Liver transplantation: Past accomplishments and future challenges

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WJ Wall. Liver transplantation: Past accomplishments and future challenges. Can J Gastroenterol 1999;13(3):257-263. Liver transplantation has evolved from a rare and risky operation of questionable therapeutic value to the preferred treatment for an extensive list of end-stage liver diseases. Superior immunosuppression (cyclosporine), and improvements in surgery and anesthesia brought liver grafting to its current level of success. Nearly 60,000 liver transplants have been performed, and survival rates are very good; however liver grafting faces serious immediate and long term challenges, mainly due to the widening gap between donor supply and recipient demand. Increasing numbers of sick candidates, recurrent disease (especially hepatitis C) and recidivism rates after transplantation for alcoholic cirrhosis will force increasingly difficult decisions on candidate selection and priority listing of potential recipients. Although xenotransplantation may be the ultimate solution, it has its own specific set of biological and societal challenges – the full extent of which should be revealed in the next several years.

Key Words: *Cirrhosis, Hepatitis, Liver disease, Liver transplantation*

Transplantation hépatique : réalisations passées, défis à venir

RÉSUMÉ : La transplantation hépatique a évolué, passant d'une intervention rare et risquée, d'une utilité thérapeutique douteuse, au statut de traitement privilégié pour de nombreuses maladies hépatiques terminales. L'amélioration des traitements d'immunosuppression (cyclosporine) et les progrès des techniques chirurgicales et anesthésiques ont procuré à la greffe hépatique le succès qu'elle connaît actuellement. Près de 60 000 transplantations hépatiques ont été effectuées et les taux de survie sont très bons, mais les greffes hépatiques font face à des problèmes graves, à court comme à long terme, surtout en raison de l'écart qui s'élargit entre l'offre et la demande d'organes. Le nombre croissant de malades, les récurrences de la maladie (surtout dans les cas d'hépatite C) et les taux de récidive après transplantation pour cirrhose alcoolique imposeront des critères de sélection des candidats encore plus stricts et l'établissement de listes de receveurs potentiels par ordre de priorité. Bien que la xénotransplantation puisse être la solution ultime, elle s'accompagne de défis biologiques et sociétaux qui lui sont propres et dont la portée devrait nous être révélée au cours des années à venir.

Transplantation is unquestionably one of the greatest achievements of modern medicine. The evolution of liver grafting from an experimental, desperate operation to routine surgery with excellent patient survival was due to several advances. The advance that is given the most credit, and appropriately so, is the development of cyclosporine. Its effectiveness as an immunosuppressant in organ grafting was demonstrated first by Calne et al (1-3), both experimentally and clinically. Cyclosporine changed the face of organ transplantation worldwide and ushered in a new era in transplantation. Thousands of organ recipients have had their lives saved or transformed because of this discovery. It was the first application of selective immunosuppression, which was particularly important for liver recipients who were dreadfully ill and at great risk of fatal infection. High dose steroids and azathioprine were really not compatible with survival in the most debilitated recipients. Immunosuppression with cyclosporine increased survival rates of liver recipients from less than 25% to greater than 75%, and it became firmly established as baseline therapy in solid organ grafting (4,5).

However, the demoralizing perioperative mortality that

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was typical during the early years of liver grafting was not solved by better immunosuppression alone. Many unique features of total hepatectomy and liver replacement required critical improvements in surgery and anesthesia. Although the operation was practised in laboratory animals, there were no experimental models comparable with the operative challenges that were encountered in sick patients with liver failure, portal hypertension and profound coagulopathies (6). Removing the diseased liver was hazardous, and the difficulty was increased in many recipients who had previously undergone extensive right upper quadrant operations to palliate their liver disease. It took the introduction of modern blood component therapy, coagulation factor replacement and surgical methods for controlling bleeding to make the operation safe (7,8). Instead of the massive blood loss that was typical of early cases, transfusion requirements were reduced to an average of 4 or 5 U of blood (9,10). Dedicated anesthesiologists played a decisive role in managing the hemodynamic and metabolic problems of what is arguably the most unphysiological of all operations. Rather than cold and acidotic patients who were hypotensive throughout most of the surgery, controlled operations characterized by patient stability became the standard. The introduction of venous bypass was a timely advance, when many new liver transplant centres were forming (11). The ability of venous bypass to support hemodynamics during the anhepatic period undoubtedly saved many patients during the early experiences in many programs. The need for venous bypass was reduced with the development of modern anesthetic approaches and refined patient monitoring; it is widely acknowledged now that venous bypass is not necessary in most cases (12-14). Nevertheless, its selective use today allows liver grafting to be performed in patients with cardiac disease and pulmonary hypertension.

