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COLOMBIAN EXPERIENCE IN THE TREATMENT OF HEPATITIS C WITH DIRECT-ACTING ANTIVIRAL AGENTS

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Abstract There are few published real-world studies on hepatitis C in Latin America. This paper describes a cohort of Colombian subjects treated with direct-acting antiviral agents. A total of 195 patients from 5 hepatology centers in 4 Colombian cities were retrospectively studied. For each patient, serum biomarkers were obtained, and Child-Pugh, MELD, cirrhosis and fibrosis stage were calculated. Additionally, viral load was quantified at initiation, end of treatment and at 12 weeks of completion. Adverse effects were recorded. Patients with liver transplant were compared with non-transplanted patients in terms of serum biomarkers. The patients had received 9 different regimes. The most prevalent viral genotype was 1b (81.5%). Overall, 186 patients (95.4%) attained sustained virologic response. When comparing transplanted vs. non-transplanted patients, those in the non-transplanted group were more likely to have cirrhosis (52.6% vs. 12.5%, p = 0.0004). Pre-treatment viral load was higher in the transplant group (1 743 575 IQR = 1 038 062-4 252 719 vs. 345 769 IQR = 125 806-842 239; p < 0.0001) as well as ALT and AST levels (82.5 IQR 43.5-115.5 vs. 37.0 IQR = 24.7-73.3; p = 0.0009 and 70 IQR = 41-140 vs. 37 IQR = 24-68; p = 0.004 respectively). Adverse events were reported by 28.7% of the patients; asthenia (5.6%) was the most prevalent. Our results are comparable with those from other countries in terms of therapy and biomarkers. However, our cohort reported less adverse events. Further research is needed in the region.

Key words: antiviral agents, drug therapy, hepatitis C, chronic hepatitis, liver transplantation, treatment outcome

Resumen ***Experiencia colombiana en el tratamiento de la hepatitis C con agentes antivirales de acción directa.*** Existen pocas publicaciones de evidencias del mundo real sobre hepatitis C en América Latina. En este estudio presentamos una cohorte colombiana de pacientes tratados con agentes antivirales de acción directa. Fueron analizados retrospectivamente 195 pacientes seleccionados en 5 centros de hepatología en 4 ciudades de Colombia. Dos tercios fueron mujeres y la mitad tenía ≥ 62 años. De cada uno se cuantificaron biomarcadores séricos, escala de Child-Pugh, MELD y grado de cirrosis y fibrosis. Se cuantificó carga viral al inicio, al final y a las 12 semanas después de completado el tratamiento. Se comparó la frecuencia de efectos adversos de medicamentos en trasplantados vs. no trasplantados. Los pacientes recibieron 9 esquemas de tratamiento diferentes. El genotipo más prevalente fue 1b (81.5%). La respuesta viral sostenida fue alcanzada por 186 pacientes (95.4%). El grupo no trasplantado tenía mayor frecuencia de cirrosis (52.6% vs. 12.5%, p = 0.0004). En los trasplantados, la carga viral pre-tratamiento era mayor (1 743 575 IQR = 1 038 062-4 252 719 vs. 345 769 IQR = 125 806-842 239; p = < 0.0001) igual que la ALT y la AST (82.5 IQR 43.5-115.5 vs. 37.0 IQR = 24.7-73.3; p = 0.0009 and 70 IQR = 41-140 vs. 37 IQR = 24-68; p = 0.004 respectivamente). El 28.7% refirió efectos adversos, siendo el más prevalente la astenia (5.6%). Nuestros resultados fueron comparables a los de estudios publicados en términos de terapia y biomarcadores pero nuestra cohorte presentó menos efectos adversos. Se requiere más investigación en la región.

Palabras clave: agentes antivirales, terapias combinadas, hepatitis C, hepatitis crónica, trasplante hepático, resultados de tratamiento

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The first attempt to ascertain the frequency of hepatitis C in Colombia dates back to 1992, when 4/497 (0.8%) health professionals were positive when voluntarily tested during a Congress of Internal Medicine held in Bogota[1]. In 1996, 10/430 serum samples from Tumaco, in the Pacific Coast, were positive both to an initial ELISA test and to a second confirmatory test[2]. In 1998, a prevalence study analyzed samples from 163 indigenous subjects from three different ethnic groups (inga, n = 15; kamsa, n = 54; wayuu, n = 94) and all were negative[3]. This apparently low hepatitis C prevalence in indigenous communities contrasted with that of hepatitis B, which is particularly high, as found by other studies in Amazonian communities of Brazil, Bolivia, Colombia, Peru, and Venezuela[4]. More recent studies, both from the Caribbean Coast[5] and from Colombian Amazonian indigenous ethnic groups, have shown higher prevalence rates[6].

