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| This Advisory statement has been prepared by the South RMOC for the South West and South East regions only |
| Background |
| Clinicians do not usually prescribe two biologic medications simultaneously. With an increasing number of biologics available, occasionally patients with co-morbidities may be considered for dual treatment with more than one biologic for different conditions e.g. asthma and inflammatory bowel disease. Evidence is lacking in this area to guide therapy and therefore combination biologics expose patients to risk. Drugs may interact, for example additive immunosuppressive effects that may be hard to predict. Conversely, clinicians may be reluctant to use beneficial combinations because of lack of supporting evidence. The use of simultaneous biologics will also, clearly, have a cost impact.The topic submitter advocates a multidisciplinary team approach to decide:• What the risks of combination therapy might be• Whether a different single therapy provides an alternative to combinations• Whether combination therapy is in the patient’s best interests even if unknowable risks are present.No national or regional registries currently exist to monitor outcomes and safety.

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| Extent of the Issue |
| The number of patients currently affected is unknown but likely to be small. One CCG estimates that from their population of 1 million there are likely to be about 10 to 20 patients who fall into this category.\* |
| Evidence  |

Combination Biologic Medication for Different Co-MorbiditiesPublished evidence on the efficacy and safety of combination biologics for different co-morbidities is very limited. A literature search of Medline and Embase databases revealed evidence only in the form of 2 case reports or series.A case series of dupilumab in combination with other biologic therapies is published as a conference abstract (oral communication/e-poster).(1) The retrospective analysis (2017 – 2019) identified 7 cases where patients were receiving dupilumab for atopic dermatitis simultaneously with other biologics:* 3 patients dupilumab + omalizumab for asthma alone or chronic spontaneous urticaria for > 6 months
* 1 patient dupilumab + omalizumab recent initiation
* 1 patient dupilumab + benralizumab
* 3 patients dupilumab + adalimumab for Crohn’s disease (2 cases, recent initiation) and Hidradentis Suppurativa

The combinations could increase the risk of adverse effects. Although the authors reported that to date no adverse reactions had been reported, it should be noted that the short duration of therapy would not give a true indication of the long-term risks of infection or cancer.A case report is published on the tolerance and efficacy with simultaneous use of two different classes of monoclonal antibodies to treat hypereosinophilic syndrome and ulcerative colitis in a single patient (2).Combination Biologic Medication for the Same Disease (Inflammatory Bowel Disease)A systematic review and narrative review were identified and although the RMOC is not endorsing this approach, the abstracts are reported below.* Dual biologic therapy with anti-TNF, vedolizumab or ustekinumab in inflammatory bowel disease: a systematic review with pool analysis. 2019

Background: Inflammatory bowel diseases patients eligible for biological therapy represent a group with considerable disease burden and biologics only achieve 40% clinical remission rates in responders after 1 year of therapy.Aims: To collect all the published data about patients treated with dual biological therapy with an Anti-TNF, vedolizumab or ustekinumab, for a period of at least 3 months and to pool the data about the effectiveness and safety. Methods: A MEDLINE, and Web of Science search of all studies published in English until 1 January 2019 was conducted. Results: We included 7 studies with a total of 18 patients. Fifteen patients were treated with a combination of an anti-TNF and vedolizumab, 3 patients were treated with vedolizumab and ustekinumab. Fifty-six percent of patients were affected by Crohn’s disease and 50% of patients were treated with an immunosuppressant drug or steroid too. A clinical improvement was obtained in 100% of patients, and an endoscopic improvement in 93% of patients. No serious adverse events were reported. Conclusions: The use of dual biological therapy is an attractive therapeutic option and may be an opportunity to better tailor and personalize the therapies for patients. Further studies, as randomized control trials, to provide comparative efficacy and safety endpoints of combination therapies, and to clarify potential advantages of combined biological therapies, are needed (3).(It should be noted that the short duration of therapy would not give a true indication of the long-term risks of infection or cancer.)* Combining Biologics in Inflammatory Bowel Disease and Other Immune Mediated Inflammatory Disorders, 2018

There are limited published data regarding the efficacy and safety of combination targeted therapy in IBD specifically, which include only 1 exploratory randomized control trial and 3 case reports or series. This review evaluates the published literature regarding this therapeutic paradigm in IBD and its extensive utilization in the treatment of other immune-mediated inflammatory disorders. The combination of biologic therapies demonstrates variable degrees of efficacy and highlights some safety concerns, depending upon the agents used and the disease state treated. A trial (Clinical Trials.gov Identifier: NCT02764762) combining vedolizumab and adalimumab is currently underway evaluating the effectiveness and safety of this approach in patients with Crohn’s disease, which should provide further insight into this treatment concept. While combination biologic therapy is an attractive strategy, the lack of consistent superior efficacy as well as safety concerns militates the need for further trials prior to its general application in IBD (4). |
| Discussion and Conclusions |
| Published evidence on the co-administration of two or more biologics for co-morbidities is lacking and limited to case reports and case series. Although the efficacy of combination biologic therapy may be inferred due to their targets, evidence to support this is lacking; and there may be risk of interactions and additive adverse effects. At the September 2020 meeting, the South RMOC agreed that there is currently insufficient evidence available for the RMOC to provide guidance. The evidence concerning dual / combination biologic therapy for the same disease is simply being documented above and such an approach is not being endorsed. Some RMOC members considered that the assessment of patients via the Individual Funding Request route was currently the most appropriate option in this scenario; following a multidisciplinary team meeting.Due to the lack of evidence, prescribing needs to be based on clinical decision following a multidisciplinary team review. |
| References |
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2. Patel B, Butterfield JH, Weiler CR, Kane SV. Tolerance and efficacy with simultaneous use of two monoclonal antibodies for a patient with hypereosinophilic syndrome and ulcerative colitis. Monoclon Antib Immunodiagn Immunother. 2016;35(6):300-303
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\*Cambridgeshire and Peterborough Clinical Commissioning Group (CCG) |
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