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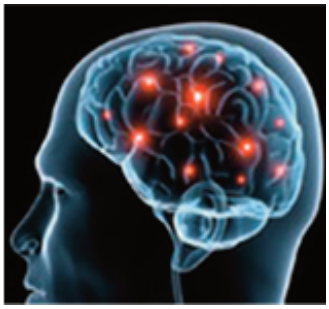

VOLUME 1 — ISSUE 6: TRANSCRIPT

Featured Cases: Incorporating MRI Results in Treatment Decision Making

Our guest author is Benjamin M. Greenberg, MD, MHS, Associate Professor, Department of Neurology & Neurotherapeutics, Pediatrics at UT Southwestern Medical Center in Dallas.

After participating in this activity, the participant will demonstrate the ability to:

- Discuss the prognostic significance of MRI findings at the time of diagnosis.
- Identify the prognostic significance of MRI changes during the course of disease modifying therapy.
- Describe how the evolving landscape of disease modifying therapies affects risk/benefit calculations when considering therapy changes.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of incorporating MRI results into this current era of expanding therapy options for patients with MS in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 1, Issue 5 *eMultipleSclerosis Review* newsletter — Incorporating MRI Results in Treatment Decision Making.

Unlabeled/Unapproved Uses
Dr. Greenberg has indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

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Guest Faculty Disclosure
Dr. Greenberg has disclosed that he has received grant support from Acorda Therapeutics, Biogen, Chugai Pharmaceutical Co., and MedImmune. He has served as a consultant for MedImmune, Novartis, and EMD Serono.

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MR. BOB BUSKER: Welcome to this *e*MultipleSclerosis Review podcast.

Today's program is a follow-up to our newsletter on the uses of *MRI Results in an Era of Expanding MS Therapy Options*. With us today is that issue's author, Dr. Benjamin Greenberg, associate professor in the Department of Neurology and Neurotherapeutics and in the Department of Pediatrics at the University of Texas Southwestern Medical Center in Dallas.

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Learning objectives for this audio program include:

- Discuss the prognostic significance of MRI findings at the time of diagnosis.
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MR. BUSKER: I'm Bob Busker, managing editor of *e*MultipleSclerosis Review. Dr. Greenberg, thank you for joining us today.

DR. GREENBERG: It's a pleasure to be here.

MR. BUSKER: In your newsletter issue, doctor, you reviewed some of the recent evidence evaluating the uses of MRI in managing multiple sclerosis — including correlations between MRI and brain volume, MRI findings relative to outcomes in early MS, and MRI lesions as a surrogate marker for relapses. You also described the concept of NEDA — or "no evidence of disease activity" — as a goal for clinical trials. Today I'd like to focus on how some of that new information can impact clinical practice. So start things off for us, if you would doctor, by describing a patient situation.

DR. GREENBERG: This is a 38 year old woman with relapsing-remitting multiple sclerosis for five years. When her MS was first diagnosed, she started therapy with interferon beta 1a in the intramuscular weekly injection formulation. Ultimately she changed to glatiramer acetate after only six months because of intolerable side effects from the interferon. Over the last 4-1/2 years on glatiramer acetate, she's had no new relapses, has complied with her medication, and has been undergoing annual MRIs to look for any evidence of new disease activity.

These MRIs have remained stable until the most recent MRI, which reveals a new, enhancing lesion in the left parietal lobe. Based on her history and exam, no obvious symptoms could be attributed to this lesion.

MR. BUSKER: She's been having annual MRIs, despite no changes in her disease status. Is that appropriate? My question really is — Is it reasonable to perform annual surveillance MRIs in patients like this when there are no clinical changes?

DR. GREENBERG: This is one of the questions that come up in clinic all the time: what is the value of an annual or even semiannual or biannual MRI in managing a patient with multiple sclerosis. In general, the view is that MRI data can be helpful for identifying suboptimal responders to any given therapy. Since 90 percent of lesions within the brain of patients with multiple sclerosis are asymptomatic, lot of disease activity can be going on without obvious clinical symptoms. While there's a lack of consensus about which MRI feature is most important — meaning you could follow T2 lesions, enhancing lesions, black holes or atrophy — identifying some sort of change on an MRI may be important for treatment decisions.

