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RESEARCH ARTICLE

Serum Thyroglobulin (Tg) assay by immunoradiometric methods (IRMA): comparison of concentrations obtained with Cisbio Bioassays vs Beckman Coulter kit in patients with differentiated thyroid cancer.

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ABSTRACT

Introduction: In clinical practice, Thyroglobulin is a tumor marker for the post-operative follow-up of differentiated thyroid cancer, provided that any thyroid residual remains are eliminated beforehand, either by simple total thyroidectomy, or most often supplemented by isotopic totalization with Iode131. The aim of this study were to compare serum Tg values measured with 02 kit manufacturers of immunoradiometric type (IRMA) and to evaluate their cost/effectiveness ratio.

Methods: We included patients followed for differentiated thyroid cancer operated and irradiated with Iodine 131 at the nuclear medicine department of Tlemcen University Hospital. Their serum Thyroglobulin was dosed in the laboratory of the department with the Tg-IRMA kit of Cisbio Bioassays taken in this study as «Gold standard» and the Tg-IRMA kit of Beckman Coulter.

Results: Ninety-nine (99) serums of patients with CDT were measured for Thyroglobulin. The correlation of the Thyroglobulin values obtained with the 02 kits is positive and significant ($r = 0.98$; $p < 0.01$). The equation of the regression line of Passing- Bablok is of type $y = 0.7 x + 0$ (with Y = Tg-IRMA Cisbio Bioassays and X = Tg-IRMA Beckman Coulter). The difference in the averages analyzed with the Bland-Altman diagram is = 0 ($p > 0.05$), indicating that there is no difference in the mean of Tg between the 02 kits. The analysis by ROC curve of the Tg-IRMA Beckman Coulter kit Thyroglobulin values at the threshold of 0.7 and 1 ng/mL finds respectively a sensitivity and a specificity of 100% and 93% with an area under the curve = 0.99.

Conclusion: There is a strong correlation between Thyroglobulin concentrations obtained with the 02 kits, so a budget reduction in the management of our patients with diffrentiated thyroid cancer is possible, in favor of the Tg-IRMA kit of Beckman Coulter with a good cost/ efficiency ratio.

Keywords: immunoradiometric assay; differentiated thyroid cancer; thyroglobulin.

Introduction

Thyroid cancer is the most common endocrine cancer[1] of which 90% are differentiated thyroid cancers (DTC). It is a cancer with low malignant potential and very good prognosis[2]. In the majority of patients with DTC, initial treatment consists of total thyroidectomy[3].

Thyroglobulin (Tg) is a glycoprotein with a molecular weight of approximately 660 kDa, which is synthesized by thyrocytes and released into the lumen of thyroid follicles[3,4]. It is the postoperative tumor marker for monitoring DTC. However, the postoperative predictive value of Tg can be influenced by several factors such as TSH concentration, anti-Tg antibody level at the moment of Tg measurement, time since total thyroidectomy and functional sensitivity of Tg[5,6]. Its assay must be performed with an ultrasensitive immunometric method of functional sensitivity < 1ng/mL using a radioactive, enzymatic or luminescent tracer, standardized on the European reference standard (CRM 457)[7].

This allows the inter-method variabilities to be reduced without removing them[8]. These variations are also due to the specificity and affinity of the primary antibody (Ab) for Tg and the matrix difference used by kit manufacturers. It is then recommended to follow patients with the same dosage and within the same laboratory[9,10,11,12]. The determination of Tg in our patients followed at the nuclear medicine department of Tlemcen University Hospital for DTC, was usually done by an immunoradiometric technique (IRMA) using the kit of the manufacturer Cisbio Bioassays, (France).

For essentially budgetary reasons, we wanted to test the Tg-IRMA kit of the manufacturer Beckman Coulter (USA) and compare its analytical performance with that of Cisbio Bioassays, while evaluating the cost/ effectiveness ratio of the 02 kits.

Materials and Methods

This is a prospective, descriptive and analytical study conducted during 2014, including patients operated for thyroid carcinoma, irradiated with an ablative dose of Iodine 131 and followed at the nuclear medicine department of the University Hospital of Tlemcen. Blood samples were taken on potassium EDTA tubes and then centrifuged. The supernatant was then aliquoted and frozen at -20 C° until analyzed. Upon receipt of the kits, the serum samples were thawed at room temperature and dosed manually according to the manufacturer's recommendations, by the same laboratory technician. The determination of Tg was done at the laboratory of the department, simultaneously with the Tg-IRMA kit of Cisbio Bioassays taken in this study as «Gold standard» and the Tg-IRMA kit of Beckman Coulter. The samples, calibrators and control levels provided by the 02 kits were dosed in duplicate. Freeze-dried and ready-to-use control serums were randomly positioned in each dosing series with 01 single level control for the Beckman Coulter kit and 02 for Cisbio Bioassays. The systematic search for Ac anti-Tg was also carried out with the IRMA dosing kit from Beckman Coulter. All patients with a value ≥ to 30 mU/l of anti-Tg were considered positive and therefore excluded from the study. The reading of the tubes was made on the automatic gamma counter WIZARD 2470

of Perkin Elmer with 05 detectors. Thus the amount of radioactivity fixed is directly proportional to the Tg concentration of the sample measured in the tubes.

