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Original article

Generalized implementation of reflex testing of hepatitis C in Galicia: Results for reflection☆

Aldara Vallejo[a,i], Luz María Moldes[b,i], Matilde Trigo[c,i], Patricia Ordoñez[d,i], Luis Rodriguez-Otero[e,i], Jorge Julio Cabrera[f,i], María José Gude[g,i], Daniel Navarro[a,i], Angelina Cañizares[b,i], Marta García-Campello[c,i], Andrés Agulla[d,i], Antonio Aguilera[a,h,i,*], en nombre del Grupo de Estudio del DUSP en Galicia[1]

[a] *Servicio de Microbiología, Complexo Hospitalario Universitario de Santiago, Santiago de Compostela (La Coruña), Spain*
[b] *Servicio de Microbiología, Complexo Hospitalario Universitario de A Coruña, La Coruña, Spain*
[c] *Servicio de Microbiología, Complexo Hospitalario de Pontevedra, Pontevedra, Spain*
[d] *Servicio de Microbiología, Complexo Hospitalario Arquitecto Marcide-Profesor Novoa Santos, Ferrol (La Coruña), Spain*
[e] *Servicio de Microbiología, Complexo Hospitalario Universitario de Ourense, Ourense, Spain*
[f] *Servicio de Microbiología, Hospital Universitario Álvaro Cunqueiro, Vigo (Pontevedra), Spain*
[g] *Servicio de Microbiología, Hospital Universitario Lucus Augusti, Lugo, Spain*
[h] *Departamento de Microbioloxia e Parasitoloxía, Universidade de Santiago de Compostela, Santiago de Compostela (La Coruña), Spain*
[i] *Instituto de Investigación Sanitaria de Santiago, Santiago de Compostela (La Coruña), Spain*

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ABSTRACT

Introduction: The implementation of reflex testing of active hepatitis C virus (HCV) infection, together with the incorporation of informative alerts in the reports, has shown that it significantly reduces the number of patients who were not referred for therapeutic evaluation.
Methods: Since the implementation in 2018 of the DUSP in the Microbiology Services of the Galician Health Service hospitals (SERGAS), new diagnoses of active HCV infection have been retrospectively identified and characterized.
Results: In 2018, a total of 258 patients with unknown active HCV infection (70,2% men, middle age 52 years) were identified through by reflex testing from consultations of primary and specialized care units in 54.8% and 39.8% respectively, as well as from other locations by 5.4%. Of the 258 patients, 81.0% were referred for therapeutic evaluation, with a median of 54 days from their diagnosis. In 58.3% of the cases the reflex testing was determined by viral load, the predominant genotype was 1a (30,7%) and 52,1% were treated, observing sustained viral response (SVR) in 93.7 % of these.
Conclusion: The generalized implementation of the HCV reflex testing together with informative alerts in Galicia has allowed us to obtain referral rates for treatment similar to those obtained in other studies. However, there is a wide variability between the different centers that require the incorporation of improvements, such as training or the use of rescue measures for optimization.

Implementación generalizada del diagnóstico en un solo paso (DUSP) de la Hepatitis C en Galicia: resultados para la reflexión

Palabras clave:
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Tratamiento

RESUMEN

Introducción: La implementación del diagnóstico en un solo paso (DUSP) de la infección activa por virus hepatitis C (VHC) conjuntamente con la incorporación de alertas informativas, ha demostrado que reduce significativamente respecto al diagnóstico tradicional la cifra de pacientes que no eran remitidos para valoración terapéutica.

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* Corresponding author.
E-mail address: antonio.aguilera.guirao@sergas.es (A. Aguilera).

Métodos: A partir de la implementación en 2018 del DUSP en los Servicios de Microbiología de los hospitales del Servicio Gallego de Salud (SERGAS), se identifican y caracterizan de manera retrospectiva los nuevos diagnósticos de infección activa por VHC.
Resultados: En 2018 se identificaron mediante DUSP un total de 258 pacientes con infección activa por VHC desconocida (70,2% hombres, mediana edad 52 años) procedentes de consultas de unidades de atención primaria y especializada en un 54,8% y 39.8% respectivamente, así como de otras localizaciones en un 5,4%. De los 258 pacientes el 81,0% fueron derivados para valoración terapéutica, con una mediana de 54 días desde su diagnóstico. En el 58,3% de los casos se determinóel DUSP mediante carga viral, el genotipo predominante fue el 1a (30,7%) y un 52,1% fue tratado, observándose respuesta viral sostenida (RVS) en el 93,7% de estos.
Conclusión: La implementación en toda Galicia del DUSP de la hepatitis C conjuntamente con alertas informativas ha permitido obtener en conjunto tasas de derivación para tratamiento similares a las obtenidas en otros estudios. Sin embargo, existe una amplia variabilidad entre los distintos centros que exigen la incorporación de mejoras, como la formación o la utilización de medidas de rescate para su optimización.

