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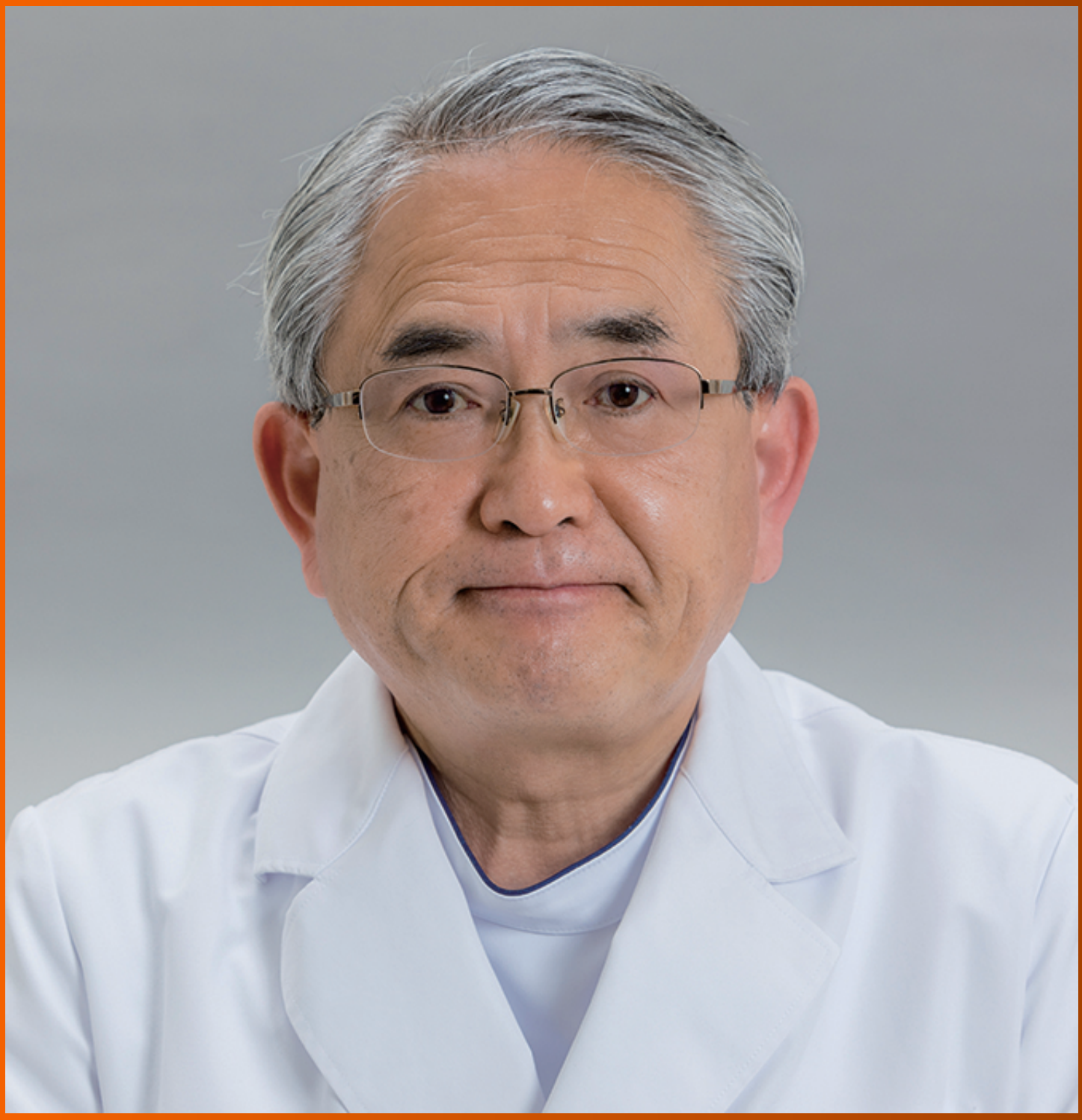

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LETTER TO THE EDITOR

Back to the drawing board: Overview of the next generation of combination therapy for inflammatory bowel disease

Jeffrey A Lowell, Michael J Farber, Keith Sultan

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Abstract

Inflammatory bowel disease (IBD) is entering a potentially new era of combined therapeutics. Triantafillidis *et al* provide an insightful review of the current state of combination therapy, with a focus on the use of a combined biologic and immunomodulator, as well as emerging data on the future potential of dual-biologic therapy (DBT). While current evidence for DBT is limited, encouraging safety profiles and ongoing trials suggest a brighter future for this approach. The importance of controlled trials should be stressed in establishing new treatment paradigms. Ongoing prospective randomized trials of DBT and perhaps future combinations of biologics and small molecule therapies will hopefully guide the next generation of IBD care.

Key Words: Inflammatory bowel disease; Biologics; Immunomodulators; Dual-therapy; Combination therapy

Core Tip: Triantafillidis *et al* thoroughly collate important studies summarizing the available evidence supporting the combination of various therapeutics used in the treatment of inflammatory bowel disease (IBD). Specifically highlighted is the importance of exploring combination therapy with biologics and immunomodulators, and in particular the emerging role of dual-biologic therapy (DBT). Given that current evidence for DBT is limited and new biologics continue to be developed, there is an urgent need for high-quality prospective trials to establish new treatment paradigms for the next generation of IBD care.

