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The Latest Therapies for MS: Weighing Respective Benefits and Risks

Narrator:
Welcome to ReachMD, and this is a special edition of On the Frontlines of Multiple Sclerosis, supported by an independent educational grant from Merck KGaA, Darmstadt, Germany.

Dr. Russell:
Welcome I am your host, Dr. John Russell. Joining me today is Doctor/Professor Antonio Uccelli, who is Director of the Center of Excellence for Biomedical Research at the University of Genoa in Italy. He and I are going to discuss the latest therapies for patients with multiple sclerosis and the benefits and risks associated with these treatment options. Professor Uccelli, welcome to the program.

Dr. Uccelli:
Thank you.

Dr. Russell:
So, let's start with a baseline – the traditional gold standard therapies for MS. What are they are what are the relative strengths and limitations?

Dr. Uccelli:
Well, nowadays there are a number of drugs that are in the market for a rather long time, and they really set up and paved the road for moving towards new strategies for treating multiple sclerosis. Now we have drugs such as interferons and glatiramer acetate that have been in the market over 20 years and they definitely clearly demonstrate good efficacy on relapse rate and MRI activity, not much about progression, but they certainly end up providing very strong evidence of safety, meaning that we can now treat patients in the early phases of multiple sclerosis with what I would say limited disease activity with a great deal of efficacy, gain, and safety. Now all the data we accumulated over the years make us feel that most of our patients in that condition can be treated for many years, as long as their disease is controlled with no major problems related to serious adverse events.

Another type of first-line therapies is the orals that have entered the market a bit more recently, and in this case, I am talking about dimethyl fumarate and teriflunomide. These new therapies probably have a relatively similar efficacy, again mainly on disease activity measured by relapse rate and MRI activity. They have the great advantage of being oral therapies and not injectables. Indeed for interferons and glatiramer acetate, the major drawback is related to the fact that they are injectables, very often with some frequent administration, such as for glatiramer acetate or certain types of interferons, high-dose interferons, and for the case of interferons, they are also associated with flu-like symptoms that are somehow cumbersome. It is interesting from the point of view of the patient because they are very much affected by these side effects that do not really worry the neurologist because we know again that we are talking about a very safe drug, but for daily life, they are kind of bothering our patients.

Also, the orals are associated with some adverse events that can be kind of bothering patients. For example, dimethyl fumarate, we have gastrointestinal or flushing that can be somehow cumbersome, but the good thing is in most cases they tend to fade out and they are limited over time, so I think good, moderate efficacy are overall limited or very minor serious adverse events over time.

Dr. Russell:
So, Professor, shifting to some of the newer medicines we have seen over the last decade, can you talk about natalizumab, fingolimod, and alemtuzumab?

Dr. Uccelli:
Oh sure. I guess that the advance of natalizumab was really a milestone in the treatment of multiple sclerosis. For the first time, we phased a new treatment with an incredibly high efficacy on relapse rates and disease activity that was an incredibly strong effect that was perceived by the scientific community and by patients, and after natalizumab, fingolimod, and more recently alemtuzumab entered the market with relatively similar profiles of efficacy. Now, this great efficacy unfortunately was associated for the case of natalizumab with the appearance of an unexpected side effect or adverse event, actually I would say, which is PML, which is encephalopathy which is induced by a virus, a virus which is harbored in our own body by almost three quarter of the population and is a virus that does not create any problem for most of us, but under certain circumstances in which the access of immune cells is limited such as for the case of natalizumab, this virus can enter the central nervous system and lead to encephalitis; again I call progressive multifocal local encephalopathy, which can be a very serious, life-threatening event. Luckily, this situation is very, very rare in patients, which is about 1/3 of the population which are JCV negative, meaning they are negative for antibodies against the virus while tend to accumulate over time, increasing the risk of developing encephalitis in those individuals that are positive for this virus, leading to relatively common habits of stopping treatments after 24 months in those individuals at high risk for PML.

Fingolimod is an oral drug that is associated with a good efficacy, very good efficacy, probably not as high as natalizumab, but with overall a good profile of safety. It is well accepted by patients and is associated just after the first administration to decrease the heart rate, which is in most, most cases, clinically irrelevant but requires a bit of monitoring for the first six hours. Then, patients have to be monitored to keep an eye on their leukocyte profile over time and enzymes, liver enzymes, over time and also they have to see an eye doctor and a dermatologist once every year to make sure that no evidence of oncology or dermatological skin events can occur, which however are extremely rare. So, overall very well tolerated drug with very good efficacy which does not have limitations over time except for those individuals that unfortunately do not respond, which is rare, but unfortunately can happen.