The biliary drainage of the transplanted liver used to be a source of tremendous morbidity and mortality. Nearly half of all recipients developed biliary complications that resulted in the deaths of one of every three recipients (15-17). The signs and symptoms of failed biliary reconstruction were often confused with other causes of graft dysfunction. Biliary obstruction or leak was frequently mistaken for rejection, and patients were unwittingly poisoned with large doses of steroids in the erroneous belief that rejection was responsible for jaundice. Faulty types of biliary drainage were gradually discarded and replaced with more reliable methods (8). Although biliary complications still occur in 5% to 10% of patients, these complications no longer have the lethal impact that they once did (18-19). Morbidity and mortality from biliary complications were also reduced by the diagnostic and therapeutic capabilities provided by modern imaging of the biliary tract. The integrity of the biliary drainage could be accurately assessed, and complications could be diagnosed promptly and corrected by surgical or nonsurgical techniques (20,21).

Although the microscopic features of rejection were well documented, the critical role of graft histology in patient management was not appreciated until post-transplant allograft biopsies were routinely performed (22,23). Great reliance is now placed on graft biopsies to confirm or exclude rejection and, just as important, to diagnose a spectrum of pathological processes that can cause allograft dysfunction. A new vista was opened for pathologists, some of whom subsequently devoted their careers solely to transplantation pathology.

Central to success was the grafting of a liver that functioned well in the recipient. Although the basic principles of core cooling of organs and hypothermic storage were known in the 1970s, their application could not revive livers that had sustained severe warm ischemic damage, the result of poor control of physiological events immediately before and during organ removal from dead donors. The establishment and acceptance of brain death criteria resulted in thoughtful rather than neglectful management of donors, enhancing immensely the viability of grafts. The introduction of University of Wisconsin solution was a major advance in organ preservation (24,25); it was superior to other solutions (26,27) and extended the safe limit of liver preservation. Long distance procurement and exchange of livers between centres became practical and routine.

The total effect of these numerous advances allowed the full impact of better immunosuppression to be seen in liver recipients. Results from the use of cyclosporine or tacrolimus-based immunosuppression are excellent (28-30). Although the debates go on about the advantages of one immunosuppressive protocol over another, the most gratifying conclusion is that there are choices of immunosuppressive agents, drugs that can be substituted as clinical circumstances require. Monoclonal antibodies are options for induction therapy (31-33), and other agents, such as mycophenolate mofetil and rapamycin, are being tested in clinical trials in liver recipients (34).

Transplantation has had an extraordinary effect on the practice of hepatology. There is virtually no hepatic-based disease, acute or chronic, for which transplantation does not have conceptual application. Inborn errors of metabolism are corrected within hours of liver grafting. Some of the most spectacular successes, in the eyes of hospital personnel at least, are the recoveries of patients from deep coma after transplantation for fulminant hepatic failure. Multivisceral grafts, with the liver as a component, are still experimental, but their place in the management of patients with an array of gastrointestinal disorders is becoming established (35-37). The protective immunological effect that the liver can confer on other transplanted tissue seems real, and elucidation of the mechanism may reveal some of the answers to transplantation tolerance.

