Overview of Gene Therapy

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- No relevant disclosures to declare

Objectives

- Describe the history and principles of gene therapy
- Provide an overview of recent developments in gene therapy
- Discuss clinical and operational considerations for the pharmacist
- Demonstrate importance of organizational readiness

Historical Overview (1 of 2)

- Early Concepts (1960s-1970s)
  - The idea of gene therapy was first proposed in the 1960s and 1970s.
  - Scientists envisioned using genetic material to correct or replace defective genes responsible for various diseases.

- Milestones in the 1980s
  - 1980: The U.S. Supreme Court ruled that living organisms could be patented, setting the stage for biotechnological advances.
  - 1989: The first approved gene therapy trial took place, treating a 4-year-old girl with a rare genetic disorder called severe combined immunodeficiency (SCID).

Historical Overview (2 of 2)

- Setbacks and Progress (1990s-2000s)
  - In the early 1990s, setbacks occurred, including the death of a patient in a clinical trial, leading to increased regulatory scrutiny.
  - Despite setbacks, progress was made, and researchers developed safer vectors (typically viruses) to deliver therapeutic genes into target cells.

- Advancements in the 21st Century
  - The 2000s and beyond saw significant advancements in gene therapy, with successful treatments for diseases like inherited blindness and certain types of leukemia.
  - CRISPR-Cas9, a revolutionary gene-editing technology, emerged, allowing for precise modification of specific genes.

Principles of Gene Therapy (1 of 2)

- Delivery Mechanisms
  - Viral Vectors: Viruses are modified to carry therapeutic genes into target cells. Adeno-associated viruses (AAVs) and lentiviruses are commonly used.
  - Non-viral Vectors: Liposomes and other non-viral methods can also be used for gene delivery.

- Types of Gene Therapy
  - Somatic Gene Therapy: Involves the modification of genes in non-reproductive cells. Changes are not passed on to future generations.
  - Germline Gene Therapy: Involves modifying genes in reproductive cells, potentially passing changes to offspring. This raises ethical concerns and is currently not widely practiced.

- Gene Editing Technologies
  - CRISPR-Cas9: This revolutionary technology allows precise editing of genes by cutting DNA at specific locations and enabling the introduction of desired changes.
  - TALENs and Zinc Finger Nucleases: Other gene-editing tools that have been used, though CRISPR-Cas9 is the most widely adopted.

Principles of Gene Therapy (2 of 2)

- Challenges and Ethical Considerations
  - Challenges include the immune response to viral vectors, off-target effects in gene editing, and the potential for unintended consequences.
  - Ethical considerations include the risk of unintended genetic changes, the potential for enhancement rather than treatment, and issues related to consent and access.

- Regulatory Landscape
  - Regulatory agencies, such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), play a crucial role in ensuring the safety and efficacy of gene therapy products.

Notable Trends and Developments (1 of 3)

- CRISPR Technology Advancements
  - The CRISPR/Cas9 gene-editing technology continued to be a major player in gene therapy.
  - Researchers were exploring ways to enhance its precision, reduce off-target effects, and address ethical concerns.

- Expansion of Approved Therapies
  - Several gene therapies received regulatory approvals for various genetic disorders and rare diseases.
  - Notable examples included Luxturna for inherited retinal disease and Zolgensma for spinal muscular atrophy.

- Advances in Delivery Systems
  - Improvements in gene delivery systems were a focus of research.
  - Scientists were working on developing more efficient and targeted delivery methods, such as viral vectors or nanoparticles, to deliver therapeutic genes to specific cells and tissues.

Notable Trends and Developments (2 of 3)

- Cancer Gene Therapies
  - There were ongoing efforts to develop gene therapies for cancer, including CAR-T cell therapies and oncolytic viruses.
  - These approaches aimed to harness the patient's immune system to target and eliminate cancer cells.

- RNA Therapies
  - Beyond DNA-based gene therapies, there was increased interest in RNA-based therapies, such as mRNA vaccines and RNA interference (RNAi) technologies.
  - mRNA vaccines, in particular, gained prominence due to their success in the development of COVID-19 vaccines.

