Introduction to What's New in Alzheimer's Disease Treatment

DISEASE MODIFYING THERAPY

MISSOURI MEMORY CENTER

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INTRODUCTION

It has been my honor and privilege to have been given the opportunity to help hundreds if not thousands of people with the challenges of diagnosing and treating Alzheimer's disease (AD). It has also been an honor to have been appointed by the Governor of the State of Missouri to the Missouri Task Force on AD; to be the primary investigator on AD research studies conducted at Missouri Memory Center; to work with the Alzheimer's Association; and to educate physicians and other medical practitioners about AD diagnosis and treatment.

We are now moving into a new era for treating Alzheimer's disease, the era of "disease modifying therapy" or "DMT". When I first started my practice of neurology, over 30 years ago, the concept of DMT for neurological disorders was still a dream. The very first DMT was not for AD. It was for multiple sclerosis (MS) and it was FDA approved in 1993. Fortunately, today, there are over 20 choices of DMTs for MS.

It just so happened that the first treatment for the symptoms of AD also gained FDA approval in 1993. However, that first AD medication, and those that followed it, were found to only help the day-to-day symptoms of AD, they did not slow the progression that always occurs in AD. The last truly new medication in this category was FDA approved 20 years ago, in 2003.

Scientists have worked diligently to seek other approaches to treating AD including searching for medications that could slow down the progression of AD symptoms, or DMTs. There have been some small successes but many big failures as these new ideas were tested.

Now the world has changed. In July 2023 Leqembi became the very first fully FDA approved medication that slows the progression of AD; it is a DMT (disease modifying therapy). This means that for some AD patients, we have the option to use medication that may slow down the progression of AD, not merely treat the day-to-day symptoms.

In my practice as a neurologist at Missouri Memory Center I have discussed the new breakthrough medication with many patients. The decision about using this new form of treatment is an individual choice to be made by each patient and their family. There is nothing at all that is "one size fits all" in AD management.

My goal in preparing this "Introduction to What's New in Alzheimer's Disease Treatment" is to give my patients, and to give you, a solid basic understanding of the issues that need to be considered about the new treatment option. This guide is not intended to provide an answer for all questions, it is a just starting point in the understanding of the many things that should be considered in deciding whether this treatment is appropriate for each individual battling AD. There are many more details that will need to be discussed for patients that decide to move forward with the new treatment. I strongly urge all patients and their family members to do their own research, but to bring any and all questions or concerns in for discussion before making their final decisions. The best medical decisions are shared decisions made with patients and their medical care provider, not by simply surfing the internet.

Please be aware that the field of AD treatment is moving quickly and that the information provided here is a starting point. Be certain that you use the most up to date information in your own decision making.

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SECTION 1: A New Treatment Era for Alzheimer's Disease

Dementia is a disorder of not only memory but also of other thinking skills. Although dementia is commonly thought of as a "memory disorder" it is really a disorder of thinking (and memory is one part of thinking).

Dementia is a word used to describe the symptoms of a thinking disorder. The word dementia does not state what is causing the symptoms. There are many different causes for dementia. To be told "you have dementia" is only part of a diagnosis. A true diagnosis is to state "you have dementia CAUSED BY…." and then knowing the cause. Knowing the cause requires some investigation. The investigation that is done to find the cause of dementia is the medical and neurological evaluation. A thorough work-up takes the diagnosis from simply "dementia" but to the more accurate diagnosis of "dementia caused by …." with the cause having been found by the work-up.

The work-up is the pivotal part of evaluating people with memory, or thinking skills disorders. Some people may have a treatable disorder and the dementia symptoms could possibly be reversible.

Alzheimer's disease (AD) is one form of dementia that most people have heard of and many people fear. AD is the most common form of dementia and is responsible for at least 2 out of 3 cases. It becomes more common with aging and the older the person the higher the chance that their dementia is due to AD.

Why is it called Alzheimer's disease? Did he have it? Did he discover it?

