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How Biosimulation Can Bring New Immuno-oncology Treatments to Patients

Immuno-oncology, which harnesses the patient's immune system to fight cancer, is one of the hottest areas in drug development today. In recent years, the Food and Drug Administration (FDA) has granted breakthrough therapy designations to multiple immuno-oncology drugs for a variety of oncology indications including advanced non-small cell lung cancer[1] and melanoma.[2] Over the last two decades, pharmacokinetics/pharmacodynamics (PK/PD) modeling and simulation (M&S) has played a growing role in oncology drug development. M&S (also known as biosimulation) can help support some of the unique challenges that immuno-oncology programs face.

A 21st century treatment with 19th century roots

When it comes to immuno-oncology treatments, everything old is new again. In the late 19th century, an intrepid physician named William Coley was struck by the case of a deathly ill cancer patient who made a seemingly miraculous recovery after contracting a serious bacterial infection.[3] This strange case inspired him to deliberately infect another cancer patient with bacteria. Again, the patient who was suffering from an advanced-stage sarcoma, recovered. Dr. Coley kept refining his treatment, known as Coley's toxins. A lack of understanding of the immune system meant that no one knew exactly how this treatment worked. Eventually, Coley's toxins fell into disuse with the emergence of radiation therapy in the early 20th century.

How the immune system targets cancer cells

In addition to protecting us from pathogens, the immune system also identifies and destroys cancer cells. Briefly, the cancer-immunity cycle works as an interplay between T-cells and tumor cells.[4] Dying tumor cells release antigens, which trigger the activation of specific T-cells. The activated T-cells migrate into the tumor where they can kill cancer cells. This causes further release of antigens and maintains the cycle.

Immunotherapy drugs rev up the immune system to fight cancer

Immuno-oncology drugs bind their pharmacologic targets to stimulate the immune response. Many targets play a general role in the immune system. Drugs selective for these targets risk causing systemic immune-related adverse reactions. On the other hand, several pharmacological targets are selective for the T-cell/tumor interaction, eg, PD-1/PD-L1.

PD-1: A key immune checkpoint in cancer

PD-1 (programmed cell death 1) is a protein that serves as an immune checkpoint. It downregulates the immune system by preventing T-cell activation. PD-1 helps reduce autoimmunity and promotes

Challenge

Immuno-oncology drug timelines tend to be highly condensed by the opportunity for fast-track approval. In addition, informing dosing using early clinical data is difficult due to a lack of early clinical biomarkers.

Solution

Biosimulation technology can help establish the relationship between drug exposure and safety/efficacy, determine the therapeutic window, predict PK in subpopulations, and assess the competitive safety/efficacy landscape.

Benefit

Modeling and simulation approaches help immuno-oncology programs to establish dosing regimens, understand the factors causing variability in exposure, inform the drug label, and make better decisions on competitive positioning.

Clinical development in immuno-oncology programs follows a condensed timeline wherein classical development phases are not readily discernible. In this compressed time line, modeling and simulation is applied continuously to answer questions; no clear separation exists between learn-confirm cycles.

self-tolerance. This checkpoint protein inhibits the immune system by promoting apoptosis in antigen-specific T-cells and, simultaneously, reducing apoptosis in regulatory T cells (suppressor T cells). Cancer cells overexpress PD-1 ligands (PD-L1/PD-L2), which bind PD-1 to suppress the immune system.

Immuno-oncology drugs can target the PD-1 signaling pathway in one of two ways. PD-1 inhibitors target PD-1 on T cells whereas PD-L1/PD-L2 inhibitors target the PD-L1/PD-L2 ligand expressed on tumor cells. These inhibitors are generally antibodies. Both types of inhibitors release the "brakes" that the tumor places on the immune system so that T-cells are able to identify and kill cancer cells.

