How real-world experience shapes clinical practice

Following one antibiotic's journey over time

While clinical trials are vital in getting drugs to market, these tightly-controlled studies are unable to address the diverse needs of many patients in the real world. Real-world experience research can bridge the gap between clinical trials and clinical practice. Recently, Dr Mark Redell of Melinta Therapeutics, USA, introduced a collection of research experiences on the real-world use of the antibiotic oritavancin (Orbactiv). Research like this has the potential to allow many more patients to benefit from a drug by opening up new treatment options for the elderly, for those with other health conditions, and many more.

Any drug used for medicinal purposes must be both safe and effective. Around the world, randomised controlled trials (where participants are randomly allocated to either an experimental or control group) are recognised as a trusted, well-established process for assessing the safety and efficacy of drugs for human use. Clinical trials of this type are used to answer very specific questions; such as, is this drug safe and effective in treating this disease? However, these traditional clinical trials are mostly separate from routine clinical practice and are designed to control variability in patients suffering from a specific infection.

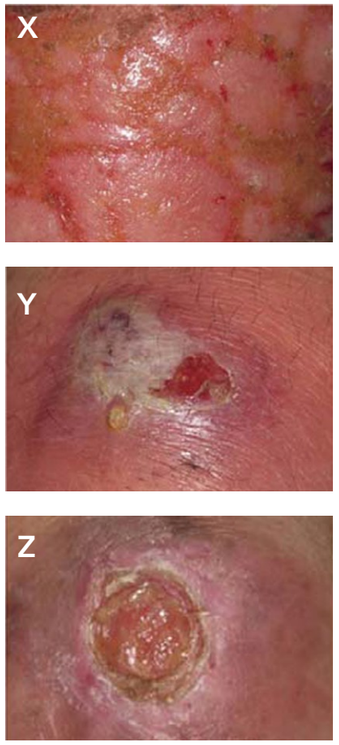
Out of necessity, patients who do not meet the narrow study inclusion criteria – the elderly, or people with health conditions who are taking other medications, for example – are excluded from, or greatly under-represented in these trials. However, in the real world, doctors treat many patients who fall within these categories with little data which can predict efficacy or safety in these patient populations.

Real-world evidence (RWE) studies have the potential to bridge the gap between randomised controlled trials and clinical practice. These post-marketing (i.e. after the drug has been released onto the market) studies can shed light on how a drug actually performs in the real world: whether it is effective and safe in patients who fall outside the population assessed by phase 3 clinical trials. RWE can come from a variety of different sources, including well controlled clinical trials, registries, health records, and insurance claim databases.

