EFFICACY OF TUMOR NECROSIS FACTOR-ALPHA THERAPY IN THE MANAGEMENT OF PAEDIATRIC PERIANAL CROHN'S DISEASE: A SYSTEMATIC REVIEW

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Introduction: Recent studies report an increased incidence of perianal Crohn's disease (PCD) in paediatric patients (up to 50.7%), which can lead to significant morbidity and reduced quality of life. Especially in children and young adults, PCD may be refractory to medical treatment, despite the most advanced pharmacological and surgical treatments, with consequent significant impact on quality of life. Although Anti- Tumor Necrosis Factor-alpha (TNF-α) therapy, primarily infliximab and adalimumab, are now increasingly used to induce and maintain disease remission in the paediatric CD population, however, the optimal use of these therapies has not yet been defined in the paediatric setting.

Methods: In accordance with a published protocol (PROSPERO registration no. CRD42019118838), we systematically and critically evaluated all published evidence on the efficacy and safety of anti-TNF-α (infliximab, adalimumab and certolizumab) in children with PCD, in the PubMed, MEDLINE, Embase, Cochrane and clinical trials.gov databases from any time until October, 18th, 2018with no language and study type restriction. The outcome measures were the proportion of patients with fistula closure, proportion of patients with response or remission, proportion of patients categorized as primary non-responders or loss of response, relapse rate at the any of the study time points and the number of patients underwent on surgical resection during anti-TNF-α therapy. The other secondary outcome measures were safety measures and withdrawals due to the adverse events.

Results: Based on the inclusion criteria, we included 29articles (yielding a total of 565PCD patients aged between 9months to 18years) in our systematic review. The included studies differed regarding the number of PCD patients treated with anti- TNF-α [n=1to 101], baseline disease severity, concomitant treatment, treatment refractoriness, remission and response criteria. Only 4studies evaluated adalimumab in PCD patients and no study evaluated certolizumab in PCD patients. Out of 565patients included in the analysis, 326(60%) achieved clinical remission and 310 (55%) had a clinical response. Overall, a complete closure of the perianal fistula was reported in 127/ 228(56%) of patients; 10/29studies including 37patients reported primary non-response rates ranged from 8% to 15%. Loss of response or secondary non-response rates ranged from 14% to 25%. The pooled incidence rate of surgical interventions required during treatment ranged from 28% to 39%. In total, adverse events were reported in 10/29studies including 105of 565PCD patients [19%; 95% CI: 16%–22%]. Anaemia and allergic reactions were the most frequent adverse effects. Among serious adverse event, leucopoenia, varicella infection and anaphylactic shock were commonly reported. Recorded discontinuation rate due to adverse effects occurred in 9% of patients [95% CI: 5–16%], with serious infections being the most common reason cited for treatment withdrawal.

Discussion and conclusion: The findings of the present review imply that according to low-quality evidence from small, uncontrolled and heterogeneous descriptive studies, and very few RCTs, nearly three-fifths children with PCD achieved remission with anti-TNF-α treatment and in approximately 40% remission was maintained after 12months, with practically low discontinuation rate due to serious adverse events. More than half of the patients achieved complete fistula closure. There is still a need for more robust evidence adequately assessing the efficacy and safety of anti-TNF-α therapy in paediatric PCD, as well as in comparison with other therapies.