



## EDITORIAL

## RDW as a Surrogate Marker for Active Crohn's Disease: Potential Utility



### RDW Como Marcador de Atividade na Doença de Crohn: Qual a Potencial Utilidade?

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Crohn's disease (CD) is a chronic and relapsing condition with the majority of patients experiencing a progressive course which leads to permanent bowel damage.<sup>1,2</sup> Early control of inflammation is now advocated by most authors in order to prevent permanent bowel damage. Current guidelines for the management of CD recommend a sequential and additive step-care paradigm.<sup>3-5</sup> Salicylates should be used solely in mild disease, corticosteroids in the acute flares, while immunosuppressives (azathioprine, 6-mercaptopurine and methotrexate) are reserved for patients with severe disease and/or who develop corticoid dependency. Currently, both infliximab and adalimumab are approved in the European Union as second-line treatments for severe, active CD not responding or being intolerant to conventional therapy.<sup>6</sup> In contrast with this more conservative approach, some authors now propose a *top-down* approach where biologics with or without immunosuppressives would be started early in the course of disease with the aim of avoiding long term structural damage to the bowel and thereby change the natural history of disease.<sup>7</sup>

The characterization of a response to medication has also evolved over time. In the past, response was based mainly on clinical symptoms, with or without biologic markers, namely C-reactive protein (CRP). However, it has been recognized that in CD there is a poor correlation between clinical symptoms and the endoscopic status of the intestinal mucosa, the paradigm being that most patients promptly respond to corticosteroids but mucosal healing (MH) is rarely observed with these agents. Furthermore, in line with the concept of avoiding long term damage, a strong emphasis has been put in MH as a desirable endpoint since some studies observed that severe endoscopic disease was associated with a more aggressive course of disease and need for surgery.<sup>8</sup> As such, some authors have proposed that, even in clinical practice, MH should become a therapeutic goal.<sup>9</sup>

However, evaluation of mucosal healing in Crohn's disease implies a total ileo-colonoscopy which is not practical nor feasible to monitor disease activity at short intervals. To improve this non-invasive monitoring of disease activity in Crohn's disease several biomarkers such as calprotectin or lactoferrin have been proposed. Still, these have not entered into the clinical arena in the sense that they are not ordered on a routine basis but mainly when doubts persist whether the patient is responding to a certain therapy.

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Also, with the therapeutic treat-to-target strategy recommended nowadays, most of CD patients remain well for extended periods of time. As they are often young people with active personal and professional lives, strategies that would allow them to decrease number of visits to the Hospital, would certainly contribute to improve their quality of life.

In this issue of GE, Oliveira et al.<sup>10</sup> examined whether Red Cell Distribution Width (RDW) could be used as a surrogate marker for disease activity in CD patients. Red cell distribution width (RDW) is a quantitative measure of variability in the size of circulating erythrocytes. It is routinely measured by automated hematology analyzers not implying additional costs. In the last years, numerous studies have shown that a higher RDW is associated with several pathologic conditions, some suggesting that it could be used as an inflammatory marker for IBD, mainly in an inpatient setting.<sup>11,12</sup> Although the mechanisms that mediate the relationship between high RDW values and increased CD activity are still unknown, it has been demonstrated that a chronic inflammatory state may contribute to ineffective erythropoiesis causing immature erythrocytes to enter the circulation, resulting in elevated RDW.

The purpose of this study was, firstly, to determine whether RDW was associated with CDAI and, secondly, to identify a possible RDW cutoff with clinical applicability for an outpatient setting. It was a cross sectional study including 119 patients with CD, observed consecutively in an outpatient setting. CD activity was determined by CDAI (active disease if CDAI  $\geq 150$ ). The authors observed an association between RDW and disease activity ( $p=0.044$ ). After adjustment for age and gender, this association remained consistent (OR 1.20, 95% CI 1.03–1.39,  $p=0.016$ ). It was also found that the association between RDW and disease activity was independent of hemoglobin and ESR (OR 1.36, 95% CI 1.08–1.72,  $p=0.01$ ) and of biologic therapy (OR 1.19, 95% CI 1.03–1.37,  $p=0.017$ ).

A RDW cutoff of 16% had a specificity and negative predictive value for CDAI  $\geq 150$  of 88% and 86%, respectively. The authors concluded that these results could contribute to the implementation of this simple parameter, in clinical practice, aiming to help therapeutic decisions.

Recently The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) program was published with the aim of identifying potential treatment targets to be used for a “treat-to-target” strategy using an evidence-based expert consensus process.<sup>13</sup> In respect to Crohn’s disease the group agreed upon clinical/patient-reported outcome (PRO) remission defined as resolution of abdominal pain and diarrhea/altered bowel. Biomarker remission (normal C-reactive protein (CRP) and calprotectin) was considered solely as an adjunctive target.

As we are now heading to a so-called era of telemedicine where patients are invited to use and report more on digital platforms, we could easily conceive the inclusion of PRO and routine blood tests, including RDW values, in a remote monitoring of disease activity in patients with CD. Telemedicine is used in many clinical specialties and across numerous healthcare settings, which range from mobile patient-centric applications to complex interactions amongst clinicians in tertiary referral hospital settings. In a recently published paper, Wilson and Maeder<sup>14</sup> review the

recent directions in telemedicine. They discuss some recent areas of significant development and progress in the field of telemedicine, with the purpose of identifying strong trends in both research and practice activities. It is concluded that two major drivers of contemporary telemedicine development are a high volume demand for a particular clinical service, and/or a high criticality of need for clinical expertise to deliver the service. These areas offer promise for further study and enhancement of applicable telemedicine methods and have the potential for large-scale deployments internationally, which would contribute significantly to the advancement of healthcare.

With respect to inflammatory bowel disease, we can say that it is a high prevalent disease, affecting mainly young people and, in the past decade, treatment of this disease has improved tremendously, with most patients being well controlled with medical therapy. Having said so, it is also recognized that highly trained specialists in this area are few and chronic bowel damage occurs in poorly controlled patients. The latter are the ones that physicians want to detect early in order to intensify therapy. We could then imagine a scenario where most patients would self report to the physician every 3–4 months (namely to detect adverse effects from therapy used) and a visit to the Hospital with more deep evaluation probably including endoscopic evaluation, would only occur every 12–18 months. Patients reporting “red flags” signs or symptoms would be appointed to come to the Hospital earlier than planned so that a full evaluation clarifies whether disease is active or not.

In the study by Oliveira et al, RDW values seem very specific with a high negative predictive value for detecting active Crohn’s disease. This gives some assurance that we are not letting go patients with active disease. In conjunction with patient-reported outcome (PRO), RDW value could be useful in identifying patients who are at risk of having active disease. It would be interesting to see how this strategy would work on a prospective basis.

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