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NEW UPDATES ON ULCERATIVE COLITIS

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Abstract:

Introduction: *Ulcerative colitis (UC) by definition is an inflammation of the mucosa of the colon, it is a subtype of inflammatory bowel diseases (IBD), and it is associated with high morbidities in affected population. During the last two decades, the treatment protocols for ulcerative colitis have changed after the introduction of biological treatment. It is very important to understand the different available biological and conventional agents and the new strategies and techniques used in treatment of UC, including new targets and small-molecule drugs*

Aim of work: *In this review, we will discuss the most recent evidence regarding the new updates on management of ulcerative colitis.*

Methodology: *We did a systematic search for the new updates on management of ulcerative colitis in the emergency department using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). We only included full articles.*

Conclusions: *Achieving remission is an essential therapeutic goal in patients with ulcerative colitis. Persistence of activity, even if mild, causes a reduction in quality of life of the patients. Dose optimization of biologic drugs might go beyond plasma levels, as tissue levels of biologic drugs in the inflamed intestine may not be associated with plasma levels. The value of therapy intensification in patients who are having full clinical remission, but persistent endoscopic lesions, still needs to be determined in ad-hoc designed studies that target to establish the chronic harms and benefits of different therapeutic strategies. The most common errors using available drugs are under-dosing and persisting in therapies that are ineffective. Applying the right doses with strict criteria for drug failure is essential in clinical practice.*

Key words: *Ulcerative colitis, new updates, diagnosis, management.*

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INTRODUCTION:

Ulcerative colitis (UC) by definition is an inflammation of the mucosa of the colon, it is a subtype of inflammatory bowel diseases (IBD), and it is associated with high morbidities in affected population [1]. In the majority of the cases, UC is usually not associated with the formation of fistulas and abscesses, and the incidence of further complications like strictures is low, thus, it is considered to be a less severe disease than Crohn's disease (CD). However, both diseases have the same negative effect on the quality of life. Such a negative effect on the quality of life is greater than the effect seen in other immune-mediated diseases like rheumatoid arthritis or asthma [2]. During the last two decades, the treatment protocols for ulcerative colitis have changed after the introduction of biological treatment. It is very important to understand the different available biological and conventional agents and the new strategies and techniques used in treatment of UC, including new targets and small-molecule drugs.

In this review, we will discuss the most recent evidence regarding the new updates on management of ulcerative colitis.

METHODOLOGY:

We did a systematic search for the new updates on management of ulcerative colitis in the emergency department using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). We only included full articles. The terms used in the search were: Ulcerative colitis, new updates, diagnosis, and management.

Current treatment patterns in UC

Currently, four classes of drugs are used in treatment of UC: aminosalicylates (5-ASA), immune-suppressants, steroids and biological agents. The choice of the best drug to use and the rout of administration are based on many factors like the severity and extension of the disease, the current treatment regimen and the patient's drug history.

Disease extension

Ulcerative colitis can be classified into three groups: proctitis, left-side colitis, or extensive colitis, according to the extension of the disease. At the time of establishing the diagnosis, the extension of the disease must be assessed. A reassessment must also be done whenever further extension is suspected based on the biomarker and symptomatic findings. In cases of mild or moderate rectal UC, topical mesalazine is considered to be the first-line of treatment, while in extensive or left-sided UC, a combination of oral and topical 5-ASA is proved to be the most effective treatment [3]. In cases where there is no responders to 5-ASA, local (in proctitis patients) or systemic corticosteroids are used. When there is a resistance for 5-ASA and corticosteroids, immunosuppressants and/or biologics are used regardless the extension of the refractory [4].

Disease severity:

- Mild-to-moderately active disease

In cases of mild or moderate UC, Mesalazine is considered to be the first-line treatment, as it has a better result in achieving clinical, endoscopic, and histologic remission, when compared to placebo [5]. 60% of patients with mild-to-moderate UC have achieved remission on mesalazine [6]. In cases of extensive and left-side UC, a combination oral and topical 5-ASA is better than lone oral therapy [7], suing 5-ASA once a day is considered to be as effective as using divided doses regardless the used formulation of 5-ASA [8]. Relapsed patients should be treated with high dose of mesalazine in order to to achieve remission.

