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Review Article

The History of Ulcerative Colitis Revealed by the Literature

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ABSTRACT: Ulcerative colitis is a chronic inflammatory disease of the large intestine. The number of patients with ulcerative colitis is rapidly increasing worldwide; it was only around 150 years ago that this disease was recognized medically. This article reviews the history of ulcerative colitis and its treatment, as per previous studies. A suspected case of ulcerative colitis was first described in modern medicine in 1768. The term "ulcerative colitis" first appeared in literature in 1875; it was only recognized as a disease in the early twentieth century. No effective treatment was found at that time, which brought the mortality rate of hospitalized patients with ulcerative colitis to almost 50%. The first case series of ulcerative colitis was reported in Japan in 1928. The development of treatment is as follows: sulfasalazine in the 1940s, corticosteroids in the 1950s, thiopurines in the 1970s, and biologics in the late 1990s. Since 2000, molecular targeted drugs have been developed one after another. I would like to express my sincere respect and appreciation to the pioneers whose tireless efforts and passion had advanced the diagnosis, treatment, and pathophysiological elucidation of ulcerative colitis. We must receive the batons from them and continue the efforts in finding the cure for ulcerative colitis.

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Introduction

Ulcerative colitis is a chronic inflammatory disease of the large intestine that extends from the rectum to the colon continuously. Its causes remain unknown. It is hypothesized that individuals with genetic predispositions are affected by environmental factors such as diet, causing abnormal intestinal immunity, and thus chronic colitis.[1] It mainly affects young people, but the age of onset ranges widely from the 10s to 60s. Epidemiologically, it has been observed that the number of patients increases as society modernizes and westernizes.[2] In the West, the number of patients started increasing from the 1960s. In Japan, the Ministry of Health, Labour and Welfare launched the Research Group for Intractable Inflammatory Intestinal Diseases in 1975, to start the registration of this disease. The number of registered patients nationwide was only 965 in 1976, compared with 2013, which recorded 166,060 cases.[3] A national epidemiological survey conducted in 2014 estimated that the number of cases in Japan was approximately 220,000.[4] Although the number of patients with ulcerative colitis is

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rapidly increasing, it was only 150 years ago that this disease was recognized medically. This article reviews the history of ulcerative colitis and its treatments, as per the previous studies.

History of Ulcerative Colitis

A suspected case of ulcerative colitis was first described in modern medicine in *The Morbid Anatomy of Some of the Most Important Parts of the Human Body*, a book written by Matthew Baillie in 1768.[5] He described the pathological anatomy of the human body in this book. There is a description in it that says: "It very commonly happens that inflammation of the intestines advances to suppuration and ulceration. Ulceration, however, does not appear to be so common in the small as in the great intestines". Ulceration is limited to the large intestine, indicating the pathological characteristics of ulcerative colitis.

The term "ulcerative colitis" first appeared in literature in 1875. At that time, most of the diseases presenting bloody stool were considered infectious dysentery. It was Sir Samuel Wilks, a British physician, who took notice that colitis could also occur through noninfectious causes and described noninfectious colitis as "simple ulceration of the large intestine" or "simple colitis" in his 1859 edition of *Lectures on Pathological Anatomy*.[6] In the 1875 edition of *Lectures on Pathological Anatomy*, Wilks and Walter Moxon first used the term "simple ulcerative colitis" for colitis that had no indication of infection, such as fever or epidemic.[7]

It was in the early twentieth century that ulcerative colitis was recognized as a disease entity. In 1909, the Royal Society of Medicine in London organized a symposium at which more than 300 cases of ulcerative colitis from several hospitals in London were recorded.[8] Surprisingly, nearly half of these cases were fatal. Ulcerative colitis is not considered a life-threatening disease today, but at the time with the absence of a definite treatment, it recorded a high mortality rate.

In Japan, Professor Ryukichi Inada of the University of Tokyo first reported 10 cases of ulcerative colitis in 1928, which he collated over a 10-year period.[9] In 1958, Professor Fujio Matsunaga of Hirosaki University reported 259 cases of ulcerative colitis, consisting of his own cases and those reported in Japan in his homework lecture at the annual meeting of the Japanese Society of Internal Medicine.[10]

History of Treatments for Ulcerative Colitis

A review of the treatment of ulcerative colitis in 1936 begins with the following sentence: "The most important factors in the successful treatment of ulcerative colitis are patience and perseverance on the part of both doctor and patient".[11] This sentence indicates that there was almost no effective medical treatment at that time. The pharmacotherapy listed in this review is only codeine, belladonna (a plant alkaloid with anticholinergic effects), charcoal, and iron. Although there was little pharmacotherapy, this review has the following interesting descriptions: "it is essential to control by endoscopy any apparent improvement, as the disappearance of symptoms may precede the disappearance of the last trace of ulceration and inflammation by several weeks. Relapse is almost certain to occur unless treatment is continued until all signs of inflammation have disappeared". "The danger of recurrence is much reduced if treatments continued until the sigmoidoscope shows no trace of inflammation, even if symptoms have already disappeared for some weeks." It is surprising that despite the immaturity of treatment and endoscopy, the importance of mucosal healing, currently the most important therapeutic goal, has already been recognized in this era.

Later, sulfasalazine was developed in the 1940s, corticosteroids in the 1950s, thiopurines in the 1970s, and biologics in the late 1990s. Since 2000, molecular targeted drugs have been developed one after another.