The past two decades have been a remarkable period in transplantation. Transplants are more successful than ever, and the rewards to patients are great, almost without parallel in medicine or surgery. Nevertheless, success has produced a new set of problems, different from the previ-

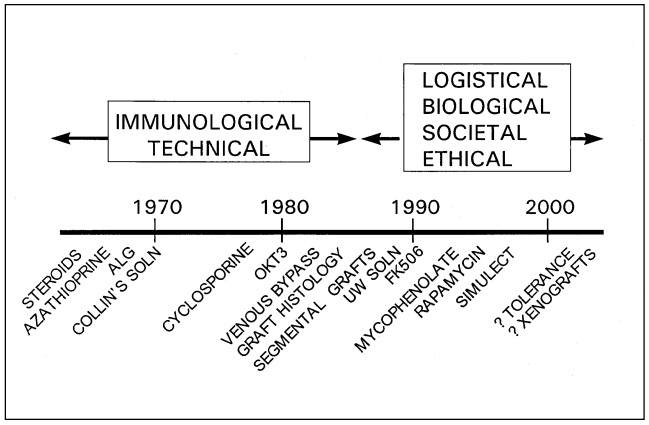

Figure 1) *Milestones and challenges in the history of liver transplantation. SOLN Solution*

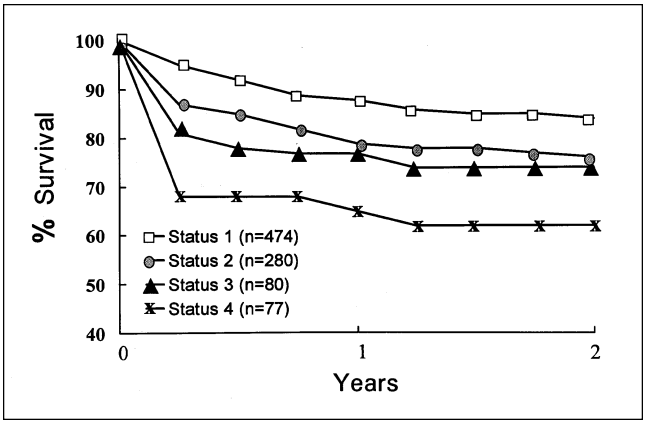

Figure 3) *Recipient survival after liver transplantation according to patient status (source: Canadian Organ Replacement Register [38])*

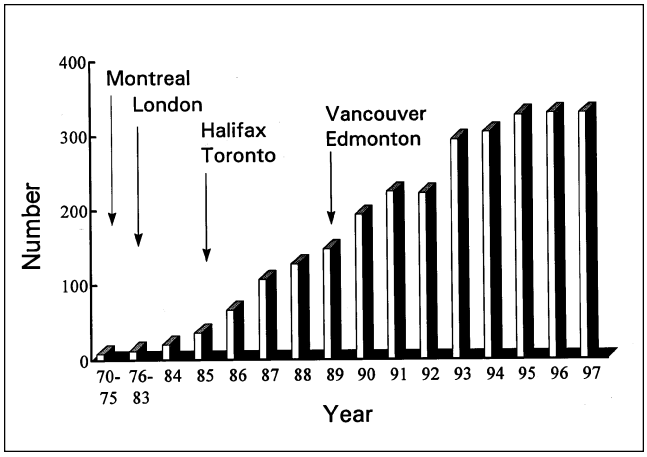

Figure 2) *Growth of liver transplantation in Canada. Arrows indicate the years in which programs were started in the corresponding cities*

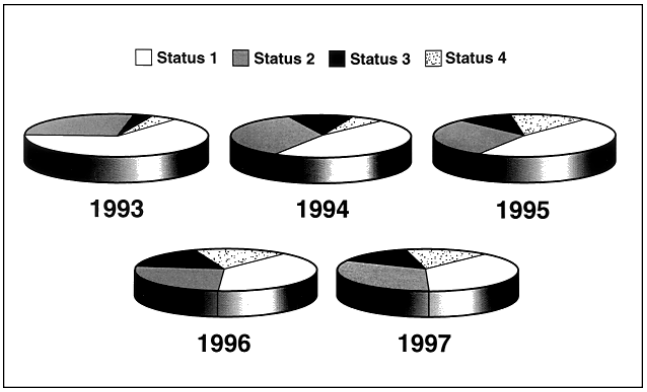

Figure 4) *Status rankings of patients who received liver transplants at London Health Sciences Centre in the 1990s*

