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Integrating Real-World Evidence into Oncology Practice: A Closer Look at Biosimilars

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Integrating Real-World Evidence into Oncology Practice: A Closer Look at Biosimilars" is sponsored by Amgen Oncology. *Amgen Oncology: advancing oncology at the speed of life.*
Your host is Dr. Charles Turck.

Dr. Turck:
Randomized controlled trials have always been considered the gold standard for guiding evidence-based therapeutic decisions in the oncology field.[1,2] But while these trials are primarily conducted in large academic settings to set the bar for treatment guidance, approximately 85% of patients are actually diagnosed and treated in community healthcare settings,[3] which may create a potential gap between RCT outcomes and clinical practice. And that's where real-world evidence, or RWE, needs to be evaluated as to whether it can bridge this gap. So what do we need to know about the emergence of RWE in the oncology field? More on that to come on today's program.
This is ReachMD, and I'm Dr. Charles Turck. Joining me to talk about real-world evidence in oncology is Dr. Jerome Goldschmidt, medical oncology specialist practicing at Blue Ridge Cancer Care and affiliated with the U.S. Oncology Network in Blacksburg, Virginia.
Dr. Goldschmidt, welcome to the program.
Dr. Goldschmidt:
Thanks, Charles. Happy to be here.
Dr. Turck:
Before we begin exploring some emerging applications of RWE, can you give us a brief overview of RCTs and where the need for RWE came from?
Dr. Goldschmidt:
Sure. As I'm sure you know, RCTs are the most trusted method available for validating new treatments based on the safety and efficacy data collected from recipients of those treatments against controls in a double-blinded setting.[4] RCTs are the gold standard by which new therapeutics achieve approval and acceptance.[1,2] The outcomes of RCTs are instrumental in guiding clinical decisions, health policies, clinical practice recommendations, and guidelines.[5]

In terms of the method, RCTs are controlled to help reduce variation, which could otherwise lead to ambiguity regarding benefits or risks during trials. RCTs are generally larger studies of hundreds to thousands of patients which will better distribute clinical variations between the control and the experimental groups, thus limiting biases.[18]

Generally, these methods use some key features such as selection of homogenous patient populations,[5] idealized controlled settings overseen by multidisciplinary teams requiring access to various technologies and treatments,[4] and randomization, which reduces bias and confounding variables.[4] Overall, these methods allow for RCTs to demonstrate clinical safety and efficacy.

So then let's fast forward to the outcomes from RCTs that get carried into clinical practice. We know that clinicians in both academic and community settings draw from these outcomes to help guide several treatment choices. But in both practice environments, and especially in community practices, the results they see are not always in sync with those reported in RCTs. And that's not a big surprise, since in day-to-day practice, or the real world as we define it here, we can't account for the same factors that RCTs can standardize, such as patient populations, disease severity, comorbidities, or concomitant medications.[2] I think this is a fundamental disconnect that creates a need to bridge RCT outcomes with real-world evidence.

Dr. Turck:
So with that background in mind, Dr. Goldschmidt, let's focus on RWE studies as potential bridges to those translational gaps you just

talked about. Can you tell us about RWE studies and their overall value proposition?

Dr. Goldschmidt:

Real-world evidence is the clinical data obtained outside of traditional RCTs.[6] Though I think of it as less of an alternative and more of a mutually complementary data source alongside RCTs. Because in my opinion, the resulting combination of information can provide very powerful evidence-based clinical guidance. RWE helps to fill in the gaps, if you will, of our knowledge base from the original gold standard, and using data provided by electronic medical records, government databases, and insurance claims among other sources.

The goal of RWE studies is to improve healthcare decision-making in dynamic settings. And the data gathered can help provide a more complete picture of the effectiveness, impact, and tolerability of treatments. But we're realizing that there's a lack of common understanding around how to interpret RWE, which creates misreads of some data, overreliance on limited data points, and varying levels of disappointment when the findings from RWE studies aren't as clear-cut as RCTs.

Compared to RCT results, RWE findings with more limited insights will sometimes appear like they're scratching the surface on specific questions without providing the cleanest answer. But remember, they're mapping uncharted waters and putting RCT hypotheses up against real-world settings, and that can have enormous value in and of itself. We see this with drug development. A drug performs very well in the initial screening process in animal studies, only to fall short in the clinical trial in humans.

Dr. Turck:

So up to this point, we've been looking at RWE studies and RCTs generally, but now let's apply RWE to the field of oncology and alongside the emergence of biosimilars. What should we know to start?

Dr. Goldschmidt:

Well, I'd like to start off by characterizing these treatments. The FDA defines biosimilar as, "a biological product that is highly similar to a U.S. licensed reference biological product for which there is no clinically meaningful differences in safety, purity, or potency." [9] This is a class of therapeutic agents that have been used in Europe for over 10 years, with well-established safety and efficacy. But it's much more recently entering the scope of oncology practice in the U.S. Biosimilars are becoming increasingly utilized alternatives to effective yet expensive cancer treatments, given their comparable efficacy and safety to the reference products.[10]

Dr. Turck:

And are the drug approval requirements similar between biosimilars and their reference products?

Dr. Goldschmidt:

Actually, they're pretty distinct. Before a biosimilar can be approved, a comparative clinical trial must demonstrate equivalence in a sensitive patient population.[11] But let's just consider that definition because the terminology comes from the FDA guidance document entitled: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry. And unless you're versed in regulatory speak, some of the nuance is lost there.