In cases of patients with amino salicylate intolerance, oral corticosteroids are considered to be the main line of therapy. Although steroid therapy has a 60–70% remission rate, it cannot maintain the state of remission, and it is associated with high rates of side effects. So in order to minimize the systemic exposure to corticosteroids and decrease the incidence of side effects, new galenic corticosteroidal preparations with local colonic release and rapid clearance have been developed including budesonide MMX [9], and beclomethasone dipropionate. Both drugs are considered to be safer and associated with higher remission rates than conventional and mesalazine. In cases where both corticosteroids and mesalazine are ineffective the use of immunosuppressants, biologics, or surgical treatment are being considered. In cases of repeated relapse with 5- ASA treatment, the use of with azathioprine and 6-mercaptopurine mist is considered. It can also be used as maintenance therapy in patients with good response to cyclosporine or tacrolimus. In the cases whit 6-MP or azathioprine induced remission, the use of thiopurines is considered to be more effective than 5-ASA in achieving steroid-free remission, clinical response (in up to 87% of patients), and endoscopic remission and in maintaining the state of remission [10].

Evidence on methotrexate used for inducing and

maintaining remission in patients with ulcerative colitis is scarce. Some previous studies have suggested that most patients with ulcerative colitis who were treated with intravenous methotrexate at doses between twenty milligrams and twenty-five milligrams showed response or remission of their disease [11]. On the other hand, a recent published study has failed to demonstrate the efficacy of intravenous methotrexate in the induction of steroid-free remission [12]. In fact, for these patients there is no enough data to support recommending methotrexate for maintaining remission in patients with ulcerative colitis.

Biologic medications and/or surgical interventions must be considered in patients who fail to improve following the use of immunosuppressant treatment. The use of anti-TNF pharmacological agents has been a huge development in the pharmacological interventions of ulcerative colitis cases. Previous trials and systematic reviews have concluded the benefits of anti-TNF medications for the induction and maintenance of clinically significant remission, inducing and maintaining healing of the mucosa, and achieving significant declines in the hospitalization rates and also enhancing the quality of life of patients [13]. During the Active Ulcerative Colitis Trials, medical interventions using infliximab decreased colectomy risk by seven percent when compared to the use of placebo [14]. It should be noted that this benefit that could not be reproduced during the Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab studies [15]. However, a systematic review concluded that anti-TNF medications decreased significantly the risks of requiring colectomies in patients with ulcerative colitis.

Large population-based studies have also found varying results [16]. Today, there are 3 anti-TNF agents approved for the use in ulcerative colitis patients: adalimumab, infliximab, and golimumab. Infliximab is considered the first anti-TNF medication that was approved for use in the induction and maintenance of remission in patients with ulcerative colitis. The efficacy of Infliximab was proven in the Active Ulcerative Colitis Trials, which concluded that patients who had moderate or severe ulcerative colitis and who were given infliximab had significantly higher rates of achieving a significant clinical response, remission, and healing of mucosa, when they were compared to ucerative colitis patients who were given placebo [17]. The ideal response to infliximab could be achieved with combination treatment. The UC-SUCCESS trial concluded that patients who were given a combination of both infliximab and azathioprine had higher likelihood to achieve steroids-free remission and healing of mucosa when compared to those who received infliximab alone. A recently published review found that the use of infliximab can be associated with higher efficacy when compared to the use of adalimumab regarding rates of healing of mucosa.

The ULTRA 1 and ULTRA 2 studies concluded that the use of adalimumab leads to higher efficacy than the use of placebo for the induction and maintenance of remission in ulcerative colitis patients with moderately active disease or severely active disease who have a history of a previous failed other treatment and also led to a decline in the number of overall and ulcerative colitis-specific hospital admissions when compared to the use of placebo [18]. Efficacy and safety with chronic use was assessed in an open study of ulcerative colitis patients who were included in the ULTRA 1 and ULTRA 2 studies. Of ulcerative colitis patients who had remission and healing of mucosa following one year of therapy, about sixty-three percent and fifty-nine percent, respectively, achieved maintenance of these clinical outcomes after 4 years of follow up, with rates of side effects staying stable over the duration of the study [19].

