Perspective

A novel player: cyclosporine therapy in the management of inflammatory bowel disease

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Abstract: Amongst other indications, cyclosporine therapy has emerged as a novel agent for the management of severe refractory ulcerative colitis (UC). In the historic population of patients receiving cyclosporine therapy—namely solid organ transplant patients—renal toxicity has proven to be a significant mitigating side effect limiting the therapeutic window. However, dose-limiting sequelae amongst patients receiving cyclosporine for inflammatory bowel disease (IBD) have not been as significant. As a result, the fear of renal toxicity as an adverse effect is less of a concern in IBD patients. The goal of this manuscript is to emphasize the need for future research to explore optimal drug dosing and extended use of cyclosporine therapy in the treatment of IBD—given its pathophysiology, efficacy, and safety profile in patients with IBD.

Keywords: Inflammatory bowel disease (IBD); Crohn's disease; ulcerative colitis (UC); cyclosporine

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Introduction

The management of acute, severe ulcerative colitis (UC) has been an arduous undertaking for clinicians. Until recently, only two therapeutic avenues were available for an acute UC flare—steroids or surgery. Patients refractory to steroid therapy would classically undergo a colectomy. However, cyclosporine has provided an additional rescue or 'salvage therapy'—reducing the incidence of colectomy.

Since the late 1980's, there has been a rapid evolution in the popularity of the drug cyclosporine (1). Cyclosporine has progressed from strictly a transplant drug, to a novel therapeutic agent for the management of inflammatory bowel disease (IBD). Historically, cyclosporine was used for solid organ transplant immunotherapy but the dose-limiting sequelae of nephrotoxicity would often occur. These sequelae have not been as significant in IBD patients. One hypothesis to explain this difference is that given IBD's bimodal incidence, half of all IBD patients present at a young age, with less co-morbidities, and normal kidney function and therefore are more capable of withstanding cyclosporine-induced renal toxicity (1). Herein, we attempt to encourage more studies to expand the role of cyclosporine therapy to other avenues in IBD by describing its pathophysiology, efficacy, and safety profile in patients with IBD.

Discussion and conclusion

Cyclosporine, an 11 amino acid lipophilic peptide, begins its mechanism of action by binding to the cytoplasmic protein—cyclophilin. This leads to selective inhibition

of calcineurin, a regulatory factor involved with the transcription of multiple cytokine genes. This causes down-regulation of interleukin (IL)-2, IL-3, IL-4, tumor necrosis factor (TNF)-alpha, granulocyte-macrophage colony-stimulating factor, and interferon-gamma. It has been theorized to also block the activation of c-Jun N-terminal kinase (JNK) and p38 signaling pathways, making it highly specific (2). Ultimately, proliferation of T lymphocytes becomes markedly reduced, making cyclosporine a potent immunosuppressive agent. IL-2 is a known mediator of inflammation in IBD, further validating cyclosporine's particular efficacy in this patient population.

Since the introduction of steroid therapy several decades ago, no new drugs were approved for severe refractory UC. The options for patients refractory to corticosteroid therapy were limited and included invasive procedures. This prompted the need for a 'last resort' or rescue drug—one that could prevent colectomy, especially in patients whose co-morbidities or personal preference precluded them from surgical intervention. Hence, this created an era in which many trials began to occur. Early open-label experience proved to be so successful to the degree that it prompted many smaller, randomized, controlled, drug trials (3). Of those, Lichtiger *et al.* conducted a randomized, double blind, control trial in which cyclosporine or placebo was administered to 20 patients. The population targeted were all patients with severe UC refractory to a minimum of seven days of steroid therapy. The results were statistically significant. 82%, or nine out of the eleven patients responded rapidly to the Intravenous (IV) cyclosporine (4). In order to explore the efficacy of cyclosporine as a long-term solution, Cohen *et al.* tested this drug over a 5-year period at the University of Chicago. Out of the 42 patients, 86% responded to cyclosporine therapy, and 62% of patients even avoided colectomy (5). In a slightly larger study, 83% of the 142 patients not only responded to cyclosporine but also avoided colectomy during hospitalization. However, after seven years 88% of them did in fact need a colectomy (6).

In a study by Present *et al.* the authors attempted to broaden the indications for cyclosporine therapy to the treatment of fistula in CD, with positive results. Fistula closure occurred in 44% of patients. Additionally, moderate improvement was noticed in another 44% and as many as 64% of patients maintained their improvement in the chronic phase (7).

Due to its narrow therapeutic window cyclosporine therapy must be closely monitored. Although nephrotoxicity can occur, permanent renal damage is less likely in patients with IBD as opposed to transplant patients, taking this medication.

In an attempt to better understand the safety profile of cyclosporine in the IBD population, Sternthal *et al.* retroactively reviewed the charts of 111 patients given IV cyclosporine followed by an oral dosage. The results highlighted the adverse effects including; seizures, paresthesias, hypertension, hyperkalemia, and gingival swelling (8).

Aside from the various adverse effects associated with cyclosporine, its innate ability to alter drug kinetics and be altered by other drugs makes it more difficult to administer. As a potent metabolite of the cytochrome P450 3A pathway, drugs such as phenytoin, carbamazepine, and octreotide reduce blood cyclosporine levels, while erythromycin and ketoconazole increase blood cyclosporine levels (9). Side effects of cyclosporine appear dose dependent. Interestingly, a double blind, randomized, controlled trial by Van Assche *et al.* showed that a low dosage regimen of 2 mg/kg/day is equally effective to the established regimen of 4 mg/kg/day (10), providing data to support the possibility of treating patients at lower doses yielding similar therapeutic results while reducing the side effect profile. Future studies would benefit on uncovering alternative dosing regimens for various indications of usage, leading to decreasing cyclosporine's adverse effects and drug toxicity.

In conclusion, while cyclosporine therapy was once only used in solid-organ transplant patients, clinicians are now becoming aware of its safety profile in patients with IBD. In particular, its role in preventing colectomy in patients with acute severe UC, has allowed cyclosporine to emerge as a novel therapeutic agent. Future studies are needed to help extend cyclosporine usage to other areas of IBD, as well as to establish optimal drug dosing for its various indications.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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