ous ones, and in many respects more challenging than those that have been overcome in the past. The obstacles to liver grafting in the 1970s and 1980s were largely technical and immunological. The technical problems have been reduced to a reasonably low level that does not lend itself to much further reduction. The complexity of the surgery will always carry a certain incidence of technical misadventure. Immunosuppression is the best it has ever been, and acute, irreversible rejection is now a rare event. But these advances have created new problems that can be categorized into four broad areas: logistical, biological, societal and ethical (Figure 1). None is mutually exclusive, and they are inter-related. Each presents unique challenges for the future of liver transplantation.

The logistical problems primarily involve the shortage of donor organs. The growth of liver transplantation in Canada is shown in Figure 2. During the formative years, organ needs were satisfied because relatively few candidates were waiting for liver transplants. As results improved, the indications for grafting expanded, more patients became candidates and donor livers failed to meet the demand everywhere. In 1997, more than 1000 patients on liver transplant waiting lists in North America died due to lack of donor organs. This is a tragedy by itself, but the organ shortage also threatens to erode the good results of liver transplantation because candidates become sicker as they wait longer for transplants. Risk factors that have been shown to correlate well with perioperative mortality, such as the state of malnutrition of patients, coexisting renal failure and level of coma, are fairly accurately reflected in the status rankings of patients on the waiting list. They are good surrogate markers of operative risk, and their effect on post-transplant mortality is clearly shown in national statistics from the Canadian Organ Replacement Register (38). The best risk patients (status 1 and 2) have much better survival rates than the higher status recipients (status 3 and 4) (Figure 3). During the past five years there has been a steady annual decrease in the number of good risk patients undergoing liver grafting at the London Health Sciences Centre. At the beginning of the decade, status 1 patients accounted for two-thirds of liver recipients (Figure 4). Their numbers have progressively decreased, and they now account for less than one-third of the total, while the number of patients in higher risk categories has increased. Maintaining good overall survival rates with increasing numbers of poor risk candi-

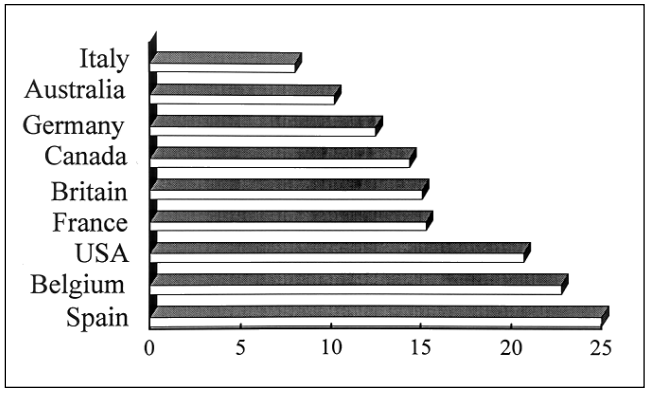

Figure 5) *National organ donor rates (per million population)*

dates is going to be very difficult. The ability of transplant centres to offer transplants to patients at the most opportune time in their illness becomes more compromised each year.

Data from the United Network of Organ Sharing Registry in the United States provide a stark picture of the situation there (39). In the 1990s, there has been a 40% increase in the number of liver transplants, but the number of patients waiting for a liver transplant increased by 340% and the mortality on the waiting list increased by 120%, despite all medical attempts to increase the donor pool by using marginal grafts (40), fatty livers (41), older organs (42,43) and segmental grafts from living donors (44). In an attempt to meet the needs, livers are now being split with the smaller fragment going to a child and the larger right lobe to a suitably sized adult (45,46). The concept is an old one that has been reintroduced because of the severe shortage of organs. It has been done a few times in Canada but has its own set of logistical problems. There is an increased demand on operating rooms and surgical teams for overlapping, if not simultaneous, procedures. Recipients have to be size matched, and liver sharing in a country the size of Canada poses significant limitations of time and distance.

