

Dosage Regimen for MAdCAM Antagonists

FIELD OF THE INVENTION

The present invention relates to dosage regimens of MAdCAM antagonist antibodies.

BACKGROUND OF THE INVENTION

5 Mucosal addressin cell adhesion molecule (MAdCAM; also known as addressin) is a member of the immunoglobulin superfamily of cell adhesion receptors. The selectivity of lymphocyte homing to specialized lymphoid tissue and mucosal sites of the gastrointestinal tract is determined by the endothelial expression of MAdCAM. MAdCAM is uniquely expressed on the cell surface of high endothelial venules of organized intestinal lymphoid tissue, such as
10 Peyer's patches and mesenteric lymph nodes, but also in other lymphoid organs, such as pancreas, gall bladder and splenic venules and marginal sinus of the splenic white pulp.

While MAdCAM plays a physiological role in gut immune surveillance, it appears to facilitate excessive lymphocyte extravasation in inflammatory bowel disease under conditions of chronic gastrointestinal tract inflammation. $\text{TNF}\alpha$ and other pro-inflammatory cytokines increase
15 endothelial MAdCAM expression and, in biopsy specimens taken from patients with Crohn's disease and ulcerative colitis (UC), there is an approximate 2-3 fold focal increase in MAdCAM expression at sites of inflammation. Similar patterns of elevated expression have been observed in experimental models of colitis. In other pre-clinical models for inflammatory conditions, such as insulin-dependent diabetes graft versus host disease, chronic liver disease, inflammatory
20 encephalopathy, and gastritis, there is also reawakening of fetal MAdCAM expression and participation of activated $\alpha_4\beta_7^+$ lymphocytes in disease pathogenesis. In these inflammatory models as well as hapten-mediated (e.g., TNBS, DSS, etc.) or adoptive transfer ($\text{CD4}^+\text{CD45Rb}^{\text{high}}$) mouse colitic models, the rat anti-mouse MAdCAM monoclonal antibody (mAb), MECA-367, which blocks the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM, reduces the
25 lymphocyte recruitment, tissue extravasation, inflammation and disease severity.

WO2005067620 discloses MAdCAM antagonist antibodies and uses thereof.

WO2006096490 discloses MAdCAM antagonist antibodies and compositions thereof.

SUMMARY

The disclosure provides embodiments as set forth below, each of which is indicated by E
30 thereto:

E1. A method for treating a patient susceptible to or diagnosed with a condition associated with an increase in MAdCAM expression comprising administering to the patient an initial dose of between about 5 mg and about 150 mg of MAdCAM antagonist antibody.

(b) obtaining SNP rs11171739 sequence from said genomic DNA; wherein the presence of risk allele (C) at rs11171739 predicts that said patient would benefit from treatment with a MAdCAM antagonist antibody.

E106. A method of treating a patient susceptible to or diagnosed with a condition associated with an increase in MAdCAM expression comprising administering to the patient an initial dose of between about 5 mg and about 150 mg of MAdCAM antagonist antibody, wherein said patient comprises risk allele (C) at rs11171739.

E107. A method of treating a patient susceptible to or diagnosed with a condition associated with an increase in MAdCAM expression comprising administering to the patient an initial dose of between about 5 mg and about 150 mg of MAdCAM antagonist antibody, wherein said is identified by any one of the method of embodiments E86-E105.

E108. A kit comprising:

(a) a detection agent for detecting the presence of a biomarker, or for measuring the level of a biomarker in a biological sample, wherein said biomarker is: (i) any one of the biomarkers listed in Tables 12, 13, 15; (ii) circulating $\alpha 4\beta 7+$ cells; (iii) rs11171739 risk allele; or (iv) any combination of the foregoing; and

(b) instructions to use said detection agent.

In one aspect, there is provided use of a MAdCAM antagonist antibody in the manufacture of a medicament for the treatment of a patient susceptible to or diagnosed with ulcerative colitis, wherein the medicament is to be administered to the patient an initial dose of between 5 mg and 150 mg.

In another aspect, there is provided a MAdCAM antagonist antibody for use as described herein.

In another aspect, there is provided a pharmaceutical composition comprising the MAdCAM antibody described herein.

