ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Innovations in Liver Transplant

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G&H Why are technologies being developed to expand or improve the liver donor pool?

MS Recently, machine perfusion technology has allowed for the use of more organs, potentially from older donors, livers with higher fat content, or donation after cardiac death livers. Nevertheless, there is still a mismatch between the number of people who need a liver transplant and how many high-quality livers are available. More livers are still urgently needed. Additionally, some people need temporary support while their liver regenerates because of severe acute liver injury (eg, from a drug, toxin, surgery, or trauma). That is another reason new technologies are needed, not just for transplant but also potentially for liver support. Innovative strategies to use bioartificial liver support can temporarily bridge an individual to transplant or eventually can help support native liver regeneration and recovery. A lot of exciting things are happening, such as trying to use genes to cure diseases so that liver transplant is not needed, gene editing to engineer livers, organoids to serve as models of disease in addition to engineering livers, and generative artificial intelligence that can touch every facet of administrative and clinical medicine. I think there will be more changes coming down the pike in liver transplant over the next several years.

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G&H Could you discuss the concept of liver organoids?

MS Liver organoids are a complicated concept that can be thought about at different levels. Organoids can recapitulate different cells or small 3-dimensional structures in the body. There is no organoid right now that is a fully functioning liver that does all aspects of what a typical liver does from start to finish because the liver has so many different functions. However, we have different models of disease based on these organoids. Right now, work is being done to put liver cells on a scaffold and bioengineer livers. We are not at a state where this is ready for prime time, but it could be conceivable that using pluripotent stem cells could enable us to potentially engineer a liver from someone's cells to grow and support either a partial liver while the patient is getting better on their own from a liver injury or serve as a bridge to liver transplant. This is an exciting future technology.

G&H Could you discuss the potential use of gene editing to reduce the need for liver transplant?

MS CRISPR, which stands for clustered regularly interspaced short palindromic repeats, is a technology that allows for the editing of genes. CRISPR technology is

being used to add or subtract genes to treat diseases such as inborn errors of metabolism (urea cycle disorders) that are programmed in the liver but also more common liver diseases such as hepatitis B or hemochromatosis. This is complex, but I think over the next few years, we may see more and more ways that CRISPR technology could potentially be used to fundamentally cure diseases and prevent the need for liver transplant for some.

G&H What advances are being made in pig-to-human liver xenotransplant?

MS There is a lot of interest right now in bioartificial liver support. A team from the University of Pennsylvania is using pigs that are genetically engineered with CRISPR technology to insert protective genes and take out genes that can cause human infection or human rejection of the pig liver using an external liver support device. Essentially, the CRISPR technology is used to engineer the pig liver so that it is better tolerated by the human and has some additional functions that are more like human functions. Early data show that this gene-modified pig liver can maintain some liver function for short periods of time in decedents. Right now, phase 1 safety trials are ongoing in patients with acute-on-chronic liver failure. Thus, it has not yet been well elucidated for whom this technology is optimal, but it is now cleared for small phase 1 studies in humans to determine safety profiles and how well the artificial liver works.

Additionally, there have been cases of genetically modified pig livers that have been transplanted into humans—that is, not external but heterotopic transplant. The success of this approach is still highly variable. I would not yet say that this technology is ready for prime time. If anything, the aforementioned external liver support is more reasonable to do and probably will be easier to implement in a short period of time. That is because the liver has a lot of different complex functions. It is still exceedingly complicated at this stage to take a pig liver, for example, and expect it to do all of the functions that a human liver does without rejection and without major problems in coagulation.

G&H What is the current status of robotic liver transplant?

MS There is a lot of interesting innovation going on in this area. Robotic surgery with a human controlling the console outside of the operating room has already been used for both deceased full liver transplant and living donor liver transplant. We know this type of surgery requires expertise but leads to less pain, shorter hospital stays, and better cosmetic results in terms of scarring.

G&H How can artificial intelligence potentially help optimize donor-recipient matching or allocation?

MS A lot more could be done in terms of sophistication of optimizing donor-recipient matching. There is a lot of potential for machine learning and advanced techniques in terms of using data to optimally match donors and recipients to have the best outcome. This is a very exciting area. However, high-quality data are needed that have more detail than that collected in our current transplant organ system. With high-quality data (the more the better) on different parameters of both donors and recipients, we can think about better matching. Nevertheless, optimal organ placement has to be balanced with other considerations, such as geography, equity, and utility (eg, maximizing the life of the transplant organ), so this is a complex issue. Advanced machine learning and computational techniques as well as high-quality, real-time data will help improve the system eventually.

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G&H How can artificial intelligence be used for digital pathology and diagnostics in liver transplant?

MS Large language models enable us to interpret images and text. These models could be used to automate what a human pathologist does and help with more rapid interpretation of pathology reports. It is important to train these models on high-quality human output. The technology should just be used to help human pathologists make a diagnosis. It is central to our implementation of artificial intelligence systems to make sure that the humans are kept in the loop. In other words, artificial intelligence is the assistant; the human, ultimately, is who makes the clinical decisions.

G&H Are there any other emerging applications of artificial intelligence in liver transplant that you would like to discuss?

MS I would like to mention other applications of large language models, which could be used at all phases of liver transplant. They could be used for donor screening; to simplify and generate patient-facing materials for education; to summarize, for example, a patient's liver transplant workups and patient selection meetings; and to automate much of the back office functions in terms of recordkeeping and what patients need in terms of management, either on the waiting list or after liver transplant. Essentially, large language models could touch nearly all facets of clinical and administrative work. We have already seen how ambient listening technology can revolutionize documentation in the clinic without having to type. There is a lot of potential for these models to improve workflows, but they have to be designed so that they are helpful and also accurate. However, not every hospital needs the same solution for the same type of scenario; large language models need to be customized to the setting.

G&H What are the biggest challenges of implementing artificial intelligence and innovation in liver transplant into daily clinical practice?

MS There are issues of trust from patients and providers involving ethics and potential breaches of confidentiality. There are also potential issues of low data quality, data drift, and biases in the data that we have to be aware of. Additionally, different data systems could be fragmented and not talk to one another. There are also costs associated with artificial intelligence deployment, and it may not be warranted for many clinical scenarios. If a model has been developed in a different system, it might not be possible to easily deploy it in clinical settings. Thus, there are a lot of system-level issues as well as human trust issues and workflow issues that are potential challenges in implementation.

Disclosures

Dr Serper has no relevant conflicts of interest to disclose.

Suggested Reading

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