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Monoclonal Antibodies & Small Molecules: What Clinicians Need to Know

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Monoclonal Antibodies & Small Molecules: What Clinicians Need to Know" is sponsored by Amgen and Novartis.
Amgen and Novartis have provided funding for this podcast and compensated the presenters for participating in this program. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
A number of small-molecule drugs and monoclonal antibodies are currently approved for a variety of common and rare diseases. While both modalities may be considered targeted therapies,[1] each has unique characteristics that may influence how they are used to treat diseases, making it essential that clinicians know the differences between the two and also appropriate uses for each.[2,3,4] These characteristics will be the central focus of today's discussion.

Welcome to ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me is Dr. Peter McAllister, Co-Founder and Chief Medical Officer at the New England Institute for Clinical Research. Dr. McAllister, welcome to the program.

Dr. McAllister:
Thank you, Jennifer. It's a pleasure to be here.

Dr. Caudle:
So, to start off, Dr. McAllister, when we refer to small-molecule drugs and monoclonal antibodies, what exactly are we talking about here? And can you give us a brief overview of these two different modalities?

Dr. McAllister:
Sure. So, small-molecule drugs, just like the name implies, are small clinical entities.[2,5] They are approximately half a kilodalton in size. They are produced through a chemical synthesis, a process that is easily controlled, and results in identical product each time you manufacture.[2,6] Now, monoclonal antibodies, on the other hand, they are biologic agents that are large complex proteins usually around 150 kD in size, which is over 100 times larger than the small-molecule drugs.[2,5,6] Both small-molecule drugs and monoclonal antibodies have unique characteristics in size, in structure and mode of synthesis,[2,3,4] and all of these characteristics can influence the eventual clinical properties of both the small-molecule drugs and monoclonal antibodies in terms of drug target and specificity.[2,4]

Dr. Caudle:
You know, that's a really interesting point that you just brought up about how form influences function. So, can you elaborate on the clinical properties of small-molecule drugs and monoclonal antibodies?

Dr. McAllister:
Sure. So the small-molecule drugs, particularly those that are lipid soluble, can be directed to intracellular or extracellular targets.[2,4] The large size of monoclonal antibodies, on the other hand, prevent the crossing of cellular membranes in target cells, and as a result, the monoclonal antibodies are typically directed toward extracellular targets only, such as receptors on the cell surface. For example, they can be designed to selectively target receptor ligand interactions,[2,6,7] which is why monoclonal antibodies are typically associated with high target specificity;[2] while small-molecule drugs have a lower specificity.[2]

Dr. Caudle:
So, how then do these characteristics affect the administration of small-molecule drugs and monoclonal antibodies respectively?

Dr. McAllister:
Yeah, that's an important question, Jennifer, because the route of administration impacts the frequency of administration. So, small-molecule drugs are typically administered orally, and they require daily dosing due to half-lives that may be measured in hours.[1,2,4] In contrast, monoclonal antibodies are biologic agents, and they are administered parenterally through intravenous, subcutaneous or intramuscular routes,[2,4,6] and they have a long half-life ranging from weeks to months,[8] and that can allow for longer dosing intervals, such as once or twice a month.[2,4,8,9]

These unique properties of dosing frequency and route of administration, it has advantages and disadvantages in terms of patient preference and ease of use. And now, for example, dosing frequency may influence patient adherence since less frequent dosing intervals can be associated with improved adherence.[4,7] Oral administration may be preferred in those patients who have some fear of needles or other injection-related concerns.[10] Now, with respect to ease of parenteral administration, the intravenous or IV route provides a rapid absorption but typically has to be administered in a healthcare facility while the subcutaneous route provides relatively slower absorption but can be self-administered in the patient's home.[4,11]

Dr. Caudle:
So, Dr. McAllister, given those distinctions, how are these 2 modalities distributed in the body once administered?

Dr. McAllister:
So, the small-molecule drugs, they generally have a wide distribution in the tissues and organs and plasma,[12] and there's 2 major pathways of metabolism[13] of the small-molecule drugs. One is metabolism by the cytochrome P450 enzymes through oxidation, which leads to excretion into the urine, and the other is conjugation reactions or glucuronidation leading to hepatic biliary excretion in the stool.[13,14]

Now, monoclonal antibodies in contrast, they have a small range of distribution,[6,12] and they're relatively confined to the vasculature.[4] Moreover, monoclonal antibodies are too large for clearance by kidney or liver mechanisms, and so they're metabolized by 2 primary pathways, nonspecific elimination via the reticuloendothelial system and target-mediated clearance via internalization of the antibody target complex where it undergoes intracellular degradation in the target cell itself.[2,3,4,15,16]

Dr. Caudle:
So, Dr. McAllister, you've given us a great understanding for how these 2 modalities differ in terms of structure, properties, administration routes and distribution. Continuing along those lines, do these unique characteristics influence their respective safety profiles?

