

ORIGINAL PAPER

Early Atherosclerosis and Acute Vascular Events in Ulcerative Colitis Patients – a Case Series

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Abstract

Introduction: In inflammatory bowel disease uncontrolled inflammation may play a role in the early progression of systemic atheromatosis with increased cardiovascular risk. Endothelial dysfunction is mediated by pro-inflammatory cytokines but also by an increased level of CRP which is involved in the expression of adhesion molecules and atheroma plaque rupture. Tailored treatment with better control of the ulcerative colitis and endoscopic healing might result in decrease risk of atherothrombotic events. **Aim:** We decided to use a well-established method (vascular Doppler ultrasound with media-intimate index measurement) to detect an increased incidence of endothelial lesions as predictors of early atheromatosis in patients with ulcerative colitis treated with biological or conventional therapy.

Material and methods: We prospectively analyzed 25 patients with RCUH with a mean age of 40 years, 16 with biological treatment. The Student t test, the Mann Whitney U test and the ANOVA test were used to compare continuous variables. **Results:** A discriminant analysis was performed with the presence of atheroma plaque as a dependent variable and several predictor variables, such as age, triglycerides, cholesterol of patients with ulcerative colitis. Univariate ANOVA analyzes revealed that the presence or absence of atheroma plaque differs in the variables predicting the age, INR and ecoIMT of patients with ulcerative colitis (in the age of patients ($F = 8.511$, degrees of freedom = 11, $p = 0.014$) Patients, INR ($F = 50.437$, degrees of freedom = 11, $p = 0.001$) and Patients' ecoIMT ($F = 7.398$, degrees of freedom = 11, $p = 0.020$) In another analysis of discriminatory function s-introduced the predictor variables specific to measuring the evolution of ulcerative colitis, respectively Mayo and Mayo E (age ($F = 0.8511$, degrees of freedom = 11, $p = 0.014$), INR ($F = 50.437$, degrees of freedom = 11, $p = 0.001$), ecoIMT ($F = 7.398$, $df = 11$, $p = 0.020$) and Mayo ($F = 14.885$, degrees of freedom = 11, $p = 0.003$). **Conclusions:** Age, endoscopic activity, and INR were correlated with predictive ultrasound changes for atheromatosis. Strengths are the prospective nature of the study and weaknesses are the limited number of patients and the fact that most patients were in remission and treated with biologicals, which could create bias in the sense of reducing the atherosclerotic risk directly correlated with active inflammation.

Keywords: inflammatory bowel diseases, ulcerative colitis, inflammation, atherosclerosis, carotid ultrasound, intima media thickness, cardiovascular risk.

Rezumat

Introducere: În bolile inflamatorii intestinale inflamația poate să joace un rol în progresia ateromatozei precoce și secundar unui risc cardiovascular crescut. Disfuncția endotelială este mediată de citokine pro inflamatorii dar și de