- Gene Editing in Clinical Trials
  - Several clinical trials were underway to assess the safety and efficacy of gene editing techniques for various genetic disorders.
  - This included not only CRISPR but also other technologies like zinc finger nucleases and TALENs.

Notable Trends and Developments (3 of 3)

- Global Collaborations and Investments
  - Gene therapy research and development saw increased collaboration between academia, biotech companies, and pharmaceutical giants.
  - There was also a rise in funding and investments in gene therapy startups.

- Ethical and Regulatory Considerations
  - As gene therapy applications expanded, ethical and regulatory discussions intensified.
  - The field faced challenges related to ensuring patient safety, addressing long-term effects, and navigating the ethical implications of gene editing.

Clinical Considerations for the Pharmacist (1 of 2)

- Patient Assessment and Education
  - Pharmacists need to be actively involved in patient assessment, ensuring a thorough understanding of the patient's medical history, existing medications, and potential drug interactions.
  - Providing patient education is critical, as gene therapies often involve novel treatments with unique mechanisms of action.
  - Pharmacists can help ensure patients understand the benefits, risks, and potential adverse events of gene therapies.

- Medication Management:
  - Gene therapies may require specialized handling and administration.
  - Pharmacists should be well-versed in the proper storage, preparation, and administration procedures for these therapies.
  - Collaborating with healthcare providers to establish protocols for monitoring and managing potential adverse effects is essential.

Clinical Considerations for the Pharmacist (2 of 2)

- Monitoring and Adverse Event Management
  - Pharmacists play a key role in monitoring patients for treatment response and potential adverse events.
  - Pharmacists should work closely with the healthcare team to establish monitoring parameters and protocols.
  - Pharmacists need to be familiar with the specific adverse event profiles associated with gene therapies and understand appropriate interventions.

- Collaboration with Healthcare Team
  - Effective communication and collaboration with other healthcare professionals, including physicians, nurses, and genetic counselors, are essential for optimal patient care.
  - Participating in multidisciplinary team meetings and contributing to treatment planning can help ensure a comprehensive approach to patient care.

Clinical Considerations for the Pharmacist (Example)

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

(yes-kar-ta)

THE MOST IMPORTANT INFORMATION TO KNOW ABOUT YESCARTA®

YESCARTA may cause side effects that are life-threatening and can lead to death. Call or see your healthcare provider or get emergency help right away if you get any of the following:

- Fever (100.4°F/38°C or higher)
- Difficulty breathing
- Chills or shaking chills
- Confusion
- Dizziness or lightheadedness
- Severe nausea, vomiting, or diarrhea
- Fast or irregular heartbeat
- Severe fatigue or weakness

It is important to tell your healthcare provider that you received YESCARTA and to show them your YESCARTA Patient Wallet Card. Your healthcare provider may give you other medicines to treat your side effects.

IMPORTANT FACTS

This is only a brief summary of important information about YESCARTA and does not replace talking to your healthcare provider about your condition and your treatment.

- Your blood cells will be sent to a manufacturing center to make your YESCARTA.
- Before you get YESCARTA, you will get 3 days of chemotherapy to prepare your body.
- When your YESCARTA is ready, your healthcare provider will give it to you through a catheter placed into your vein (intravenous infusion). The infusion usually takes less than 30 minutes.
- You will be monitored where you received your treatment daily for at least 7 days after the infusion.
- You should plan to stay close to the location where you received your treatment for at least 4 weeks after getting YESCARTA. Your healthcare provider will help you with any side effects that may occur.
- You may be hospitalized for side effects and your healthcare provider will discharge you if your side effects are under control, and it is safe for you to leave the hospital.
- Your healthcare provider will want to do blood tests to follow your progress. It is important that you do have your blood tested. If you miss an appointment, call your healthcare provider as soon as possible to reschedule.

ABOUT YESCARTA

YESCARTA is a prescription medicine used to treat two types of non-Hodgkin lymphoma:

- large B-cell lymphoma when your first treatment did not work or your cancer returned within a year of first treatment, OR when at least two kinds of treatment have failed to control your cancer.
- follicular lymphoma when at least two kinds of treatment have failed to control your cancer.

YESCARTA is different than other cancer medicines because it is made from your own white blood cells, which have been modified to recognize and attack your lymphoma cells.

