

METHODS OF DISEASE ACTIVITY PROFILING FOR PERSONALIZED THERAPY MANAGEMENT

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 61/484,607, filed May 10, 2011, U.S. Provisional Patent Application No. 61/505,026, filed July 6, 2011, U.S. Provisional Application No. 61/553,909, filed October 31, 2011, U.S. Provisional Application No. 61/566,509, filed December 2, 2011, and U.S. Provisional Application No. 61/636,575, filed April 20, 2012, the disclosures of which are hereby incorporated by reference in their entirety for all purposes.

BACKGROUND OF THE INVENTION

[0001a] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

[0002] Inflammatory bowel disease (IBD) which includes Crohn's disease (CD) and ulcerative colitis (UC) is a chronic idiopathic inflammatory disorder affecting the gastrointestinal tract. Disease progression of CD and UC includes repeated episodes of inflammation and ulceration of the intestine, leading to complications requiring hospitalization, surgery and escalation of therapy (Peyrin-Biroulet *et al.*, *Am. J. Gastroenterol.*, 105: 289-297 (2010); Langholz E., *Dan. Med. Bull.*, 46: 400-415 (1999)).

Current treatments such as anti-tumor necrosis factor-alpha (TNF- α) biologics (e.g., infliximab (IFX), etanercept, adalimumab (ADL) and certolizumab pegol), thiopurine drugs (e.g., azathioprine (AZA), 6-mercaptopurin (6-MP)), anti-inflammatory drugs (e.g., mesalazine), and steroids (e.g., corticosteroids) have been shown to reduce disease activity. In some clinical trials of CD, mucosal healing which is described as the absence of intestinal ulcers, was induced in patients on combination therapy of corticosteroids, IFX and ADL. Furthermore, MH was maintained in patients receiving IFX.

[0003] Other studies have shown that mucosal healing can be a hallmark of suppression of bowel inflammation and predict long-term disease remission (Froslie *et al.*, *Gastroenterology*, 133: 412-422 (2007); Baert *et al.*, *Gastroenterology*, (2010)). Long-term mucosal healing has been associated with a decreased risk of colectomy and colorectal cancer in UC patients, a decreased need for corticosteroid treatment in CD patients, and possibly a

decreased need for hospitalization (Dave *et al.*, *Gastroenterology & Hepatology*, 8(1): 29-38 (2012)).

an autoimmune disorder (e.g., rheumatoid arthritis, Crohn's Disease, ulcerative colitis and the like.). In this method, by assaying the subject for the correct or therapeutic dose of anti-TNF α antibody, i.e., the therapeutic concentration level, it is possible to predict whether the individual will be responsive to the therapy.

[0030] In another embodiment, the present invention provides methods for monitoring IBD (e.g., Crohn's disease and ulcerative colitis) in a subject having the IBD disorder, wherein the method comprises assaying the subject for the correct or therapeutic dose of anti-TNF α antibody, i.e., the therapeutic concentration level, over time. In this manner, it is possible to predict whether the individual will be responsive to the therapy over the given time period.

[0030a] According to another aspect, there is provided a method for selecting a therapy regimen to promote mucosal healing in an individual diagnosed with inflammatory bowel disease (IBD), said method comprising:

(a) measuring the levels of an array of mucosal healing markers at time point t_0 to generate a mucosal healing index at t_0 ;

(b) measuring the levels of an array of mucosal healing markers at time point t_i to generate a mucosal healing index at t_i ;

(c) comparing the change in the mucosal healing index from t_0 to t_i ; and

(d) selecting the therapy regimen for the individual to promote mucosal healing.

[0031] Other ~~objects~~, features, and advantages of the present invention will be apparent to one of skill in the art from the following detailed description and figures.

[0031a] Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] **Figure 1** shows a personalized IBD activity profile as described in Example 1.

[0033] **Figure 2A** show various patient infliximab concentrations as a function of treatment time. **Figure 2B** shows patient ranks over a course of treatment with events (infliximab falling below a threshold concentration) noted.

[0034] **Figure 3A** show various patient HACA (ATI) concentrations as a function of treatment time. **Figure 3B** shows patient ranks over a course of treatment with events (HACA detection or appearance) noted.

[0035] **Figure 4A** illustrates an association between the presence of ATI and the level of IFX in patient samples. Samples with no detectable level of ATI had a significantly higher IFX median concentration, compared to sample with detectable ATI. **Figure 4B** illustrates that the presence of ATI correlates with higher CDAI. **Figure 4C** shows that concurrent immunosuppressant therapy (*e.g.*, MTX) is more likely to suppress the presence of ATI.