The reason it is called Alzheimer's disease is because in 1906 Dr. Alzheimer was studying the brain of a patient who had died with dementia. He used the best scientific tests that were available in 1906 and he discovered things that no one had ever seen before. He saw two different things under his microscope that turned out to be the buildup of abnormal proteins. These proteins are called amyloid and tau. For many decades some doctors would say "we think it might be Alzheimer's disease, but we can't be 100% sure until we do your autopsy". Why would they have said that? Because proof that amyloid and tau protein have built up in the brain is required for the 100% accurate diagnosis of AD. Fortunately, in the last 10 years our ability to accurately diagnose AD has greatly improved, in part due to 21st century technology which is a bit more advanced than was available to Dr. Alzheimer in 190%. Fortunately, scientific breakthroughs have given us the ability to detect amyloid and tau protein building up in living people. These new inventions are called "biomarkers". Biomarkers are tests that can be done on living people (long before the autopsy) to look for the brain changes of AD. These biomarker tests for AD include amyloid PET brain scans and spinal fluid testing. We may soon see other types of biomarker tests for AD, including blood tests, but those are not yet considered to be accurate enough for making decisions on treatment with the newest medications for AD.

Why bother diagnosing AD?

There are many ways that we can help the patient with AD as well as their family members and care providers. Knowledge is power, and knowing how to handle things now and what to expect in the future is part of giving good care. There are medications that have been available for several decades for treating AD symptoms. These pill form medications can help some patients with the day-to-day symptoms of AD and they are currently considered to be part of the standard of care for many AD patients. These older medications may help with AD symptoms in the short-run, but they do not slow down the progressive worsening of memory and other thinking skills that always happens with AD.

What's new today in Alzheimer's disease treatment?

Scientists have discovered that amyloid builds up in the brain for years, even decades before the patient has any noticeable memory or thinking problems. They have found that the amyloid build up starts first and then the other protein discovered by Dr. Alzheimer in 1906, tau protein, builds up later, both long before the symptoms begin. Since Dr. Alzheimer's initial discoveries, scientists have determined

that the amyloid and tau protein build up is only part of what happens in the brain as AD progresses. Because the amyloid build up starts very early (even as long as decades before the memory and thinking symptoms start) the questions have been: "Does amyloid build up trigger the changes that come later as the dementia symptoms progress?"; and, "Could removing the abnormal amyloid protein build up in the brain help slow down the worsening that always happens with AD?"

For many years scientists have worked on several different ideas on how to address the amyloid protein buildup in the brain. Unfortunately, for many years nothing was proven to make a difference for patients with AD.

More recently scientists have invented ways to design "immunotherapies" for many medical conditions. This is a technology where antibodies, which we all have to fight off infections, can be custom made to do other jobs, including removing amyloid protein from the brain. Not all of the amyloid removing drugs that have been tested have helped patients with the symptoms of AD (meaning they have not changed the progression memory or other thinking problems with AD), until recently.

For the first time ever, we now have medication that has been fully FDA approved to treat AD that has been shown to slow the progression of the symptoms of AD. Although not a cure for AD, this is a breakthrough in the field. However this treatment is not appropriate for all AD patients. Each and every patient will need to consider the potential benefits as well as the possibility of side effects before considering this option.

SECTION 2: Leqembi for Early Alzheimer's Disease Treatment

For the first time ever, we can now consider fully FDA approved medication options for the treatment of Alzheimer's disease (AD) for patients who are at the early stages of the disease.

The availability of Leqembi now, and likely other medications in the future, offers patients with the earlier stages of AD the opportunity to consider treatment that may slow down the rate of progression of AD. In medical terms this is called "disease modifying therapy", meaning the treatment may slow down the progression of AD. Other medications used to treat the symptoms of AD may help with the day-to-day symptoms, but they do not slow down the progression of AD. The chance to consider disease modifying therapy, with the hope of slowing the progression of the symptoms of AD, is a brand new option for some patients.

Science has proven that AD changes start in the brain long before the memory changes of AD show up. Currently, disease modifying therapy for AD is only approved for use in people who have developed symptoms related to AD and are in the earliest stages of AD.

Although there are several different systems used to rate the stages of AD, this discussion uses a simplified version based on the severity AD symptoms.

Symptomatic Alzheimer's disease can be broken down into four general stages.