History of 5-Aminosalicylic Acid (5-ASA)

5-ASA preparations are the first-line treatment for patients with mild-to-moderate ulcerative colitis. The first 5-ASA preparation is sulfasalazine (also called as salazosulfapyridine or salazopyrin), developed by Nanna Svartz, professor of medicine at Karolinska Hospital in Stockholm. This drug was initially developed for rheumatoid arthritis. At that time, there was a hypothesis that rheumatoid arthritis was caused by an infection in the joint. Svartz then thought that a drug combining sulfonamide, an antibacterial drug, and salicylic acid, an anti-inflammatory drug, could be ideal for rheumatoid arthritis and developed sulfasalazine, an azo compound of sulfapyridine and 5-ASA. She also administered sulfasalazine to patients with ulcerative colitis, based on the hypothesis that ulcerative colitis was also caused by an infection. She reported in 1942 that all nine patients with ulcerative

colitis who received sulfasalazine responded to the drug.[12]

John Lennard-Jones et al. of St. Mark's Hospital reported in 1962 the results of a double-blind controlled trial, examining the efficacy of sulfasalazine for induction of remission in patients with active ulcerative colitis.[13] In this trial, 50 patients with ulcerative colitis were assigned to receive sulfasalazine, placebo, or salicylazosulphadimidine. In the sulfasalazine group, 16 out of 20 had endoscopic improvement, compared with only 8 out of 20 in the placebo group. In 1973, Sydney Truelove et al. reported that sulfasalazine was also effective in maintaining remission.[14]

The efficacy of sulfasalazine for ulcerative colitis had been shown, but it remained unknown, which has the active moiety, sulfapyridine or 5-ASA. Truelove et al. reported in 1977 the results of a blinded controlled study in which patients with ulcerative colitis were assigned to receive rectal administration of sulfapyridine, 5-ASA, or salazosulfapyridine.[15] In this study, clinical improvement was observed in approximately three quarters of patients receiving sulfasalazine or 5-ASA and in only 30% of those receiving sulfapyridine. This study demonstrated that 5-ASA is an active moiety in ulcerative colitis.

The azo-bond of sulfasalazine is digested by the gut microbiota, and 5-ASA is released in the colon, which acts directly on the colonic mucosa to suppress inflammation. Sulfapyridine, one of the moieties of sulfasalazine, may cause side effects such as bone marrow suppression, rash, headache, and liver damage, but when 5-ASA alone is administered orally, most of it is absorbed in the small intestine. Thus, various formulations have been devised to deliver 5-ASA to the colon efficiently. The efficacy of a pH-sensitive polymer coating formulation (Asacol®) was reported in 1987,[16] and a slow-releasing capsule formulation (Pentasa®) was reported in 1993.[17]

History of Corticosteroids in the Treatment of Ulcerative Colitis

Corticosteroids are the first-line treatment for induction of remission in patients with moderate-to-severe ulcerative colitis. The efficacy of corticosteroids for ulcerative colitis was first proven in 1955 by a control-controlled trial by Truelove and Witts.[18] In this trial, patients with ulcerative colitis were assigned to receive cortisone or placebo intravenously. Patients who received cortisone showed higher rates of improvement and remission than those in the control group. In addition, 9 of 38 patients (23.7%) died in the control group versus 3 of 43 (7.0%) in the cortisone group. It can be concluded that corticosteroids help in reducing the mortality of ulcerative colitis.

History of Thiopurines

Thiopurine is used to maintain remission in patients with ulcerative colitis. At Burroughs-Wellcome pharmaceutical company (later GlaxoSmithKline), George Hitchings and Gertrude Elion synthesized a variety of purine derivatives to develop anticancer drugs that inhibit DNA replication and stop cell growth. They finally developed 6-mercaptopurine (6-MP), which was initially used to treat acute lymphoblastic leukemia. Hitchings and Elion subsequently developed various drugs, including azathioprine, allopurinol, trimethoprim, acyclovir, nelarabine, and azidothymidine, for which they received the Nobel Prize in Physiology or Medicine in 1988.

Azathioprine, a prodrug of 6-MP, has also been shown to suppress immune cell proliferation and has been used in the treatment of rejection after organ transplantation. The use of azathioprine in patients with ulcerative colitis was first reported in 1966.[19] In 1972, the results of a placebo-controlled study showed the efficacy of azathioprine in maintaining remission in ulcerative colitis.[20]

History of Biologics for Ulcerative Colitis

The first monoclonal antibody used for the treatment of inflammatory bowel disease is infliximab, an anti-TNFα antibody. Infliximab was developed in collaboration of Centocor, a venture biotechnology company and later acquired by Johnson & Johnson, and Professor Jan Vilček of New York University.[21]

Infliximab was initially developed for rheumatoid arthritis and sepsis, but a case report published in *The Lancet* in 1993 showed that it was effective in treating a 12-year-old girl with colonic Crohn's disease refractory to corticosteroids, mesalamine, and azathioprine.[22] This case report paved the way for biologics era in the treatment of inflammatory bowel disease.

The results of a pilot study utilizing infliximab for ulcerative colitis were reported in 2001;[23] 4 years later, the results of large-scale randomized controlled studies were reported in 2005.[24] Currently, five biologics are available for the treatment of ulcerative colitis: infliximab, adalimumab, and golimumab (anti-TNFα antibodies), vedolizumab (anti-α4β7 integrin antibody), and

ustekinumab (anti-IL-12/23 p40 antibody).

Conclusions

The history of ulcerative colitis has been presented as per the previous literature. It was only 150 years since ulcerative colitis was established as a disease entity. A hundred years ago, there was no definite treatment for ulcerative colitis, making its mortality rate high; however in recent years, developments for the treatment of the disease have rapidly advanced, making ulcerative colitis nonfatal. Finally, I would like to express my sincere respect and appreciation to the pioneers whose tireless efforts and passion advanced the diagnosis, treatment, and pathophysiological elucidation of ulcerative colitis. We must receive the batons from them and continue the efforts in finding the cure for ulcerative colitis.

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Education and Training

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