[0036] **Figure 5A** shows that patients with ATI are more likely to develop a poor response to treatment. **Figure 5B** illustrates that the inflammatory marker CRP is associated with increased levels of ATI.

[0037] **Figure 6** illustrates that the protein levels of an array of one or more inflammatory and tissue repair markers correlate to the formation of antibodies to IFX.

[0038] **Figure 7A** illustrates that an array of inflammatory markers can be used to establish an inflammatory index what correlates with the presence of ATI and/or disease progression.

WHAT IS CLAIMED IS: CLAIMS

1. A non-invasive method for measuring mucosal healing in an individual diagnosed with inflammatory bowel disease (IBD) receiving a therapy regimen, the method comprising:

(a) measuring the levels of an array of mucosal healing markers in a sample
5 from the individual;

(b) comparing the levels of an array of mucosal healing markers in the individual to that of a control to compute the mucosal healing index of the individual, wherein the mucosal healing index comprises a representation of the extent of mucosal healing; and

10 (c) determining whether the individual undergoing mucosal healing should maintain the therapy regimen.

2. A method for monitoring therapeutic efficiency in an individual with inflammatory bowel disease (IBD) receiving therapy, the method comprising:

(a) measuring the levels of an array of mucosal healing markers in a sample
15 from the individual at a plurality of time points over the course of therapy with a therapeutic antibody;

(b) applying a statistical algorithm to the level of the one or more markers determined in step (a) to generate a mucosal healing index;

(c) comparing the individual's mucosal healing index to that of a control; and

20 (d) determining whether the therapy is appropriate for the individual to promote mucosal healing.

3. A method for selecting a therapy regimen for an individual with inflammatory bowel disease (IBD), the method comprising:

(a) measuring the levels of an array of mucosal healing markers in a sample
25 from the individual at a plurality of time points over the course of therapy, the individual receiving a therapeutic antibody;

(b) applying a statistical algorithm to the level of the one or more markers determined in step (a) to generate a mucosal healing index;

(c) comparing the individual's mucosal healing index to that of a control; and

30 (d) selecting an appropriate therapy regimen for the individual, wherein the therapy regimen promotes mucosal healing.

4. A method for reducing or minimizing the risk of surgery in an individual diagnosed with inflammatory bowel disease (IBD) being provided a therapy regimen, said method comprising:

(a) measuring an array of mucosal healing markers at a plurality of time points over the course of therapy with a therapeutic antibody;

(b) generating the individual's mucosal healing index comprising a representation of the presence and/or concentration levels of each of the markers over time;

(c) comparing the individual's mucosal healing index to that of a control;

and

(d) selecting an appropriate therapy regimen to reduce or minimize the risk of surgery.

5. The method of claim 4 wherein the control is a healthy control.

6. A method for selecting a therapy regimen to promote mucosal healing in an individual diagnosed with inflammatory bowel disease (IBD), said method comprising:

(a) measuring the levels of an array of mucosal healing markers at time point t_0 to generate a mucosal healing index at t_0 ;

(b) measuring the levels of an array of mucosal healing markers at time point t_i to generate a mucosal healing index at t_i ;

(c) comparing the change in the mucosal healing index from t_0 to t_i ; and

(d) selecting the therapy regimen for the individual to promote mucosal healing.

47. The method of any one of claims 1 to 3 or 6, wherein the IBD comprises Crohn's disease or ulcerative colitis.

8. The method of claim 6 wherein the mucosal healing index is determined using a statistical algorithm.

9. The method of any one of claims 1 to 3, wherein the therapy is selected from the group consisting of TNF α inhibitor therapy, an immunosuppressive agent, a corticosteroid, a drug that targets a different mechanism, nutrition therapy, and combinations thereof.

10. The method of claim 9, wherein said TNF α inhibitor therapy comprises an anti-TNF α antibody selected from the group consisting of infliximab, etanercept, adalimumab, certolizumab pegol, and combinations thereof.

11. The method of claim 9 or claim 10, wherein said nutrition therapy comprises a special carbohydrate diet.

12. The method of any one of claims 9 to 11, wherein said immunosuppressive agent is a member selected from the group consisting of azathioprine, 6-mercaptopurine, methotrexate, and combinations thereof.

13. The method of any one of claims 9 to 12, wherein said drug that targets a different mechanism is a member selected from the group consisting of an IL-6 receptor inhibiting antibody, an anti-integrin molecule, a JAK-2 inhibitor, a tyrosine kinase inhibitor, and combinations thereof.