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un nivel crescut al CRP care este implicată în supra expresia moleculelor de adeziune și ruptura plăcii de aterom; ipoteza noastră este ca o boală bine controlată terapeutic cu vindecare endoscopică ar conduce la o scădere a riscului cardiovascular. **Scop:** Am decis să folosim o metodă consacrată (ecografia Doppler cu măsurarea indicelui intima medie) pentru a decela ateromatoza precoce în dorința de a vedea dacă există o incidență crescută a leziunilor endoteliale la pacienții cu RCUH tratați cu terapie biologică sau convențională și să încercăm să validăm această metodă ca instrument în monitorizarea pro activă a pacienților. **Material și metode:** Au fost analizați prospectiv 25 de pacienți cu RCUH vârsta medie 40 de ani, tratament biologic 16. Testul t student, testul Mann Whitney U și testul ANOVA au fost utilizate pentru compararea variabilelor continue. **Rezultate:** O analiză discriminantă s-a realizat având prezența plăcii de aterom ca variabilă dependentă și mai multe variabile predictor, ca de exemplu, vârsta, trigliceridele, colesterolul ale pacienților cu colită ulcerativă. Analizele ANOVA univariate au relevat că prezența sau absența plăcii de aterom diferă la nivelul variabilelor predictor vârsta, INR-ul și ecoIMT-ul pacienților cu colită ulcerativă (la nivelul vârstei pacienților ($F=8,511$, grade de libertate= 11, $p=0,014$), INR-ului pacienților ($F=50,437$, grade de libertate=11, $p=0.001$) și ecoIMT-ului pacienților ($F=7,398$, grade de libertate=11, $p=0.020$). Într-o altă analiză a funcției discriminative s-au introdus și variabilele predictor specifice măsurării evoluției colitei ulcerative, respectiv Mayo și Mayo E (vârsta ($F=0,8511$, grade de libertate= 11, $p=0,014$), INR ($F=50,437$, grade de libertate= 11, $p=0,001$), ecoIMT ($F=7,398$, $df=11$, $p=0,020$) și Mayo ($F=14,885$, grade de libertate=11, $p=0,003$). **Concluzii:** În această serie de cazuri vârsta, activitatea endoscopică și valoarea INR s-au corelat cu modificările ecografice predictive pentru ateromatoză. Punctele forte sunt caracterul prospectiv și analiza statistică a pacienților (parte a unui lot de 80 de pacienți) iar punctele slabe faptul că majoritatea pacienților erau în remisiune clinică și endoscopică fiind tratați biologic în mod proactiv, ceea ce ar putea valida ipoteza noastră conform căreia o terapie eficientă cu o remisiune profundă a bolii digestive duce la un risc cardiovascular mai redus.

Cuvinte cheie: boli inflamatorii intestinale, colită ulcerativă, ateroscleroză, ecografie Doppler carotidiană, indicele intima-medie, risc cardiovascular.

INTRODUCTION

Patients with inflammatory bowel disease (IBD) seem to have an increased risk of cardiovascular events and IBD disease activity has been reported as an independent risk factor after adjustment for traditional cardiovascular risk factors¹. Uncontrolled systemic inflammation might be the factor involved in the pathogenesis of early atherosclerosis and associated increased risk of cardiovascular events in these patients.²

Treatment with biologic and small molecules may lower the risk of cardiovascular events due to their anti-inflammatory properties; this is not proven for conventional therapy with thiopurines. Steroids on the other hand are related to an increased cardiovascular risk; however the data is conflicting in different studies^{3,4,5}.

Previous studies showed that and intima-media thickness IMT is a reliable marker for early atherosclerosis². The aim of our study was to evaluate the presence of early atherosclerosis in a group of subjects with ulcerative colitis using Doppler ultrasonography measurement of the IMT as a marker of subclinical atherosclerosis.

MATERIALS AND METHOD

Study design and population

We prospectively analyzed 25 patients with RCUH with a mean age of 40 years, 16 with biological treatment. The patients included in the study had an established UC diagnosis, based on clinical, endoscopic, and histological criteria, according to the current guidelines with a minimum disease duration of at least one year. The inclusion criteria for the IBD group were age ≥ 18 years and patients willing to undergo evaluation of the carotid arteries by ultrasonography. The exclusion criteria were current cardiovascular conditions (known heart disease, hypertension, history of vascular events), diabetes, smoking and dyslipidemia. The local research ethics committee at the Bucharest Emergency University Hospital approved the research protocol.

Clinical evaluation

Demographic data, nutritional status, disease duration, surgical history, past and current medication, possible comorbidities and risk factors were collected. At the moment of the evaluation patients were assessed using biomarkers (CRP, calprotectin), colonoscopy and carotid ultrasound. Ulcerative colitis was classified by

extension (proctitis, proctosigmoiditis, left colitis and pancolitis) and endoscopic severity was graded using the partial Mayo. Patients were treated and monitored proactively according to the treat to target criteria firstly introduced for Crohn's disease⁶.

Doppler ultrasonography of the carotid arteries

The Doppler ultrasonography of the carotid arteries was performed using a General Electric Ultrasound Machine Vivid E90, equipped with a 7.0-MHz linear ultrasonic transducer and an image recording system.

