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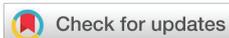***Corresponding author:** Eleazar Chaib, M.D, PhD, FRCS, Associate Professor of Surgery, School of Medicine, University of São Paulo, Av. Dr. Arnaldo 455, 3rd floor, suite 3208, 01246-903, São Paulo, Brazil, Tel: +55 11 30618319; Fax: +55 11 30617270; E-mail: eleazarchaib@yahoo.co.uk

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Research Article

Impact of HCV antiviral therapy on the Liver Transplantation Waiting-List assessed by mathematical models

Abstract

In this paper we analyze, through a mathematical model, the potential impact of HCV antiviral therapy on the liver transplantation waiting list (LTWL) in the State of Sao Paulo, Brazil.

In previous papers, we projected the size of the waiting list by taking into account the incidence of new patients per year, the number of transplantations carried out in that year, and the number of patients that died in the waiting list. In the present work, we projected the LTWL size for the next 30 years and we introduced the anti-HCV treatment, which was assumed to half the incidence of patients in the LTWL and that the recovery of patients in the list would triple. The liver transplantation rate was assumed to not be affected by the anti-HCV treatment. Our mathematical model demonstrates that anti-HCV therapy would have a remarkable impact on the size of the LTWL, in the State of Sao Paulo, dropping from twenty-four thousand to approximately twelve hundred patients in the next 30 years.

Introduction

Prevalence of hepatitis C virus (HCV) infection is found worldwide however country prevalence ranging from less than 1% to greater than 10%. The highest prevalence has been reported in Africa and Middle-East, with a lower prevalence in the Americas, Australia, and Northern and Western Europe [1].

Sao Paulo is the first Brazilian state to perform liver transplantation in 1968 [2]. Since then the recipient waiting list has increased; now approximately 150 new cases per month are referred to the single list at the central organ procurement organization [3].

HCV infection is considered a major public health problem [4] with a global prevalence rate of 2.8%, equating to over 185 million infections, and more than 350,000 deaths annually.

An estimated 3 million to 4 million new cases of HCV infection emerge every year, worldwide [5]. Furthermore, the HCV-related mortality is increasing and HCV infection is projected to be the most important leading cause of viral hepatitis-related mortality in the near future [4,6].

End-stage liver disease due to HCV is currently the leading indication for liver transplantation (LT) in both the United State of America (USA) and Brazil, mainly in the State of Sao Paulo accounting for over 30% and 40% of all transplants annually, respectively (8,9). However, treatment for chronic HCV infection, with elimination of HCV infection, has revolutionized in the past 5 years with the approval of second-generation direct-acting antiviral agents.

The number of patients on the liver transplantation waiting list (LTWL) in the State of Sao Paulo jumped 2.71-fold in the past ten years, almost 50% of them due to HCV consequently the number of deaths on LTWL moved to a higher level increasing 2.09-fold [7-11].

Our aim is to analyze, through a mathematical model, the potential impact of HCV antiviral therapy on the LTWL in the State of Sao Paulo, Brazil

Materials and Methods

This is a theoretical work and we used mathematical models designed to mimic the LTWL's dynamics and which represent improvements on works previously published. In previous papers Chaib et al. [3-5], projected the size of the waiting list, L, by taking into account the incidence of new patients per year, I, the number of transplantations carried out in that year, Tr, and the number of patients that died in the waiting list, D. The dynamics of the waiting list is given by the recurrent equation:

$$L_{t+1} = L_t + I_t - D_t - Tr_t \qquad (1)$$

that is, the list size at time *t+1* is equal to the size of the list at the time *t*, plus the new patients getting into the list at time *t*, minus those patients who died in the waiting list at time *t*, and minus those patients who received a graft at time *t*. The variables I, and D, from 2006 onward were projected by fitting an equation by maximum likelihood, in the same way that we did for Tr.

In this paper we improved the list dynamics by considering a continuous-time model as follows:

$$\frac{dL(t)}{dt} = (\beta - \alpha - Tr)L(t) \qquad (2)$$

where β is the incidence rate of patients with the model for end-stage liver disease (MELD) criteria to get into the LTWL, α is the death rate and T_r is the transplantation rate of patients in the LTWL, respectively. We used the Latin Hypercube sampling method [7], to find the values of the parameters that would explain the observed data.

Equation (2) has the following solution:

$$L(t) = L(0)\exp\left[-(\beta - \alpha - Tr)t\right] \qquad (3)$$

Data used in the work has been collected in the Service of Transplantation of the State Secretary of Health of Sao Paulo.

Ethical issues

This work has been approved by the Institutional Review Board of the School of Medicine, University of Sao Paulo, under the protocol number 2018-3954-7.

Results

Table 1 shows the value of the variables that entered the model. From the time variation in each of the variables, we estimated the rates of equation (2)

Figure 1 shows a comparison between the actual number of patients in the liver transplantation waiting-list from 2006 until 2017, an exponential fitting and the integral of equation (2).

As can be observed in the figure, the set of parameters used retrieves the actual data with the same accuracy as the exponential fitting. This should be expected since the solution of equation (1) is also an exponential function (equation (2)). However, the remarkable tally of the models output with the exponential fitting was obtained by optimizing the value of the parameters through the latin hypercube sampling technique used.

We the projected the result of equation (3) for the next 30 years, under the assumption that all the conditions would remain the same. Next, we introduced the anti-HCV treatment, which was assumed to halve the incidence of patients in the LTWL and that the recovery of patients in the list would triple.

