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Clinical Sensitivity and Specificity of Anti–CCP IgG, RF, and CRP Assays Singly or in Combination to Aid in the Diagnosis of Rheumatoid Arthritis

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Clinical Sensitivity and Specificity of Anti–Cyclic Citrullinated Peptide IgG, Rheumatoid Factor, and C-Reactive Protein Assays Singly or in Combination to Aid in the Diagnosis of Rheumatoid Arthritis

Abstract

Background: In 2009, the new rheumatoid arthritis (RA) criteria released by the American College of Rheumatology (ACR) and the European League Against Rheumatism included the measurement of anti–cyclic citrullinated peptide (CCP) antibodies to aid in the classification of RA.[1,2] As is true for the other serological markers mentioned in the criteria, rheumatoid factor (RF) and C-reactive protein (CRP), elevated anti-CCP IgG is predictive of RA. RF has good sensitivity (50%–90%) but low specificity for RA,[3] whereas anti-CCP IgG is highly specific (82%–98%) with comparable diagnostic sensitivity (60%–85%).[4]

Objective: The objective of this study was to determine if the combination of the IMMULITE® 2000 Anti-CCP IgG*, Dimension Vista® RF, and Dimension Vista hsCRP or CRP assays improved the diagnostic sensitivity and specificity for RA diagnosis.

Methods: The fully automated IMMULITE 2000 Anti-CCP IgG assay[5] is a two-cycle chemiluminescent immunoassay for the detection of specific IgG autoantibodies to CCPII. Samples were measured for RF, and CRP on the Dimension Vista according to the package insert. If the hsCRP result exceeded the assay range, the value was then obtained with the CRP assay.

Results: The clinical sensitivity, specificity, and overall agreement for 339 samples (138 confirmed rheumatoid arthritis [7 samples were excluded from final analysis] and 201 apparently healthy patients) tested with the IMMULITE 2000 Anti-CCP IgG assay were 79%, 100%, and 91%, respectively. When tested with the Dimension Vista RF, the clinical sensitivity, clinical specificity, and overall agreement were 83%, 98%, and 92%, respectively. Receiver operator curve analysis for anti-CCP IgG, RF, and hsCRP demonstrated areas under the curve (AUCs) of 0.93, 0.93, and 0.79, respectively. The clinical sensitivity, specificity, and overall agreement for the combination of anti-CCP IgG and RF assays were 93%, 98%, and 96%, respectively.

Conclusion: Overall, the IMMULITE 2000 Anti-CCP IgG assay performed comparably to the Dimension Vista RF assay for the diagnosis of rheumatoid arthritis, and in combination, the clinical sensitivity was improved from 79% (anti-CCP) and 83% (RF) to 93%. The overall average level for CRP was significantly higher (15.91 mg/L) in the rheumatoid arthritis samples than in normal samples (2.49 mg/L).

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*Not available for sale in the U.S. and its future availability in the U.S. cannot be guaranteed.
Not all product offerings are available in all countries.

Background

In 2009, the new rheumatoid arthritis (RA) criteria released by the American College of Rheumatology (ACR) and the European League Against Rheumatism included the measurement of anti–cyclic citrullinated peptide (CCP) antibodies to aid in the classification of RA.[1,2] As is true for the other serological markers mentioned in the criteria, rheumatoid factor (RF) and C-reactive protein (CRP), anti-CCP IgG are predictive of RA. RF has good sensitivity (50%–90%) but relatively low specificity for RA,[3] whereas anti-CCP IgG is more specific (82%–98%) with comparable sensitivity (60%–85%).[4]

Objective

The objective of this study was to determine if the combination of the IMMULITE® 2000 Anti-CCP IgG*, Dimension Vista® RF, and Dimension Vista hsCRP or CRP assays improved the sensitivity and specificity for RA diagnosis.

Methods

A total of 339 samples consisting of 201 apparently normal samples and 138 confirmed RA samples (meeting ACR 1987 guideline criteria) were measured for anti-CCP, RF, and CRP according to the manufacturer's instructions. If the hsCRP result exceeded the assay range, the value was then obtained with the CRP assay.