Table 1 Main features of the 02kits.

Kit	Tg-IRMA Cisbio Bioassays (France)	Tg-IRMA Beckman Coulter (USA)
Principle	Sandwich	Sandwich
Standardization	CRM 457	CRM 457
Specimen collection	Serum/plasma	Serum/plasma
monoclonal Ab	Tube coated with 4 Human anti-Tg Ab + 1 Radio labelled Ab to ^{125}I	Tube coated with 3 Human anti-Tg Ab + 1 Radio labelled Ab to ^{125}I
Standards	(S1 - S7)	S0+ (S1 - S7)
Control serum	2	1
Measurement range	0,2-500 ng/mL	0,3-600 ng/mL
Detection limit	0.2 ng/mL	0,3 ng/mL
Time incubation	1st Incubation 3h at 18 -25°C 2nd incubation 16-20H	1st Incubation 2h at 18 25°C 2nd incubation 18-24H
Detection	Gamma counter	Gamma counter

Ab: Antibody; 125I: Iodine 125;
S: Standards (Calibrators).

Statistical analysis

The analysis of the results was done with the software SPSS version 21 (Statistical Package for the Social Sciences-USA). The Pearson bivariate correlation test was used to assess the degree of correlation between quantitative variables. The Passing-Bablok regression line and the Bland-Altman mean difference diagram for matched samples were used to evaluate the linearity of the values and the difference of the means obtained with the 02 kits.

A ROC curve was also used to test the sensitivity and specificity of Beckman Coulter's Tg-IRMA kit at different functional sensitivity thresholds.

Results

A total of 99 serums were included in this study. Different levels of concentrations were obtained. Tg values measured in ng/mL with the Cisbio Bioassays kit range from 0.18 to 1351.12 ng/mL with an average of 93.96 ± 307.17 ng/mL. For the Beckman Coulter kit, values range from 0.17 to 1706.34 ng/mL with an average of 103.53 ± 353.56 ng/mL.

The statistical analysis showed a good correlation between the Tg concentrations

obtained with the two kits. The Pearson bivariate correlation coefficient is positive and significant (r = 0.98; p < 0.01) and the Passing-Bablok regression line equation is y = 0.7 x + 0 (with Y = Tg-IRMA Cisbio Bioassays results and X = Tg-IRMA Beckman Coulter results). The difference of the Tg means obtained by the Bland-Altman diagram is = 0 with p = 0.215 (> 0.05). Nevertheless, there is a dispersion of some Tg values between the two kits. For the ROC curve at the threshold of 0.7 and 1 ng/mL, the sensitivity and specificity of the Tg-Beckman Coulter kit is 100% and 93% respectively with an area under the curve = 0.99.

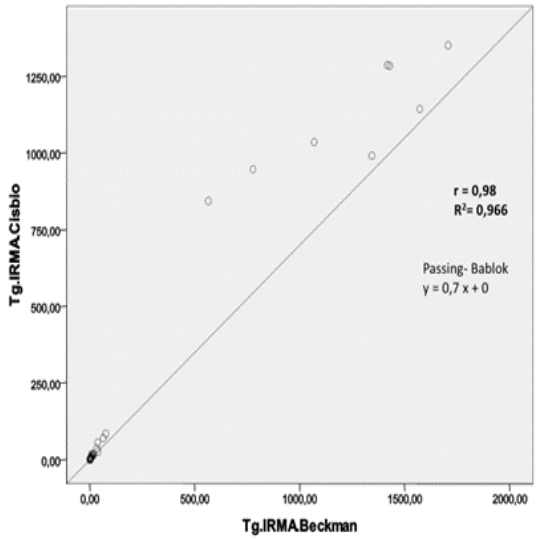

Figure 1: Pearson correlation coefficient between the 02 kits and the Passing-Bablok line.