BEFORE RECEIVING YESCARTA, TELL YOUR HEALTHCARE PROVIDER ALL ABOUT YOUR MEDICAL PROBLEMS, INCLUDING IF YOU HAVE OR HAVE HAD:

- Neurologic problems (such as seizures, stroke, or memory loss)
- Lung or breathing problems
- Heart problems
- Liver problems
- Kidney problems
- A recent or active infection

Tell your healthcare provider about all the medications you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

HOW YOU WILL RECEIVE YESCARTA

- Since YESCARTA is made from your own white blood cells, your blood will be collected by a process called "leukapheresis" (loo-kah-fur-ee-sis), which will concentrate your white blood cells.

WHAT TO AVOID AFTER RECEIVING YESCARTA

- Do not drive, operate heavy machinery, or do other dangerous things for 8 weeks after you get YESCARTA because the treatment can cause sleepiness, confusion, weakness, and temporary memory and coordination problems.
- Do not donate blood, organs, tissues, or cells for transplantation.

THE POSSIBLE OR REASONABLY LIKELY SIDE EFFECTS OF YESCARTA

The most common side effects of YESCARTA include:

- Fever (100.4°F/38°C or higher)
- Low white blood cells (can occur with a fever)
- Low red blood cells
- Low blood pressure (dizziness or lightheadedness, headache, feeling tired, short of breath)
- Fast heartbeat
- Confusion
- Difficulty speaking or slurred speech
- Nausea
- Diarrhea

These are not all the possible side effects of YESCARTA. Call your healthcare provider about any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

GET MORE INFORMATION

- This is only a brief summary of important information about YESCARTA. Talk to your healthcare provider to learn more.
- Visit www.YESCARTA.com or call 1-844-454-KITE (5483).

Source: Kite, A Gilead Company - Yescarta (April 2022)

Operational Considerations for the Pharmacist (1 of 2)

- Supply Chain Management
  - Gene therapies may have unique supply chain requirements due to their specialized nature.
  - Pharmacists need to work closely with suppliers and manufacturers to ensure a consistent and reliable supply of these therapies.
  - Managing inventory, including proper storage conditions and expiration date monitoring, is crucial to prevent product wastage.

- Billing and Reimbursement
  - Understanding the complexities of gene therapy reimbursement is essential.
  - Pharmacists can play a role in facilitating the billing process by ensuring accurate documentation of the therapy administration and supporting the reimbursement application process.

Operational Considerations for the Pharmacist (2 of 2)

- Regulatory Compliance
  - Staying abreast of regulatory requirements is critical in the evolving field of gene therapy.
  - Pharmacists need to ensure that their practices align with local, national, and international regulations governing the administration and monitoring of gene therapies.
- Staff Training and Development
  - Given the specialized nature of gene therapies, ongoing training and development for pharmacy staff are crucial.
  - This includes staying updated on the latest advancements, safety protocols, and best practices in gene therapy administration.
- Information Management
  - Proper documentation and information management are essential for tracking patient responses, adverse events, and treatment outcomes.
  - Pharmacists should ensure that electronic health records accurately reflect the details of gene therapy administration and monitoring.

Organizational Readiness (1 of 4)

- Efficient Implementation
  - Organizations that are ready for change can implement new interventions more efficiently.
  - This readiness involves having the necessary infrastructure, policies, and processes in place to support the integration of new practices seamlessly.
- Staff Engagement and Buy-In
  - When an organization is ready for change, it fosters a culture of openness and collaboration.
  - Staff members are more likely to be engaged and supportive of the changes, leading to better acceptance and adoption of new practices.
- Resource Allocation
  - Organizational readiness ensures that appropriate resources, including financial, human, and technological, are allocated to support the implementation of new interventions.
  - This prevents unnecessary delays or disruptions in the process.