In another aspect, there is provided use of a MAdCAM antagonist antibody described herein in the preparation of a medicament for the treatment of ulcerative colitis

In another aspect, there is provided a method for assessing the presence or absence of a beneficial response in an ulcerative colitis (UC) patient after administering a MAdCAM antagonist antibody at an initial dose of between about 20 mg and about 75 mg of MAdCAM antagonist antibody, comprising:

(a) measuring the level of a biomarker in a biological sample from said patient, wherein said biomarker is: (i) any one or combination of the biomarkers selected from the group consisting of: Fecal calprotectin, sMAdCAM, hsCRP, AR, CHI3L1, CXCL1, CXCL11, CXCL13, CXCL9, Dkk-1, EGF, EN-RAGE, EPO, FGF-21, GH, IL-17C, IL-6, IL-7, IL-8, MIP-1 alpha, MMP-1, MMP-10, MMP-12, MMP-3, NT-pro-BNP, OSM, PTPN22, PTX3, REG-4, RETN, TNFRSF4, TRANCE, and VEGF-A; (ii) CCR9; (iii) circulating $\alpha 4\beta 7+$ cells; or (iv) any combination of the foregoing; and (b) comparing said level with a sample obtained from a healthy individual; wherein a decrease in the level of biomarker, as compared to the control, is predictive of a beneficial response in said patient

In another aspect, there is provided a method for identifying an ulcerative colitis (UC) patient who would benefit from treatment with a MAdCAM antagonist antibody to be administered at an initial dose of between about 20 mg and about 75 mg, comprising:

(a) measuring the level of a biomarker in a biological sample from said patient, wherein said biomarker is: (i) any one or combination of the biomarkers selected from the group consisting of: Fecal calprotectin, sMAdCAM, hsCRP, AR, CHI3L1, CXCL1, CXCL11, CXCL13, CXCL9, Dkk-1, EGF, EN-RAGE, EPO, FGF-21, GH, IL-17C, IL-6, IL-7, IL-8, MIP-1 alpha, MMP-1, MMP-10, MMP-12, MMP-3, NT-pro-BNP, OSM, PTPN22, PTX3, REG-4, RETN, TNFRSF4, TRANCE, and VEGF-A; (ii) CCR9; (iii) circulating $\alpha 4\beta 7$ + cells; or (iv) any combination of the foregoing;

(b) comparing said level with a sample obtained from a healthy individual; wherein a decrease in the level of biomarker, as compared to the control, predicts that said patient would benefit from treatment with a MAdCAM antagonist antibody; and

(c) selecting said patient for treatment with a MAdCAM antagonist antibody.

In another aspect, there is provided a method for identifying an ulcerative colitis (UC) patient who would benefit from treatment with a MAdCAM antagonist antibody to be administered at an initial dose of between about 20 mg and about 75 mg, comprising:

(a) assaying a biological sample that comprises genomic DNA from said patient; and

(b) obtaining SNP rs11171739 sequence from said genomic DNA;

wherein the presence of risk allele (C) at rs11171739 predicts that said patient would benefit from treatment with a MAdCAM antagonist antibody.

In another aspect, there is provided a kit comprising:

(a) a detection agent for detecting the presence of a biomarker, or for measuring the level of a biomarker in a biological sample, wherein said biomarker is: (i) any one or combination of the biomarkers selected from the group consisting of: hsCRP, AR, CHI3L1, CXCL1, CXCL11, CXCL13, CXCL9, Dkk-1, EGF, EN-RAGE, EPO, FGF-21, GH, IL-17C, IL-6, IL-7, IL-8, MIP-1 alpha, MMP-1, MMP-10, MMP-12, MMP-3, NT-pro-BNP, OSM, PTPN22, PTX3, REG-4, RETN, TNFRSF4, TRANCE, and VEGF-A; (ii) CCR9; (iii) circulating $\alpha 4\beta 7$ + cells; (iv) rs11171739 risk allele; or (v) any combination of the foregoing; and (b) instructions to use said detection agent.

The disclosure provides as a further embodiment that may be used independent or in combination with any of the previous embodiments, a method for the treatment of a patient susceptible to or diagnosed with a condition associated with an increase in MAdCAM expression comprising administering to the patient an initial dose of between about 5 mg and about 150 mg of MAdCAM antagonist antibody following one or more doses of tofacitinib.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Clinical remission rate based on total mayo score at week 12 (treatment failure approach).

Figure 2: Clinical remission rate based on naïve and experience population at week 12 (treatment failure approach).

Figure 3: Clinical response and mucosal healing rates at week 12 (treatment failure approach).

Figure 4: Analysis results of placebo corrected clinical remission rate, clinical response rate and mucosal healing rate based on total mayo score at week 12 (cmh method, central read, mitt population).