In 1998, when the Pan American Health Organization warned about the risk of transmission of the virus through transfusions, Chile, Colombia, Costa Rica, and Venezuela had already made tests for the virus mandatory in all their blood banks[7]. The prevalence of the virus was then estimated at 0.45% in a sample of 41 575 blood donors in Santander[8]. In 2007, in a total of 6009 blood bank records from donations received in 2004-2005, 38 (0.6%) hepatitis C cases were detected by a third generation ELISA[9]. On the other hand, of 1840 Colombian women participating in a human papillomavirus study in 2015, 46 (2.5%) were positive for hepatitis C[10].

A systematic review published in 2007[11] analyzed the prevalence of hepatitis C in intravenous drug abusers from 57 countries, and Bogota (with 2%), had the lowest figures in Latin America. On the other hand, Sepúlveda et al.[12] found positive titers for hepatitis C in 16/71 (22.5%) intravenous drug abusers in a psychiatric hospital in Pereira, which contrasts with the finding of Bautista et al., who found none in a population of 259 illicit drug users in Bucaramanga (of which only 11 used intravenous drugs)[13]. In Armenia (Colombia), the prevalence was 22.3% in a sample of 265 intravenous drug users[14].

With regards to genotype frequency, in 2002, in a sample of 40 patients with hepatitis C from Medellin, Yepes et al. found that the predominant genotype and subtype were 1, and 1a, respectively, with an apparent relative increase of genotype 1b in the previous few years[15], suggesting transfusions as the main transmission mechanism. In 2005, a study led by the Colombian National Institute of Health analyzed 500 patients who had received ten or more transfusions, from 4 blood banks in Bogota (n = 279) and Medellin (n = 221)[16]. The number of subjects sampled and the percentages that were positive, according to the 5 diagnoses included, were: cancer (n = 236, 3.4%), hemophilia (n = 90, 32.2%), chronic hemodialysis (n = 82, 6.1%), acute bleeding (n = 78, 2%), and sickle cell anemia (n = 14, 7.1%). The study by Yepes et al. in the Caribbean Coast[5] had found a history of transfusion in 44/55 affected individuals. Another study from a dialysis unit in Cali found reactivity in 29/999 patients (2.9%)[17].

The distribution of hepatitis C subtypes in a sample of 185 positive sera from voluntary blood donors was: 1b (82.8%), 1a (5.7%), 2a (5.7%), 2b (2.8%), and 3a (2.8%)[18]. The most recent study of serotypes and genotypes, based on 1538 isolates of hepatitis C virus from 1527 patients, found genotype 1 in 88.6%, distributed as follows: subtype 1b 70%, subtype 1a 13.5 %, and not determined 5.1% of cases; genotype 2 was found in 5.4% of cases, 3 in 2%, and 4 in 4%; 0.8% had mixed genotypes[19].

In Colombia, hepatitis C is the main indication for liver transplantation[20]. The natural history of hepatitis C changed radically with the development of direct-acting antiviral agents[21-23]. Their efficacy and safety have not been yet properly studied in Latin American population[24]. This study presents "real-world evidence" from hepatology centers in four Colombian cities.

Materials and methods

This retrospective multicenter study included all patients treated with direct-acting antiviral agents from five reference centers in hepatology, in four Colombian cities (Barranquilla, Bogota, Cartagena, and Medellin) during 2015-2017. Patients were not preselected according to any specific complaints and tests were done as part of their routine evaluation.

Adults with a diagnosis of hepatitis C were included in the study. The diagnosis of hepatitis C was defined as a positive test for anti-HCV antibodies confirmed by a positive HCV viral load. Additionally, patients should have initiated treatment with any of the available pharmacological schemes. Treatments were chosen by each treating hepatologist who was aware of the patient's diagnosis, following national[25] and international guidelines[26-29]. There were no excluded patients. Standard protocol approvals, registrations and patients' consents were obtained.