~~5. The method of any one of claims 1 to 3, wherein the IBD comprises Crohn's disease.~~

614. The method of any one of claims 1 to ~~513~~, wherein the mucosal healing marker is a member selected from the group consisting of AREG, EREG, HB-EGF, HGF, NRG1, NRG2, NRG3, NRG4, BTC, EGF, IGF, TGF- α , VEGF-A, VEGF-B, VEGF-C, VEGF-D, FGF1, FGF2, FGF7, FGF9, TWEAK and combinations thereof.

~~7. The method of any one of claims 1 to 6, wherein the markers are measured in a sample selected from the group consisting of serum, plasma, whole blood, stool, peripheral blood mononuclear cells (PBMC), polymorphonuclear (PMN) cells, and a tissue biopsy.~~

~~8. The method of any one of claims 1 to 7, wherein the therapy is selected from the group consisting of TNF α inhibitor therapy, an immunosuppressive agent, a corticosteroid, a drug that targets a different mechanism, nutrition therapy, and combinations thereof.~~

~~9. The method of claim 8, wherein the TNF α inhibitor therapy comprises an anti-TNF α antibody.~~

~~10. The method of claim 9, wherein the anti-TNF α antibody is a member selected from the group consisting of REMICADETM (infliximab), ENBRELTM (etanercept), HUMIRATM (adalimumab), CIMZIA[®] (certolizumab pegol), and combinations thereof.~~

5 ~~11. The method of claim 8, wherein the immunosuppressive agent is a member selected from the group consisting of azathioprine, 6-mercaptopurine, methotrexate, and combinations thereof.~~

10 ~~12. The method of claim 8, wherein the drug that targets a different mechanism is a member selected from the group consisting of an IL-6 receptor inhibiting antibody, an anti-integrin molecule, a JAK-2 inhibitor, a tyrosine kinase inhibitor, and combinations thereof.~~

~~13.~~ The method of claim 8, wherein the nutrition therapy comprises a special carbohydrate diet.

~~14.~~ The method of any one of claims 1 to 13, wherein the array of mucosal healing markers further comprises at least one member selected from the group consisting of an anti-TNF α antibody, an anti-drug antibody (ADA), an inflammatory marker, an anti-inflammatory marker, a mucosal healing marker, and combinations thereof.

~~15.~~ The method of claim 14, wherein the anti-TNF α antibody is a member selected from the group consisting of REMICADETM (infliximab), ENBRELTM (etanercept), HUMIRATM (adalimumab), CIMZIA[®] (certolizumab pegol), and combinations thereof.

15. The method of any one of claims 1 to 3, wherein the array of mucosal healing markers further comprises at least one member selected from the group consisting of an anti-TNF α antibody, an anti-drug antibody (ADA), an inflammatory marker, an anti-inflammatory marker, a mucosal healing marker, and combinations thereof.

16. The method of claim 15, wherein said anti-TNF α antibody is a member selected from the group consisting of infliximab, etanercept, adalimumab, certolizumab pegol, and combinations thereof.

~~16~~17. The method of claim ~~14~~15 or claim 16, wherein ~~the said~~ anti-drug antibody (ADA) is a member selected from the group consisting of a human anti-chimeric antibody (HACA), a human anti-humanized antibody (HAHA), a human anti-mouse antibody (HAMA), and combinations thereof.

~~17~~18. The method of ~~claim 14~~any one of claims 15 to 17, wherein ~~the said~~ mucosal healing marker is a member selected from the group consisting of AREG, EREG, HB-EGF, HGF, NRG1, NRG2, NRG3, NRG4, BTC, EGF, IGF, TGF- α , VEGF-A, VEGF-B, VEGF-C, VEGF-D, FGF1, FGF2, FGF7, FGF9, TWEAK and combinations thereof.

~~18~~19. The method of ~~claim 14~~any one of claims 15 to 18, wherein ~~the said~~ inflammatory marker is a member selected from the group consisting of GM-CSF, IFN- γ , IL-1 β , IL-2, IL-6, IL-8, TNF- α , sTNF RII, and combinations thereof.

1920. The method of ~~claim 14~~any one of claims 15 to 19, wherein ~~the said~~ anti-inflammatory marker is a member selected from the group consisting of IL-12p70, IL-10, and combinations thereof.