Dr. McAllister:
Yes, Jennifer, there are implications for their safety profiles in several respects. Now, for example, the small-molecule drugs have the potential to cross the blood-brain barrier, which may result in increased risk of central nervous system- or CNS-related adverse events.[2,17] The monoclonal antibodies, on the other hand, they don't readily cross the blood-brain barrier because of their large size, and as a result they have minimal distribution in the CNS,[2] and so they are typically not associated with central nervous system-related toxicity.[4,18,19,20,21]

Now, additionally, because small-molecule drugs share a common metabolic and elimination pathway via either the kidney or the liver, concomitant use of these drugs can result in drug-drug interactions.[13,14] Evaluating the likelihood of drug-drug interactions when using the small-molecule drugs is therefore an important part of our clinical consideration.[6] Now, by contrast, since the metabolism and elimination of the monoclonal antibodies doesn't involve the cytochrome P450 enzymes,[6,13] concomitant use of small-molecule drugs and monoclonal antibodies has low potential for drug-drug interactions.[6]

Dr. Caudle:
And as the use of monoclonal antibodies in the clinical setting continues to evolve, what can you tell us about potential toxicities?

Dr. McAllister:

Toxicities may be associated with the monoclonal antibodies, and they are generally classified as on-target effects, also called target-related toxicities, and target-independent toxicities, such as immunogenicity,[2,6] for example. Now, with on-target toxicity adverse events may result from intended cellular effect on intended target tissues. Now, for example, monoclonal antibodies that deplete immune cell expression of CD20 may reduce inflammation, but depletion of immune cells can also increase the risk of opportunistic infections.[2,22] Another example of on-target toxicity may include unintended cellular effects due to monoclonal antibody interactions with target antigens at unintended tissues.[2] Now, example here, think of a monoclonal antibody that inhibits angiogenesis to reduce tumor growth. That may also reduce growth of new blood vessels in healthy tissues leading to, for example, gastrointestinal perforations or complications due to wound healing.[23] Now, immunogenicity, that's a delayed hypersensitivity reaction involving an anti-antibody host response to the specific monoclonal antibody. Immunogenicity is independent of the monoclonal antibody target, and it's a risk with all the monoclonal antibodies.[2,12]

Dr. Caudle:
So with these safety profile differences in mind, I'd like to touch upon any factors we should prioritize regarding the use of either modality in special patient populations. So, can you share some top-of-mind considerations there?

Dr. McAllister:
Certainly. Because of the routes of elimination, the clearance of the small-molecule drugs may be altered in patients with renal or hepatic impairment.[5,6,24,25] Immunogenicity of the monoclonal antibodies may also be a concern in patients who have, say, an upregulated or downregulated immune system.[26] For the monoclonal antibodies and small-molecules, patient types that would necessitate some special attention include pediatric patients, patients[25] with obesity,[16] and pregnant or breastfeeding women.[27-31] For example, in pregnancy, placental drug transfer is dependent on the properties of the placental membrane as well as the pharmacologic properties of the medication.[32] Now, most low molecular weight drugs simply diffuse through the placental tissue while drugs with a higher molecular weight require active transport across the placenta. Now, for the monoclonal antibodies, only a specific class of antibody known as IgG is transferred across the placenta with the transfer being minimal in the first trimester and then increasing throughout the second and third trimesters.[33]

Dr. Caudle:
Well, clearly we've covered a lot of ground today, Dr. McAllister, but before we close out this program, are there any parting comments or takeaway messages you'd like to share with our audience?

Dr. McAllister:
Yeah, sure. I'd just like to reiterate that small-molecule drugs and monoclonal antibodies have unique characteristics and properties that clinicians really need to take into account, particularly when considering treatment in specific patient populations.

Dr. Caudle:
Well, that's a great thought to carry us with, and with that I'd really like to thank my guest, Dr. Peter McAllister, for sharing his expertise and insights on the characteristics of monoclonal antibodies and small-molecule drugs. Dr. McAllister, it was great having you on the program.

Dr. McAllister:
Thank you, Jennifer. It's a pleasure to be here.

Announcer:
This program was sponsored by Amgen and Novartis and is the first in a series of discussions relevant to the practice of neurology. This is ReachMD. Be part of the knowledge.

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