Journal of Crohn's and Colitis (2014) **8**, 903–918

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REVIEW ARTICLE

Nanotechnology in the treatment of inflammatory bowel diseases

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Received 27 November 2013; received in revised form 26 February 2014; accepted 26 February 2014

KEYWORDS
Inflammatory bowel diseases;
Nanoparticles;
Microparticles;
Therapy;
Drug delivery;
Compliance

Abstract

Background and aims: Treatment of inflammatory bowel diseases (IBD) is only aimed to block or inhibit the pathogenetic steps of the inflammatory cascade. Side effects of systemic therapies, poor targeting of orally administered topical drug and low adherence to prescription represent frequent therapeutic challenges. Recent observations suggest that nanotechnology could provide amazing advantage in this field since particles having dimension in the nanometer scale (nanoparticles) can modify pharmacokinetic step of biologic and conventional therapeutic agents with a better delivery of drugs within the intestinal inflammatory cells. The aim of this review was to provide the clinician with an insight into the potential role of nanotechnology in the treatment of IBD.
Methods: A systematic search (PubMed) for experimental studies on the treatment of intestinal inflammation using nanotechnology for the delivery of drugs.
Results and conclusions: The size of the pharmaceutical formulation is inversely related to specificity for inflammation. Nanoparticles can penetrate epithelial and inflammatory cells resulting in much higher, effective and long-acting concentrations than can be obtained using conventional delivery systems. From a practical point of view, this should lead to improvements in both efficacy and adherence to treatment, providing patients with the prospect of stable and

Abbreviations: IBD, inflammatory bowel diseases; 5-ASA, 5-aminosalicylic acid, mesalazine; UC, ulcerative colitis; CD, Crohn's disease; nm, nanometer; NPs, nanoparticles; μm, micrometer; PEG, polyethylene glycol; DSS, dextran sodium sulfate; TNBS, trinitrobenzene sulfonic acid; LPS, lipopolysaccharide; TNFα, tumor necrosis factor α; IL, interleukin; IFN, interferon; MPO, myeloperoxidase; PLGA, poly(lactic-co-glycolic acid); PLA, poly-lactic acid (polylactide); PVA, poly-vinyl alcohol; PCL, poly-caprolactone; NiMOS, NPs in microsphere oral system; siRNA, short interfering RNA; Map4k4, mitogen-activated protein kinase kinase kinase kinase 4; NF-kB, nuclear factor-kB; ROS, reactive oxygen species; GALT, gut associated lymphoid tissue; KPV, Lys-Pro-Val.

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http://dx.doi.org/10.1016/j.crohns.2014.02.024

prolonged remissions with reduced drug loadings. Reduced systemic side effects could also be expected.

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1. Introduction

A definitive cure for inflammatory bowel diseases (IBD) is still lacking and patients continue to be treated with agents aimed at blocking or inhibiting the immune-inflammatory cascade at various levels. In active ulcerative colitis (UC), mesalazine (5-aminosalicylic acid: 5-ASA) is effective in mild to moderate diseases, while steroids, cyclosporine and biologics becoming necessary in severe presentations.[1] For active Crohn's disease (CD), for which cyclosporine is ineffective and 5-ASA has a limited role, it is still debated whether biologics should be used as first line treatment or only for patients who prove refractory to steroids.[2] With regard to the maintenance of remission, biologic drugs, immunosuppressants and 5-ASA can each in their own way prove effective.[1,2] Biologics have been studied in recent years and some concern exists about the real burden of long-term adverse effects including opportunistic infections and malignancies.[3] Moreover, it is not clear when they can be stopped or which is the best exit strategy.[4] Immunosuppressants are effective and strongly indicated for steroid-dependent patients, but doubt remains regarding their safety for applications longer than 5 years.[1,2] 5-ASA, on the other hand, has been in use from more than 70 years, with proven efficacy and only modest long-term side effects, with limitations however, regarding its topic action and complex therapeutic protocol.[5–10] In fact, in UC and in prevention of recurrence in CD, the major problem is to maintain an adequate concentration of the drug in the inflamed mucosa in order to obtain a reduction of recurrences and reduce the need of steroids and hospitalization.[11–15] These results, sometimes may require multiple daily administrations of large numbers of pills — together with enemas, suppositories or foam, a practice that has the effect of reducing a full adherence to treatment in about half of patients with a fivefold increased risk of recurrence.[16,17] Thus, the ideal drug to treat IBD should focus specifically on inflamed tissues with the fewest systemic involvement, simplifying therapeutic protocols and assuring maximum adherence to treatment. To date, only the recent formulation MMX 1200 mg, aside the possibility of a once-a-day administration, allows a reduction in the number of pills and a wider colonic targeting.[18,19]

In the last years, new technologies provided opportunities for advances in this field. In particular, nano- and micro-particles have turned out to be promising tools for the targeted delivery of drugs to specific anatomical sites.[20–22] Nanomedicine, which refers to the application of nanotechnology to medicine, is an emerging area, which focuses in imaging, early diagnosis, pathological tissue analysis and especially in drug delivery. In particular, it can allow not only the development of new therapeutic agents, but also the improvement in efficacy of existing drugs.[23–28]

The aim of this paper is twofold: to provide an overview of the literature aimed to synthesize the main physico-chemical characteristics of nano- and micro-particles and to explore the potential role of nanotechnology in the treatment of intestinal inflammation.

2. Methods

A literature search was conducted using PubMed with the search terms "inflammatory bowel diseases", "intestinal inflammation", "nanotechnology", "nanoparticles", "microparticles", "drug targeting", and "therapy". All the