Clinical sensitivity and specificity for RA diagnosis was determined, and ROC analysis was performed using the Analyse-it® Method Evaluation Edition (Analyse-it Software, Ltd. Leeds, UK). In addition, distributions of the analytes' values in the study population were determined. The cutoff for diagnosis of RA for the IMMULITE 2000 Anti-CCP IgG assay was 4 U/mL, and the cutoff for the Dimension Vista RF assay was 15 IU/mL. Seven samples were excluded from the final analysis because of instrument error.

Results

The RF and anti-CCP assays performed comparably in the diagnosis of RA, and both performed better than the hsCRP/CRP assays (Table 1 and Figure 1).

Table 1. Area under the curve and 95% confidence interval for the diagnosis of RA using the IMMULITE 2000 anti-CCP IgG assay, and the Dimension Vista RF, *hs*CRP, and CRP assays.

Assay	AUC	SE	*P*	AUC (95% CI)
hsCRP/CRP (mg/L)	0.794	0.0251	<0.0001	0.745 to 0.844
RF (IU/mL)	0.929	0.0174	<0.0001	0.895 to 0.963
Anti-CCP (U/mL)	0.926	0.0167	<0.0001	0.893 to 0.959

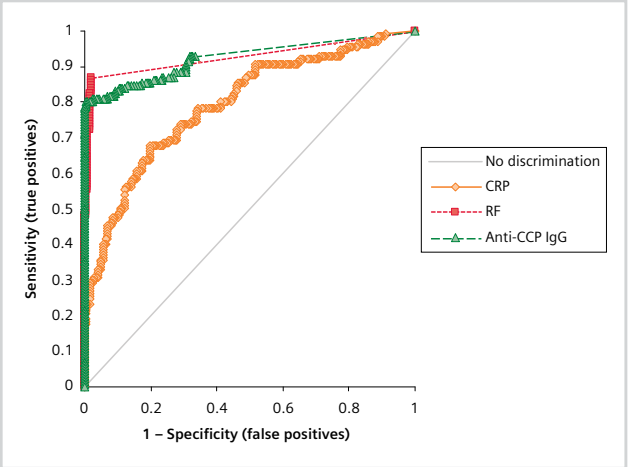

Figure 1. ROC analysis of the IMMULITE 2000 anti-CCP IgG assay, and the Dimension Vista RF, *hs*CRP and CRP assays vs. clinical status.

The IMMULITE 2000 Anti-CCP IgG assay demonstrated excellent clinical specificity and good agreement with RA status (Table 2). The Dimension Vista RF assay also demonstrated excellent clinical specificity and good agreement with RA status (Table 3).

Table 2. Clinical sensitivity, clinical specificity, and agreement of IMMULITE 2000 Anti-CCP IgG assay with RA status.

	Anti-CCP IgG		
RA Status*	Negative	Positive	Total
Negative	201	0	**201**
Positive	29	109	**138**
Total	**230**	**109**	**339**

Clinical sensitivity = 79%
Clinical specificity = 100%
Total agreement = 91%

*Determined by 1987 ACR criteria.

Table 3. Clinical sensitivity, clinical specificity, and agreement of the Dimension Vista RF assay with RA status.

	RF		
RA Status*	Negative	Positive	Total
Negative	197	4	**201**
Positive	23	115	**138**
Total	**220**	**119**	**339**

Clinical sensitivity = 83%
Clinical specificity = 98%
Total agreement = 92%

*Determined by 1987 ACR criteria.

The combination of the anti-CCP and RF assays demonstrated better clinical sensitivity than either assay alone, comparable specificity, and good agreement with RA status (Table 4).

Table 4. Clinical sensitivity, clinical specificity, and agreement of the IMMULITE 2000 anti-CCP IgG and the Dimension Vista RF assays for RA diagnosis.

	RF and Anti-CCP IgG		
RA Status*	Negative	Positive	Total
Negative	197	4	**201**
Positive	10	128	**138**
Total	**207**	**132**	**339**

Clinical sensitivity = 93%
Clinical specificity = 98%
Total agreement = 96%

*Determined by 1987 ACR criteria.

Normal samples had lower values for anti-CCP, RF, and CRP than RA-confirmed samples (Figures 2–4).