As mentioned in the newsletter, Dr. Sormani and colleagues examined multiple patients in an analysis of trials looking at MRI lesions as a surrogate for relapses, and when they collected all the data in a meta-analysis, they found a correlation between the ability to suppress new MRI lesions like the one this patient had and the ability to suppress relapses.[1] Thus, some data suggest that using annual surveillance MRI to show that the disease modifying therapy you're using is suppressing new lesions may be a surrogate for preventing relapses over the long run.

MR. BUSKER: She comes in, as you noted, with a new, enhancing lesion in her left parietal lobe. Is this an indication that changes in her therapy should be considered?

DR. GREENBERG: When taking a disease modifying therapy, clinicians and patients constantly have to ask themselves whether the therapy is being tolerated and whether it is achieving the intended goal. Specifically, is it suppressing the disease activity; is it putting a patient into remission?

The question then comes up, what are the indications and when should a therapy be switched? When a patient comes in with either new disease activity or side effects, the clinician and the patient have to ask themselves several questions.

First, is the patient actually taking the medication? When someone comes in with breakthrough disease, compliance and adherence are critical. If a patient is not taking a medication as prescribed, it's hard to define whether they are having a suboptimal response or breakthrough disease or failure of the medication because they're not getting a full dose effect.

Second, clinicians and patients have to look for evidence of clinical progression or relapses. Has the patient had any new symptoms or events that would suggest breakthrough disease? Are old symptoms slowly getting worse, suggesting a progression of underlying disease? Or in general, could the medication be producing side effects that make their symptoms worse?

Third, clinicians and patients must consider the MRI. Is there evidence of breakthrough disease, as we've seen in this case, even in the absence of symptoms, even when a patient is complying with the medication? As we saw from Dr. Sormani and colleagues, the MRI findings can correlate to disease activity and can predict relapses, but using the MRI as a surrogate of disease activity in clinical practice remains controversial.[1]

Most of the evidence suggests that when an MRI changes, it predicts future disability. Indeed, in the newsletter, Dr. Maghzi and colleagues indicated that even in early multiple sclerosis, magnetic resonance imaging changes, whether new lesions, enhancing lesions, or volume changes, would precede changes in disability.[2] Thus, it is reasonable for clinicians and patients to consider MRI data when deciding a patient should or shouldn't remain on a disease modifying therapy.

Ultimately, this leads us to ask how high should we set the bar. With all the therapeutic options we have available, the temptation is to set the bar high, meaning we should keep all of our patients in complete remission with no evidence of disease activity — but for each individual patient, the benefit/risk ratio has to be considered. If the alternative drug we are considering has individual risks or safety concerns, when patients and clinicians may opt to remain on a suboptimal therapy, even in the face of relapses or MRI changes because the risks to that individual may be too great to change the therapy. Thus, all of these decisions have to be individualized during a conversation between each patient and their clinician.

MR. BUSKER: When you're talking about how high to set the bar, are you referring to NEDA; that is, "no evidence of clinical disease activity"?

DR. GREENBERG: The idea of NEDA, or no evidence of disease activity, is deciding how we monitor patients. As it's currently defined, NEDA includes a patient who has no evidence of relapses, no evidence of progression of disability as measured by the expanded disability status scale or EDSS, no evidence of new T2 hyperintense lesions, and no evidence of new post-gadolinium enhancing lesions.

In the current literature NEDA means that a patient has had all four of those. It's like a trifecta: you have to have all of them to be included in that category. It is used as a level of evidence to say we have put the patient into full remission.

So the first question that needs to be asked about NEDA is, as it's currently defined, do patients who achieve that goal go on to have a good course, good quality of life, lack of disability? The flip side is, are patients who fail to meet that goal destined to have disability? The second question, then, is, if that definition of NEDA is not predictive, what is an alternate, more accurate definition?

Currently, NEDA is being considered as the goal in MS. But as we saw in the newsletter from Dr. Rotstein and colleagues in Boston, who reported on the evaluation of NEDA activity in a seven-year

longitudinal multiple sclerosis cohort of patients in the CLIMB study, some elements of NEDA were not predictive. Specifically, some patients achieving NEDA overwhelmingly went on to have no disability over the seven years,[3] but other patients who had some evidence of disease activity during those seven years were not progressing in disability.

