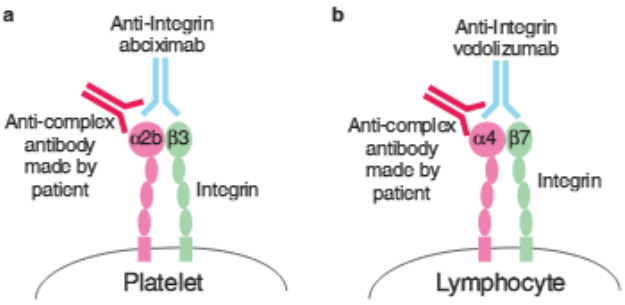

Figure 1. To illustrate the biological plausibility of an unexpected biologic process resulting in reduced specificity of an anti-adhesion therapy, consider the case of abciximab, an anti $\alpha_{IIb}\beta_3$ integrin monoclonal. In panel **a**, when patients develop anti-complex antibodies, these stabilize the interaction between the anti-integrin antibody and its target, reducing the specificity of the interaction. Rather than binding only platelets with activated $\alpha_{IIb}\beta_3$ integrins, this less-specific binding leads to binding of all platelets and to significant bleeding. Similarly, it is plausible to envision (**b**) that a similar anti-complex antibody could bind both vedolizumab and the α4 integrin molecule. This would strengthen the binding between vedolizumab and the α4 integrin, potentially leading to less-specific binding of α4 integrins (including α4β1 integrins on brain-specific lymphocytes). This unlikely but biologically plausible event could effectively turn vedolizumab into an α4-specific antibody (i.e., natalizumab) in these rare patients. This type of rare anti-complex antibody might be more frequent in patients with an autoimmune diathesis.

physicians and pharmaceutical companies that PML could occur.

This brings us to the topic of the biological plausibility of the rare event of PML in association with anti-adhesion therapies. We offer as a cautionary example the unexpected immunologic effect of serum antibodies to Abciximab. This monoclonal antibody therapy was designed to bind to the activated form of platelet glycoprotein IIb/IIIa (aka integrin $\alpha_{IIb}\beta_3$), and prevent clotting during endovascular procedures without an excess of clinically important bleeding in most patients. However, some patients developed antibodies against the abciximab/platelet complex, which reduced the specificity of this interaction (3). When one of these rare patients is treated with abciximab, severe thrombocytopenia occurs, and rapid bleeding from all mucosal surfaces ensues. Although it is unlikely that a similar mechanism might reduce the specificity of other anti-integrin monoclonal therapies, it is not impossible.

That this has previously occurred in patients treated with another anti-integrin monoclonal antibody, and that patients with inflammatory bowel disease (IBD) are prone to autoimmune reactions, makes it unlikely but possible that an unforeseen mechanism in rare patients could reduce the specificity of an anti-α4β7 monoclonal therapy (**Figure 1**). Sufficient sample size can change a very rare event to a reasonably likely event.

We would like to reiterate that the rule of 3s provides the upper limit of the 95% confidence interval, not the actual estimate of the risk of an event. We agree with the letter writers that PML cases associated with vedolizumab, if they occur at all, will be rare events, and that there are many factors that could affect an estimate of the frequency of rare events, including biological plausibility, latency, and other risk factors.

We are hopeful that anti-adhesion therapies will prove beneficial to millions of patients with IBD worldwide, but we should be prepared for the possibility of rare events, including PML. We hope that if PML does occur in the future in association with the newer anti-adhesion therapies, gastroenterologists, the Food and Drug Administration, and the general public will thoughtfully consider the frequency of rare events and embrace the richness of human diversity. To paraphrase Miranda in Shakespeare's The Tempest (V,i), O brave new world, that has such biologic processes in it!

To dismiss the past (abciximab) and deny the possibility of rare risks in the future would make us ill-prepared for an important potential complication. As vedolizumab leaves the island of clinical trials for the wider world of clinical practice, rare events might occur, but we should not panic or overreact to them. Instead, we should thoughtfully consider the frequency and magnitude of benefits in relation to the frequency and magnitude of rare risks.

CONFLICT OF INTEREST

P.D.R.H. has participated in clinical trials of the anti-adhesion therapies vedolizumab, AMG181, and PF-00547659 as a site investigator.