A total of 195 patients were tested for HCV genotype, viral load, cirrhosis and fibrosis stage according to the fibroscan scale. Serum biomarkers as bilirubin, ALT, AST, INR, hemoglobin, platelets and creatinine were measured. Child-Pugh and MELD scores were calculated for each patient. All samples were taken under the routine examination and none of them was acquired during liver or renal crisis or under any acute illness. Samples were processed by the laboratory of the correspondent center from which the sample was obtained.

Patients were classified initially according to their treatment status into: patients who had not received any treatment, non-responders, partial responders, patients with virologic relapse, patients with liver transplant. Patients were considered to be non-responders when the HCV RNA serum level remained detectable throughout the treatment and was formally defined as < 2 Log_{10} decline in HCV RNA between the baseline and week 12[25]. Patients were considered to have a virologic relapse when HCV RNA decreased and remained below the limit of detection during the treatment, but became detectable again after the discontinuation of the treatment[25]. Finally, patients were considered to be partial responders if the HCV RNA decreased ≥ 2 Log_{10} during the treatment but did not fulfill the responder requirements.

According to current practice, each patient had viral load quantified at the beginning and end of treatment, as well as at 12 weeks of completion, to ascertain sustained virologic response (SVR), which is considered the main outcome.

Additionally, all participants in the study were asked about adverse effects. These were classified in three categories: most common adverse effects, adverse effects that lead to the discontinuation of the treatment and serious adverse effects. The following serious adverse effects were taken in account: liver decompensation, anemia, diarrhea, hepatotoxicity and kidney failure. Hepatotoxicity was defined as presenting hepatic encephalopathy, ascites, esophagus variceal bleeding and/or presenting a bilirubin level three times higher than the reference, or ALT/AST- ratio between concentration of aspartate transaminase (AST) and alanine transaminase (ALT) level five times higher than the reference.

Data were summarized and analyzed in two expert meetings. In the first one, the required sociodemographic and clinical information was agreed upon. In the second one, the entire data were analyzed, and missing, or inconsistent information was reviewed by the entire team.

Information was summarized using commercially available software Excel 2016 [Microsoft® Office 365®]. Statistical analyses were performed using commercially available software GraphPad Prism 6 [GraphPad Software Inc.]). Patients were considered separately according to their transplantation status and a comparison was made between transplanted and non-transplanted. Furthermore, they were classified according the treatment they were receiving, and the virologic response as well as the adverse effects described.

For comparison between transplanted and not transplanted patients, normality was assessed using Shapiro-Wilk test. When the normality condition was satisfied, mean and standard deviation were reported. If the normality test was not satisfied, median and interquartile range were reported. For comparison between transplanted and not transplanted groups, the T-test with Welch correction was performed, and when proportions and nominal data were being compared, the Mann-Whitney test was used to compare two continuous distributions and/or non-parametric samples.

Following the indications of Resolution 8430 of 1993 from the Colombian Ministry of Health, which establishes national research ethics recommendations, this study was classified as "without risk". Confidentiality was preserved throughout the study. The protocol was approved by the ethics committee and by each center's institutional review board.

Results

Information was collected from 195 subjects. Demographics are shown in Table 1. Almost two thirds were women, and half of the patients were ≥ 62 years old. They had been treated with 9 different regimens including paritaprevir/ritonavir-ombitasvir and dasabuvir (ProD), daclatasvir/asunaprevir (DCV/ASV), ProD + rivirin (ProD + RBV), sofosbuvir/DCV + RBV (SOF/DCV + RBV), DCV/simprevir + RBV (DCV/SMV + RBV), SOF/DCV, SOF/ledipasvir + RBV (SOF/LDV + RBV) and SOF/RBV.

The most prevalent genotype was 1b (81.5%) and less than half of our cohort members presented cirrhosis. Especial characteristics (liver transplant, chronic kidney disease, and HIV infection) were present in 19.5%. Baseline biomarkers of the entire cohort are described in Table 1.