What is lacking is long-term outcomes, meaning at the 20 year mark would those individuals with evidence of clinical or MRI breakthrough be destined to have disability? We just don't know the answer yet.

What was most notable from the study, though, was about 15 percent of patients who had no evidence of MRI disease activity at year 7, did have clinical evidence of progression, raising the question of how good are MRI surrogates of activity for predicting clinical progression.

Thus, I think the overall goal of inducing complete remission is correct, but we need long-term studies to validate the criteria for achieving NEDA; for example, should we be including brain atrophy in the definition of NEDA? These things require further study.

MR. BUSKER: Based on what we've just been discussing, how would you recommend treating this patient?

DR. GREENBERG: This patient has had a four year experience with glatiramer acetate without new symptoms but now has evidence of a new enhancing lesion on the MRI. I think she should have a serious conversation with her clinician about changing disease modifying therapies. And the critical portion of that conversation would be an assessment of that patient's notion of risk.

Glatiramer acetate had an incredible safety record over many years now, and a lot of the alternatives we would consider come with heightened risk. At the same time, we would remind the patient that there's risk of the disease progressing and we have opportunities to put her into long-term remission.

So in general, if this patient is willing to change the risk ratio or the therapy she takes, I would probably recommend looking at one of the FDA approved oral therapies or natalizumab, depending on her JC antibody status, as a very appropriate medication to consider switching to.

MR. BUSKER: Thank you for that case and discussion, doctor. And we'll return, with Dr. Benjamin Greenberg from UT Southwestern Medical Center, in just a moment.

MR. BOB BUSKER: Hello. This is Bob Busker, Managing Editor of *e*MultipleSclerosis Review.

If you found today's program on iTunes or on the web, please be sure to subscribe. This podcast is part of Johns Hopkins *e*MultipleSclerosis Review, an educational program providing monthly activities certified for CME credit. *e*MultipleSclerosis Review provides expert commentary and useful practice information for clinicians treating patients with multiple sclerosis.

For additional information, or to subscribe to receive our newsletters and podcasts without charge, please visitt www.eMultipleSclerosisReview.org. Thank you.

MR. BUSKER: Welcome back to this *e*MultipleSclerosis Review podcast. I'm Bob Busker, managing editor of the program. We've been talking with Dr. Benjamin Greenberg from the University of Texas Southwestern Medical Center in Dallas about Incorporating MRI Results into this Current Era of Expanding Therapy Options for Patients with MS. So Dr. Greenberg, let's continue by going back to the clinic.

DR. GREENBERG: Let's return to this same patient but add some information and go back to her initial presentation. This is the same 38 year old woman with relapsing-remitting MS. Her original presentation was with a right-sided optic neuritis, but now I want to tell you about her baseline MRI.

When she first came in, the MRI revealed a significant disease burden with diffuse T2 hyperintense lesions. She had several T1 black holes and already had atrophy out of proportion to her age. This patient started on interferon, as you recall, and ultimately switched to glatiramer acetate because of side effects. She has remained on glatiramer acetate for 4-1/2 years until coming in with the new enhancing lesion but without symptoms.

MR. BUSKER: A patient with this kind of presentation — talk about her prognosis. What's concerning and what's reassuring?

DR. GREENBERG: When making an initial decision about disease modifying therapy, clinicians and patients have to take all the data available and discuss prognosis. Is the patient in a category where we're concerned about rapid progression of disability, or is the patient in a category where they are more likely to have a relatively benign course of the disease? No prognostics in MS are perfect. These rules get broken all the time, but in general, since it is better to be a woman than a man with this disease, her gender would be reassuring.

While it is better to have nonmotor symptoms at first event, her optic neuritis is relatively reassuring, compared to somebody who has difficulty walking as their first presentation. But what is concerning about this patient is her baseline MRI. The presence of diffuse T2 lesions, the black holes, and the atrophy, each independently is a poor prognostic indicator for ultimate disability.

MR. BUSKER: When evaluating that baseline MRI, doctor, which findings would you consider most significant?

DR. GREENBERG: When we're talking about MRI and what's most significant or concerning, it really depends on what you're interested in. The T2 burden on the MRI gives you a sense of the person's prior disease history. Clearly she has been having events, as shown by scar tissue left over from prior events, and if she has diffuse T2 changes it means she has probably been dealing with the disease a long time before presenting at your office.