The examination was performed with subjects were placed in supine position, with a slight hyperextension of the neck. The common carotid artery was assessed in multiple longitudinal planes, proximal to the carotid bulb in order to obtain the best resolution for calculating the carotid intima-media thickness, defined as the distance from the lumen-intima interface to the media-adventitia interface of the artery wall. The measurement was made at the end of the diastole, approximately 1 cm proximal to the bifurcation.

The CIMT values lower than 0.9 mm were considered normal, values in between 0.9 mm and 1.2 mm were classified as a moderate thickening, while values greater than 1.2 mm were considered subclinical atherosclerosis, similar to the data from the METEOR study⁷.

Statistics

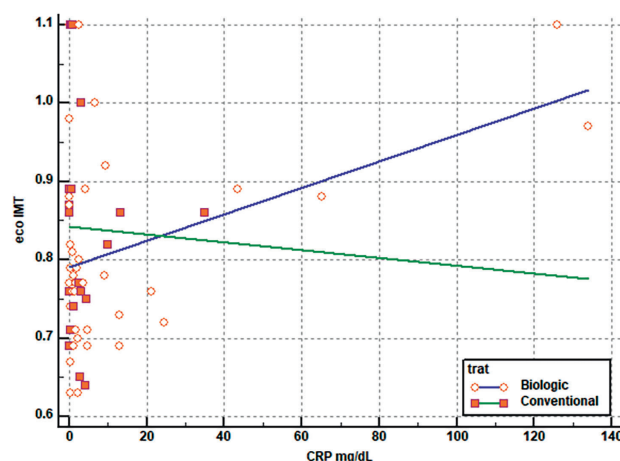
Student's t-test, Mann Whitney U test, and ANOVA test were used for comparison of continuous variables. Fisher's exact test and chi-square test were performed for comparison of proportions. The statistical analyses and sample size calculation were performed using INSERT PROGRAM. IBM SPSS version 20.0 for Windows (IBM Corp., Armonk NY, USA). Multivariate logistic regression and multiple linear regression analyses were performed. The regression models built were adjusted for age, INR, CRP, Iron, Triglycerides, Cholesterol levels, BMI and disease duration. A p -value < 0.05 was considered significant.

RESULTS

In the conventional therapy group, the median age was higher compared to the biological therapy group [$p=0.064$].

The partial Mayo score was higher in the biological treatment group, as expected, with a tendency towards statistical significance [5.00 (3.00-8.00) vs

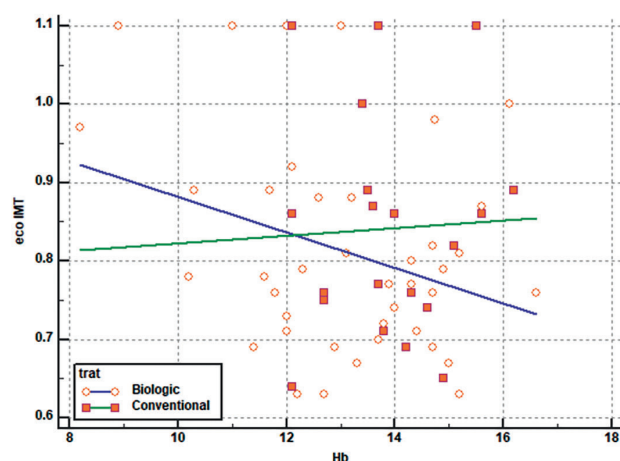
3.00 (3.00-4.00), $p=0.087769$]. No other statistically significant differences were observed between the two treatment groups. The CRP mg/dL ($p=0.054$) and Hb ($p=0.05$) values, both either important severity criteria or indicators of an inflammatory bowel disease flare almost reached statistical significance (figures 1 and 2).



$$\text{trat="Biologic": } y = 0.7903 + 0.001695 x$$

$$\text{trat="Conventional": } y = 0.8431 + -0.0005036 x$$

Figure 1. Eco IMT and CRP correlations



$$\text{trat="Biologic": } y = 1.1087 + -0.02267 x$$

$$\text{trat="Conventional": } y = 0.7733 + 0.004875 x$$

Figure 2. Eco IMT and Hemoglobin value correlations

The INR value is significantly higher in the conventional treatment group, despite none of the patients receiving anticoagulant therapy and it is strongly correlated with the presence of atherosclerotic plaques, reaching statistical significance (OR=645.6; 95% CI, $p<0.001$).