Regarding previous treatment, 128 (65.6%) had not received any prior treatment, 42 (21.5%) were non-responders to previous treatment, 8 (4.1%) had received an unknown treatment, 13 (6.7%) had a virologic relapse, and 4 (2.1%) were partial responders; 24 patients (12.3%) had received a liver transplant.

Comparison between patients with and without a liver transplant was made (Table 2). Concerning demographics, there were more females in the non-transplant group than in the transplant group and the most prevalent viral genotype in both groups was 1b. Patients were comparable regarding body mass index (BMI), fibroscan score, and albumin levels. Members of the non-transplanted group were more likely to have cirrhosis than transplanted patients. Pre-treatment viral load was higher in the transplanted group than in the non-transplanted group. Bilirubin was higher in the transplanted group than in the non-transplanted group, as well as ALT and AST. INR was higher in the non-transplanted group, as well as hemoglobin and platelets. Creatinine was higher on the transplanted group.

Regarding safety, 28.7% patients reported adverse effects, as summarized in Table 3. Of these, the most common were asthenia and adynamia. Ten were considered to have a serious adverse effect (encephalopa-

TABLE 1.– *General characteristics of the study population, in a cohort of Colombian hepatitis C patients treated with direct-acting antiviral agents*

	All subjects (n = 195)
Female, n (%)	118 (60.5)
Age in years	
Median (IQR)	62 (55-68)
Body mass index	
Mean (SD)	26.2 (4.2)
Genotype, n (%)	
1a	31 (15.9)
1b	159 (81.5)
1	4 (2.1)
2	1 (0.5)
Fibroscan, n (%)	
Unknown	40 (20)
0	21 (10.7)
1	19 (9.7)
2	21 (10.7)
3	21 (10.7)
4	73 (37.4)
Cirrhosis	93 (47.7)
Special groups, n (%)	
Liver transplant	24 (12.3)
Chronic kidney disease	11 (5.6)
HIV positive	3 (1.5)
Pre-treatment viral load (UI/ml)	
Median (IQR)	421 863
(137 016 – 1 288 674)	
Bilirubin	
Median (IQR)	0.9 (0.62-1.3)
ALT U/l	
Median (IQR)	41 (26-82)
AST U/l	
Median (IQR)	40 (25.25-72.5)
INR	
Median (IQR)	1.06 (1-1.2)
Hemoglobin	
Median (IQR)	14.1 (13.2-15.5)
Platelets	
Median (IQR)	154 500 (111 250-233 000)
Albumin	
Median (IQR)	4.01 (3.8-4.4)
Creatinine	
Median (IQR)	0.8 (0.7-1.0)
Child-Pugh	5 (5-6)

IQR: interquartile range; SD: standard deviation

thy 1, cholelithiasis 1, diarrhea 2, hepatotoxicity 3, and anemia 3). Six patients receiving PrOD + RBV (n = 3), DCV / ASV (n = 2) and DCV / SMV + RBV (n = 1) discontinued treatment because of adverse effects (cholelithiasis, diarrhea, and hepatotoxicity). However, 3 of them maintained a SVR despite discontinuing therapy.

Additionally, two of the transplant recipients (8.3%) stopped treatment because of hepatic decompensation; both were receiving PrOD + RBV.

Most patients in our cohort were treated with ProD (33%). SVR was attained by 186 patients (95.4%). The proportion attaining SVR according to each therapy is summarized in Table 4.

Discussion

To our knowledge this is the first Latin American study that provides real-world evidence for the efficacy of direct-acting antiviral agents in the therapy of hepatitis C.

In the study population, as previously described in our country, the most frequent genotype is 1b (81.5%) followed by 1a (15.9%), which suggests that the sample of this study is representative of Colombian cases, and that having received a transfusion (prior to 1998) would be the main risk factor. The majority of the studied cases were women, perhaps more prone to this particular risk factor. Additional studies, however, are required in the target population to clarify the role of this and other risk factors for hepatitis C virus transmission in Colombia.

