S12-4 Development of drug delivery system with microspheres targeting intestinal immune cells for inflammatory bowel disease

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Many patients with ulcerative colitis (UC) have been successfully treated with steroidal drugs as well as immunosuppressants. Among these, glucocorticosteroid is known to be very effective for the treatment of UC. However, because of a variety of systemic side effects, the administration of glucocorticosteroids by the oral and intravenous routes is often restricted to patients with severe or acute UC. Therefore, to circumvent such side effects, topical rectal administration of glucocorticosteroid and, its alternative regimens have been used for IBD patients. However, some patients are still resistant to these treatments. It is well-known that macrophages and dendritic cells play important roles in the regulation of immunoresponses in the gastro-intestinal tract as antigen-presenting cells. Microfold (M) cells, which exist in the follicle-associated epithelium overlying the lymphoid follicles of Peyer's patches, take up various macromolecules, bacteria, viruses, and protozoa and transport them to the follicular areas for uptake by macrophages. Therefore, the regulation of macrophages and M cells is thought to be very important as therapeutic strategies for patients with IBD. Considerable attention has been paid to the use of polymer microspheres for the sustained release of various drugs and the targeting of therapeutic or diagnostic agents to their site of action. The use of biodegradable microspheres is particularly preferable from the perspective of avoiding the accumulation of foreign materials in the body. It was reported that biodegradable poly-D,L-lactic acid (PDLLA) microspheres can be efficiently taken up by macrophages and M cells. Therefore, the direct uptake of anti-inflammatory agents by macrophages, achieved with the use of microspheres, appears to have a superior immunosuppressive effect and to be more useful for the treatment of patients with IBD.

We have successfully incorporated dexamethasone (Dx) into microspheres using a solvent double emulsion method, and developed a new therapy using PDLLA microspheres containing Dx (Dx-microspheres) which directly targets macrophages and M cells. We have already demonstrated that administration of Dx-microspheres attenuate both murine and rat colitis model. Now, we start a open-label clinical trial with Dx-microspheres for patients with active UC.