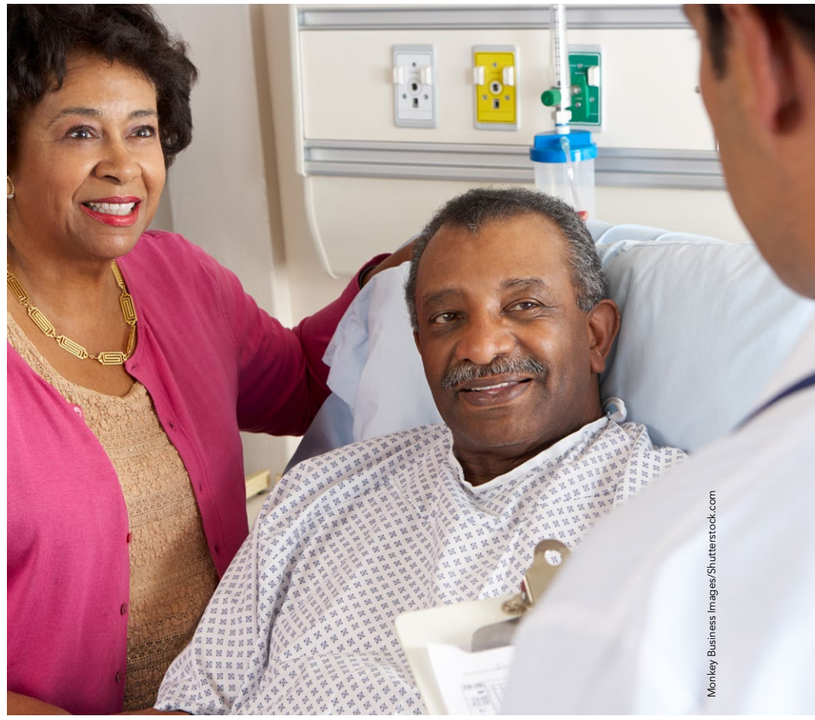
ANTIBIOTICS IN THE REAL WORLD

Prescribers considering using a newly-approved antibiotic in a patient who falls outside the narrow population covered by phase 3 clinical trials face a challenge. How can they know whether the antibiotic will cure an infection, or whether it carries an undue risk, for example, in obese or immunosuppressed patients? Can it be used to treat infections caused by other pathogens not studied pre-marketing or in other infection types? In a real-world setting, only post-approval experiences can answer these questions. Rather than waiting for additional clinical studies from a sponsor, which are costly and may take several years, publication of real-world experiences can address data gaps and share implementation strategies in natural and real-life healthcare settings.

Sharing real-world experiences and data can help prescribers make sound clinical judgements. Reasonably-sized real-world registries study patients who reflect the prescriber's day-to-day patient demographics but do not necessarily reflect those enrolled in clinical trials for a specific drug. Publication of these data and findings help prescribers and researchers to understand how the drug works in patients with complex infections and multiple comorbidities (when a patient has one or more additional conditions, alongside their primary illness). Often, a prescriber has limited treatment options for patients in these situations. Access to RWE resources could help to meet this medical need. Registries of RWE lack the scientific rigour of clinical trials: data is collected retrospectively, and they are typically non-comparative and non-randomised. Nevertheless, RWE data can validate and complement the knowledge gathered from clinical trials on the benefits and risks of a treatment.



X (cellulitis), wound (Y) and abscess (Z).



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Real-world evidence (RWE) data can validate and complement the knowledge gathered from clinical trials on the benefits and risks of a treatment.

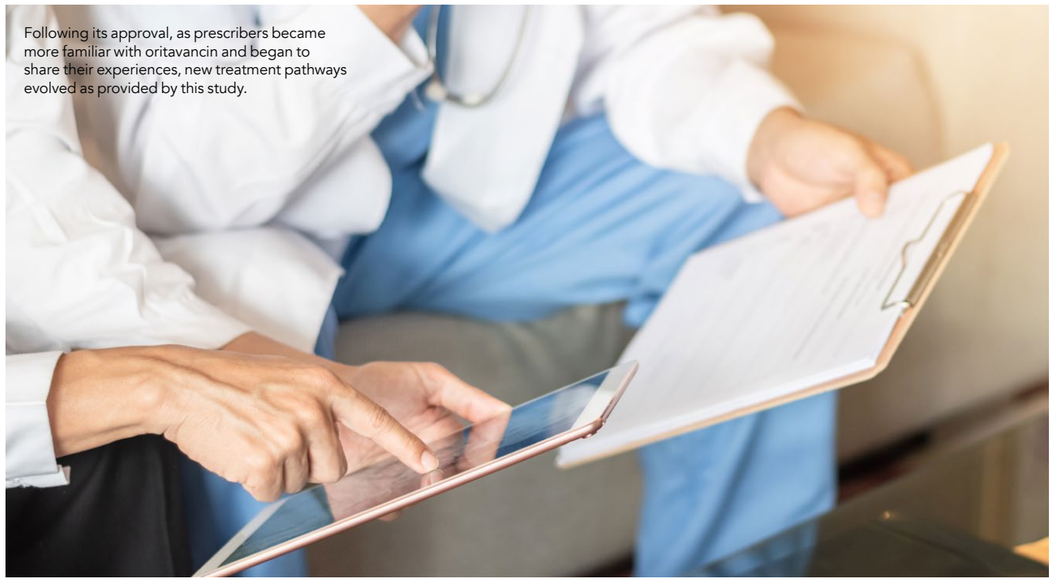
Recently, Dr Mark Redell, an expert in post-marketing research at Melinta Therapeutics, introduced a collection of studies in the journal *Drugs – Real World Outcomes* on the antibiotic oritavancin (Orbactiv). Oritavancin is designed to treat acute bacterial skin and skin structure infections, such as those linked to cellulitis, abscesses and wounds. The drug is administered as a single dose over the course of three hours. Oritavancin was approved for use in the US in August 2014 and in the EU in March 2015. A number of different Gram-positive bacteria (i.e. bacteria with a particular type of cell wall), including methicillin-resistant *Staphylococcus aureus* (MRSA) are known to be susceptible to oritavancin.

Real-world evidence studies have the potential to bridge the gap between randomised controlled trials and clinical practice.