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IP-10 In Pediatric Celiac Disease and Food Allergy

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To the Editor: We have carefully read the paper recently published in *AJG* (1), in which the authors have described an approach to differentiate the diagnosis of celiac disease (CD) from that of non-celiac patients with

gluten sensitivity. On the other hand, some other authors have recently also shown the utility of detection of interferon-γ (IFN-γ) and IFN-γ-inducible protein-10 (IP-10) by ELISA or IFN-γ ELISpot for the detection of gluten-reactive T cells in HLA-DQ2.5+ associated CD (2). With this in mind, we aimed to study the importanceof the detection of IP-10 levels in patients with a debut confirmed diagnosis of CD and to compare these with levels in children affected with food allergies.

Patients with CD had a wide spectrum of gastrointestinal symptoms, isolated or not, including abdominal discomfort, nausea, vomiting, failure to thrive, constipation, or abdominal pain with iron deficiency. All patients of the CD group were positive for anti-transglutaminase antibodies (Tgt Abs), which were detected using anti-IgA fluoroenzymoimmunoanalysis against human and recombinant Tgt (EliaTM Immunocap 250), and for anti-deaminated gliadine antibodies, which were detected using standard ELISA (Quanta LiteTM Gliadin IgA II). The allergy group consisted of subjects with food allergies and hypersensitivity I symptoms as described elsewhere (3). A healthy control group consisted of patients who had assisted in the study of drug allergies and who were negative for either anti-TgT or anti-Gliadin antibodies. Informed consent from patients and/or controls was obtained. The ethics committee approved the study (PI: 35/11 and PI: 12/14).

IP-10 levels measured using Immunoassay (Procarta, Affymetrix) and read by flow cytometry (Luminex) were higher (statistically significant by the Kruskal–Wallis nonparametric method for three groups) in CD patients ($n=19$; average of 212 pg/ml) compared with control patients ($n=10$; 111 pg/ml). However, levels in CD patients were significantly lower than those in patients with a food allergy ($n=18$; 627 pg/ml). As it has been reported that duodenal biopsies of pediatric CD patients have shown an inflammatory profile consisting of augmented IL8 and IL17 (4,5), we also measured these cytokines. In our sample, IL8 and IL17 were also clearly elevated, thus confirming the possibility of an immunotherapeutic intervention at this point.

It is known that IP-10 is secreted by several cell types such as monocytes, endothelial cells, and fibroblasts in response to IFN-γ. IP-10 has been attributed several roles, such as chemoattraction for monocytes/macrophages. It is possible that the IP-10 levels before intervention are predictive of a favorable response and have a supporting role in differential diagnosis of CD and food hypersensitivity.

CONFLICT OF INTEREST

Guarantor of the article: Victor Matheu, MD, PhD.

Specific author contributions: Yvelise Barrios and Paloma Poza conceived the original idea and were mainly responsible for the work. Inmaculada Sanchez-Machín and Ruperto Gonzalez were responsible for control patients and responsible for the following up of patients with food allergy along with Paloma Poza. Andres Franco was responsible for the *in vitro* assays along with Y. Barrios. Honorio Armas was responsible for following up the patients with celiac disease. Victor Matheu was the senior researcher responsible for the work, had financial support, and wrote the final version of the manuscript. All authors approved the final version of the manuscript.

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Potential competing interests: Yvelise Barrios, Paloma Poza, Andres Franco, Inmaculada Sanchez-Machín, Ruperto Gonzalez, Honorio Armas, and Victor Matheu declare that they do not have any conflict of interest.

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A Fatal Case of Diffuse Enteritis After Colectomy for Ulcerative Colitis: A Case Report and Review of the Literature

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To the Editor: Colectomy is considered curative in patients with refractory ulcerative colitis (UC). However, case reports exist of patients developing *de novo* jejunitis years after colectomy for UC. We present a case of a fatal severe enteritis that developed immediately following colectomy in a patient with UC, and a review of the literature.

A 56-year-old woman was admitted to our center with hematemesis, high ileostomy output, and lethargy 11 days after a total proctocolectomy for refractory UC. She had a 12-year history of left-sided UC, but relapsed in the last 6 months despite mesalamine. During her preceding admission, enteric infections and cytomegalovirus (CMV) were excluded. She failed to respond to 5 days of IV steroids and salvage therapy with IV cyclosporine. She underwent a proctocolectomy with ileal j-pouch formation, and a diverting loop ileostomy, with a normal-appearing small