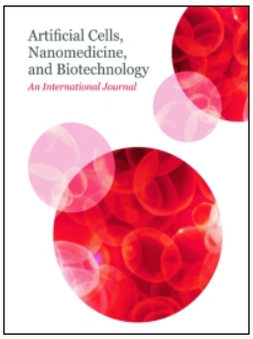

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Artificial Organs as a Bridge to Transplantation

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ABSTRACT

Current organ shortage is estimated to keep outpacing demand for years to come. Among the advocated strategies, artificial and bioartificial devices may prove beneficial to a wide category of patients on transplant waiting lists. Bionic organ science allows to reproduce organ architecture and function through a complex interplay of cellular and mechanical elements. Some bioartificial organs may well be used to replace anatomical defects, while others allow to compensate for failing organ functions and to bridge patients to transplantation. Among these latter, bioartificial liver (BAL) systems bear the highest potential for clinical application, even if their use is raising several controversial issues. These latter regard the identification and stratification of patients fit for transplantation, timing and type of transplantation after recovery, appropriateness of double-blind, randomized clinical trials and safety

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of animal and/or human cell lines. Nonetheless, bionic organ science needs to be regarded as a useful adjunct in the armamentarium of organ replacement therapies for the third millennium.

INTRODUCTION

At the turn of the second millennium the scientific community is faced with the issue of organ shortage. Paradoxically, the achievements in organ transplantation over the last few decades in terms of both organ survival rates and patients' quality of life have resulted in a dramatic increase in organ demand (United Network for Organs Sharing (UNOS), 1999). Currently, the number of patients on transplant waiting lists worldwide is rapidly outstripping the donor pool and new strategies are strongly advocated to meet the demand. Among the highly favored policies are the use of live donation, the adoption of marginal donors, graft splitting techniques, xenogeneic allografts, cell transplantation and artificial organs.

The idea of artificial systems to sustain organ functions and bridge patients to transplantation is nothing new. What lies beneath the concept of modern bionic science is to reproduce organ function through a complex interplay of cellular and mechanical elements. Bionic science is based on two lines of technological achievements: the use of ultra-thin, biocompatible, and selectively permeable polymer membranes which can allow solute exchanges between a cellular or tissue graft and its environment, and the synthesis of novel materials, some biostable, some bioresorbable, which can serve as scaffolding for tissue regrowth (Galletti, 1991).

Aim of the current paper is to illustrate the state of the art of artificial organs as a bridge to transplantation with particular regard to bioartificial liver systems and to comment on their role in the current clinical practice.

THE CURRENT SCENARIO

Artificial organs are entirely mechanical devices and were the first to be introduced for use in clinical practice. They have come quite a long way since the first hollow-fiber dialyzers and currently encompass a wide host of external and implantable systems. On the other hand, bionic organs consist of both a mechanical and a cellular component coupled as to reproduce organ architecture and function, to allow solute exchanges and tissue regrowth. Some of them, such as bionic bone segments and skin flaps, may be used to replace anatomical defects, while others have been devised to compensate for failing depurative and synthetic functions.

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Undoubtedly, the organ that has become most symbolic with bionic organ science is the bioartificial liver (BAL), because of its potential as a bridge-to-transplantation device. The shortage of liver donors and the excellent results of orthotopic liver transplantation (OLT) have rekindled the interest in bionic liver systems and have urged many an author to work on novel strategies of liver replacement therapies (Chamuleau, 1998; Dixit and Gitnick, 1998; Watanabe and Millis, 2000).

Liver replacement strategies include a wide range of therapeutic options, some of which have definitively entered the clinical practice and have become the standard of reference for most physicians. Biologic and/or bioartificial options include OLT, split liver grafting, hepatic cell transplantation, whole liver perfusion, xenotransplantation and BAL. Artificial options consist of plasma exchange techniques and depurative support devices, however lacking the synthetic functions of biologic systems.

BIOARTIFICIAL LIVER

The ideal bioartificial liver should reproduce the whole spectrum of liver depurative and synthetic functions without hemodynamic alterations, should be safe and easy to use. Unfortunately, not all of these criteria are met by currently available systems and several concerns still exist as regards their application (Dixit and Gitnick, 1998; Watanabe and Millis, 2000). Most BALs incorporate a biologic (hepatocytes) and a synthetic housing component (plastic housing shells and semipermeable membranes) coupled as to facilitate the delivery of liver functions. Of the several BAL designs, only the hollow-fiber systems have been developed for practical use and clinical trials. They are basically off-the-shelf dialyzers that have been modified as artificial livers.