Golimumab is another agent that is a fully human anti-TNF antibody and can be administered through the subcutaneous route. The PURSUIT study concluded that when compared to the use of placebo, the use of golimumab can be considered a beneficial therapy for the induction and maintenance of remission in moderately active ulcerative colitis or severely active ulcerative colitis for up to one year. This trial also concluded that golimumab is beneficial for the induction and maintenance of healing of mucosa at weeks thirty and fifty-four.

An alternative to anti-TNF therapy in patients with ulcerative colitis who fail to achieve remissions on corticosteroids and or other immunosuppressants is the drug vedolizumab. It is a humanized monoclonal antibody that blocks the α4β7-integrin, which acts by blocking the recruitment of lymphocytes into the guts. The GEMINI I trial has concluded the efficacy of vedolizumab in the induction of maintenance of remission in moderate and severe cases of ulcerative when it was compared to the use of placebo. At six weeks, the rate of response was forty-seven percent in patients who were treated with vedolizumab and twenty-five percent for those who were given placebo (p value less than .001). At fifty-two weeks, patients remaining on vedolizumab treatment had forty-two

percent (every eight-week dosing) and forty-five percent (every four-week dosing) rates of achieving remission when compared to sixteen percent among those who were given placebo. Healing of mucosa and corticosteroid-free remission were also higher among patients who were treated with vedolizumab when compared to patients in the placebo group [20].

Vedolizumab is another agent that has a relatively safe profile. In a previous study of about 2,800 patients who received Vedolizumab for a duration of five years it was not found to be linked with higher rates of developing severe or opportunistic infections, nor there were any cases that developed progressive multifocal leukoencephalopathy and the risk of cancers was similar to that classically seen in patients with inflammatory bowel diseases [21].

Therapeutic monoclonal antibodies pharmacological agents have a complicated profile in which levels of the agent do not have a linear correlation with the dose that is given. Factors that can usually affect clearing the drug include metabolism rates, binding to the target, cellular uptake, presence of Brambell receptors, and the presence of antidrug antibodies. Immunogenicity usually correlates with less serum levels of the drug and a failure to response [22].

- Severe-fulminant disease:

Severe cases of ulcerative colitis can be potentially fatal and linked to significant complications, and a rate of mortality that is about one percent of cases [23]. All patients who have severe ulcerative colitis must be admitted to the hospital to confirm the diagnosis, exclude the presence infections and get proper therapy.

During hospital admission, patients must get sufficient intravenous fluids, nutritions supplements, and low-molecular-weight heparins to achieve thromboprophylaxis, and cessation of any medication that might lead to the development of colonic dilatation. Additionally, electrolyte disturbance and anemia (if present) must be treated [4]. IV steroids are considered to be the first choice for therapy in severe flare cases. Guidelines generally recommend using of IV hydrocortisone 4 times every day or methylprednisolone. About sixty percent of patients will show sufficient response to IV steroid monotherapy and about 33% of patients will need to receive the rescue therapy.

The response to IV corticosteroids must be evaluated on the third day following the initiation of treatment. In corticosteroid-refractory cases, therapeutic options can include cyclosporine, infliximab, tacrolimus or surgical interventions. Medical interventions are generally preferred as second-line interventions, as there is not much evidence to support using tacrolimus in severe ulcerative colitis when compared to the use of cyclosporine or infliximab. In these cases, cyclosporine or infliximab are the most likely used second-line interventions. Studies that compared the use of 'rescue therapy' with infliximab or cyclosporine found that no significant difference was found between the two treatment groups regarding clinical [24].

Criteria for treatment failure

Common mistakes during the management and treatment of ulcerative colitis cases include the use of drugs at less than optimal therapeutic doses, and long-duration treatments with medications even after they are proven to be ineffective in inducing remission following the recommended period of exposure. Before therapy is called as a 'failure', it is essential to exclude the presence of other possible causes of medication refractoriness like the presence of an infection or ischemic colitis, assess compliance with treatment, and improve therapeutic doses.

5-ASA doses that are recommended for inducing remissions are one-gram suppository every day for the treatment of proctitis, whereas for left-side or extensive extension with mild activity disease or moderate-activity disease more than 2.4-grams through the oral route. Patients who have moderate ulcerative colitis might benefit from the use higher doses of the medication. To achieve complete maintenance following remission, the generally recommended doses of mesalazine are three-grams per week in patients with proctitis and two grams per day in patients with left-side or extensive extension. Based on this, refractoriness to treatment with 5-ASA is generally known as persistence of clinical manifestations following application of proper treatment for four to eight weeks at doses higher than four grams [25].

