are not in Mo's or someone else's clinic; they are patients that you and your Practice team are probably seeing at least once a year and that's where the opportunity is to intervene with what is potentially a fairly straightforward, but clinically impactful choice that you and your patients could make.

Whether or not we should be doing it in primary care? Historically, we haven't done that, but is that just for historical reasons rather than any other good reason? We are closer to our patients and I know it might sound like it's difficult to get hold of your GP at the minute, but it's a lot harder to get hold of your lipidologist or your cardiologist, for sure, even though we have our access challenges. We know the patients pretty well, we've got excellent data systems and architecture, so I do not see any fundamental reason why we can't launch new medicines in primary care. I do think it has to be in collaboration with colleagues in secondary care. I think that was another oversight at the beginning of these programme. I think the powers that be thought that GPs could just get on with it without being able to pick up the phone and speak to your local cardiologist or lipidologist. But I don't see why we can't do it and again, looking at the pipeline of medicines coming down the road, there is likely to be more examples in the not-too-distant future. So we do think that's an important discussion we should have as GPs about what we need, to be able to do that. I know that some of it's money, but there are more things than just money – skills and training and education and all the rest. So I'd like to say, that's my position. I know that it won't land well with everybody, but that's what I would say.

ME: The only [additional] thing is; use Advice and Guidance if you are not happy about certain decision. Advice and Guidance has changed the way we do lipids in my locality, at least, and it can be very helpful, to get someone from cardiology or someone from a lipid clinic to help answer your queries and get you to do anything you are in doubt about.