20.—A method for reducing or minimizing the risk of surgery in an individual diagnosed with inflammatory bowel disease (IBD) being administered a therapy regimen, said method comprising:

(a) measuring an array of mucosal healing markers at a plurality of time points over the course of therapy with a therapeutic antibody;

(b) generating the individual's mucosal healing index comprising a representation of the presence and/or concentration levels of each of the markers over time;

(c) comparing the individual's mucosal healing index to that of a control; and

~~d) selecting an appropriate therapy regimen to reduce or minimize the risk of surgery.~~

~~21. The method of claim 20, wherein the mucosal healing marker is a member selected from the group consisting of AREG, EREG, HB-EGF, HGF, NRG1, NRG2, NRG3, NRG4, BTC, EGF, IGF, TGF- α , VEGF-A, VEGF-B, VEGF-C, VEGF-D, FGF1, FGF2, FGF7, FGF9, TWEAK and combinations thereof.~~

~~22. The method of claim 20 or 21, wherein the control is a healthy control.~~

~~23~~21. The method of ~~any one of claims 20 to 22~~claim 4 or claim 6, wherein the therapeutic antibody or, respectively, the therapy regimen comprises an anti-TNF antibody.

~~24~~22. The method of claim ~~23~~21, wherein ~~the said~~ anti-TNF antibody is a member selected from the group consisting of ~~REMICADE™~~ (infliximab), ~~ENBREL™~~ (etanercept), ~~HUMIRA™~~ (adalimumab), ~~GIMZIA®~~ (certolizumab pegol), and combinations thereof.

~~25. The method of any one of claims 20 to 24, wherein the markers are measured in a sample selected from the group consisting of serum, plasma, whole blood, stool, peripheral blood mononuclear cells (PBMC), polymorphonuclear (PMN) cells, and a tissue biopsy.~~

~~26~~23. The method of ~~any one of claims 20 to 25~~claim 4 or claim 5, wherein the plurality of time points comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, or more time points.

~~24.~~ The method of any one of claims 4, 5, or 23, wherein the first time point in the plurality of time points is prior to the course of therapy with the therapeutic antibody, or wherein the first time point in the plurality of time points is during the course of therapy with the therapeutic antibody.

~~27. The method of any one of claims 20 to 26, wherein the IBD comprises Crohn's disease or ulcerative colitis.~~

~~28. The method of any one of claims 20 to 27, wherein the first time point in the plurality of time points is prior to the course of therapy with the therapeutic antibody.~~

~~29. The method of any one of claims 20 to 27, wherein the first time point in the plurality of time points is during the course of therapy with the therapeutic antibody.~~

~~30. A method for selecting a therapy regimen to promote mucosal healing in an individual diagnosed with inflammatory bowel disease (IBD), said method comprising:~~

(a) measuring the levels of an array of mucosal healing markers at time point t_0 to generate a mucosal healing index at t_0 ;

(b) measuring the levels of an array of mucosal healing markers at time point t_1 to generate a mucosal healing index at t_1 ;

(c) comparing the change in the mucosal healing index from t_0 to t_1 ; and

(d) selecting the therapy regimen for the individual to promote mucosal healing.

~~31. The method of claim 30, wherein the mucosal healing marker is a member selected from the group consisting of AREG, EREG, HB-EGF, HGF, NRG1, NRG2, NRG3, NRG4, BTC, EGF, IGF, TGF- α , VEGF-A, VEGF-B, VEGF-C, VEGF-D, FGF1, FGF2, FGF7, FGF9, TWEAK and combinations thereof.~~

~~32. The method of claim 30 or 31, wherein the mucosal healing index is determined using a statistical algorithm.~~

~~32. The method of any one of claims 30 to 32, wherein the therapy regimen comprises an anti-TNF antibody.~~

~~34. The method of claim 33, wherein the anti-TNF antibody is a member selected from the group consisting of REMICADE™ (infliximab), ENBREL™ (etanercept), HUMIRA™ (adalimumab), CIMZIA® (certolizumab pegol), and combinations thereof.~~

~~35~~25. The method of any one of ~~claims 30 to 34~~the preceding claims, wherein the markers are measured in a sample selected from the group consisting of serum, plasma, whole blood, stool, peripheral blood mononuclear cells (PBMC), polymorphonuclear (PMN) cells, and a tissue biopsy.

~~36~~26. The method of ~~any one of claims 30 to 35~~claim 5, wherein the levels of an array of mucosal healing markers are measured at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, or more additional time points.

~~37. The method of any one of claims 30 to 36, wherein the IBD comprises Crohn's disease or ulcerative colitis.~~