The T1 black holes on the MRI give you a sense of severity of attacks. Specifically, these form when there's axonal transaction and axonal damage. Somebody who has lots of T2 lesions but relatively few T1 black holes, it may give you a sense of their ability to compensate or repair from attacks, and the presence of T1 black holes gives you a sense that a person is not recovering as well from an immune-mediated attack on the brain.

The enhancing lesions will suggest how robust the immune response is, how active the disease is. More enhancing lesions means at that moment in time their immune system is causing more active damage than in the past. Finally, atrophy is a global measure of brain injury. So if you are trying to get a sense of what's happened in the past, the T2 burdens and the atrophy and the T1 black holes play a role, but if you are trying to get a sense of what's happening right now in front of you, the enhancing lesions are the most suggestive.

MR. BUSKER: What's known about how these MRI findings correlate to long-term disability?

DR. GREENBERG: Studies have looked at these different MRI measures in relation to disability. In the newsletter we referred to the Maghzi and colleagues article that came out in 2014. That study looked at T2 lesions, T1 lesions, and atrophy.[2] They found early in MS that atrophy is a poor prognostic indicator for future disability. That would stand out to me more than anything else as a concerning feature.

MR. BUSKER: So when making initial treatment decisions, what role should the patient's baseline MRI characteristics play?

DR. GREENBERG: Like anything else, when making an initial treatment decision, we start with patient preference and their ability to assess risk of a treatment and risk of a disease. But patients often want to know how active or how severe their disease is, so an MRI with a lot of changes, T1 black holes, T2 hyperintensities or atrophy, can work to inform the patient that they are at a higher risk for disease progression.

Patients who hear that they're at low risk of disability could afford trials of medications that have lower risk profiles, while patients who are in a high risk situation may have to consider drugs that are classically described as second line therapies. We have to individualize the options for each patient, taking into account all the data, including MRI.

MR. BUSKER: And in the clinician's monitoring decisions? Same question — what role should those baseline MRI characteristics play?

DR. GREENBERG: Once a disease modifying therapy is initiated, we have to monitor patients to determine whether are they responding. This can entail a lot of things; the basis of it is clinical exams and history taking, but we also use MRIs. How frequently the patient will be monitored clinically and with MRI, and what types of monitoring you will use, could be dictated by the severity of the person's MS.

If their baseline MRI characteristics put them in the high risk/high severity category, regardless of their clinical status, they should probably be followed more frequently and more intensely because the room for error is lower. The next relapse and the next lesion could leave them with irreversible disability in a way that's easier than someone with less severe MRI changes.

So while all of these decisions needed to be individualized to the patient, the baseline MRI characteristic should inform a clinician's decision how frequently and how intensely to monitor the patient.

MR. BUSKER: So bottom-line: the patient you described — how would you treat her?

DR. GREENBERG: This 38 year old who presented with the optic neuritis and no other symptoms had an MRI that had significant changes. While the decision to start interferon beta 1a and then ultimately glatiramer acetate is a very personal decision, I would put her in a category where we should be offering therapies that are traditionally defined as second line. With that severe a change on MRI, the atrophy and the black holes — if she said she wanted to start one of the oral therapies or natalizumab, I would consider it a very appropriate choice, based on that baseline MRI characteristic.

MR. BUSKER: Dr. Greenberg, normally at this point I'd ask you bring us another patient, but I think we'll be better served by continuing with this one. So if you would, doctor —

DR. GREENBERG: This same 38 year old woman who presented with the severe disease started on interferon, switched to glatiramer acetate because of side effects, and then came in with the new enhancing lesions and no symptoms, now comes in to discuss a change in therapy. The question is, for whatever reason you want to make a change, how do you decide that and which therapy should you chose?

MR. BUSKER: Before you make the decision to change therapy, what factors help you determine when a patient has legitimately failed their current disease modifying therapy?

DR. GREENBERG: The first part of the equation is exactly how you put it: has she failed or not? For me, the term failure, which is used quite a bit, is somewhat troubling. I prefer to say suboptimal response — and this not just political correctness or coming up with a nicer sounding term. I prefer suboptimal responder over the term failure for a very specific reason. When a patient hears that they have failed a therapy, it assumes that a change must occur; whereas when we talk about suboptimal response, it gives you the wiggle room to say, yes, you're not responding ideally but this still may be the best drug for you and we have to individualize it.