Introduction

Hepatitis C virus (HCV) infection is a global public health problem affecting approximately 1% of the population and is the leading cause of persistent liver disease associated with the development of cirrhosis, hepatocellular carcinoma, liver failure and death[1–3]. The latest data available in the Spanish general population estimate a seroprevalence of 0.85%, while the rate of active infection stands at 0.22%[4].

In 2016, the World Health Organization adopted a strategy aimed at eliminating viral hepatitis and, as part of this, HCV infections[5]. The World Health Organization's vision for eliminating these infections is based upon the global targets set for 2030 to reduce the incidence of chronic infections by 90% and attributable mortality by 65%.

In the absence of an effective vaccine, the cornerstone upon which HCV elimination and control rests is the treatment of all patients with the new direct-acting antivirals (DAAs), which yield cure rates in excess of 95%[6–9]. Therefore, patients must be previously diagnosed and referred to treatment centres for therapeutic evaluation.

However, a major barrier to HCV treatment and elimination is directly related to the diagnosis of active infection, as there are significant variations between different regions, countries and populations at risk[9,10].

Proper and timely diagnosis is an essential element with regards to controlling the infection. The lack of continuity between diagnosis and subsequent clinical evaluation means that many patients who have been diagnosed do not receive treatment or do so with unnecessary delay. Moreover, this also leads to an increase in the number of visits to the specialist, resulting in the indirect effect of losing the follow-up of the patient[11]. For this reason, reflex testing diagnosis, which consists of conducting the necessary tests, RNA or HCV core antigen (HCcAg)[12] for a definitive diagnosis of hepatitis C in the same specimen[10,13,14], followed by the effective communication of results through an information alert, is the key to combating this lack of continuity and facilitating access to treatment for diagnosed patients. This has already been demonstrated in a pilot study conducted in 2017, as the implementation of reflex testing significantly reduced the number of patients diagnosed by the traditional algorithm who were not referred for therapeutic evaluation from 35% to 16%[15]. Additionally, reflex testing, like universal screening, is a cost-effective tool compared to routine clinical practice based on the traditional algorithm[16–18] as it further facilitates access to treatment[19–21] and, in addition, indirectly ensures that consultations are not overloaded by patients who have already resolved their infection[22].

In Galicia, all the microbiology departments of the hospitals of the Servicio Gallego de Salud [Galician Health Service] (public health) implemented reflex testing during 2018, so the aim of this study was to evaluate its first results.

Methodology

Design and characteristics

A retrospective and anonymised study was carried out in the microbiology departments of all the Galician Health Service hospitals, representing the health districts of La Coruña, Ferrol, Lugo, Pontevedra, Orense, Pontevedra, Santiago and Vigo, to evaluate the results of the implementation of reflex testing for hepatitis C on the referral of diagnosed patients to receive the corresponding treatment during 2018. The inclusion of the various hospitals into the study was progressive throughout 2018 and occurred at the time they implemented this reflex testing strategy.

Detection of active HCV infection in the reflex testing strategy was performed on samples which were positive for HCV antibodies in serological screening by detecting viral load by real-time RT-PCR with TaqMan probes (Roche Diagnostics COBAS® AmpliPrep/COBAS® TaqMan® HCV 2.0/COBAS® 6800) or by detecting HCV core antigen by chemiluminescence immunoassay (Abbott Diagnostics).

For the study, a database was constructed in Excel format in which the data from the diagnosed cases of active HCV infection by reflex testing were collected anonymously from the laboratory information system (LIS) files of the microbiology departments. The variables collected for the study were: age, gender, place of origin, health care origin of referral, referral or not to specialised care (hepatology), days elapsed from diagnosis to referral, method used to diagnose active infection (HCV core antigen or HCV-RNA), genotype, treatment and cure, the latter being understood as the absence of detectable viral load 3 months after the end of treatment.

Patients diagnosed for the first time with active HCV infection were included, while those whose active infection was previously known about were excluded, regardless of whether or not they had been therapeutically evaluated by the specialist. In all diagnosed cases of active HCV infection, the report issued to the sender, from primary or specialised care, was accompanied by an information alert for referral to hepatology for therapeutic evaluation.

