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Discussing the Latest in MS Treatment and Disease-Modifying Therapies

Dr. Turck:
The World Health Organization, or WHO, has introduced three disease-modifying therapies for multiple sclerosis, or MS, into its Essential Medicines List. So how effective are these therapies? And moreover, what implications do these additions to the list hold for our approach to treating MS?

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and here to discuss these treatments is Dr. Jay Avasarala, who is the Director of the Comprehensive Care Center for Multiple Sclerosis and Neuroimmunology at the Kentucky Neuroscience Institute in Lexington. He was also part of the international team that was responsible for submitting the list of medications that were later approved by the WHO.

Dr. Avasarala, welcome to the program.

Dr. Avasarala:
And thank you for having me, Charles.

Dr. Turck:
Now just for some context, Dr. Avasarala, would you explain what the WHO's Essential Medicines List is? And have other disease-modifying therapies for MS been added before?

Dr. Avasarala:
I guess the inclusion of any therapeutic agent on the WHO model list of essential medicines, referred to as EML, is an initial step to potentially increase their availability worldwide, and in some fashion, it would also serve as a guide for the development of national and institutional EMLs. So, it promotes inclusion, and it also updates essential and affordable medicines and health products for neurological disorders in national EMLs, which is the essential medicines list as guided by this WHO list. In multiple sclerosis, no treatment prior to this were listed, and I think there was an earlier one submitted in 2018 where the drugs that were submitted were glatiramer acetate, fingolimod, and ocrelizumab, but that was rejected, that list, and so we put together another list, this time around December of 2022. And then this was taken forward, and now they have approved it.

So what does it mean? Like I said, it means access, affordability, safety, efficacy; all those factors come together. And this is a broad guideline, if you will, across the globe and not targeting one area or the other. And this is done in collaboration with the Cochrane MS group, and systematically, they assess, and we as a group put the list together. We also looked at on-label and off-label drugs for MS.

Dr. Turck:
And what you participated in, as you described, was a large international effort with researchers from around the globe coming together to recommend these three therapies. I was wondering if you could say a little bit more about what the nitty-gritty of the group's research looked like and who was involved.

Dr. Avasarala:
I think I would have, obviously, an entire list of participants, but essentially, if you think of this group as MS experts, and then the other stakeholders would be organizations dealing with MS, such as MSIF, the MS International Federation, for example, the American Academy of Neurology, for example, which I represented, and then there's a host of representations across the world. So those organizations, as well as individual MS experts, including patients and caregivers and most importantly the MS International Federation, which put together, the entire group, form the crux of who participated.

And how was the evidence looked at? Like I said, the Cochrane Group, for example, which is an international network with headquarters based in the UK, so not-for-profit organization, it's a member of the UK National Council for Voluntary Organizations, and so Cochrane is a group organization, if you will, for anyone interested in high-quality information to make healthcare decisions. And then this was also fortified by great evidence to decision framework, which is I think mostly based in Canada, the best I know. And then it uses associated balance of benefits and harms and certainty of evidence, cost and effectiveness, especially in the low- to middle-income countries, and also looking at health outcomes valued by patients with a view to reduce healthcare inequities, feasibility, and availability. So it's a cornucopia, if you will, of multiple experts, organizations, and stakeholders.

Dr. Turck:
Now let's talk about the medications that were approved. How did your team decide on rituximab, cladribine, and glatiramer acetate?

Dr. Avasarala:
So what we did as a group was that part of the analysis done, including every study and any study that had an on-label or off-label disease-modifying drug therapy for MS, descriptors and publications were systematically assessed and analyzed, and part of the analysis centered on the Cochrane MS group, as well as the use of what is called as the GRADE Evidence to Decision framework on the basis of balance of benefits and harms and certainty of evidence. Also taken into considerations were cost and cost-effectiveness in low-income, as well as middle-income countries, and finally, health outcomes valued by patients and with the potential to reduce health inequities and acceptability, feasibility, and availability in those countries were of equal importance. The availability of generic and biosimilar versions were also considered, and the needs of special populations were also taken into consideration. So three drugs were rituximab, cladribine, and glatiramer acetate, as you know. And in those countries where rituximab is an off-label drug, the substitution with ocrelizumab as an alternative agent can be complex or prohibited in some countries, were selected for inclusion in the application submitted.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Jay Avasarala about disease-modifying therapies for multiple sclerosis, or MS, that were recently added to the WHO's Essential Medicines List.