The logistical issues imposed by the shortage of organs are directly tied to societal obstacles to organ donation. The public is not well informed about the effectiveness of transplantation, and there is a lack of awareness of the need for organs. Only half of all adults have signed a donor card. The majority of people have not discussed donation with their families, and most do not know the wishes of their relatives (unpublished data). Transplant coordinators realize more than anyone that grief-stricken relatives find it much easier to give consent for donation when they know it was the wish of the deceased. Professional barriers exist too. Surveys of intensive care unit nurses and physicians in Canada show that although both groups are heavily in favour of organ donation and transplantation, there is a gap in their own willingness to donate, and the percentage that have signed a donor card is only marginally higher than that of the general public (47,48). The majority feel unease at approaching families about donation, and half are not familiar with how to refer a potential organ donor. With 12 to 14 donors per million population, Canada's donor rate is mediocre compared with that of other countries (Figure 5). Spain is the acknowledged leader, the result of a coordinated national effort to educate the public and to make donation routine in virtually every hospital with an intensive care unit (49). If Canada had an organ donation rate similar to Spain, the liver transplant waiting list in this country would be reduced by two-thirds within one year. Although legislative approaches to increasing donation by such laws as required request, mandated choice or presumed consent have been proposed, they have not been successful in North America or are against public wishes. An educational approach seems far more logical than legislation, but changing attitudes takes time and effort. Meanwhile, the unmet need for human organs is the greatest problem that limits the provision of life-saving and life-enhancing transplants to patients with organ failure.

Whereas logistical and societal issues are immediate concerns, biological challenges relate more to long term outcome of patients and what will happen in the next 10 to 20 years. As more patients live longer after grafting, increasing attention has to be given to late mortality and causes of graft loss. A picture is emerging that is worrisome. Recurrence of the original disease for which liver transplantation was performed accounts for 30% of all graft losses (50-52). Recurrent viral hepatitis is the major concern. Hepatitis B can be controlled with antiviral therapy although indefinite hepatitis B immune globulin treatment has many drawbacks, and already there is viral resistance to lamivudine (53). Of much greater importance is the impact that cirrhosis from the hepatitis C virus (HCV) has on liver transplantation. Nearly one of every four adult patients who receives a liver graft is HCV-positive, and persistence of viremia is not only universal after transplantation but is also heightened by immunosuppression (54). Although it had been hoped that the course of hepatitis C after transplantation would mirror its slow natural history, aggressive hepatitis leading to early graft loss occurs in some patients. The most ominous finding is that many patients develop end-stage cirrhosis over the long term. In one study, mild or moderate hepatitis was present in 90% of all HCV-positive recipients one year after grafting, and by five years it had progressed to the stage of cirrhosis in almost 20% (55). It seems inescapable that substantial numbers of patients who have been transplanted for HCV-related cirrhosis are destined for late graft failure. Even if it takes twenty years for the virus to destroy the allograft, the eventual consequences are enormous when one considers the thousands of patients who have been and continue to be transplanted for HCV-related cirrhosis. Already there is controversy over the appropriateness of retransplantation for recurrent hepatitis C. The biological problem of recurrent disease is not restricted to viral hepatitis. Primary biliary cirrhosis, autoimmune chronic active hepatitis and primary sclerosing cholangitis may all recur in the transplanted liver. Al-

though the reports so far are isolated and immunosuppression may actually help to prevent recurrence of these diseases, it is premature to conclude that longer follow-up will not yield many more recurrences resulting in late graft failure.

The impact of chronic rejection in this scenario should not be dismissed. Chronic rejection is the most common cause of retransplantation, and how prevalent it will become and how many grafts it will destroy are unknown (56,57). Retransplantation is the only solution for chronic graft failure, regardless of the cause. Unfortunately, retransplantation creates a double jeopardy. Patients awaiting retransplantation compete with candidates waiting for primary grafts. Not only is the burden on the waiting list increased, but also the results of retransplantation are inferior compared with those of primary transplantation. Graft and patient survival rates are 15% to 20% less, and the results are very poor if the patients become sick while awaiting retransplantation. Survival rates of only 20% have been reported in patients retransplanted for chronic graft failure who are critically ill (58).