[1] Other members of the DUSP Study Group in Galicia are listed in Appendix A.

Table 1
General demographic characteristics of patients diagnosed with active HCV infection in Galicia by reflex testing during 2018 as a whole and according their referral for therapeutic evaluation.

	Total (100%) (n = 258)	Referred (81%) (n = 209)	Not referred (19%) (n = 49)	*p*
Age in years, median (IQR)	52 (45–60)	52 (46–59)	51.50 (43–75.25)	NS
Gender, n (%)				
Female	77 (29.8)	61 (79.2)	16 (20.8)	NS
Male	181 (70.2)	148 (81.8)	33 (18.2)	NS
Health care origin of referral, n (%)				
Primary Care	142 (54.8)	117 (82.4)	25 (17.6)	NS
Specialised Care	103 (39.8)	81 (78.6)	22 (21.4)	NS
Medical departments	81	65 (80.3)	16 (19.7)	NS
Surgical departments	22	16 (72.7)	6 (27.3)	NS
Other	13 (5.4)	11 (78.6)	2 (21.4)	NS

NS: not significant.
Medical departments: Internal Medicine, Cardiology, Gastroenterology, Psychiatry, Dermatology, Rheumatology, Pulmonology, Haematology, Endocrinology, Nephrology, Neurology, Oncology.
Surgical departments: Vascular Surgery, Cardiac Surgery, Maxillofacial Surgery, Ophthalmology, Gynaecology.

Statistical analysis

In our study, the Kolmogorov–Smirnov test was used to check whether or not the age distribution and referral days followed a normal distribution, while the χ^2 test and the Student's t test or the Mann–Whitney U test were used to make comparisons of qualitative and quantitative variables, respectively, for which the SPSS v. 20.0 (IBM Corp.) statistical package was used. Statistical significance was set at $p < 0.05$ in all cases.

Results

The demographic characteristics of the 258 patients in the study who were diagnosed with active HCV infection in Galicia during 2018 after the widespread implementation of reflex testing are listed in Table 1. Of these new diagnoses, 181 were in men (70.2%) and 77 in women (29.8%), with a median age for both genders of 52 years (IQR: 45–60). Overall, 54.8% of patients were in primary care, 39.8% in specialised care, and 5.4% in other units (prisons, drug addiction care units, etc.). No significant differences were found in the demographic characteristics of the patients (age, gender and place of origin) in terms of their referral or non-referral for therapeutic evaluation.

Table 1 also shows that a total of 209 patients (81.0%) were referred to hepatology units (gastroenterology, internal medicine or infectious diseases departments) for therapeutic evaluation, with no differences observed in the proportions of patients referred according to gender or the health care origin of referral from primary or specialised medical care and, within this, if it was a medical or surgical department.

In the study as a whole, and as can be seen in Table 2, the median number of days from the issuance of the diagnosis and the corresponding information alert to referral was 54 days, with no statistical significance ($p = 0.136$, not shown in the table) in the differences of the medians found for primary and specialised care. However, the referral rates as a whole and by health care origin of referral, as well as the corresponding referral times from the diagnosis, varied considerably among the different health districts involved in the study (La Coruña, Ferrol, Lugo, Pontevedra, Orense, Santiago and Vigo), as well as the consultations or units from which they came.

As shown in Table 2, as a whole the referral percentages by health district ranged between 93.4% in Santiago de Compostela and 63.6% in Orense; within primary care, referral ranged from 100% in Lugo to 61.1% in La Coruña; while in specialised care it was between 100% in Pontevedra and 53.8% in Orense. In addition, and regardless of the health care origin of the referral, the median number of days required for referral ranged from 25.5 days (IQR: 7.5–51.25) in the health district of Vigo to 77 days (IQR: 32.75–118.75) in La Coruña, with an overall median of 54 days (IQR: 18.25–80.25).

Regarding the diagnostic method used to confirm active HCV infection, in 58% of cases HCV viral load was used and in 42% the HCV core antigen was used, without differences between the mean values of these determinations (4,185 fmol/l of HCcAg vs 2,656,657 IU/ml of HCV-RNA), after formulating the corresponding conversion[23].

Furthermore, in our study, in the new diagnoses of active HCV infection in Galicia during 2018, the genotype found most often (in 30.7%) was genotype 1, subtype 1a. In the total number of patients diagnosed, the distribution of HCV genotypes was as follows: GT1 60.2% (subtype 1a 30.7% and 1b 28.2%), GT2 3.9%, GT3 20.3% and GT4 14.7%, as shown in Table 3.