Alemtuzumab is another monoclonal antibody and very, very effective, although there is no head-to-head study against natalizumab. I would say that we can imagine a drug with a similar profile of efficacy. It is administered intravenously and again a very significant effect on relapse rate and disease activity on MRI.

Again, the cons of these drugs associated with the possibility for serious adverse events, in this case, patients have to be monitored for their leukocyte counts. They need to be very careful because in one third of the cases thyroid problems can occur that eventually may require treatment. They need to follow up for the appearance of a secondary autoimmunity again, against thyroid but also can occur against platelets and kidneys, and all these secondary autoimmunity events can be potentially quite dangerous and therefore requires careful monitoring. So, overall, I say that the pros of this drug are a great deal of efficacy definitely superior to what is observed for first-line therapies. On the other side, the rare but not so rare appearance of a serious adverse event, rarely but sometimes life threatening, requires very careful monitoring.

Dr. Russell:
So, Professor, it sounds like these medicines have lower relapse rates and have improved the quality of life of your patients, are there any other newer emerging medicines that you are starting to see in the literature that you are starting to use?

Dr. Uccelli:
Absolutely. There are now new drugs that are entering or have just entered the market that are providing us with great expectations of efficacy. One of these is ocrelizumab, which is a different type of approach leading to B-cell depletion. It is similar to natalizumab and alemtuzumab, a monoclonal antibody that depletes the lymphocytes from the circulation of patients with multiple sclerosis. The results that have been published one year ago show extremely high efficacy against an active comparator, interferon beta-1a high dose, and a high level of efficacy on relapse rates and extremely high efficacy on MRI measures that are a measure of disease activity.

It is important to emphasize that ocrelizumab is the first drug that has shown some evidence of efficacy in progressive MS, and this is very important because no other drug has succeeded in doing so, but at the same time it needs to be emphasized that efficacy in progressive MS means not at all that the patient will recover or reverse disease progression but will slow down the progression of the disease and disability; however, again I think this is a very important result; this is the first time that a drug shows this level of efficacy.

Daclizumab is a drug that is administered subcutaneously, so a novel type of administration and also a different kind of mechanics of action, is a drug that, as I said, similar to fingolimod has a very good effect on relapse rates and activity measured by MRI, again with an active comparator that was interferon with 1a once a week. The adverse events associated with this drug are quite unusual for the neurological community because there are adverse events which are usually mild to moderate but we are all waiting for this drug to see how we can manage this event. Other minor but still relevant issues are associated with liver problems, meaning increase of enzymes

that needs to be monitored quite carefully.

Now, there are other drugs that are likely to enter the market in a short time, and we have great expectations, for example, cladribine. Cladribine is a drug that has a significant effect on immune cells, mainly on lymphocytes while it leaves some of the innate immunity still properly working and therefore this is likely to support quite limited problems that have been associated in terms of infections. The efficacy that cladribine has shown in the pivotal phase 2 and 3 studies have shown a significant effect on disease activity measured by MRI but at the same time a very strong effect on relapse rate. This is another drug that we can imagine together with alemtuzumab, ocrelizumab, natalizumab that is likely to have a very, very, very strong impact on patients with multiple sclerosis.

Dr. Russell:
So, Professor, based on everything we talked about, it sounds like we have lots of choices right now. So, what do you think is the best therapeutic approach that carry the best benefits-to-risks ratio for our patients with multiple sclerosis?

Dr. Uccelli:
This is a very important question; however, it is difficult to provide you with a single answer. I would say that the best thing is to try to identify the best patients for our different types of drugs. So, when we talk about personalized medicine, we are now really in a situation in which we can identify the best drug for our own patients. In my opinion, it is extremely important to detect MRI and clinical signs that provide good or bad progressive factors and based on that, go to our first-line therapies for those individuals with a milder type of disease and eventually start with more efficacious drugs, even in the early phase of disease, for example, through an approach that can suggest a strong hit at the beginning of the disease in order to stop the most aggressive forms of multiple sclerosis. In this case, I would say that we already have clinical evidence or MRI evidence that allow us to select those patients that are at a higher risk of developing in a short a time disability. In those cases, I strongly support the use of the most efficacious therapies. Regardless of the fact that it exposes them to a bit higher risk of adverse events, but as I always say to my patients, I think the highest risk you have is to let the disease move in on and lead you to disability, and that is something that we cannot reverse.

Dr. Russell:
That certainly makes a whole lot of sense. Professor Uccelli, thank you so much for sharing your expertise in multiple sclerosis today with our ReachMD listeners.

Dr. Uccelli:
Thank you very much. It was a great time to be with you.

Narrator:
The preceding program was a special edition of On the Frontlines of Multiple Sclerosis, supported by an independent educational grant from Merck KGaA, Darmstadt, Germany. Thank you for watching!