

Treatment of Hyperlipidemia in the Heart Transplant Patient: A Challenge of the 21st Century

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Hyperlipidemia is one of the most common complications in heart transplant patients (HT), and it has been reported in more than 90% of the survivors within 10 years of the transplantation. (1) HT inherent factors, such as immunosuppressant therapy or better intestinal absorption, and other factors not associated with transplantation, such as dietary or genetic tendency, contribute to the disease high prevalence.

In the last decades, hyperlipidemia has become an important therapeutic purpose, as it is one of the main non-immunologic factors involved in the development and progress of the graft vessel disease (GVD), current main limiting factor for transplant patient survival.

GVD, (2) unlike atherosclerosis in heart transplant patients, is a diffuse disease involving both epicardial arteries and microvasculature. Due to graft denervation, its clinical manifestation is often late and may present as heart failure, AMI, arrhythmia or even sudden death. Currently, we lack non-invasive diagnostic techniques for highly accurate and sensitive prediction. And unfortunately, available therapies for established GVD are poorly effective.

Therefore, preventing GVD development is certainly one of the big challenges of HT in the 21st century. Along these lines, the development of new immunosuppressant drugs, improved organ preservation techniques and an appropriate monitoring of cholesterol levels appear to be determinant to reduce GVD incidence and progress in this subset of patients. (2)

Although we currently lack specific guidelines on clinical management and purposes of the treatment of hyperlipidemia in the heart transplant patient, it seems reasonable to consider (at least) the same objectives as in patients belonging to the overall population with heart disease (LDL < 100 mg/dl).

Treatment of hyperlipidemia in the heart transplant patient includes an approach at different levels. Firstly, dietary recommendations and a good estimated monitoring should be considered, although these actions are not often enough to get a good lipid profile, thus requiring drug therapy.

Clinical and experimental trials have shown that statins (HMG CoA reductase inhibitors) effectively reduce cholesterol levels in transplant patients, GVD

development and short- and long-term mortality. In 1990s, Kobashigawa et al.(3) showed that the use of pravastatin in heart transplant patients significantly reduced the number of acute rejections, rejections with hemodynamic involvement and GVD incidence, while significantly increasing survival. Subsequently, Wenke et al. (4) showed that the use of simvastatin markedly reduced LDL levels and thus GVD incidence. Both authors confirmed their outcomes in the long term, with a 5- and 8-year (6) follow-up, respectively.

Subsequent studies showed that atorvastatin, with a similar safety profile, achieved a significant decrease in overall cholesterol, triglycerides and C-LDL in this subset of patients.

When heart transplant patients have a suboptimal lipemic control despite the use of statins, those in whom the use of statins is contraindicated or adverse events have been documented associated with its administration seem to benefit from ezetimibe, a tried-and-true and well-tolerated agent after the transplantation. (7) **However, there are still no studies documenting this benefit in clinical outcome, including rejections, GVD or survival.**

The overall population has a longer experience with ion-exchange resins, nicotinic acid and gemfibrozil than heart transplant patients and, therefore, it should be carefully used.

The lipid-lowering effect of statins does not explain all benefits attributed to them in HT patients; therefore, other effects such as antiproliferative and immunomodulator have been suggested. Consequently, it is recommended that the treatment with HMG CoA reductase inhibitors starts early, preferably within the first two weeks after HT.

However, the treatment with statins is not free of risks, including potential rhabdomyolysis (1: 1,000,000), hepatotoxicity, muscle pain and single increased creatine phosphokinase (CPK). In our experience (8) and, in accordance with literature data, (3-7, 9) the incidence of adverse events attributed to treatment with statins is low (12.2%) when analytical monitoring and clinical follow-up are near. In our series of patients, the need to remove this type of lipid-lowering drugs was < 5%.

Therefore, the treatment with statins in the heart transplant patient should be considered a first-line

treatment and, if there are no contraindications for its use, it should be administered early.

There are other parameters, such as high homocysteine and lipoprotein (a) [Lp(a)] levels which have been considered risk factors for development of heart coronary disease and have been proposed as GVD risk factors.

It is well-known that Lp(a) levels are reduced during the first 6 months after the transplantation and remain low during the first year of transplantation. (10) However, their effect on GVD development is currently controversial. (11, 12)

Retrospective and observational studies suggest that high homocysteine levels are involved in GVD development. However, a bimodal effect has been recently described with the use of folic acid as prevention/treatment of hyperhomocysteinemia in heart transplant patients. (13) The treatment with folates appears to delay GVD development in HT patients with high homocysteine levels, whereas the use of folic acid appears to augment intimal hyperplasia in patients with normal homocysteine levels.

Masson et al., in their paper **“Management of Dyslipemia in Heart Transplant Patients. Findings on New Risk Factors”**, (9) under this edition of *Revista*, report high homocysteine (> 15 mg/dl) and Lp(a) (> 30 mg/dl) levels in almost half of their series of patients undergoing an orthotopic HT. They ask for prospective randomized and controlled studies to determine the involvement of Lp(a) and homocysteine in GVD pathogenesis, thus setting their clinical and therapeutical implications in this subset of patients.

To sum up, GVD is the main limiting factor for transplant patient mid- and long- term survival. The great prevalence of hyperlipidemia in HT patients and its involvement in GVD development make achieving a good lipid monitoring one of the purposes of follow-up after HT. Statins are to be regarded as first-line therapy in HT patients due to its lipid-lowering, antiproliferative and immunosuppressant effect, and they should be administered, except for contraindications, as soon as possible. Research on other risk factors as Lp(a) implication and homocysteine in GVD

pathogenesis opens new lines of potential therapeutic acting in these patients.

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