Finally, 52.1% of patients referred for therapeutic evaluation started treatment with DAAs and 93.7% of those who completed treatment during the course of this study had a sustained virological response.

Discussion

In our study, the widespread and staggered implementation of reflex testing[24,25] in Galicia alongside information alerts for the diagnosis of active HCV infection yielded response times for therapeutic evaluation and referral rates in line with those obtained in similar studies[15,26]. This is an improvement on those obtained by the traditional algorithm, and this study therefore supports its recommendation by various associations and societies[7,13,27].

Regarding referral for access to treatment with DAAs, as a whole no differences were found in terms of gender or the health care origin of referral in the absolute percentages of patients referred to hepatology units, so these factors are not decisive in this case, as in other studies similar to ours[26].

However, in our study, despite the overall result for Galicia of 81%, we found significant variations in terms of referral percentages, with ranges of variability around 30% between the different health districts. Excellent rates of referral were observed, higher than 90% in some cases, but there were also low rates at around 60%. These differences increase even more when the results are broken down according to the health care origin of referral, with differences for primary care of almost 40% and almost 55% for specialised care.

In our study, we found a median referral time of 54 days (IQR: 19.25–80.25), similar to that found in other studies in which the impact of reflex testing was measured[15,26]. However, this figure is likely to be improved with the consolidation of this strategy. In our case, variation was also seen in the median referral time for

Table 2
Referral of patients (% and median days) from reflex testing in Galicia by health district and health care origin of referral during 2018.

Health district	Patients, n (%)	Referral, n (%)	Days to referral, median (IQR)	PCU referral, n (%)	PCU: days to referral, median (IQR)	SC: referral, n (%)	SC: days to referral, median (IQR)	Other: referral n (%)	Other: days to referral, median (IQR)
Santiago de Compostela	76 (30)	71 (93.4)	48.5 (8.25–68.5)	42 (93.3)	28 (8.0–59.5)	22 (95.7)	56 (8.0–75.0)	7 (87.5)	86.5 (48.75–133.5)
La Coruña	71 (27)	46 (64.7)	77 (32.75–118.75)	22 (61.1)	77 (26.75–123.75)	20 (66.7)	67 (29.75–118.75)	4 (80.0)	108 (83–261.25)
Pontevedra	36 (14)	33 (91.6)	56 (19.25–101.25)	14 (82.4)	52 (16.75–72.0)	19 (100.0)	74 (30.25–123.5)		
Ferrol	31 (12)	27 (87.1)	54 (33.0–70.0)	20 (95.2)	54.5 (29–66.75)	7 (70.0)	52 (31.75–127.50–3)		
Orense	22 (8)	14 (63.6)	49 (24.25–148.0)	7 (77.8)	49 (13.0–66.0)	7 (53.8)	145 (N/A)		
Vigo	12 (5)	9 (75.0)	25.5 (7.5–51.25)	6 (75.0)	22 (10.0–46.5)	3 (75.0)	29 (N/A)		
Lugo	10 (4)	9 (90.0)	58 (42.25–93.75)	6 (100.0)	66.5 (46.5–106.25)	3 (75.0)	42.5 (N/A)		
Total (Galicia)	258 (100)	209 (81.0)	54 (19.25–80.25)	117 (82.4)	50 (14.5–74.0)	81 (78.6)	56 (29.0–102.0)	11 (84.6)	108 (54.25–133.5)

IQR: interquartile range; N/A: not applicable; PCU: Primary Care Units; SC: specialised care.

Table 3
Distribution of genotypes in the total population studied compared to the study conducted by Navarro et al. in Galicia (2005–2015).

HCV Genotypes	Navarro et al. n = 4,469 (2005–2015) as a %	Vallejo et al. n = 231 (2018) as a %	*p*
1	62.4	60.2	NS
1a	27.5	30.7	NS
1b	30.3	28.2	NS
NA	4.6	1.3	0.02
2	3.4	3.9	NS
3	21	20.3	NS
4	12.6	14.7	NS
5	0.1	0	NA
Mixed	0.4	0.9	

NA: genotype 1 not assigned (no subtype); NS: not significant.

all of Galicia, which is four days shorter in primary care and two days longer in specialised care, although it increases significantly in patients from drug addiction units, peaking at 108 days (IQR: 54.25–133.5). However the limited number of cases does not allow significant conclusions to be drawn.