Echo-IMT ($p < 0.001$) is an independent predictor of the atherosclerotic process, reaching statistical significance, with values considerably higher among patients with atherosclerotic plaques.

Multivariate logistic regression models were built, introducing variables that either reached or were close to statistical significance in the univariate logistic regression analysis, using the stepwise method. In relation to the presence of atherosclerotic plaques, age continues to be an independent predictor, reaching statistical significance, each 1 unit increase of this variable, multiplying the risk of plaque formation by 1.27 times (OR: 1.2766; 95% CI: 1.0296, 1.5830; $p = 0.0261$). INR values also significantly correlate with the presence of atherosclerotic plaques, reaching statistical significance, each 1 unit increase in INR value augmenting the risk of plaque formation by 212×10^3 times (OR: 212×10^3 ; 95% CI: 5.0751, 8.82×10^9 ; $p = 0.0239$). The model obtained had an AUC of 0.973 (95% CI: 0.895–0.998) and was able to explain 46.60% to 78.95% of the obtained data (Cox & Snell $R^2 = 46.60\%$, Nagelkerke $R^2 = 78.95\%$).

Simple, as well as multiple linear regression analyses, were consecutively conducted in order to assess the relationship between echo-IMT (an independent predictor, strongly associated with the presence of atherosclerotic plaque, as shown by the logistic regression model) and commonly known risk factors, both patient and disease-related.

Simple linear regression analysis of variables commonly associated with an increased cardiovascular risk and echo-IMT showed that disease duration ($\beta = 0.008343$, 95% CI: 0.001265, 0.01795, $p = 0.087576$) and endoscopic severity in ulcerative colitis patients ($\beta = -0.05230$, 95% CI: 0.1141, 0.009459, $p = 0.093130$), assessed by the Mayo score, show a tendency toward statistical significance.

The results obtained are in line with those of previous studies and can once again highlight the possibility of an accelerated atherosclerotic process in patients with active or longer-lasting severe inflammatory bowel disease.

As mentioned before, patients receiving biological therapy included in our study have had a more severe disease, CRP and Hb being criteria used to assess severity/activity.

Multiple regression models were built, adjusting for age, INR, CRP mg/dL, Hb, Cholesterol, Triglycerides, Iron levels, BMI and disease duration.

In the biological therapy group, age ($\beta = 0.005645$, $p < 0.0001$), INR value ($\beta = 0.1728$, $p = 0.0089$) and Iron value ($\beta = -0.0008147$, $p = 0.04$) remain strong predictors of an increased echo-IMT, maintaining statistical significance. In the conventional therapy group, age ($\beta = 0.006658$, $p < 0.001$) was the only variable maintaining statistical significance. It can be observed that the results obtained through regression analysis in the conventional therapy, respectively biological therapy subgroups, are similar to those obtained when analyzing the entire group of subjects.

DISCUSSION

In patients with active ulcerative disease (high endoscopic, clinical and biological markers of activity) we observed increased values of the echo IMT.

Ultrasound evaluation of IMT might serve as an useful tool in predicting cardiovascular risk and adjusting therapy in IBD patients although data regarding the effect of therapy is conflicting^{8,9,10,11}.

With the new biologic therapies that can alter the course of the disease^{12,13,14} a strategy where treatment can be tailored not only with a step up/add on approach of their biologic treatment but also by adding statin therapy or other therapeutic measures targeting cardiovascular risk might be implemented using echo IMT¹⁵.

