neutrophils, macrophages and dendritic cells contribute to IBD. T lymphocytes, for instance, infiltrate the mucosa of the gastrointestinal tract through coordinated interactions between adhesion molecules on the surface of the T lymphocyte and their cognate ligand on the endothelium. For example, α4β7 integrin which expressed on the surface of some T and B lymphocytes directs the migration of these cells by binding to one of its ligands, mucosal addressin cell adhesion molecule 1 (MAdCAM-1) on endothelial cells of the GI tract. Chemokine receptors and ligands, *e.g.*, the receptor CCR9 and its ligand CCL25 also play a role in the migration of inflammatory cells, *e.g.*, effector memory T helper cells into the intestine epithelium in IBD.

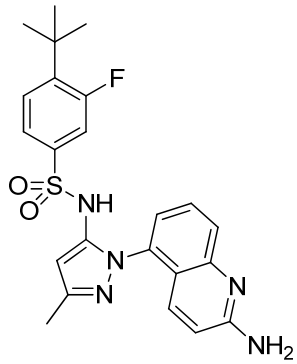
[0006] Current therapies for treating IBD include surgery or use of anti-tumor necrosis factor (anti-TNFα) antibodies, *e.g.*, infliximab and adalimumab, aminosalicylates, systemic corticosteroids, immunosuppressants, *e.g.*, thiopurines and methotrexate, and combinations thereof. Unfortunately, some patients with IBD do not respond to or cannot tolerate such drug treatments.

[0007] In view of the above, it is apparent that effective treatment regimens for IBD that are able to block multiple pathways and/or multiple cell types associated with lymphocyte infiltration can be useful for treating the disease. The present invention provides such therapies along with pharmaceutical compositions and related methods of treatment.

BRIEF SUMMARY

[0008] The present disclosure provides a method of treating or reducing the development of inflammatory bowel disease in a mammal, said method comprising administering a suitable amount of a CCR9 chemokine receptor inhibitor with an anti-α4β7 integrin blocking antibody. In some embodiments, the inflammatory bowel disease is Crohn's disease (CD) or ulcerative colitis (UC).

[0008a] In a first aspect, the present disclosure provides a use of a CCR9 chemokine receptor inhibitor and an anti-α4β7 integrin blocking antibody in the manufacture of a medicament for treating or reducing the development of inflammatory bowel disease in a

mammal wherein the CCR9 chemokine receptor inhibitor is  or a pharmaceutically acceptable salt thereof.

[0008b] In a second aspect, the present disclosure provides a composition for use in treating or reducing the development of inflammatory bowel disease in a mammal, said composition comprising a therapeutically effective amount of a CCR9 chemokine receptor inhibitor, a therapeutically effective amount of an anti-α4β7 integrin blocking antibody, and a pharmaceutically acceptable carrier or excipient, wherein the CCR9 chemokine receptor inhibitor is selected from the compound in claim 1.

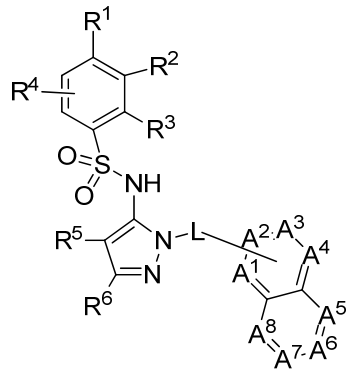
[0008b] In a third aspect, the present disclosure provides a use of a CCR9 chemokine receptor inhibitor and an anti-α4β7 integrin blocking antibody in the manufacture of a medicament for treating or reducing the development of inflammatory bowel disease in a mammal wherein the CCR9 chemokine receptor inhibitor is vercirnon (Traficet-EN).

[0009] In some embodiments, the CCR9 chemokine receptor inhibitor is a small molecule receptor inhibitor having a molecular weight of less than 1500. The CCR9 small molecule receptor inhibitor can have a molecular weight of about 1495, 1450, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, 500, or less.

In other embodiments, the CCR9 chemokine receptor inhibitor is a small molecule receptor inhibitor having a molecular weight of less than 750. The CCR9 small molecule receptor

inhibitor can have a molecular weight of about 745, 700, 650, 600, 550, 500, 450, 400, 350, 300 or less.

[0010] In some embodiments, the CCR9 small molecule inhibitors provided herein may be represented by formula (I) or salts thereof:



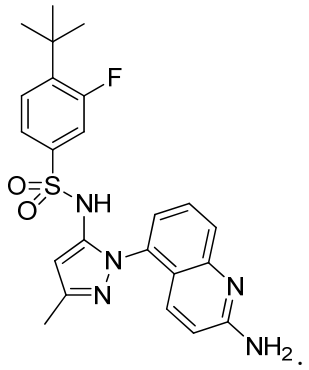
(I)

where R^1, R^2, R^3, R^4, R^5, R^6, L, A^1, A^2, A^3, A^4, A^5, A^6, A^7, and A^8 are as defined below.

[0011] In some embodiments, the anti-α4β7 integrin blocking antibody is vedolizumab (ENYVIO®), or a biosimilar, biobetter, or bioequivalent thereof. In other embodiments, the anti-α4β7 integrin blocking antibody is vedolizumab (ENYVIO®).

[0012] In some embodiments, the CCR9 chemokine receptor inhibitor and the anti-α4β7 integrin blocking antibody are administered in a combination formulation. In other embodiments, the CCR9 chemokine receptor inhibitor and the anti-α4β7 integrin blocking antibody are administered sequentially. In yet other embodiments, the CCR9 chemokine receptor inhibitor is administered prior to the anti-α4β7 integrin blocking antibody. In another embodiment, the CCR9 chemokine receptor inhibitor is administered after administration of the anti-α4β7 integrin blocking antibody.