A SVR was achieved by 95.4% (186/195) of our patients, which is comparable with the SVR described in the literature for naive and treatment-experienced patients, which is usually 80-90[26-29]. At week 12 after starting treatment, 100% of the patients treated with ProD and SOF/DCV+RBV presented SVR, which is comparable to figures described for these therapies in other countries[30]. The association SOF/SMV presented the lowest response rate in this cohort (75%), which is different from the virologic response found in other studies[31]. However, in our cohort only 4 patients were being treated with this scheme and the small sample can be responsible for the difference. Usually, “special patients” are considered difficult to treat as they have higher event rates and poor SVR rates[32]. In this cohort, 122 cases (62.6%) were in this group, as they have presented with cirrhosis (n 93, 47.7%), with liver transplant (24, 12.3%), with CKD (11, 5.6%), or co-infected with HIV (3, 1.5%). Despite this high percentage of special patients, the entire cohort achieved an acceptable SVR.

Furthermore, a large proportion of patients (60, 30.8%) received medication schemes currently considered suboptimal (in this case daclatasvir/asunaprevir) which was then the only option. The 93% SVR in these patients is similar to a large series of Korean cases treated with this

TABLE 2.– *Differences between transplanted and non-transplanted subjects in a cohort of Colombian hepatitis C patients treated with direct-acting antiviral agents*

	Non-transplant patients (n = 171)	Liver transplant patients (n = 24)	P value
Female, n (%)	111 (64.9)	7 (29.1)	0.0038
Age in years,			
Median (IQR)	62 (55-68)	57 (46.5-65.3)	0.05
Body mass index			
Mean (SD)	26.1 (4.3)	27 (3.3)	0.2
Genotype, n (%)			
1a	27 (15.8)	4 (16.7)	
1b	140 (81.9)	19 (79.4)	
1	3 (1.8)	1 (4.2)	
2	1 (0.6)	0 (0.0)	
Fibroscan	3 (1 - 4)	2 (0-3.8)	0.1
Cirrhosis, n (%)	90 (52.6)	3 (12.5)	0.0004
Decompensated cirrhosis, n (%)	5 (2.9)	2 (8.3)	0.2
Pre-treatment viral load			
Median (IQR)	345 769		
(125 806 – 842 239)	1 743 575		
(1 038 062 – 4 252 719)	<0.0001		
Bilirubin			
Median (IQR)	0.9 (0.6-1.3)	1.0 (0.8-1.6)	0.02
ALT U/l			
Median (IQR)	37 (24.7-73.3)	82.5 (43.5-115.5)	0.0009
AST U/l			
Median (IQR)	37 (24-68)	70 (41-140)	0.0043
INR			
Median (IQR)	1.08 (1.0-1.2)	1.0 (0.9-1)	0.006
Hemoglobin			
Median (IQR)	14.4 (13.5-15.6)	13.5 (12.5-14.0)	0.0038
Platelets			
Median (IQR)	152 000		
(107 000-234 000)	165 000		
(122 000-226 000)	0.6		
Albumin			
Median (IQR)	4.1 (3.7-4.4)	4.1 (3.7-4.3)	0.8
Creatinine			
Median (IQR)	0.8 (0.7-0.9)	1.02 (0.8-1.2)	0.0008

IQR: interquartile range; SD: standard deviation

combination[33]. Other schemes with suboptimal response rates were daclatasvir/simeprevir + ribavirin, sofosbuvir/simeprevir, and sofosbuvir/simeprevir.

Additionally, when comparing transplanted with non-transplanted patients, we found differences in terms of cirrhosis, pretreatment viral load, bilirubin, ALT and AST, INR, hemoglobin and platelets.

About viral load on the transplanted group, it has become clear in the literature that the recurrence of detection of HCV RNA is nearly universal in transplanted patients[34]. It has been described that viral load usually decreases immediately post-transplantation, but when patients are followed further in time, there is a significant increase reaching the pre-transplant viral load levels 48 hours

TABLE 3.– *Overall report of adverse effects*

Symptom	Number of reports (n=195)	%
Asthenia	11	5.6
Adinamia	9	4.6
Headache	8	4.1
Fatigue	8	4.1
Nauseas	5	2.5
Hepatotoxicity	3	1.5
Anemia	3	1.5
Rash	2	1
Diarrhea	2	1
Cholelithiasis	1	0.5
Pruritus	1	0.5
Vomit	1	0.5
Anxiety	1	0.5
Encephalopathy	1	0.5

Ten of these patients were considered to have a serious adverse effect (1 patient with cholelithiasis, 2 patients with diarrhea, 3 patients with hepatotoxicity, 3 patients with anemia and 1 with encephalopathy).