No liver disease encompasses more biological, societal and ethical issues than alcoholic liver disease (ALD). After the report of Starzl et al in 1998 (59) demonstrated equally good survival in patients transplanted for ALD compared with those with non-ALD, the numbers of patients transplanted for this condition steadily increased. They now account for more than one-quarter of the total adult liver recipients (with or without HCV) in the United States (60). The ethical arguments for and against giving transplants to patients with ALD and for giving them equal priority with other patients on the waiting list are regularly debated. To deny ALD patients the same opportunity as others would be a moral judgement of far reaching significance. Such a prejudicial policy should and would trigger a vigorous challenge, championed by patient advocates and legal experts. So far the debates have centred around ethical theories and principles, but they will undoubtedly be fuelled by current information on alcohol relapse after transplantation. Many centres have reported short term relapse rates of 15%, but after several years the incidence increases, and relapse rates of 30% or higher are now being reported (61-63). Subsets of these patients incur substantial morbidity from continued drinking. Unfortunately, criteria that might seem logical in predicting relapse such as employment, marital support and education have not correlated well with recidivism after transplantation (62,64,65). The failure to totally rehabilitate patients to lifestyles that do not include alcohol has the potential to seriously undermine the credibility of liver transplant efforts. Programs risk the loss of public support and confidence. An idea of the public's perception of the worth of liver transplantation for ALD can be gauged by the conclusions reached by legislators in the state of Oregon who attempted to set priorities on health care. After seeking wide public opinion and consensus, more than 700 condition/ treatment pairs were ranked, taking into consideration cost, length and quality of life, and effectiveness of treatment. Cirrhosis of the liver without mention of alcohol was ranked in the middle third, slightly behind renal transplantation and cataract surgery. However, when alcoholic cirrhosis was the specific condition mentioned, its priority dropped almost to the very bottom of the list, next to hemorrhoids (66). These conclusions were reached in 1990, before there was substantial documentation of relapse rates after transplantation for ALD. Dare we hazard a guess at what the public reaction would be to current transplant efforts in view of the recidivism rates that are now being reported? A selection bias against candidates with ALD may have already crept in at the professional level. Patients in some transplant centres have more advanced disease by the time they receive a transplant and seem to be less likely to get a second transplant than patients with non-ALD (67).

Liver transplantation has reached a level of success that not many would have predicted two decades ago. Nevertheless, the problems confronting us now and others that are on the horizon are formidable. When discussing the treatment of sick patients Hippocrates said, "It is not enough for the physician to do what is necessary, but the patient and attendants must to do their part as well, and circumstances must be favourable". At present, many of the circumstances surrounding liver transplantation are distinctly unfavourable. The therapeutic potential of life-saving transplants is thwarted by the increasing disparity between the supply and demand for organs. Transplant programs are faced with the task of striking a balance between medical needs and the chance of a successful outcome each time a recipient is chosen. Although the attempt is aimed at balancing utilitarian, egalitarian and libertarian theories of justice in the allocation of donor organs, in reality it is not possible. In dealing with lifestyle-related illnesses, transplant specialists find themselves dealing with the many uncertainties and intangibles of human behaviour. Recurrent disease in the transplanted liver, viruses that cannot be eradicated and the spectre of huge numbers of recipients with late graft failure will create even worse situations for equal and fair treatment of everyone. Xenotransplantation, if it is possible, has the potential to make all of our current problems irrelevant. Recent progress in the understanding of xenograft rejection and ways to overcome it using genetically modified animals is encouraging (68-70). But xenotransplantation brings its own set of biological and societal issues. For liver grafting specifically, there is the problem of pig proteins, especially complement, and their physiological compatibility with humans. Public and professional resistance to xenotransplantation has already shown signs of entrenchment, with arguments dominated by the threat of infecting patients and the public with animal viruses. It seems unlikely that all the concerns will be satisfied before the actual clinical trials are performed. Fruitful debate should be encouraged but should not obstruct the implementation of life-saving transplants when scientifically sound regulatory guide-

lines are in place. Accountability and ethically acceptable medical decision-making will never be more important for transplant centres than they will be in the future.