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TO THE EDITOR

The authors of the present review should be commended for their exhaustive effort analyzing a broad overview of data to the present date on the use of combinations of therapies for the treatment of patients with inflammatory bowel disease (IBD)[1]. With the emergence of new biologics targeting varying mechanisms of the inflammatory system, the prospect of new combinations of dual therapy becomes both enticing and intimidating for gastroenterologists and supports the importance and timeliness of the current review. To the work of the authors, we offer our own brief editorial on the topic addressing key findings presented.

It is worth restating that the term combination therapy (CT) for IBD has over the years become almost synonymous with the use of a biologic [typically a tumor necrosis factor (TNF)-α inhibitor] in combination with an immunomodulator (IMM) such as mercaptopurine, azathioprine, or methotrexate. Though the authors do well to present evidence of multiple scenarios where an IMM has value in combination with a TNF-α inhibitor, the majority of clinical evidence and guideline recommendations focus on the scenario with the greatest level of evidence: the initial therapy of IMM along with infliximab (IFX)[2,3]. In this regard, it has become accepted that the major benefit to this combination is through IMM induced suppression of anti-drug antibodies to IFX, in support of IFX drug levels, rather than through the combined direct therapeutic benefit of the IMM itself. While the short-term benefits of this CT are now generally accepted, the long-term use of IMMs with anti-TNFs comes at a cost of potentially increased rates of infection and malignancy in the form of lymphoproliferative disorders or nonmelanoma skin cancer[4]. Even with years of study, the risks *vs* benefits of indefinite CT remain unclear, both for the individual patient and the health care system as a whole.

Further, despite a thorough discussion on the role of antibiotics combined with biologics, mesalamine combined with corticosteroids, and other time-worn issues, there is an element of "burying the lead" in the current review. Specifically, the authors clearly see and appropriately note that the future CT debate and area of investigation goes beyond these established scenarios. The real future lies in the brave new world of dual therapy-combinations of multiple biologics, or biologics with newer small molecules such as the Janus kinase inhibitors. This appears to be the next generation of CT, as the field strives to achieve additive benefit from combining existing effective therapies. To this, we would like to add two specific observations.

First, high-quality data to support this next generation of CT is still very scarce. The field still awaits controlled trial data, as was the case with SONIC in which a clinical hypothesis generated from retrospective observations was tested and resulted in a new lasting treatment paradigm[5]. Within the body of the review the authors touch on the two prospective trials that investigated dual-biologic therapy (DBT) for IBD. The first, by Sands *et al*[6] compared IFX alone to IFX in combination with natalizumab for the treatment of Crohn's disease (CD). In this trial, the results were not clinically significant and as the authors themselves point out this combination "should be avoided" due to the risks of multifocal leukoencephalopathy. The second prospective trial is the recent VEGA trial, by Feagan *et al*[7]. This trial enrolled ulcerative colitis (UC) patients, comparing clinical outcome and safety for patients across three arms: golimumab alone, guselkumab alone, or the combination of both together. The authors observed a benefit from DBT over golimumab alone, but no significant benefit *vs* guselkumab monotherapy. Safety across the arms was comparable. Certainly, a partial victory for DBT, but not the paradigm-shifting moment needed in the treatment of IBD.

Second, in addition to a lack of high-quality data on efficacy of DBT in IBD, there is also only limited safety data available. Again, this is largely due to the need for longitudinal patient studies and the multiple combinations of biologics available. Recent meta-analyses of mostly retrospective observations suggest an acceptable safety profile of DBT when utilized in IBD, with no significant increase in serious adverse events reported; however, data on specific combinations is limited[8-10]. Notably, the authors highlight that the strong safety profiles of newer biologics such as ustekinumab and the gut-targeted vedolizumab make each appealing choices for use in combination with each other or TNF-α inhibitors. Indeed, the most studied DBT regimens consist of vedolizumab combined with a TNF-α inhibitor or with ustekinumab. An even greater information gap exists for the potential combination of different biologics with small molecule drugs such as the Janus kinase inhibitors and the sphingosine-1-phosphate receptor modulators.

Our third point is perhaps a more hopeful one. In their conclusion, the authors address the quality of evidence of DBT as limited by a lack of adequate financial support. While the current lack in available published evidence supports this statement, the future might be a bit brighter. The recently reported and encouraging safety profile of triple therapy found

in the EXPLORER trial[11], along with actively enrolling trials of DBT such as the DUET-CD (ClinicalTrials.gov Identifier: NCT05242471) and DUET-UC (ClinicalTrials.gov Identifier: NCT05242484) studies, with support from pharmaceutical companies, suggest that this may be changing. In the future it appears we will see the kind of high-quality prospective work that clinicians will need to guide the next generation of IBD care.

FOOTNOTES

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