The liver transplantation rate was assumed to not be affected by the anti-HCV treatment. Figure 2 shows the results of this simulation.

It can be seen from figure 2 that the anti-HCV treatment would have a remarkable impact on the size of the LTWL, dropping from around 24 thousand patients to around 1.2

Table 1: Value of the variables that entered into the model

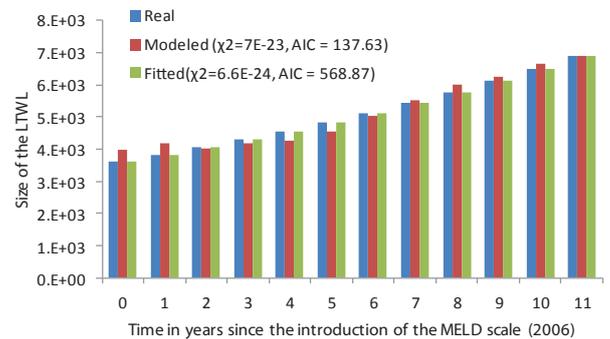| Year	Previous # Patients in the LTWL	Incidence of New cases per year	Number of Transplants	Recovered	Deaths
1	4183	1565	510	24	840
2	4013	1022	440	44	708
3	4165	1212	545	54	461
4	4266	1287	693	45	448
5	4544	1415	744	37	356
6	5023	1576	688	15	394
7	5537	1490	599	18	359
8	5998	1520	653	12	394
9	6262	1378	665	16	433
10	6643	1451	655	19	396
11	6916	1316	623	21	399
12	7181	1385	620	28	472

Figure 1: Number of patients in the LTWL since 2006. Real data (blue) is compared with the simple fitting procedure (green) and the model (equation (3), Red).
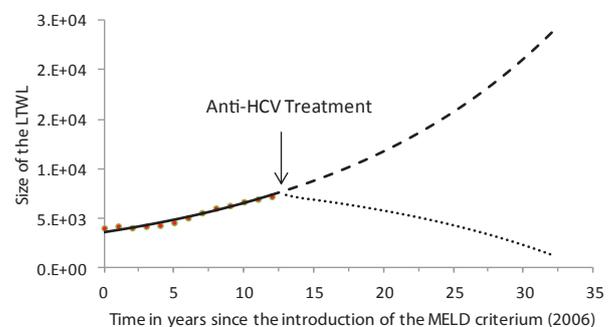

Figure 2: Impact of Anti-HCV treatment on the size of the LTWL. Red dots represent real data, gross-dotted line represents the projection of the size of the LTWL in the absence of treatment and finely-dotted line the theoretical reduction in the size of the LTWL as a result of treatment introduce at time 12.5 years.

thousand patients in 30 years. This reduction would obviously more accentuated if the transplantation capacity of the system would increase, such that by doubling the transplantation rate from year 12, the LTWL would be reduced to zero after less than ten years.

Discussion

In this work we propose an improvement of mathematical models aimed to mimicking the LTWL's dynamics previously published in order to assess the theoretical impact of anti-HCV treatment on the size of the list. It represents an important contribution to the understanding of the possible impact of anti-HCV treatment on the number and rate of new liver failure cases in an affected community because HCV-related end-stage cirrhosis is currently the first cause of liver transplantation [5]. The risk for developing cirrhosis 20 years after initial HCV infection among those chronically infected varies between studies, but is estimated at around 10–15% for men and 1–5% for women. Once cirrhosis is established, the rate of developing hepatocellular carcinoma (HCC) is at 1–4% per year [12].

The health care burden caused by hepatitis C is projected to increase significantly in the next 20 years, on the basis of modeling estimates of cirrhosis, hepatic decompensation, and HCC likely to be seen in this population in the future [13].

Currently, chronic hepatitis C virus-infection-related cirrhosis is the most common indication for liver transplantation in the USA and most parts of the world. While the incidence of new hepatitis C virus cases has decreased, the prevalence of infection will not peak until the year 2040. In addition, as the duration of infection increases, the proportion of new patients with cirrhosis will double by 2020 in an untreated patient population. In previous papers our group [14-19], proposed a series of mathematical models dealing with distinct aspects of liver transplantation. Some of the models were simple like the present one and some more complex. In spite of the mathematical simplicity of the current model, it may serve as a benchmark to test a crucial hypothesis related to the size of the waiting list in countries with a rather limited supply of grafts, namely, how a new tool of public health control (in this case a new therapy) will impact the rate at which liver-failure patients could be transplanted as soon as possible. We think that the present simple model can represent an important step forward in understanding and controlling this rather important public health issue.

Finally, it important to highlight the model's limitations such as the simplicity of the assumptions behind the equations. However, the role of mathematical models as applied to real-world problems consists in helping the understanding of the phenomenon and to provide tools of predictive capacity that may be used to guide decision-making, in particular in critical health issues such as liver transplantation. We hope that this model may be of clinical use related to the optimal distribution of anti-HCV treatment as a control tool to end-stage liver failure.

Conclusion

Our mathematical model demonstrates that anti-HCV therapy would have a remarkable impact on the size of the LTWL, in the State of Sao Paulo, dropping from twenty-four thousand to approximately twelve hundred patients in the next 30 years.

Author contributions

Chaib E, Pessoa JLE, Medeiros M and Massad E designed the research; Pessoa JLE, Medeiros M performed the research; Pessoa JLE, Medeiros M and Massad E analyzed the data; Chaib E and Massad E wrote the paper; Chaib E; Pessoa JLE, Medeiros M and Massad E revised the manuscript prior to submission.

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