Figure 5: Analysis results of placebo corrected clinical remission rate, clinical response rate and mucosal healing rate based on total mayo score at week 12 (cmh method, local read, mitt population).

CLAIMS

1. Use of a MAdCAM antagonist antibody in the manufacture of a medicament for the treatment of a patient susceptible to or diagnosed with ulcerative colitis, wherein the medicament is to be administered to the patient an initial dose of between about 20 mg and about 75 mg.
- 5 2. The use of claim 1, wherein a subsequent dose is to be administered in an amount that is about the same or less than the initial dose, said subsequent dose being provided between about 1 week and about 12 weeks after the initial dose.
3. The use of claim 1 or 2, wherein either or both of the initial dose or subsequent dose of the MAdCAM antagonist antibody is dosed at a range whose lower limit is selected from the group
10 consisting of 5 mg, 6 mg, 7 mg, 7.5 mg, 8 mg, 9 mg, 10 mg, 12 mg, 15 mg, 20 mg, 22.5 mg, 25 mg, 30 mg, 35 mg, 45 mg, 50 mg, 55 mg, 65 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, and whose upper limit is selected from the group consisting of 22.5 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, less than 75 mg, 75 mg, 80 mg, 85 mg, 90 mg, t 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg,
15 less than 150 mg, and 150 mg.
4. The use of claim 1 or 2, wherein an initial dose and one or more subsequent doses of between 22.5 mg and 75 mg of MAdCAM antagonist antibody is to be administered to the patient.
5. The use of any one of claims 2-4, wherein the subsequent dose is to be administered about 4 weeks after the initial dose.
- 20 6. The use of any one of claims 2-4, wherein the subsequent dose is to be administered about 8 weeks after the initial dose.
7. The use of any one of claims 1-6, wherein the observed clinical remission rate at about 12 weeks after initial dose, as determined using the MAYO score, is at least about 3%.
8. The use of any one of claims 1-7, wherein the clinical response rate at about 12 week after
25 the initial dose is at least about 28%.
9. The use of any one of claims 1-8, wherein mucosal healing rate at about 12 week after the initial dose is at least about 10%.
10. The use of any one of claims 1-9, wherein the patient is not taking a TNF antagonist or TNF inhibitor.
- 30 11. The use of any one of claims 1-10, wherein an initial dose of about 50 mg of MAdCAM antagonist antibody, followed by one or more subsequent doses of the MAdCAM antagonist antibody in an amount that is about the same as the initial dose is to be administered to the patient, and wherein the one or more subsequent doses are doses about every 4 weeks.
12. The use of any one of claims 1-11, wherein an initial dose of about 100 mg of MAdCAM
35 antagonist antibody, followed by one or more subsequent doses of the MAdCAM antagonist

antibody in an amount that is about the same as the initial dose is to be administered to the patient, and wherein the one or more subsequent doses are doses about every 8 weeks.

13. The use of any one of claims 1-12, wherein the MAdCAM antagonist antibody comprises a light chain whose CDRs are according to the CDRs of SEQ ID NO:3, and a heavy chain whose CDRs are according to the CDRs of SEQ ID NO:4.

14. The use as claimed in any one of claims 1-13, further comprising

(a) measuring the level of a biomarker in a biological sample from said patient, wherein said biomarker is: (i) any one or combination of the biomarkers selected from the group consisting of: Fecal calprotectin, sMAdCAM, hsCRP, AR, CHI3L1, CXCL1, CXCL11, CXCL13, CXCL9, Dkk-1, EGF, EN-RAGE, EPO, FGF-21, GH, IL-17C, IL-6, IL-7, IL-8, MIP-1 alpha, MMP-1, MMP-10, MMP-12, MMP-3, NT-pro-BNP, OSM, PTPN22, PTX3, REG-4, RETN, TNFRSF4, TRANCE, and VEGF-A; (ii) CCR9; (iii) circulating $\alpha 4\beta 7^+$ cells; or (iv) any combination of the foregoing; and

(b) comparing said level with a sample obtained from a healthy individual;

such that a decrease in the level of the biomarker, as compared to the control, is predictive of a beneficial therapeutic response in the condition.

15. A MAdCAM antagonist antibody for use in accordance with any one of claims 1-14.

16. A pharmaceutical composition comprising the MAdCAM antibody of claim 15.

17. Use of a MAdCAM antagonist antibody of claim 15 in the preparation of a medicament for the treatment of ulcerative colitis.