FOUR STAGES OF SYMPTOMATIC AD

4. SEVERE AD DEMENTIA

3. MODERATE AD DEMENTIA

2. MILD AD DEMENTIA

1. MILD COGNITIVE IMPAIRMENT (MCI) due to AD (also called MCI-AD).
   These are patients who have cognitive changes caused by AD, but who have not yet progressed into the dementia stage of AD.

Patients with Stages 3 and 4 AD, (moderate AD dementia and severe AD dementia stages) are not candidates for the new disease modifying therapies, but they can still possibly benefit from the older medications that are used to treat the day-to-day symptoms. Stage 2 (mild AD dementia) patients may also benefit from some of the day-to-day symptom treatment medications. The medications used to treat day-to-day symptoms of AD have been studied for Stage 1 (MCI-AD) but the studies did not show benefit for the Stage 1 patients.

The new disease modifying therapies for AD are appropriate to use for many, but not all, patients with Alzheimer's disease who are at Stage 1 (MCI-AD) and Stage 2 (mild AD dementia). Some patients at these early AD stages may have medical or other neurological disorders that exclude them from taking this type of medication. Some patients who might be candidates may not wish to take the new medications due to the diagnostic steps that are needed to determine if the treatment is appropriate for them, or the schedule of testing and IV medication infusion that has very strict timing, or they may review the potential benefits and the possible risks (possible side effects) and decide that this is not a treatment they wish to take. Careful consideration needs to be given in each individual case before proceeding with the new disease modifying treatment for AD.

How to determine if you might be a candidate for treatment with Leqembi

ALL of the following are needed to be a possible treatment candidate:

1. Have an accurate clinical diagnosis that fulfills the diagnostic criteria for Stage 1 (MCI-AD) or Stage 2 (mild AD dementia). The first step is a thorough medical and neurological history and physical exam. This includes the standard blood work and MRI brain scan that are required as part of a detailed work-up.
2. Have a family member or other care partner that can help provide support for the process of receiving this type of treatment.
3. Age 55-85 years old.
4. Can have MRI scans done, because multiple brain MRI scans are part of the treatment protocol. (MRI-conditional medical devices may or may not be allowed due to care planning needs.)
5. Have a positive biomarker for AD. Currently the only acceptable biomarker tests are amyloid PET scan and/or spinal fluid testing. (Other types of biomarkers, including blood tests, are being developed but they have not yet reached the degree of accuracy needed for determining candidacy for the new treatments.)
6. Have good veins for starting an IV, because the new treatments are given by IV.
7. Can come in to the infusion center on a regular schedule (Leqembi is given by IV infusion every two weeks.)

ANY of the following excludes taking this type of treatment:

1. Any current medical or neurological treatment that would make the treatment less beneficial.
2. Any other current medical, neurological or psychiatric problem that may be a cause for the memory loss.
3. Abnormalities on brain MRI that would be contraindication for treatment.
4. Any reason to be unable to keep on a rigorous schedule for IV infusions and/or MRI scans.
5. Any stroke or TIA within the preceding 12 months.
6. Any history of having a seizure.
7. Any history of immunologic disease (for example: lupus, rheumatoid arthritis, Crohn's disease) or systemic treatment with immuno suppressants, immunoglobulins, or monoclonal antibodies or their derivatives.
8. Any form of bleeding disorder or blood work abnormalities that increased the risk for bleeding.
9. Any use of any anti-coagulant medications including: Eliquis (aprixaban), Coumadin (warfarin), Pradaxa (dabigatran), Savayasa (edoxaban), Xarelto (rivaroxaban), Bevyxxa (betrixaban), or heparin.
10. Any unstable medical conditions (for example: cardiac, respiratory, gastrointestinal, kidney, cancer).
11. The use of the "blood clot buster" medication called TPA is not recommended for patients on Leqembi.

Each patient that may be a candidate for Leqembi needs to review their overall health status with their care provider to decide if Leqembi is a good choice for them. This type of joint decision making, based on all the details of each person's case is very important.