CONCLUSION

We can assume that a better therapeutic disease control might result in a decrease of the cardiovascular risk but further studies are necessary to support this conclusion due to the small number of patients which were treated intensively in a top down or accelerated step up manner.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

References

1. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005;352:1685–95.
2. Daza L, Aguirre M, Jimenez M, Herrera R, Bollain JJ. Common carotid intima-media thickness and von Willebrand factor serum levels in rheumatoid arthritis female patients without cardiovascular risk factors. *Clin Rheumatol*. 2007 Apr;26(4):533-7.
3. Bruzzese V, Palermo G, Ridola L, Lorenzetti R, Hassan C, Izzo A, Zullo A. Preclinical atherosclerosis in patients with inflammatory bowel diseases: a case-control study. *Ann Transl Med*. 2017 Apr;5(7):158.
4. Principi M, Mastrodonato M, Scicchitano P, Gesualdo M, Sassara M, Guida P, et al. Endothelial function and cardiovascular risk in active inflammatory bowel diseases. *J Crohns Colitis*. 2013 Nov;7(10):e427-33.
5. Cappello M, Licata A, Calvaruso V, Bravatà I, Aiello A, Torres D, et al. Increased expression of markers of early atherosclerosis in patients with inflammatory bowel disease. *Eur J Intern Med*. 2017 Jan;37:83-89.
6. Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, Danalioglu A, Novacek G, Armuzzi A, Hébuterne X, Travis S, Danese S, Reinisch W, Sandborn WJ, Rutgeerts P, Hommes D, Schreiber S, Neimark E, Huang B, Zhou Q, Mendez P, Petersson J, Wallace K, Robinson AM, Thakkar RB, D'Haens G. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet*. 2018 Dec 23;390(10114):2779-2789. doi: 10.1016/S0140-6736(17)32641-7. Epub 2017 Oct 31.
7. Crouse JR, Raichlen JS, Riley WA, et al Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR trial. *JAMA* 2007;297:1344-53.
8. Filimon AM, Negreanu L, Doca M, Ciobanu A, Preda CM, Vinereanu D. Cardiovascular involvement in inflammatory bowel disease: Dangerous liaisons *World J Gastroenterol* 2015 21(33): 9688-9692
9. Gallino A, Aboyans V, Diehm C; European Society of Cardiology Working Group on Peripheral Circulation, et al. Non-coronary atherosclerosis. *Eur Heart J*. 2014;35:1112–1119.
10. Simon A, Megnien JL, Chironi G. The value of carotid intima-media thickness for predicting cardiovascular risk. *Arterioscler Thromb Vasc Biol*. 2010;30:182–185.
11. Papa A, Santoliquido A, Danese S, Covino M, Di Campli C, Urgesi R, Grillo A, Guglielmo S, Tondi P, Guidi L, De Vitis I, Fedeli G, Gasbarrini G, Gasbarrini A. Increased carotid intima-media thickness in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2005 Nov 1;22(9):839-46.
12. Magro F, Soares JB, Fernandes D. Venous thrombosis and prothrombotic factors in inflammatory bowel disease. *World J Gastroenterol*. 2014;20(17):4857–72.
13. Lowe SC, Sauk JS, Limketkai BN, Kwaan MR. Declining Rates of Surgery for Inflammatory Bowel Disease in the Era of Biologic Therapy. *J Gastrointest Surg*. 2020 Nov 2. doi: 10.1007/s11605-020-04832-y.
14. Amiot A, Bouguen G, Bonnaud G, Bouhnik Y, Hagege H, Peyrin-Biroulet L; French National Consensus Clinical guidelines for the management of IBD study group. Clinical guidelines for the management of inflammatory bowel disease: Update of a French national consensus. *Dig Liver Dis*. 2021 Jan;53(1):35-43.
15. Nuñez P, García Mateo S, Quera R, 15.Gomollón F. Inflammatory bowel disease and the risk of cardiovascular diseases. *Gastroenterol Hepatol*. 2021 Mar;44(3):236-242