Organizational Readiness (2 of 4)

- Training and Development
  - Readiness involves preparing the workforce for the changes ahead.
  - This includes providing training and development opportunities to enhance the skills and knowledge of staff members, ensuring they are equipped to handle new technologies or therapies such as gene therapy.
- Quality and Safety Assurance
  - Organizational readiness is critical for maintaining quality and safety standards during the implementation of new interventions.
  - Adequate preparation helps identify and address potential risks, ensuring patient safety and positive treatment outcomes.
- Adaptability to Change
  - Healthcare environments are dynamic, and readiness allows organizations to be more adaptable to changes in the industry.
  - Being ready means having a culture that values continuous improvement and is responsive to emerging trends and technologies.

Organizational Readiness (3 of 4)

- Regulatory Compliance
  - Readiness involves understanding and complying with regulatory requirements associated with new interventions.
  - Organizations that are well-prepared can navigate regulatory processes more effectively, reducing the risk of legal or compliance issues.

- Patient-Centric Approach
  - An organization that is ready for change often prioritizes a patient-centric approach.
  - This involves tailoring services and care delivery to meet the needs and preferences of patients, ultimately enhancing the overall patient experience.

Organizational Readiness (4 of 4)

- Sustainability of Interventions
  - Organizational readiness contributes to the sustainability of new interventions.
  - When an organization is prepared, it is more likely to maintain and build upon the changes over the long term, preventing the intervention from becoming a short-term initiative.

- Measurable Outcomes
  - Readiness facilitates the establishment of measurable goals and outcomes.
  - Organizations can set benchmarks, track progress, and evaluate the success of the implementation, allowing for continuous improvement and optimization.

Approved Gene Therapies as of Q2 2023 (1 of 2)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Gendicine	recombinant p53 gene	2004	Head and neck cancer	China	Shenzhen SiBiono GeneTech
Oncorine	E1B/E3 deficient adenovirus	2005	Head and neck cancer; nasopharyngeal cancer	China	Shanghai Sunway Biotech
Rexin-G	mutant cyclin-G1 gene	2006	Solid tumors	Philippines	Epeius Biotechnologies
Neovasculgen	vascular endothelial growth factor gene	2011	Peripheral vascular disease; limb ischemia	Russian Federation, Ukraine	Human Stem Cells Institute
Imlygic	talimogene laherparepvec	2015	Melanoma	US, EU, UK, Australia	Amgen
Strimvelis	autologous CD34+ enriched cells	2016	Adenosine deaminase deficiency	EU, UK	Orchard Therapeutics
Kymriah	tisagenlecleucel-t	2017	Acute lymphocytic leukemia; diffuse large B-cell lymphoma; follicular lymphoma	US, EU, UK Japan, Australia, Canada, South Korea, Switzerland	Novartis
Luxturna	voretigene neparvovec	2017	Leber's congenital amaurosis; retinitis pigmentosa	US, EU, UK, Australia, Canada, South Korea	Spark Therapeutics (Roche)
Yescarta	axicabtagene ciloleucel	2017	Diffuse large B-cell lymphoma; non-Hodgkin's lymphoma; follicular lymphoma	US, EU, UK, Japan, Canada, China, Australia	Kite Pharma (Gilead)
Collategene	beperminogene perplasmid	2019	Critical limb ischemia	Japan	AnGes
Zolgensma	onasemnogene abeparvovec	2019	Spinal muscular atrophy	US, EU, UK, Japan, Australia, Canada, Brazil, Israel, Taiwan, South Korea	Novartis
Zynteglo	betibeglogene autotemcel	2019	Transfusion-dependent beta thalassemia	US	bluebird bio

Source: Gene, Cell, + RNA Therapy Landscape Report - Q2 2023 Quarterly Data Report (ASGCT)