The implications of BALs include the treatment of fulminant hepatitis (FH) and acute liver failure (ALF), irrespective of their etiology; chronic liver failure (CLF); posttransplant delayed graft function (DGF) or primary non-function (PNF), and regeneration after liver surgery (Kelly and Sussman, 1994; Watanabe and Millis, 2000). Patients treated by means of BAL may be addressed to OLT, according to their age, clinical performance status, prognostic factors and organ availability. To date, no universal algorithm for patients undergoing BAL exists and recovering patients may be treated conservatively, transplanted or simply followed-up, according to the medical staff's clinical experience. Much effort still needs to be done in order to identify common treatment strategies, stratify patients by presence of prognostic risk factors and allocate them to the best therapeutic options.

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BALs synthetic functions are usually provided with by human or porcine hepatic cells. Human cells are often hybridomas of genetically altered hepatoma cell lines, while porcine hepatic cells may be fresh or cryopreserved, according to system designs. The use of a cellular component is accompanied by several risks, including the potential for antigen transfer in the liquid or solute compartment and the consequent sensitization in potential recipients of liver grafts; transmission of animal diseases, such as the porcine endogenous retrovirus (PERV), and production of cellular by-products. Such risks and cell retrieval techniques hamper a wider clinical application of BALs and deserve long-term trials to assess their safety on larger scales (Pitkin and Mullon, 1999).

Three major BAL systems are currently being tested in clinical trials, the HepatAssist 2000 (Circe Biomedical, Inc.), the ELAD system device (Vitagen Inc.) and the C3ASLI (Custer and Mullon, 1998; Sussman et al., 1994; Watanabe and Millis, 2000). The HepatAssist 2000 is a hollow-fiber dialyzer containing primary porcine hepatocytes. It is currently being evaluated in a phase II/III clinical trial involving several US and European centers and enrolling more than a hundred patients. The system uses plasma separation through convective currents, which allows for high flow rates and effective molecule exchange. On the opposite, its application should be limited to no more than six hours a day, the use of citrate for plasma separation may precipitate hypocalcemia, thus fatal bleedings and coagulation defects. Even if retrieval of porcine liver cells is quite easy, concerns are raised by the potential for transfer of porcine immunogenic molecules and PERV (Custer and Mullon, 1998).

The ELAD artificial liver system is a hollow-fiber dialyzer whose extracapillary space is inoculated with cloned immortalized human hepatic cells. The cells attach to the external membranes of the hollow-fiber capillaries and begin to replicate and grow. The ELAD system uses whole blood, which is circulated through the extracapillary spaces, detoxified by the immortalized liver cells that also produce protein and clotting factors. It is currently being tested in a phase I/II clinical trial in the US and UK (Sussman et al., 1994).

The C3ASLI liver system differs from the ELAD in that it uses transformed human hepatic cells, the C3A human line and is currently under investigation in a phase II clinical trial in the US. Both the ELAD and the C3ASLI systems use immortalized human cell lines, bearing a reduced risk of patient's sensitization, use larger cell masses and allow for continuous treatment. However, the regrowth rate of immortalized hepatic cells and the risk of cancer cell line seeding should be fully elucidated (Watanabe and Millis, 2000).

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CONCERNS

BALs are no longer investigational devices, but their introduction in current clinical practice needs clarification of potential risks and evaluation of controversial issues raised by their application (Chamuleau, 1998; Dixit and Gitnick, 1998; Watanabe and Millis, 2000).

1. How to bridge patients to transplantation? To date, no definitive data exist regarding this question. No universal agreement has so far been reached concerning patients that may or may not profit from BAL and whether they should be addressed to OLT or conservative treatment after recovery of liver function. Timing and type of OLT after BAL replacement therapy are also basic issues in an era of organ shortage.
2. Is there any need for clinical trials? Once BALs safety has been established in phase I clinical trials, is it justified and ethical to perform phase II and III trials and exclude patients from the potential advantages of BALs? Double-blind, randomized clinical trials should not be applied to patients in poor conditions and with a very dismal prognosis.
3. What is the best BAL system? Porcine cell BAL bear the risk of immunogenic molecule transfer and recipient sensitization prior to OLT, while BAL based on immortalized human hepatic cells have the potential of tumor transfer from bioactive cell lines. Plasma separation devices cannot be used for more than a few hours a day, while whole blood systems allow for continuous treatment.
4. Quality control. How to organize BAL industrialization in order to meet quality controls and commercial requirements and how to keep industries in pace with technological improvements is still matter of debate.

CONCLUSION

Current organ shortage is estimated to keep outpacing organ demand for years to come. Bionic organ science may be a valid option allowing to relieve some patients on waiting lists and bridge them to transplantation. However, concerns still exist regarding patients' stratification and allocation criteria, timing and type of transplantation after organ recovery and long-term risks of transmittable animal diseases and transfer of immunogenic molecules. However, bioartificial organs should actually be

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regarded as a part of the wide armamentarium to offer patients with failing organ function.

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