First, let's talk about this comparative clinical trial, since that's an important point of distinction. Most approvals for reference products are based on significant clinical trial data, but only one clinical trial is required for the approval of a biosimilar.[12]

And that clinical trial often uses response rate as the endpoint, which can be disconcerting when we may be used to seeing overall survival, or progression-free survival as endpoints. Response rate is used here because it often provides a quicker measure of assessing biosimilarity than a survival endpoint, which makes it possible for biosimilars to keep costs down. Also, the purpose of the trial is to compare the two agents in a clinical setting, not to change or otherwise informed treatment, which is why response rate is used as an endpoint.

Next, there is the concept of demonstrating equivalence. Prior to beginning the trial, there's an agreement made with the health authorities on an equivalence margin for the differences in the response rate, and the confidence interval needs to fall within that margin.[14,15] We compare the response rate of both agents by looking at either the difference, one minus the other, or the ratio, one divided by the other. For the difference, we're looking for a number very close to zero, like 35 minus 35 equals zero. And for the ratio, we're looking for a number very close to one, like 35 divided by 35 equals one, both with narrow confidence intervals. Usually, the confidence interval is set at a plus or minus 15%. Although with the health authorities' approval, wider or narrower margins can be used. And that margin shows what will be accepted as equivalent. So results falling above the upper bound, would suggest superiority, while results falling below the lower bound would suggest inferiority.

And finally, we need to define what a sensitive population is. Since this word causes a lot of concern, as in, are patients being pre-selected to guarantee a win? The answer is no. But these trials need to reduce as many variables as possible from the patient population to isolate the impact of the treatment and enable head-to-head comparisons where possible. So you're looking for a patient population that's not heavily pretreated. Ideally, where single agent therapy is recommended.

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Jerome Goldschmidt about the integration of RWE studies into oncology practice. So Dr. Goldschmidt, taking those factors into account, it sounds like there are some potential gaps or blind spots that can emerge from these narrower approval requirements for biosimilars.

Dr. Goldschmidt:
Exactly, but this is where RWE comes in, since RWE studies can help bridge gaps formed, sometimes from biosimilar approval processes that incorporate just one trial with one endpoint in a patient population that may not represent where that agent is most frequently being used. RWE studies can tell us a lot about the different patient types and clinical settings for where a product is being used. We can identify differences or disparities in care, and we can see when, where, and how a biosimilar is being incorporated, and whether it's used in new patients or patients who have been previously exposed to the reference product.

Dr. Turck:
But I take it that within the oncology field, RWE won't solve every issue on its own. So what challenges persist for oncologists with respect to biosimilars in the integration of RWE?

Dr. Goldschmidt:
First, a product has to be used in the real world, to generate real-world evidence. But biosimilar adoption can largely depend on the position of each biosimilar being marketed. And this creates an issue of uptake for real-world data. Since the first biosimilar to be marketed will often get the bulk of the market share, sometimes for up to one and a half years following launch, this can prolong the time interval needed to obtain real-world data on other products entering the market.

Second, there's the broadness of the uptake. RWE can be of particular interest in certain tumor types that were approved based on data extrapolation without direct clinical testing. But a challenge here is that the actual use of RWE can be low either because of a relatively low incidence of those particular tumor types, or because of a reluctance to use a product without much existing clinical data in that setting.[16] So once again, we're confronting that need for a product to be used in the real world in order to generate RWE.

Third, there's occasional confusion among my colleagues toward the fundamentals of biosimilars and the variety of ways we can generate and interpret RWE to assess them.[10] Is this a study that looks at insurance claims database or EMRs? Are these live people looking at the data? Or is it based on algorithms? Data is only as good as the organization and completeness of information contained in those databases or charts. So if any fields are left incomplete, incorrect, or missing altogether, results can be significantly skewed.

Lastly, but most importantly from my vantage point, there's still a general lack of awareness for biosimilars from providers to patients.[10] But I think that's changing. A recently launched Community Oncology Alliance, or COA, campaign has been aimed at educating community oncologists on the approval process and use of biosimilars, and this has helped to increase the likelihood of providers prescribing a biosimilar.[17]

Dr. Turck:
Well, Dr. Goldschmidt, this is clearly a multifaceted topic between the introduction of biosimilars in oncology and the evolving role of RWE alongside it. But before we close, are there any takeaways on RWE that you'd like our audience to keep in mind?

Dr. Goldschmidt:
So the key takeaway for me is that RWE closes knowledge gaps between randomized controlled trial settings and community practice settings, and takes into account different patient populations, tumor types, and practice conditions compared to RCTs. For biosimilars, RWE provides strong setting-specific evidence to encourage adoption of biosimilars with confidence by providing additional efficacy and safety data within patient populations that aren't otherwise represented in biosimilarity trials. And that's an important factor influencing whether clinicians use reference products by default or consider using biosimilars.

Dr. Turck:
Thank you for sharing those important takeaways on this new approach to guiding evidence-based therapeutic decisions as we come to the end of today's program. I want to thank my guest, Dr. Jerome Goldschmidt, for helping us better understand this emergence of real-world evidence in the oncology field.
Dr. Goldschmidt, it was great speaking with you today.
Dr. Goldschmidt:
Thanks so much for having me!
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