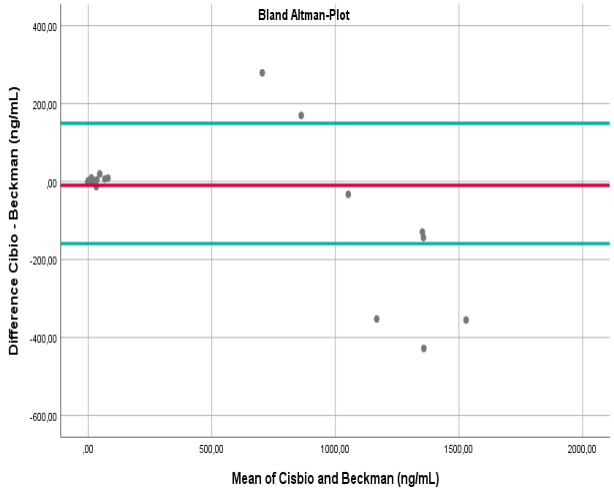

Figure 2: Bland Altman test for mean differences between the 02 kits.

Discussion

Thyroglobulin is a protein exclusively produced by the thyroid. Its assay is used as a tumor marker for post-operative monitoring of DTC and monitoring of recurrent carcinomas[13,14]. This is conditioned by the prior elimination of any thyroid remnant likely to produce residual Tg, either by simple total thyroidectomy, or most often supplemented by ablative dose treatment of Iode131[13,15,16].

Our study showed that there is a strong correlation between the Tg values obtained with the two kits (r=0.98; p< 0.01). Given that these 02 kits use principles of immunometric assays of type «sandwich» using the same types of antibodies, this correlation is not surprising. Nevertheless, we noted a dispersion of values in 07% of patients (n=07/99) whose Tg concentrations varied between 500 and 1700 ng/mL, without having a major impact on their therapeutic management. Numerous studies have shown that the dosing technique used affects changes in Tg values[11,17,18,19].

This individual difference in one of our patients could be explained by the specificity of each kit used in this study. This depends essentially on the number of monoclonal Ab engaged in the reaction and directed against the epitopes of the Tg molecule; there are 04 Ab for the Tg IRMA kit of Cisbio bioassays + 01 Ab radiolabelled at 125I and 03 Ab for the Tg IRMA kit of Beckman Coulter + 01 Ab radiolabelled at 125I. These Ab are directed against epitopical areas not recognized by the majority of anti-thyroglobulin autoantibodies present in many thyroid pathologies, thus avoiding the need for a systematic overload test. The difference in the Tg means analyzed by the Bland-Altman diagram is = 0 (p > 0.05), indicating that there are no differences in mean between the 02 kits. However, the functional sensitivity must be low to make the method as sensitive as possible in order to detect thyroid residues during post-operative follow-up of the DTC. It should be less than 1ng/mL[20]. The sensitivity of the dosages is rather appreciated by the functional sensitivity than the overly optimistic analytical sensitivity. It corresponds to the concentration measured by imprecision profile at a coefficient of variation of 20%. It is determined according to a very specific protocol[21]. The reason why, we wanted to evaluate the analytical performance by ROC curve of Tg values obtained with Beckman Coulter's Tg kit at different thresholds, especially at the threshold of 0,7 ng/mL corresponding to the functional sensitivity of the Cisbio Bioassays kit and the threshold of 1ng/mL corresponding to the decision threshold for detecting recurrence. The results showed that the sensitivity and specificity of Beckman Coulter's Tg-IRMA kit are as excellent as that of Tg-IRMA Cisbio Bioassays with a sensitivity of 100%; 95% CI [83.4-100] and 93% specificity; 95% CI [83.9-97.4] with an area under the curve = 0.99. The positive predictive value for the Beckman Coulter kit is 83.3%; 95% CI [64.5-93.7] and negative predictive value is 100%; 95% CI [93.2-100].

The limit of our study, concerns the fact that the Tg IRMA kit of Cisbio Bioassays, is taken as «Gold standard», while it would be wise to make a comparative study with kits of other manufacturers for a better interpretation of the results.

Conclusion

There is a strong correlation between the Cisbio Bioassays Tg IRMA kit and the Beckman Coulter Tg IRMA kit for serum Tg determination. Thus a budget reduction in the management of our patients with CDT is possible, in favor of the Tg-IRMA kit of Beckman Coulter with a good cost/ efficiency ratio.