So the definition of success in multiple sclerosis therapy has to be individualized. A new, nonenhancing lesion could mean something different to a patient whose MS was diagnosed just two years earlier versus somebody who had been stable on a drug for ten years or more. Those patients are very different. So just defining a new lesion as failure and not taking into account the patient's characteristics is a difficult thing to do.

In general, any evidence of breakthrough disease, clinical or radiographic, suggests that the patient responds suboptimally to the medication, and you have to decide the risks and benefits of a switch. What we're deciding is the risk of disease progression in that suboptimal response state versus the safety concerns of any medication you would switch to.

MR. BUSKER: Assuming that you are considering a switch, how do you determine which DMT to switch to? What issues should be considered?

DR. GREENBERG: Both the patient and the clinician have to consider a list of things when jumping into that switch scenario. The first is prior therapy. If a person has shown either side effects or breakthrough disease of any kind on an interferon, in the past we might have tried different interferons, but in general today we consider switching to a different class of therapy.

Then we have to consider the patient's state, how healthy or disabled or symptomatic they are. If someone is already acquiring disability based on their last relapse, we may consider going to a higher efficacy, more robust drug, even if it comes with more risk. But we have to consider risk stratification, and this comes into comorbid issues.

The best current example in disease modifying therapies is natalizumab, where we use the JC virus

antibody test to stratify an individual's risk of developing progressive multifocal leukoencephalopathy, or PML, while on natalizumab. So we have to do an assessment of the patient to decide what drugs may or may not be appropriate for their situation and medical history.

Since the majority of our patients are women, often between the ages of 30 and 40, we have to have discussions about their reproductive plans. Even with teriflunomide, where the label suggests counseling about reproductive risks for both men and women on the medication, this is now a conversation we have to have with all of our patients, regardless of gender, so we can counsel about medication safety if and when a patient decides that they want to become pregnant.

Ultimately we have to consider patient preference. Some patients have moved away from injectable therapies and prefer infusion or oral therapies, while other patients' preferences center solely around side effects, tolerability, or risk. Patient preference is very important because that's what dictates adherence and compliance. It's great to prescribe medication for patients, but if they won't take it, it is of no value.

Finally, unfortunately in today's world, with our payer system and insurance rules, we have to consider cost and accessibility. The costs of these medications are all extremely high, and if patients cannot afford copays or do not have access to the medications, it doesn't matter what the decision is about disease modifying therapy, we have to ensure they can get access.

All of these issues have to be taken into account when deciding which therapy to switch to.

MR. BUSKER: What can you tell us about the comparative efficacy of the different DMT therapies?

DR. GREENBERG: That is a great question and one we are asked all the time at meetings with our colleagues and from our patients — which drug is best? There are two parts to the answer. First is defining what we mean by which drug is best." In my view, want a drug that will put a patient into remission. The best way we have to measure remission is the currently used No Evidence of Disease Activity metric. Meaning, which patients, how many patients will go into a remission where they have no relapses, no progression of their disability, and no new lesions on their MRI.

MR. BUSKER: "No evidence of disease activity" — abbreviated as NEDA. What do the clinical trials show?

DR. GREENBERG: When we look at the data from controlled trials, we could ask ourselves what percentage of a patient population would go into remission hen on a drug? The data from these controlled trials suggest that there are different tiers to various medications' ability to achieve NEDA status. The FDA approved drugs alemtuzumab and natalizumab probably have the highest rate of achieving the NEDA. It was interesting that the decision about tiering these oral drugs based on efficacy was made despite a complete lack of head-to-head trials.

In the newsletter we reviewed data from an article published by Dr. Nixon and colleagues where they used mathematical modeling to do indirect comparisons between the oral therapies and this is a little controversial because it's all taking published data, applying statistics to it, but understanding that the cohorts of patients enrolled in those trials for teriflunomide, dimethyl fumarate and fingolimod were different cohorts.[4] So they came up with mathematical models to compare them and in their analysis, no matter which way they cut the numbers, fingolimod appeared to have a higher rate of achieving remission for patients than either teriflunomide or dimethyl fumarate. So there is a sense that from an efficacy perspective natalizumab, alemtuzumab and fingolimod are probably the most potent drugs, but what we have to remember is that there are responders and nonresponders to every drug. Meaning there are patients on glatiramer acetate, there are patients on interferon, teriflunomide, who go into complete remission, but the percent of the population who achieve that is less with those drugs. But at the same time, for those patients, there may be different risk or lower risks than the natalizumab or alemtuzumab or fingolimod.