SECTION 3: Leqembi and APOE Gene Testing

As science has advanced and disease modifying therapies for Alzheimer's disease (AD) have been discovered, scientists have determined that the benefits and risk of side-effects (specifically ARIA –amyloid related imaging abnormality) vary between people. One factor that makes a difference is the person's APOE gene type.

The APOE gene does not cause AD, but it has been known for many years the type of APOE gene you are born with changes your risk for developing AD. The type of APOE gene that is most significant is called E4. Some people do not have the E4 type of APOE. Some people have one E4 gene (they are called heterozygotes). Some people have two copies of E4 (they are called homozygotes). Having APOE gene type E4 does not cause AD, but it does raise the risk of developing AD. Many people with E4 genes do not develop AD and many people without any E4 genes do develop AD. It is recommended that people who have gene testing receive genetic counselling to explain the implications of the results.

For Leqembi, and other medications that work in a similar manner to reduce brain amyloid in AD, it has been shown that the types of APOE genes a person has been born with changes the risk for the side effect called ARIA and possibly the chances of benefitting from the medication.

1. APOE AND THE CHANCES OF GETTING THE SIDE EFFECT OF ARIA FOR LEQEMBI

For Leqembi, the chances of having the side effect called ARIA (amyloid related imaging abnormality) is higher for people who have the APOE gene type E4.

There are two types of ARIA, called ARIA-E and ARIA-H.

ARIA-E (amyloid related imaging abnormality – edema or effusion) and the APOE gene.

Overall, for ALL patients treated with Leqembi in the main study – 12.6% had ARIA-E.

However, the risk of ARIA-E is increased for patients having E4 genes.

For patients with:

No E4 gene – 5.4% had ARIA-E

One copy of E4 (heterozygotes) – 10.9% had ARIA-E

Two copies of E4 (homozygotes) – 32.6% had ARIA-E

ARIA-H (amyloid related imaging abnormality - hemosiderin) and the APOE gene.

Overall, for ALL patients treated with Leqembi in the main study – 12.6% had ARIA-H

However, the risk of ARIA-H is increased with patients having E4 genes.

For patients with:

No E4 gene – 11. 4% had ARIA-H

One copy of E4 (heterozygotes) – 14% had ARIA-H

Two copies of E4 (homozygotes) – 39% had ARIA-H

2. APO-E AND AMOUNT OF SLOWING OF AD WITH LEQEMBI

In the main clinical study the whole group of Leqembi treated patients had slowing of the progression of AD symptoms by 27% compared to the placebo treated patients at the end of the 18 month study. This was based on the results of the primary outcome measure, called the CDR-SB (CDR Sum of Boxes).

However, in an exploratory analysis of the patients treated with Leqembi who had two copies of the E4 APOE gene (homozygotes) there was no improvement on the main outcome measure (CDR-SB) for the Leqembi treated group when compared to the patients treated with placebo. There were some improvements noted in the Leqembi treated patients on some of the other testing outcomes, but not on the CDR-SB test.

Each patient that may be a candidate for Leqembi needs to review their overall health status, and their APOE gene type, with their care provider to decide of Leqembi is a good choice for them. This type of joint decision making, based on all the details of each person's case is very important.

SECTION 4: Leqembi - Balancing the Treatment Decision

Leqembi is the first medication that has ever received full FDA approval as a treatment to slow the progression of Alzheimer's disease (AD). This is a breakthrough as there have previously been no treatments proven to slow AD. It is expected that there will soon be other treatments available.

Alzheimer's disease is a disorder that comes on gradually. Many times patients and families cannot tell exactly when things started. The brain process of AD is very complicated but it has been known since Dr. Alzheimer discovered the buildup of the proteins called amyloid and tau that these changes come on gradually. More recent studies have shown that the amyloid and tau protein buildup occurs very gradually over many years and probably decades before the changes in memory and thinking skills show up. Although we now know that what Dr. Alzheimer found is only part of the process of AD, scientists have tried to determine if treating the amyloid buildup would prevent the further changes in the brain that promote the loss of memory and thinking skills.