Conflict of Interest:

None

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References:

1. Pacini F, Castagna MG, Brilli L, Pentheroudakis G, on behalf of the ESMO Guidelines Working Group. Thyroid cancer: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23 (Suppl7):vii110-vii119. DOI: 10.1093 / annonc/mds230

2. Aschebrook-Kilfoy B, Ward MH, Sabra MM, Devesa SS. Th yroid cancer incidence patterns in the United States by histologic type, 1996-2006. Thyroid. 2014;21:125-34. http://dx.doi.org/10.1089/thy.2010.0021.DOI:10.1089/thy.2010.0021

3.Prpić M, Franceschi M, Romić M, Jukić T, Kusić Z. THYROGLOBULIN AS A TUMOR MARKER IN DIFFERENTIATED THYROID CANCER - CLINICAL CONSIDERATIONS. Acta Clin Croat. 2018 Sep;57(3):518-527. DOI: 10.20471/acc.2018.57.03.16

4. Malthiéry Y, Lissitzky S. Primary structure of human thyroglobulin deduced from the sequence of its 8448-base complementary DNA. Eur J Biochem. 1987;165:491-8. DOI: 10.1111/j.1432-1033.1987.tb11466.x

5. Giovanella L, Ceriani L, Maffioli M. Postsurgery serum thyroglobulin disappearance kinetic in patients with differentiated thyroid carcinoma. Head Neck. 2010;32:568-571. DOI: 10.1002/hed.21214

6. Gurleyik E, Dogan S. Accuracy of unstimulated Basal serum thyroglobulin levels in assessing the completeness of thyroidectomy. J Clin Med Res. 2014;6:369-373. DOI: 10.14740/jocmr1873w

7. Feldt-Rasmussen U, Profilis C, Colinet E, et al. (1996).Human thyroglobulin reference material (CRM 457).1st part: assessment of homogeneity, stability and immunoreactivity. PMID: 9092300

8. Sadouk, M., W. Schneider, et al., Comparison of diagnostic performance of three thyroglobulin assays in the monitoring of diferentiated thyroid carcinoma. 75th Annual Meeting of the ATA (abstract), 2003.

9. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL,Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer DOI: 10.1089/thy.2009.0110

10. Haugen BR, Ridgway EC, McLaughlin BA, McDermott MT. Clinical comparison of whole-body radioiodine scan and serum thyroglobulin after stimulation with recombinant human thyrotropin. Thyroid 2002;12:37 43. DOI: 10.1089/105072502753451959

11. Giovanella L, Clark P, Chiovato L, Duntas LH, Elisei R, FeldtRasmussen U, et al. Thyroglobulin measurement using highly sensitive assays in patients with differentiated thyroid cancer: a clinical position paper. Eur J Endocrinol 2014;171:R33–46. DOI: 10.1530/EJE-14-0148

12. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, Gilbert J, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold K, Taylor J, Thakker RV, Watkinson J, Williams GR; British Thyroid Association. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf). 2014 Jul;81 Suppl 1:1-122. DOI: 10.1111/cen.12515. PM ID: 24989897.

13. Spencer CA, LoPresti JS, Fatemi S, Nicoloff JT. Detection of residual and recurrent differentiated thyroid carcinoma by

serum thyroglobulin measurement. Thyroid. 1999;9:435–441.patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–214. DOI: 10.1089/thy.1999.9.435

14. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016 Jan;26(1):1-133. DOI: 10.1089/thy.2015.0020. PMID: 26462967; PMCID: PMC4739132.

15. Dunn JT. Clinical usefulness of serum thyroglobulin assays.In: Hamburger JI, editor. Diagnostic methods in clinical thyroidology. New York: Springer Verlag; 1989. p 127–157. https ://link. springer.com / chapter /10.1007 / 978-1-4612-3612-2_7

16. Schlumberger M, Pacini F, Wiersinga WM, et al. Follow-up and management of differentiated thyroid carcinoma: a European perspective in clinical practice. Eur J Endocrinol 2004;151:539–548. DOI : 10.1530 /eje.0.1510539

17. Ignjatovic V., Matovic M., Vukomanovic V. Comparison of Thyroglobulin Concentrations Measured by Two Immunoradiometric Assay. Experimental and Applied Biomedical Research (EABR). 2020;21(2): 121-125. DOI:10.2478/sjecr-2018-0031

18. Stanojevic M, Savin S, Cvejic D, et al. (2009). Correlation of thyroglobulin concentrations measured by radio immuno assay and immunometric assay and the influence of thyroglobulin antibody. J Immuno assay Immunochem, 30:197-207. DOI: 10.1080/15321810902782897

19. Schlumberger M, Hitzel A, Toubert ME, et al. (2007).Comparison of seven serum thyroglobulin assays in the follow-up of papillary and follicular thyroid cancer patients. J Clin Endocrinol Metab, 92:2487–2495. DOI: 10.1210/jc.2006-0723

20. Spencer, C. A., M. Takeuchi et al., Current status and performance goals for serum thyroglobulin assays. Clinical Chemistry, 1996. 42: 164-173. PMID: 8565221

21. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al. Guidelines committee, National academy of clinical biochemistry. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 2003 ;13 3-126. DOI: 10.1089/105072503321086962.