So when making a change in therapy, efficacy is important, but it also comes with a tradeoff between an escalation in efficacy and a risk of complication.

MR. BUSKER: So to return to the patient you described — she wants to change her therapy. How are you going to advise her?

DR. GREENBERG: So in this patient who had the severe MRI to begin with, who is having evidence of breakthrough disease within the four years, I would be leaning towards using one of the drugs with a better batting average relative to putting her into complete remission, with the sense that she has less room for error.

So depending on her JC antibody status, I would either recommend probably natalizumab or fingolimod at this point. If she were JC antibody negative, natalizumab would be a perfectly appropriate choice, if she were positive fingolimod could be considered, but in the world we live in today where complications are reported with both, that decision would be individualized based on her risk assessment of these two choices.

MR. BUSKER: That "world we live in today," as we all know, is rapidly changing. What do you see as the most significant changes likely to happen over the next 10 years or so?

DR. GREENBERG: The world of multiple sclerosis has been and continues to be very exciting relative to therapeutics, and the last 10 years has seen a revolution in the number and type of disease modifying therapies we have.

The next 10 years will probably bring three significant changes. The first is surrogate markers for treatment response — can we put somebody on a drug and know they are or are not responding early in the disease. I'm thrilled to see clinical trials for drugs to repair the damage done by multiple sclerosis. Finally, on the horizon we're going to see drugs that will treat progressive disease, something we've been lacking. All three of those things will change the way we practice over the next 10 years.

MR. BUSKER: Thank you for today's discussion, Dr. Greenberg. To wrap things up, let's review what we've talked about today in light our learning objectives. So to begin: the prognostic significance of MRI findings at the time of diagnosis.

DR. GREENBERG: This learning objective was most directly related to case two, where we discussed how different MRI findings at the onset of disease relate to the different aspects of both the biology of multiple sclerosis and the prognosis for disability, and how those findings can be incorporated into treatment decisions. Data suggests that baseline MRI findings in a patient with MS can be prognostic for disability status, and both clinicians and patients should consider that when making a treatment decision.

MR. BUSKER: And our second objective: the prognostic significance of MRI changes during the course of disease modifying therapy.

DR. GREENBERG: In the first case we considered, the patient was stable clinically on glatiramer acetate but had a new, asymptomatic MRI change while on therapy. This raises the question of how o MRI findings prognosticate for outcome during therapy and how should those findings be incorporated into treatment decisions? Incorporating the articles reviewed in the newsletter there is ample evidence to suggest that MRI changes, even in the absence of clinical events, can be a harbinger of disability or relapses to come, so routine MRI surveillance of a patient is appropriate, and incorporating disease activity findings from MRI should be used in treatment decisions.

MR. BUSKER: And finally: how the evolving landscape of disease modifying therapies affects risk/benefit calculations when considering therapy changes.

DR. GREENBERG: This learning objective of considering how far we've come and where we're going relative to disease modifying therapies was encapsulated in case three, specifically, you've defined a patient as having a suboptimal response, now what do you do? With a lack of head to head trials, we reviewed literature that uses statistical analysis to compare different therapies to categorize them based on the relative efficacy. While this approach is not ideal, it is the best we have. We have found that with an increasing proportion of patients placed into remission by a drug, there tends to be a trend toward increasing risk of complications. Thus, the treatment decisions have to be individualized based on the patient's comorbid conditions and risk factors to balance the risks and benefits of any therapeutic decision.

We found that within the injectable, infusible, and oral therapies, there are differences that have to be taken into account when either initiating or changing a therapy for a patient with MS.

MR. BUSKER: Dr. Benjamin Greenberg from the UT Southwestern Medical Center in Dallas — thank you for participating in this *e*MultipleSclerosis Review Podcast.

DR. GREENBERG: Bob, it's been a pleasure, I hope your listeners find it helpful and insightful as they care for patients with multiple sclerosis.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.eMultipleScelrosisReview.org/test.

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