Leqembi is a treatment that targets very specific forms of amyloid and removes the buildup of amyloid (called amyloid plaques) from the brain. In fact, many patients treated with Leqembi have been shown to have the amyloid plaque buildup in the brain reduced to the point it is no longer at elevated levels. Although this is very interesting from a scientific perspective, amyloid plaque removal is not the only goal of treating a person for AD. The most important goal of treatment is to slow down the progression of dementia symptoms in patients with AD.

Leqembi does not change or reverse the memory loss that has already occurred. The research study that led to full FDA approval of Leqembi showed that, on average, it slowed the progression of memory and day-to-day functioning skills by 27%. This was an 18 month long clinical trial of about 1,800 patients; half were treated with Leqembi and half with placebo. At the end of the study the Leqembi treated patients had a 27% slowing of progression of AD symptoms as measured on a test called CDR Sum of Boxes (CDR-SB). The CDR-SB is a standard test that measures a combination of both memory and home functioning. Another way to describe this outcome: at the end of the 18 month study the Leqembi patients were a bit more than 5 months better on the CDR-SB than the placebo patients. More studies are ongoing to look at longer duration of treatment with Leqembi. As with all studies, averages are reported, meaning some patients could do better than average and some could do worse than average.

It is important to know that Leqembi was only tested on patients with the very earliest stages of AD. These are patients who are at Stage 1 (MCI-AD) and Stage 2 (mild AD dementia) of AD. Leqembi is not indicated for use in patients who have progressed past these early AD stages. Also, there are things specific to each and every patient that need to be considered to determine if a patient is a candidate for Leqembi.

Once a patient and their medical care provider have gone through the case details and have decided it is reasonable to consider the option of using Leqembi for AD treatment, then two major additional tests need to be discussed:

1. Getting a biomarker test. This is needed to be sure that the brain has amyloid buildup due to AD. Since Leqembi is a medication which has been specifically designed to target amyloid, it is necessary to verify that amyloid is building up in the brain. Biomarker testing is required for a patient to be a candidate for Leqembi. It is part of the FDA prescribing information and it is required by Medicare for coverage. There are currently two biomarkers that are considered to be accurate for making this treatment decision: amyloid PET scanning and/or spinal fluid testing. Both are relatively easy to do and both have their own pros and cons. Other forms of biomarker testing, including blood testing, are not FDA approved and are not considered to have the accuracy at this time for making the decision to treat with Leqembi.

2. Getting an APOE gene test. It is strongly recommended that patients who are considering Leqembi have APOE testing done. This is a blood test, but it is not a biomarker test for AD. It is a test to determine what type of APOE genes a person has been born with. It is known that a certain form of the APOE gene called E4 puts people at a higher risk for getting AD, but APOE testing does not diagnose AD. Not everyone with the E4 gene will get AD and there are a lot of people without the E4 gene who will get AD. For Leqembi, the APOE testing is not part of diagnosing AD. It is important to consider the APOE gene type because if the E4 gene is present it changes the discussion on possible risks and potential benefits. This is important to consider when deciding whether Leqembi is the right choice for an individual patient.

UNDERSTAND POSSIBLE SIDE EFFECTS WHEN CONSIDERING LEQEMBI.

Leqembi can possibly have side-effects. The most common are infusion reactions and amyloid related imaging abnormalities (ARIA).

1. Infusion Reactions

Since Leqembi is given as an IV infusion, there is the chance of having what is called "an infusion reaction". This type of reaction can occur with any type of infusion medication given by vein. In the main Leqembi study an infusion reaction occurred in about 1 out of 4 treated patients (26.4%). This also means that about 3 out of 4 people did not get an infusion reaction with Leqembi.

Common symptoms of an infusion reaction may include:

Fever, chills, headache, rash, nausea, vomiting, abdominal discomfort, and elevated blood pressure.

Most infusion reactions are mild to moderate in severity. Infusion reactions, if they occur, usually happened with the first 2 treatments. Symptoms can start during the infusion or up to several hours after the infusion. Infusion reaction symptoms typically resolve on their own within 24 hours and can usually be managed at home. For patients with more severe symptoms medications can be used to treat the infusion reaction symptoms. Uncommonly, patients have needed to be hospitalized for infusion reactions.