Approved Gene Therapies as of Q2 2023 (2 of 2)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Tecartus	brexucabtagene autoleucel	2020	Mantle cell lymphoma; acute lymphocytic leukemia	US, EU, UK, Australia	Kite Pharma (Gilead)
Libmeldy	atidarsagene autotemcel	2020	Metachromatic leukodystrophy	EU, UK	Orchard Therapeutics
Breyanzi	lisocabtagene maraleucel	2021	Diffuse large B-cell lymphoma; follicular lymphoma	US, Japan, EU, Switzerland, UK, Canada	Celgene (Bristol Myers Squibb)
Abecma	idecabtagene vicleucel	2021	Multiple myeloma	US, Canada, EU, UK, Japan	bluebird bio
Delytact	teserpaturev	2021	Malignant glioma	Japan	Daiichi Sankyo
Relma-cel	relmacabtagene autoleucel	2021	Diffuse large B-cell lymphoma; follicular lymphoma	China	JW Therapeutics
Skysona	elivaldogene autotemcel	2021	Early cerebral adrenoleukodystrophy (CALD)	US	bluebird bio
Carvykti	ciltacabtagene autoleucel	2022	Multiple myeloma	US, EU, UK, Japan, Australia	Legend Biotech
Upstaza	eladocagene exuparvovec	2022	Aromatic L-amino acid decarboxylase (AADC) deficiency	EU, UK	PTC Therapeutics
Roctavian	valoctocogene roxaparvovec	2022	Hemophilia A	EU, UK, US	BioMarin
Hemgenix	etranacogene dezaparvovec	2022	Hemophilia B	US, EU, UK	uniQure
Adstiladrin	nadofaragene firadenovec	2022	Bladder cancer	US	Merck & Co
Elevidys	delandistrogene moxeparvovec	2023	Duchenne muscular dystrophy	US	Sarepta Therapeutics
Vyjuvek	beremagene geperpavec	2023	Dystrophic epidermolysis bullosa	US	Krystal Biotech

Source: Gene, Cell, + RNA Therapy Landscape Report - Q2 2023 Quarterly Data Report (ASGCT)

Expected FDA Approvals (2024)

Anticipated Decision Year	Drug Name	Company Name	Therapeutic Approach	Indication
2023	Omidubicel	Gamida Cell	Cell Therapy	Hematological malignancies
2023	B-VEC	Krystal Bio	Gene Therapy	Dystrophic epidermolysis bullosa
2023	SRP-9001	Sarepta Therapeutics	Gene Therapy	Duchenne muscular dystrophy
2023	Roctavian	BioMarin Pharmaceutical	Gene Therapy	Hemophilia A
2023	Remestemcel-L	Mesoblast	Cell Therapy	Steroid-Refractory Acute Graft Versus Host Disease
2023	HPC cord blood	StemCyte	Cell Therapy	Unrelated Donor hematopoietic progenitor cell transplantation
2023	Lifileucel	Iovance	TIL Therapy	Metastatic melanoma
2023/2024	Afami-cel	Adaptimmune Therapeutics	Cell Therapy	Advanced synovial sarcoma
2023/2024	bb1111	bluebird bio	Gene Therapy	Sickle cell disease
2023/2024	Tab-cel	Atara Biotherapeutics	Cell Therapy	Epstein-Barr virus-associated post-transplant lymphoproliferative disorder
2023/2024	CTX001	Vertex Pharmaceuticals & CRISPR Therapeutics	Gene Editing Therapy	Sickle cell disease, β-thalassemia
2024	CT-053	CARsgen Therapeutics	CAR-T Therapy	R/R multiple myeloma
2024	Libmeldy	Orchard Therapeutics	Gene Therapy	Metachromatic leukodystrophy (MLD)
2024	Upstaza	PTC Therapeutics	Gene Therapy	Aromatic L-amino acid decarboxylase (AADC) deficiency
2024	Fidanacogene elaparvovec	Pfizer Inc	Gene Therapy	Hemophilia B (Factor IX Deficiency)

Source: [BioSpace: FDA Braces for Looming Boom in Cell and Gene Therapy Submissions (21-Jun-2023)]

Conclusion

- Gene therapy is a revolutionary field in medicine that aims to treat or prevent diseases by modifying or replacing the genetic material within a person's cells.
- Gene therapy continues to evolve, with ongoing research and clinical trials exploring its potential for treating a wide range of genetic and acquired diseases.
- While challenges persist, the field holds great promise for transforming the landscape of medicine and providing innovative solutions to previously untreatable conditions.
- Pharmacists play a crucial role in the clinical and operational aspects of healthcare, and their involvement is essential for the safe and effective implementation of various medical interventions, including gene therapy.
- Pharmacists can contribute significantly to the successful integration of gene therapies into clinical practice, ensuring the best possible outcomes for patients.
- As of Q2 2023, 26 gene therapies are approved (including genetically modified cell therapies).

References

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