18. A method for assessing the presence or absence of a beneficial response in an ulcerative colitis (UC) patient after administering a MAdCAM antagonist antibody at an initial dose of between about 20 mg and about 75 mg of MAdCAM antagonist antibody, comprising:

(a) measuring the level of a biomarker in a biological sample from said patient, wherein said biomarker is: (i) any one or combination of the biomarkers selected from the group consisting of: Fecal calprotectin, sMAdCAM, hsCRP, AR, CHI3L1, CXCL1, CXCL11, CXCL13, CXCL9, Dkk-1, EGF, EN-RAGE, EPO, FGF-21, GH, IL-17C, IL-6, IL-7, IL-8, MIP-1 alpha, MMP-1, MMP-10, MMP-12, MMP-3, NT-pro-BNP, OSM, PTPN22, PTX3, REG-4, RETN, TNFRSF4, TRANCE, and VEGF-A; (ii) CCR9; (iii) circulating $\alpha 4\beta 7^+$ cells; or (iv) any combination of the foregoing; and

(b) comparing said level with a sample obtained from a healthy individual;

wherein a decrease in the level of biomarker, as compared to the control, is predictive of a beneficial response in said patient.

19. A method for identifying an ulcerative colitis (UC) patient who would benefit from treatment with a MAdCAM antagonist antibody to be administered at an initial dose of between about 20 mg and about 75 mg, comprising:

(a) measuring the level of a biomarker in a biological sample from said patient, wherein said biomarker is: (i) any one or combination of the biomarkers selected from the group consisting of: Fecal calprotectin, sMAdCAM, hsCRP, AR, CHI3L1, CXCL1, CXCL11, CXCL13, CXCL9, Dkk-1, EGF, EN-RAGE, EPO, FGF-21, GH, IL-17C, IL-6, IL-7, IL-8, MIP-1 alpha, MMP-1, MMP-10, MMP-12, MMP-3, NT-pro-BNP, OSM, PTPN22, PTX3, REG-4, RETN, TNFRSF4, TRANCE, and VEGF-A; (ii) CCR9; (iii) circulating $\alpha 4\beta 7^+$ cells; or (iv) any combination of the foregoing;

(b) comparing said level with a sample obtained from a healthy individual; wherein a decrease in the level of biomarker, as compared to the control, predicts that said patient would benefit from treatment with a MAdCAM antagonist antibody; and

(c) selecting said patient for treatment with a MAdCAM antagonist antibody.

20. The method of claim 18 or 19, wherein said biomarker is: (i) fecal Calprotectin, sMAdCAM, or hsCRP; (ii) CCR9; (iii) circulating $\alpha 4\beta 7^+$ cells; or (iv) any combination of the foregoing.

21. The method of claim 18 or 20, wherein said biological sample is to be obtained at least about 4 weeks after administering a MAdCAM antagonist antibody, and optionally from about 4 weeks to about 12 weeks after administering a MAdCAM antagonist antibody.

22. The use of any one of claims 1-14 or the method of any one of claims 18-21, wherein said patient further comprises risk allele (C) at rs11171739.

23. A method for identifying an ulcerative colitis (UC) patient who would benefit from treatment with a MAdCAM antagonist antibody to be administered at an initial dose of between about 20 mg and about 75 mg, comprising:

(a) assaying a biological sample that comprises genomic DNA from said patient; and

(b) obtaining SNP rs11171739 sequence from said genomic DNA;

wherein the presence of risk allele (C) at rs11171739 predicts that said patient would benefit from treatment with a MAdCAM antagonist antibody.

24. A kit comprising:

(a) a detection agent for detecting the presence of a biomarker, or for measuring the level of a biomarker in a biological sample, wherein said biomarker is: (i) any one or combination of the biomarkers selected from the group consisting of: hsCRP, AR, CHI3L1, CXCL1, CXCL11, CXCL13, CXCL9, Dkk-1, EGF, EN-RAGE, EPO, FGF-21, GH, IL-17C, IL-6, IL-7, IL-8, MIP-1 alpha, MMP-1, MMP-10, MMP-12, MMP-3, NT-pro-BNP, OSM, PTPN22, PTX3, REG-4, RETN, TNFRSF4, TRANCE, and VEGF-A; (ii) CCR9; (iii) circulating $\alpha 4\beta 7^+$ cells; (iv) rs11171739 risk allele; or (v) any combination of the foregoing; and

(b) instructions to use said detection agent.