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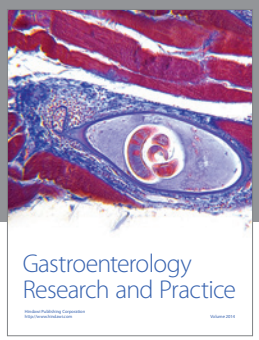

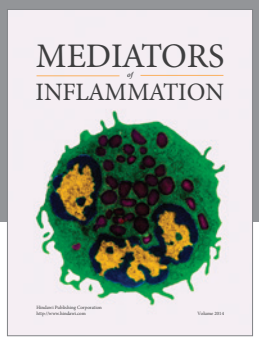

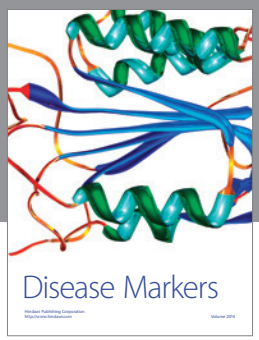

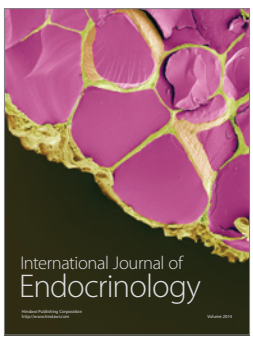

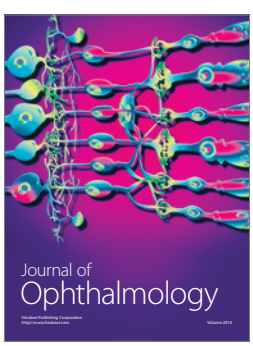

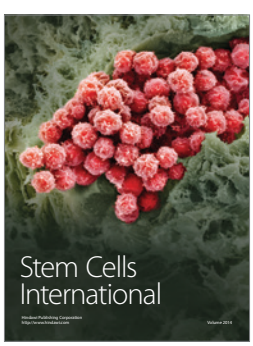

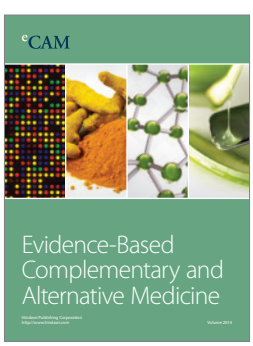

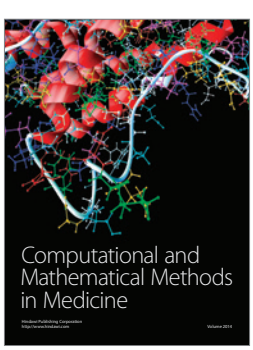

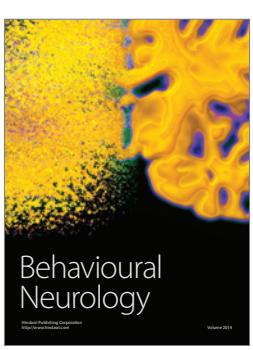

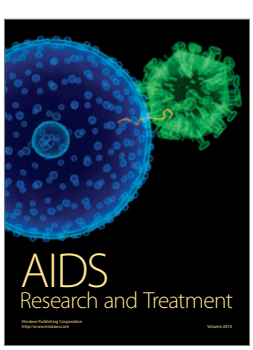

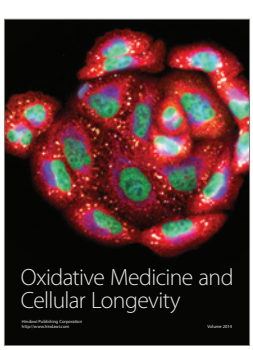

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