[0013] In some embodiments, the CCR9 chemokine receptor inhibitor is a compound having the formula:



[0014] The present disclosure also provides a composition for treating or reducing the development of inflammatory bowel disease in a mammal, said composition comprising a therapeutically effective amount of a CCR9 chemokine receptor inhibitor, a therapeutically effective amount of an anti-α4β7 integrin blocking antibody, and a pharmaceutically acceptable carrier or excipient.

[0015] In some embodiments, the inflammatory bowel disease is Crohn's disease (CD) or ulcerative colitis (UC).

[0016] In some embodiments, the CCR9 chemokine receptor inhibitor is a small molecule receptor inhibitor having a molecular weight of less than 1500. In other embodiments, the CCR9 chemokine receptor inhibitor is a small molecule receptor inhibitor having a molecular weight of less than 750. The CCR9 chemokine receptor inhibitor compound may be represented by formula (I) or salt thereof, as described herein.

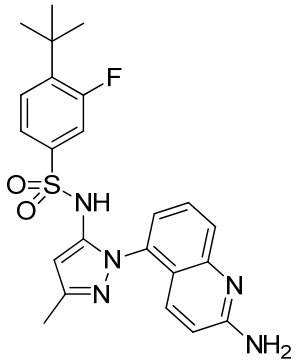
[0017] In some embodiments, the anti-α4β7 integrin blocking antibody is vedolizumab (ENYVIO®), or a biosimilar, biobetter, or bioequivalent thereof. In other embodiments, the anti-α4β7 integrin blocking antibody is vedolizumab (ENYVIO®).

[0018] The present disclosure also provides a kit for treating or reducing the development of inflammatory bowel disease in a mammal, said kit comprising a

therapeutically effective amount of a CCR9 chemokine receptor inhibitor, a therapeutically effective amount of an anti-α4β7 integrin blocking antibody, and instructions for effective administration.

[0019] In some embodiments, the CCR9 chemokine receptor inhibitor and the anti-α4β7 integrin blocking antibody are formulated for sequential administration. In other

WHAT IS CLAIMED IS:

1. Use of a CCR9 chemokine receptor inhibitor and an anti-α4β7 integrin blocking antibody in the manufacture of a medicament for treating or reducing the development of inflammatory bowel disease in a mammal wherein the CCR9 chemokine receptor inhibitor is  or a pharmaceutically acceptable salt thereof.

2. The use of claim 1, wherein the inflammatory bowel disease is Crohn's disease (CD) or ulcerative colitis (UC).

3. The use of claim 1, wherein the anti-α4β7 integrin blocking antibody is vedolizumab (ENYVIO®), or a biosimilar, or bioequivalent thereof.

4. The use of claim 1, wherein the anti-α4β7 integrin blocking antibody is vedolizumab (ENYVIO®).

5. The use of claim 1, wherein the CCR9 chemokine receptor inhibitor and the anti-α4β7 integrin blocking antibody are to be administered in a combination formulation.

6. The use of claim 1, wherein the CCR9 chemokine receptor inhibitor and the anti-α4β7 integrin blocking antibody are to be administered sequentially.

7. The use of claim 6, wherein the CCR9 chemokine receptor inhibitor is to be administered prior to the anti-α4β7 integrin blocking antibody.

8. The use of claim 6, wherein the CCR9 chemokine receptor inhibitor is to be administered after administration of the anti-α4β7 integrin blocking antibody.

9. A composition for use in treating or reducing the development of inflammatory bowel disease in a mammal, said composition comprising a therapeutically effective amount of a CCR9 chemokine receptor inhibitor, a therapeutically effective amount of an anti-α4β7 integrin blocking antibody, and a pharmaceutically acceptable carrier or excipient, wherein the CCR9 chemokine receptor inhibitor is selected from the compounds in claim 1.

10. The composition for use of claim 9, wherein the anti-α4β7 integrin blocking antibody is vedolizumab (ENYVIO®), or a biosimilar, or bioequivalent thereof.

11. The composition for puse of claim 9, wherein the anti-α4β7 integrin blocking antibody is vedolizumab (ENYVIO®).

12. Use of a CCR9 chemokine receptor inhibitor and an anti-α4β7 integrin blocking antibody in the manufacture of a medicament for treating or reducing the development of inflammatory bowel disease in a mammal wherein the CCR9 chemokine receptor inhibitor is vercirnon (Traficet-EN).

13. The use of claim 12, wherein the inflammatory bowel disease is Crohn's disease (CD) or ulcerative colitis (UC).

14. The use of claim 12, wherein the anti-α4β7 integrin blocking antibody is vedolizumab (ENYVIO®), or a biosimilar, or bioequivalent thereof.

15. The use of claim 12, wherein the anti-α4β7 integrin blocking antibody is vedolizumab (ENYVIO®).

16. The use of claim 12, wherein the CCR9 chemokine receptor inhibitor and the anti-α4β7 integrin blocking antibody are to be administered in a combination formulation.

17. The use of claim 12, wherein the CCR9 chemokine receptor inhibitor and the anti-α4β7 integrin blocking antibody are to be administered sequentially.

18. The use of claim 17, wherein the CCR9 chemokine receptor inhibitor is to be administered prior to the anti-α4β7 integrin blocking antibody.

19. The use of claim 17, wherein the CCR9 chemokine receptor inhibitor is to be administered after administration of the anti-α4β7 integrin blocking antibody.