The pharmaceutical industry has jumped on the "PD-1 bandwagon." Two anti-PD-1 drugs (nivolumab[5] and pembrolizumab) have been approved and at least nine other PD-1/PD-L1 drugs are in varying stages of clinical development. Likewise, a rising trend is combining immuno-oncology drugs with other anticancer treatments including standard chemotherapies, targeted therapies, other immuno-modulators, and anticancer vaccines.

Anti-PD-1 treatments show promise

Initial clinical results of anti-PD1 treatments have been promising. Objective response (OR) rates observed in multiple cancer types were well beyond the rates achieved with the present standard of care (SOC). In the meantime, these drugs also improved overall survival (OS) for cancer patients. Specifically in advanced melanoma, superior efficacy was observed compared to dacarbazine, the pre-immunotherapy SOC, as well as compared to ipilimumab, a CTLA-4 inhibitor and the first immune checkpoint inhibitor. Patient PD-L1 status appears to predict the anti-PD-1 drug response.[6] Since PD-1 inhibitors block PD-1 from interacting with its tumor cell ligands to "revive" the immune system, it's no surprise that patients with PD-L1 positive tumors have better outcomes than PD-L1 negative patients.

Clinical development in immuno-oncology

The standard clinical development trajectory follows a phased, linear course. Clinical pharmacology characterization is largely done through dedicated healthy volunteer studies in phase I. For these programs, M&S is applied in learn-confirm cycles which inform the next phase of development and generally take place around well-defined milestones in the program.

In contrast, clinical development in immuno-oncology programs thus far has followed a much more condensed time line wherein the classical drug development phases are not readily discernible. Clinical pharmacology is generally characterized as part of safety/efficacy studies rather than through healthy volunteer studies. In this compressed timeline, M&S is continuously applied to address a variety of questions; no clear separation exists between learn-confirm cycles.

Challenges and opportunities in immuno-oncology clinical development

The unique trajectory of immuno-oncology programs means that their sponsors face distinct challenges. For example, the timelines for development tend to be highly condensed by the opportunity for fast-track approval. In addition, a lack of early clinical biomarkers means informing dosing using early clinical data is difficult.

Immuno-oncology has its upsides as well. Opportunities frequently arise for extending the drug to multiple oncology indications. M&S can help leverage the data from one indication to support development, and ultimately, approval for another. Moreover, the potential for developing multiple combination treatments can increase a drug program's value.

Leveraging biosimulation increases the probability of regulatory and commercial success

PK/PD M&S can be leveraged throughout the development of an immuno-oncology drug. Early in development, M&S can help translate pre-clinical data from mouse xenograft models to support establishing the clinical dose regimens. Once a drug candidate moves into the clinic, its safety and efficacy profile must be characterized. Pharmacometrics can help establish the relationship between drug exposure and safety and efficacy parameters to support and justify the dosing regimen and determine the drug's therapeutic window.

Regulatory agencies expect sponsors to understand the intrinsic and extrinsic factors that might cause variability in drug exposure. In the absence of dedicated clinical pharmacology studies, population PK analysis can be performed on sparsely sampled PK data from patients to understand which factors significantly impact exposure. Furthermore, semi-physiological approaches can be used to predict PK at the site of action. These models can also help predict PK in other populations that the sponsor might want to include in the drug label.

Finally, regulatory success alone is no guarantee of commercial success. By understanding the competitive landscape, sponsors are better positioned to make critical decisions. Model-based meta-analysis (MBMA) of publicly available clinical trial data can be used to assess a compound's safety and efficacy profile compared to the SOC and/or competitor drugs in development. MBMA enables indirect comparison, taking into account the impact of treatment, patient population, and trial characteristics. This type of analysis can help estimate the probability that a drug can differentiate itself in terms of efficacy and/or safety from competitors in the same drug class or across drug classes. In the quickly evolving immuno-oncology landscape, MBMA and associated clinical trial outcome databases allow sponsors to stay on top of new developments and understand the relative merits of their drug. By incorporating biosimulation approaches into the fabric of an immuno-oncology program, sponsors will be better positioned to deliver safer and more effective medications to patients.

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