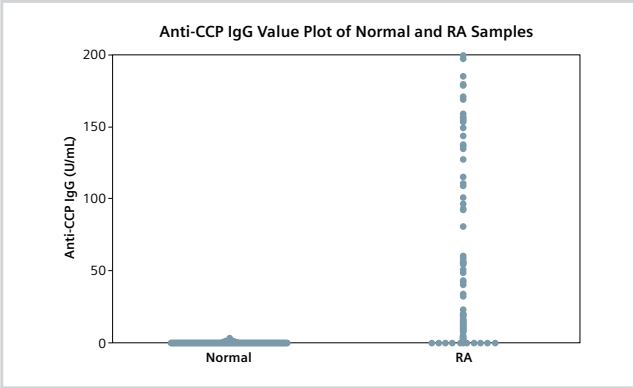

Figure 2. Distribution of IMMULITE 2000 anti-CCP IgG values in normal (N = 201) and RA samples (N = 131).

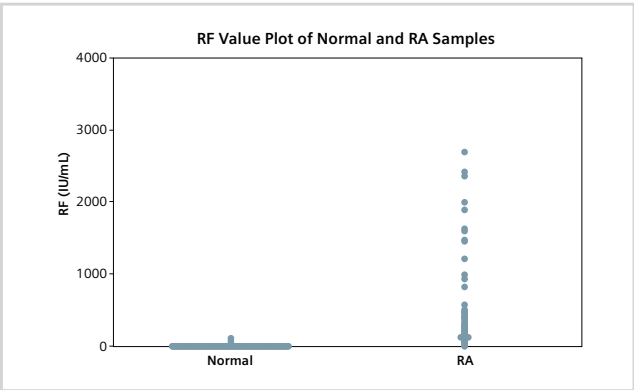

Figure 3. Distribution of Dimension Vista RF values in normal (N = 201) and RA samples (N = 131).

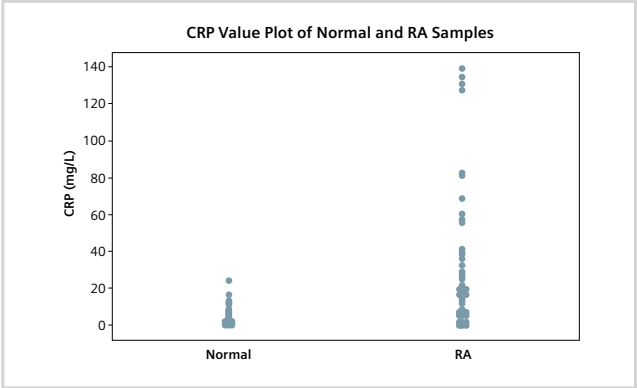

Figure 4. Distribution of the Dimension Vista *hs*CRP/CRP values in normal samples (N = 201) and RA samples (N = 131).

Conclusions

- Overall, the IMMULITE 2000 Anti-CCP IgG assay performed comparably to the Dimension Vista RF assay in the diagnosis of rheumatoid arthritis.
  - The IMMULITE 2000 Anti-CCP IgG assay demonstrated a clinical sensitivity of 79%, a clinical specificity of 100% (Table 2), and an AUC of 0.926 (Table 1 and Figure 1). Similarly, the Dimension Vista RF assay had a clinical sensitivity of 83%, a clinical specificity of 98% (Table 3), and an AUC of 0.929 (Table 1 and Figure 1).
- When the Anti-CCP IgG and RF assays were used in combination, the 93% clinical sensitivity for RA diagnosis was better than for either assay alone: 79% for anti-CCP and 83% for RF (Table 4).
- In contrast to the Anti-CCP and RF assays, the hsCRP/CRP assays, indicative of inflammation and not specific for RA, displayed a lower AUC of 0.794 (Table 1 and Figure 1).
  - Even though CRP is not a specific marker for RA, our study indicated that the overall average for CRP was significantly higher (15.91 mg/L) in the rheumatoid arthritis samples than in normal samples (2.49 mg/L) as shown in Figure 4, consistent with the RF and anti-CCP IgG profiles for normal and RA samples (Figures 2 and 3).

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