REAL-WORLD USE OF ORITAVANCIN

Four separate studies described RWE on the use of oritavancin in treating bacterial skin and skin structure infections. Overall, these studies covered 451 patients, who were treated with oritavancin in emergency rooms, outpatient units and general hospital wards. The various investigators used both single-centre and multi-centre databases, covering observational and retrospective cohorts. The patients receiving oritavancin were compared to outcomes associated with other accepted and widely used therapies and management styles, called standard-of-care.

Four studies suggested that certain treatment pathways with oritavancin could allow patients to be discharged earlier, or even avoid hospitalisation altogether. In particular, seeking the advice of a pharmacist at an early stage, in collaboration with case management and infectious disease specialists, identified patients best



Following its approval, as prescribers became more familiar with oritavancin and began to share their experiences, new treatment pathways evolved as provided by this study.

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suited to oritavancin treatment. Early discharge was not only beneficial to the patient's health, but also saved money by reducing hospital resources and the length of hospital stay.

Three additional studies looked at RWE with oritavancin and other infection types. Although not approved for use, these studies examined oritavancin as a treatment for Gram-positive osteomyelitis (an infection in the bone) and septic arthritis (infection of a joint). Both the number of doses and the timing of the doses differed between studies, making a comparison difficult, but success in treatments were favourable and comparable to past studies with other drugs.

However, together the results suggest that oritavancin may reduce length of hospital stay and likelihood of readmission in patients with these conditions, which are often challenging and time-consuming to treat. Oritavancin also appeared to carry a low risk of adverse effects in these conditions, suggesting that it could be a convenient, effective and safe treatment option in bone and joint infections.

While the data are promising, more studies should be conducted to confirm the findings of the authors of these real-world studies.

POST-MARKETING PROGRESS

Following the approval of oritavancin, many prescribers used the drug for its approved indication, as expected: acute bacterial skin and skin structure infections. At the time of drug approval, there was obviously no real-world clinical experience with oritavancin which could supplement the efficacy and safety data collected during clinical trials. However, as prescribers became more familiar with the antibiotic and began to share their experiences, new treatment pathways evolved as provided by the studies published in the journal.

Post-marketing RWE allows a wider, more diverse population of patients to potentially benefit from antibiotics such as oritavancin.

The new clinical options, developed through shared experience of benefits and risks in real-world settings, allowed oritavancin to meet several important clinical needs. In particular, RWE allowed the drug to benefit a more diverse spectrum of patients, many of whom would have been ineligible for the original clinical trials. Questions such as who should receive the drug, appropriate settings for administration, and efficacy in deep-seated and severe Gram-positive infections, could begin to be answered. Real-world knowledge of the antibiotic demonstrated that economic benefits could be maximised, through either early discharge or removing the need for hospital admittance.

In the real world, patients suffering from skin infections can be a varied and complicated group. Post-marketing RWE allows a wider and more diverse population of patients to potentially benefit from a drug like oritavancin. The ever-growing store of knowledge and experiences can also be used to support the precision medicine model, in which therapies and treatments are tailored to a specific subgroup of patients, or even individuals. This idea, rather than a "one-drug-fits-all" approach, allows the full potential of a medication, in helping as many patients as possible. Finally, RWE can answer questions that traditional randomised controlled trials simply cannot.

Behind the Research

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Research Objectives

Real-world studies provide additional information on the safety and efficacy of an antibiotic, oritavancin, in patients not studied pre-marketing and may guide treatment decisions by addressing several knowledge gaps.

Detail

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Funding
Melinta Therapeutics

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References

Redell, M. 2020. Real-World Evidence Studies of Oritavancin Use in GramPositive Infections Augment Randomized Controlled Trials to Address Clinical and Economic Outcomes. *Drugs – Real World Outcomes* 7 (Suppl 1):S2-S5. doi:10.1007/s40801-020-00189-5

Articles which follow in this supplement are provided as open access.

Personal Response

Are there many other drugs for which the RWE has been studied and drawn together in this way?

Several antibiotics have been studied in the post-marketing phase and include platforms such as registries, case series, and comparative studies. Common goals include efficacy and safety of such agents in patient populations not studied in phase 3 clinical trials, but also to better understand how prescribers use these agents once available in the marketplace. RWE also provide ideas for additional studies in patients with few therapy options and sometimes can result in powerful studies for additional approval by regulatory committees.