So you effectively looked at a very large list of disease-modifying therapies and filtered it down to those three—rituximab, cladribine, and glatiramer acetate. I was wondering if, Dr. Avasarala, you would speak a little bit about these medications' safety and efficacy, what you found in your research.

Dr. Avasarala:
Right. So rituximab, we'll take as the first drug. It's an off-label drug. It is now listed in the WHO EML, and the benefits are large if you look at the benefit section for relapsing-remitting forms of MS and moderate benefit for primary-progressive MS. And if you look at the downside of the drug, it is small in the subcohort of patients with relapsing forms of MS and small to trivial in the progressive forms of MS. And if you look at pregnancy and breastfeeding as another indicator, it's safer to avoid as far as possible but can be managed with careful timing.

And then if you look at cladribine, which is an on-label drug, which is now listed in the EML drug list, the benefits for relapsing forms of MS is large, and the harms for relapsing-remitting MS is trivial. And as far as pregnancy and breastfeeding are concerned, it is contraindicated, and pregnancy can be planned outside the treatment period, but the drug is obviously contraindicated if someone is planning pregnancy and certainly doing breastfeeding.

Glatiramer acetate, the final drug that is now listed, is an on-label drug in the US. Benefits include a large benefit, if you think of relapsing forms of MS, moderate in the progressive forms of MS. And the downside includes trivial harm with minimal serious adverse

events, probably four fewer per thousand compared to other line of drugs that we looked at. Can be used during pregnancy and breastfeeding.

And so as a combination, these three drugs that were listed give you different flavors and efficacy, as well as their effectiveness, and I guess, complications are the downside of using those drugs.

Dr. Turck:
Now, Dr. Avasarala, looking globally, what does this updated list that the WHO accepted into the Essential Medicines List—what does it mean for the treatment of MS for patients everywhere?

Dr. Avasarala:
Right. That's a great question—number one, I think, broadly speaking, this could serve as a blueprint for EML applications, the Essential Medicines List for other neurological disorders. Number two, it provides access to therapies. Obviously, there will be challenges as to how this is implemented, and that's a step moving forward. So some of these disease-modifying treatments, for example, some of them might have some patent issues. I don't think the ones that we talked about won't have any issues like that, but I'm talking about how moving forward, when you talk about a drug to be included in the WHO EML list, those issues we need to be mindful of those. And we talked about this in the past as well; I mean on prior questions as well. Additional schemes must be considered to make these drugs affordable, so affordability and availability in countries and access to healthcare, which is not, obviously, uniform, as you know globally. Those aspects need to change, and this list is the first step in that direction.

A lot obviously needs to be done to improve neurological services in low and resource-poor locations, not just to access for medication but also the diagnosis and management, and this is the management portion of it, and a lot depends on infrastructure and training need to be in place and how these treatments that can be used safely and effectively.

So I think, again, this is a large 30,000-feet overview of how these proposals are meant to work. It will be a crucial first step is what I would say to ensure that people with MS will be able to access treatment options for the first time.

Dr. Turck:
And before we close, Dr. Avasarala, are there any other thoughts or key takeaways you'd like to leave with our audience today?

Dr. Avasarala:
I think the key takeaways for me is that it's a great first step forward for the world of patients afflicted with this chronic disease, A; and B, like I said, this could well be a model for other neurological disorders moving forward. So again, I think if my information is correct, in the past 40 decades, nothing of this sort has ever been successful, but to cut it to run this last was attempted—I believe, like I said, it was 2018—and so we feel vindicated that patients who have multiple sclerosis and their caregivers for the first time can look towards a guideline or a blueprint, if you will, based on those things that we discussed as to how these drugs might become useful. And so I think the recognition of multiple sclerosis as a global healthcare issue by the WHO in approving this list needs to be underscored. I think we are glad that the WHO took this step in the right direction.

Dr. Turck:
Well, this was a great discussion, and I want to thank my guest, Dr. Jay Avasarala, for providing insights into his work in getting these important medications added to the WHO's Essential Medicines List.

Dr. Avasarala, thanks for joining us today.

Dr. Avasarala:
Thank you for having me, Charles.

Dr. Turck:

For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit ReachMD.com/NeuroFrontiers where you can Be Part of the Knowledge. Thanks for listening!