When treating patients who were admitted to the hospital with severe activity of their condition, absent clinical and biological improvements to corticosteroids following day three of treatment should be considered a failure. The generally recommended dose of azathioprine in these patients is 2.5 mg/kg every day and for mercaptopurine 1–1.5 mg/kg. Failure of Thiopurine therapy is known as the progression of disease activity or the occurrence of relapses despite administrating therapy with an appropriate dose of the medication for more than

three months [26].

Failure to achieve remission following anti-TNF medications use could happen as either a primary non-response or a secondary loss of response. Despite the absence of a clear definition of either terms, it is generally known that primary non-responders are who's who show no improvement in manifestations while they are on induction active therapy. Secondary loss of response, on the other hand, is categorized as those who respond to treatment after an induction therapy, but later fail to respond during the maintenance therapy. Assessment of primary response to anti-TNF medications must be done during week fourteen. Loss of response should be taken into consideration in patients who are undergoing induction treatment with later worsening in clinical manifestations, and the presence of an active disease must be documented using endoscopy.

Therapeutic objectives: clinical vs. endoscopic remission

In every day practice, the achievement of a complete control of clinical manifestations is an essential target for any used therapy. A direct association has been found between higher quality of life and decreased activity of the disease patients with inflammatory bowel diseases. In ulcerative colitis, specifically, when present, even mild symptoms can be linked to significantly worse quality of life, with declines of quality of life scores in ulcerative colitis patients who have Mayo scores higher than two. Based on these results, it is important that about sixty-five percent of ulcerative colitis patients and thirty-eight percent of healthcare providers believe that remission does not always mean achieving completely absent clinical manifestations of the disease [27]. Another important point to be considered while planning therapeutic goals in patients with ulcerative colitis is the proper determination whether or not reaching remission is enough, or if we must additionally target achieving of complete healing of the mucosa. Achieving complete healing of the mucosa in patients who have ulcerative colitis has been correlated with improved prognosis.

The relationship between clinical manifestations and diagnosed endoscopic lesions is not clearly understood. A significant association has been found in different studies between the full Mayo score, that includes an endoscopic component, and the partial Mayo score, that does not include an endoscopic component and only includes clinical manifestations like the number of stools every day, the presence of blood in stool, and the general assessment by the physician. additionally, a significant associated has been found between indices of activity which have endoscopic components, and other indices that do not include endoscopic components. Factor analysis concluded that these results are because of the fact that these endoscopy items in composite indices are generally linked with the frequency of stool and stool blood items.

For every day practice, ulcerative colitis patients who have persistent and progressing symptoms must undergo an upper endoscopy to assess whether or not their manifestations originate from the continuing presence of their lesions. It must be kept in mind that some patients with ulcerative colitis will still have progressive diarrhea despite achieving complete healing of mucosa. In cases of observing persistent lesions, treatment must become more intense to achieve complete remission of the disease, and if lesions cannot be observed, other etiologies of the diarrhea must be considered. The potential benefits of therapy intensification in patients, who have persistent endoscopic lesions despite achieving complete remission, still need further studies to be determined. While for patients who are receiving a maintenance therapy of mesalazine, an increase of the dose could be accepted, the harms/benefits ratio of using immunosuppressants in patients with these conditions still needs to be investigated in properly designed studies.

CONCLUSIONS:

Achieving remission is an essential therapeutic goal in patients with ulcerative colitis. Persistence of activity, even if mild, causes a reduction in quality of life of the patients. Dose optimization of biologic drugs might go beyond plasma levels, as tissue levels of biologic drugs in the inflamed intestine may not be associated with plasma levels. The value of therapy intensification in patients who are having full clinical remission, but persistent endoscopic lesions, still needs to be determined in ad-hoc designed studies that target to establish the chronic harms and benefits of different therapeutic strategies. The most common errors using available drugs are under-dosing and persisting in therapies that are ineffective. Applying the right doses with strict criteria for drug failure is essential in clinical practice.

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