2. ARIA

This has become a new word in the vocabulary of everyone in the AD field. ARIA stands for "amyloid related imaging abnormality". This means that there may be changes seen on brain MRI scans when a patient is on an amyloid lowering medication, like Leqembi. This is not unique to Leqembi and has been seen in many drugs that have been tested for reducing the AD amyloid protein level in the brain. ARIA is the reason that routine MRI scanning is part of the Leqembi treatment protocol. It is also why patients taking Leqembi who experience a change in neurological symptoms need to be evaluated and possibly have a non-scheduled MRI scan on an urgent basis. This is another reason why patients have to be able to take brain MRI scans to be a candidate for treatment with Leqembi.

THERE ARE TWO TYPES OF ARIA, CALLED ARIA-E AND ARIA-H.

ARIA-E stands for amyloid related imaging abnormality with edema or effusion. This means that on a brain MRI scan there are changes in the brain that are related to fluid leakage from the blood vessels. This was seen in 12.6% of the patients treated with Leqembi in the main study. Most of the ARIA-E cases were seen only on MRI scans and the patients had no symptoms. Some of the patients with ARIA-E had symptoms (2.8%). When symptoms occur with ARIA-E they can range from mild to severe.

ARIA-H stands for amyloid related imaging abnormality with hemosiderin deposition. This means that the brain MRI scan shows evidence of hemosiderin, from blood, deposited in the brain. This MRI finding indicates that there has been leakage of blood from blood vessels in the brain. ARIA-H was seen in 17.3% of the patients treated with Leqembi in the main study. Most of the ARIA-H cases were seen only on MRI scans and the patients had no symptoms. Some of the patients with ARIA-H had symptoms (0.7%). When symptoms occur with ARIA-H they can range from mild to severe.

All cases of ARIA are important. Although most occur without symptoms, some can have symptoms and they can range from mild to severe. If ARIA occurs, with or without symptoms, a careful decision needs to be made by the care provider and the patient about whether the treatment should continue. There can be severe cases of ARIA that lead to hospitalization and there have been cases of death due to ARIA.

These were the most common symptoms in the mild to moderate symptomatic ARIA cases:

- Headache
- Confusion
- Visual changes
- Dizziness
- Nausea
- Gait difficulty

These symptoms occurred in the severely symptomatic ARIA cases:

- Seizures including prolonged seizure
- Severe confusion
- Difficulty staying awake
- Stroke-like symptoms
- Death (in some severe cases)

It is very important for patients treated with Leqembi to report any new symptoms or worsening of previous symptoms. An urgent evaluation should be conducted and an urgent brain MRI is often needed to sort things out.

Considering APOE gene testing results and how the E4 gene changes the risk of having ARIA are important. The risk of ARIA is higher for people with APOE testing that shows they have the E4 gene. This is why it is recommended to have APOE testing done prior to considering the benefits and risks of Leqembi for each individual person.

Each patient that may be a candidate for Leqembi needs to review their overall health status, and their APOE gene type, with their care provider to decide if Leqembi is a good choice for them. This type of joint decision making, based on all the details of each person's case, is very important.

CLOSING COMMENTS

I hope that this "Introduction to What's new in Alzheimer's Disease Treatment" has not only answered some of the basic questions but has helped you discover more questions that you will need to take in to your medical provider to get the answers that best fit your particular circumstance. Remember, there is no "one size fits all" treatment plan for patients with AD. To get the best advice, each person needs their own special circumstances evaluated by a trusted medical provider who knows their individual case.

What's happening today is not the end of the story for disease modifying therapy for AD; it is the beginning of a new treatment era. We expect to see even more options for patients in the near future and in future years. However, for our patients with AD, time is of the essence. Passage of time means the disease continues. Some even say that for AD patients, "time is brain". If DMTs are to help, many experts in the field, including me, feel time is of the essence.

Do your own research now. Bring your questions and concerns in to your medical care provider soon. There is never a better time than right now to get the right answers.

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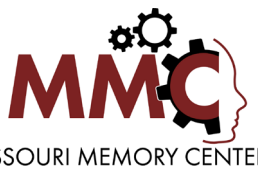
For your notes and questions



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