As expected, the median number of days to referral also varies significantly between different health districts. Among the causes of this variability are probably the different experiences with reflex testing depending on its implementation date, the effectiveness of the alerts and the level of insistence on communicating the results to the requesting service, as well as the training of health personnel or their knowledge of the existence of HCV elimination programmes based on the detection and rapid referral of infected patients to hepatology units for the treatment of active virus infection.

In our study, it is noteworthy that, despite the low number of patients already mentioned, the referral rate found in the group that includes those from prisons and drug addiction units is higher than the group that includes patients in primary and specialised care, regardless of the days observed until referral. In terms of patients who are not referred, the non-referral rate is higher from primary care units than from specialised care units and, within the latter, from surgical departments. Regarding the medical departments, despite having a higher referral rate, the non-referral rate of the psychiatric units is striking, accounting for 19% of all non-referrals (data not shown in Table 1). These results suggest the need to implement a special referral programme for those patients with reflex testing when they are admitted for severe mental disorder in order to access treatment with DAAs[28].

In this regard, it is essential to implement and insist on the training of healthcare professionals who care for infected patients outside the hepatology setting, in addition to implementing strategies that confirm the patient's access to treatment from microbiology, such as active referral through direct communication or rescue by reviewing and confirming the patient's referral with reflex testing. In this sense, and in order to harmonise the different referral rates found between the different health districts, the professionals involved should audit them periodically to check and correct, with the intervention of the health authorities if necessary, the measures proposed above to promote access to treatment.

Other notable aspects in our study are the indistinct use of HCV core antigen or HCV-RNA as part of reflex testing[12] to confirm active infection, with surprisingly similar quantification results, and to have found in the new diagnoses an HCV genotype distribution similar to that of the last study carried out in Galicia[29], as can be seen in Table 3, although with a slight increase in genotypes 1a and 4 associated in Spain with young people and parenteral and sexual transmission, respectively[30].

The high percentage of referred patients who did not start treatment (47.9%) observed in our study is also striking. We could

deduce that, although the implementation of reflex testing is highly recommended to expedite diagnosis and response times, there are still gaps to be filled in terms of its ultimate goal, which is the treatment and consequent cure of all patients in order to decrease associated morbidity and mortality and virus transmissibility. If reflex testing does not result in the treatment of practically all patients diagnosed, the implementation of this strategy will not be useful, so improvement actions should be proposed and the necessary measures taken by clinical hepatology to increase treatment rates (52.1% in our study) and prevent this from happening.

The limitations of our study include the fact that some centres were only in the study for a short time due to the late implementation of reflex testing, resulting in a number of new diagnoses that is not in line with the centre's size, as well as the limitation of information loss during data collection inherent in all retrospective studies.

To summarise, our study shows that the mere implementation of reflex testing, with the information alert and no additional strategies, is recommended but not sufficient to achieve the objectives of eliminating the disease[5,10]. Improvements to get us closer to that goal would require the creation of multidisciplinary teams to enhance results in areas such as the training of healthcare workers, the active search for infection and the use of rescue measures for optimisation.

Conflicts of interest

The authors declare that they received no funding for the drafting of this document and have no conflicts of interest.

Appendix A. Reflex testing study group in Galicia

María Luz Moldes and Angelina Cañizares (Complexo Hospitalario Universitario de A Coruña [A Coruña University Hospital Complex]), Patricia Ordoñez and Andrés Agulla (Complexo Hospitalario Arquitecto Marcide-Profesor Novoa Santos de Ferrol [Arquitecto Marcide-Profesor Novoa Santos de Ferrol Hospital Complex]), María José Gude and María Pilar Alonso (Hospital Universitario Lucus Augusti de Lugo [Lucus Augusti de Lugo University Hospital]), Luis Rodríguez-Otero and Juan García-Costa (Complexo Hospitalario Universitario de Orense [Orense University Hospital Complex]), Matilde Trigo and Marta García-Campello (Complexo Hospitalario Universitario de Pontevedra [Pontevedra University Hospital Complex]), Aldara Vallejo, Daniel Navarro and Antonio Aguilera (Complexo Hospitalario Universitario de Santiago de Compostela [Santiago de Compostela University Hospital Complex]) and Jorge Julio Cabrera and Sonia María Pérez Castro (Hospital Universitario Álvaro Cunqueiro de Vigo [Álvaro Cunqueiro de Vigo University Hospital]).

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