TABLE 4.– *Proportion of patients that attained sustained virologic response*

Therapeutic scheme	n	SVR	%
PrOD	65	65	100
DCV/ASV	60	56	93
PrOD+RBV	41	38	93
SOF/DCV+RBV	10	10	100
DCV/SMV+RBV	9	8	89
SOF/SMV	4	3	75
SOF/DCV	3	3	100
SOF/LDV+RBV	2	2	100
SOF+RBV	1	1	100
Total	195	186	95.4

PrOD: paritaprevir; DCV: daclatasvir; ASV: asunaprevir; RBV: ribavirin; SOF: sofosbuvir; SMV: simeprevir; LDV: ledipasvir; (PTV)/ritonavir (RTV)/ombitasvir; (OMV)/dasabuvir (DSV); SVR: sustained virologic response

after the transplant and increasing up to 10 to 100 fold the pre-transplant viral load in the following month[35,36], this information is consistent with what is found in this cohort, with the transplanted patients viral load higher than the non-transplanted ones.

Moreover, three patterns of recurrence have been described. In the first one, only transaminases are elevated as it refers to an acute hepatitis[35]. The second one is a chronic hepatitis which leads to cirrhosis in the 25% of patients in the following 5 years[37], in this one, mainly low levels of albumin can be seen. In the third type, a fibrosing cholestatic hepatitis is presented with high viral loads associated with high transaminase loads and usually high bilirubin levels[35]. In this cohort, higher levels of ALT, AST and bilirubin were found in the transplanted patients, which could be also correlated with the higher viral load. However, further studies should be made taking in account time after transplantation to correctly identify and differentiate the causes of these higher liver function marker levels, as they can variate widely over time.

Traditionally, anemia has been described after liver transplantation and its incidence varies between 4.3% and 28.2%, depending on diagnostic criteria used[38]. The cause of anemia is not always clear, but it can be associated with certain medications (tacrolimus, cyclosporine A, azathioprine), with viral infections as parvovirus B19 and cytomegalovirus, or immunologic bone marrow suppression[38]. Therapeutic schemes with RBV have been associated with higher anemia rates[39]. In this cohort, lower levels of hemoglobin were found in the transplanted patients, even though the median was not in the anemia range, but in the lower limit of normality. This result is expected and correlates with the results found in the literature.

Thrombocytopenia has been described in chronic HCV infection[40]. Whereas it has been described as transitory in transplant patients, it has also been reported as persistent in up to 57% of the cohort[41]. In this cohort, platelet count was lower in the transplanted group. According to the literature, spleen size and platelet counts before transplantation can be correlated with platelet levels after the transplant[42], however this should be furthered studied in this cohort as spleen was not measured, but could be an explanation for these results.

Additionally, adverse effects and discontinuation of treatment were described in this cohort. Fifty-six patients reported presenting adverse effects (28.7%), contrary to what is described in the literature in which some cohorts reach even 90% of patients reporting adverse effects[43], this could be due to under-reporting in this cohort due to different reasons as time given for the medical interview. Nevertheless, even when the percentage between the symptoms reported varies from study to study, the reported adverse effects are consistent with other reports[44, 45]. In this cohort, the most reported adverse effect was asthenia, followed by adynamia, headache, fatigue and nausea.

A limitation of this study is the quality of information collected, a common problem in real-world evidence studies. All participant researchers used common and well stablished criteria for diagnosis and follow-up, which gives credibility to our data on efficacy. Safety, however, seems

to be a serious problem, since information on adverse events was not recorded properly in the clinical records, except for major adverse events, or those that required interruption of treatment.

Further research in Colombia should point towards the characterization of the safety of the regimes and correlation between precise regimes, specific adverse effect and the premature discontinuation of each regime, in order to provide better quality information.

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[…] La civilización, bajo su aspecto moral, es un conjunto de cualidades artificialmente desarrolladas, proviniendo de aquí la diferencia entre el individuo civilizado y el salvaje. Éste depende del medio en que ha nacido; el otro es su colaborador inteligente.

Leopoldo Lugones (1874-1938)

El Imperio Jesuítico (1904). Buenos Aires: Hyspamérica, 1985. Epílogo, p 251