Dermatol. 2007;156: 990-996), DVT and pulmonary embolism (Shimanovich I. et. al. Treatment of severe pemphigus with protein A immunoadsorption, rituximab and intravenous immunoglobulins Br J. Dermatol 2008;158:382-388) including death from septic shock (Tournadre A, et al. Polymyositis and pemphigus vulgaris in a patient successful treatment with rituximab Jt Bone Spine 2008;75:728-729). Accordingly, there is a need for new therapies that can treat PV effectively and related diseases without causing or at least reducing serious side effects compared to the standard of care in treating pemphigus.

Summary

In one aspect, the present disclosure provides the use of a therapeutically effective amount of a BTK inhibitor in place of or in combination with a corticosteroid in the manufacture of a medicament, for treating an acute inflammatory and/or autoimmune disease in a mammal in need thereof, wherein the corticosteroid is to be used as the first or second line therapy; and optionally, said BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

In another aspect, the present disclosure provides the use of a therapeutically effective amount of a BTK inhibitor in place of or in combination with a corticosteroid in the manufacture of a medicament, for treating an inflammatory and/or autoimmune disease in a mammal in need thereof, wherein the corticosteroid is to be used as the first or second line maintenance therapy; and optionally, said BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

In another aspect, the present disclosure provides the use of a therapeutically effective amount of a BTK inhibitor in place of or in combination with a corticosteroid in the manufacture of a medicament, for eliminating or reducing therapeutic dose of the corticosteroid to be used in the treatment of an inflammatory and/or autoimmune disease in a mammal in need thereof, wherein the corticosteroid is to be used as the first or second line in chronic maintenance therapy; and optionally, said BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

In a further aspect, the present disclosure provides the use of a therapeutically effective amount of a BTK inhibitor in the manufacture of a medicament, for treating an autoimmune and/or inflammatory disease in a mammal in need thereof for a treatment period sufficient to treat acute flares of the autoimmune disease.

Detailed Disclosure of Embodiments

In a recent study conducted by the Applicant in which a dog suffering from pemphigus foliaceus (PF) was administered (R,E)-2-(3-(4-amino-3-(2-fluoro-4-phenoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile, a Bruton Tyrosine Kinase (BTK) inhibitor, as a single agent, it was surprisingly discovered that inhibition of BTK is effective and safe for the treatment of PF.

In addition, it was surprisingly discoved that the manifestation of clinical response with (R,E)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile, was as rapid and comparable to that observed with systemic corticosteroid therapy. Additionally, none of the well-known corticosteroid-like adverse effects in canines, such as polyuria, polydipsia, polyphagia or weight gain, was observed.

Accordingly, the present disclosure provides methods of treating a blistering disease, such as pemphigus vulgaris (PV) or pemphigus foliaceous (PF) with a BTK inbibitor in a mammal, use of a BTK inhibitor as a replacement therapy for corticosteroid therapy for diseases treatable with a corticosteroid (such as autoimmune or inflammatory disease and in particular where corticosteroids are used as first or second line therapy), where a rapid clinical response is desirable. Also, disclosed are methods of treating automimmune and/or inflammatory diseases with a BTK inhibitor at a specific phase of the disease process (such as acute phase and/or at onset and duration of an acute flare) and for a limited amount of time so as to maximixe short term relief, minimize long term progression of the disease, and minimize long term toxicological and other adverse effects.

Accordingly, in a first aspect, provided is a method of treating an autoimmune blistering disease in a mammal in need thereof which method comprises administering to the mammal in need of said treatment a therapeutically effective amount of a BTK inhibitor.

What is Claimed:

1. Use of a therapeutically effective amount of a BTK inhibitor in place of or in combination with a corticosteroid in the manufacture of a medicament, for treating an acute inflammatory and/or autoimmune disease in a mammal in need thereof, wherein the corticosteroid is to be used as the first or second line therapy; and

optionally, said BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

2. Use of a therapeutically effective amount of a BTK inhibitor in place of or in combination with a corticosteroid in the manufacture of a medicament, for treating an inflammatory and/or autoimmune disease in a mammal in need thereof, wherein the corticosteroid is to be used as the first or second line maintenance therapy; and

optionally, said BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

3. Use of a therapeutically effective amount of a BTK inhibitor in place of or in combination with a corticosteroid in the manufacture of a medicament, for eliminating or reducing therapeutic dose of the corticosteroid to be used in the treatment of an inflammatory and/or autoimmune disease in a mammal in need thereof, wherein the corticosteroid is to be used as the first or second line in chronic maintenance therapy; and

optionally, said BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

4. Use of a therapeutically effective amount of a BTK inhibitor in the manufacture of a medicament, for treating an autoimmune and/or inflammatory disease in a mammal in need thereof for a treatment period sufficient to treat acute flares of the autoimmune disease.

5. The use of any one of Claims 1 to 4, wherein the autoimmune and/or inflammatory disease is chosen from Table (I) or (II) below:

Table (I)

Acute indications for corticosteroid therapy
Initial presentations or flares of rheumatic disorders such as psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, bursitis, tenosynovitis, gout, synovitis of osteoarthritis, epicondylitis

Initial presentation or flares of collagen disease such as systemic lupus erythematosus (SLE), dermato/polymyositis, rheumatic carditis, vasculitis
Initial presentations or flares of dermatologic diseases such as pemphigus, Stevens-Johnson syndrome, exfoliative dermatitis, mycosis fungoides, severe psoriasis, severe seborrheic dermatitis
Control of incapacitating allergic reactions including asthma, contact or atopic dermatitis, serum sickness, drug hypersensitivity
Initial presentations or flares of ophthalmic diseases including allergic corneal ulcers, herpes zoster of the eye, anterior or posterior inflammation/uveitis or choroiditis, sympathetic ophthalmia, allergic conjunctivitis, keratitis, chorioretinitis, optic neuritis, iritis, iridocyclitis
Initial presentations or flares of respiratory diseases including symptomatic sarcoidosis, Loeffler's syndrome, berylliosis, fulminating or disseminated tuberculosis, aspiration pneumonitis
Initial presentations or flares of hematologic disorders including idiopathic thrombocytopenic purpura, secondary thrombocytopenia, autoimmune hemolytic anemia, erythroblastopenia, congential hypoplastic anemia
Acute nephrotic syndrome of SLE
Initial presentations or flares of gastrointestinal disease such as ulcerative colitis, Crohn's disease
Acute neurological trauma to reduce swelling

Table (II)

Indications for Prednisone tablets
Endocrine disorders: • Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice: synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance). • Congenital adrenal hyperplasia • Nonsuppurative thyroiditis • Hypercalcemia associated with cancer
Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: • Psoriatic arthritis • Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy) • Ankylosing spondylitis • Acute and subacute bursitis • Acute nonspecific tenosynovitis • Acute gouty arthritis • Post-traumatic osteoarthritis

- Synovitis of osteoarthritis
- Epicondylitis

Collagen diseases:
During an exacerbation or as maintenance therapy in selected cases of:
- Systemic lupus erythematosus
- Systemic dermatomyositis (polymyositis)
- Acute rheumatic carditis

Dermatologic diseases:
- Pemphigus
- Bullous dermatitis herpetiformis
- Severe erythema multiforme (Stevens-Johnson syndrome)
- Exfoliative dermatitis
- Mycosis fungoides
- Severe psoriasis
- Severe seborrheic dermatitis

Allergic states:
Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:
- Seasonal or perennial allergic rhinitis
- Serum sickness
- Bronchial asthma
- Contact dermatitis
- Atopic dermatitis
- Drug hypersensitivity reactions

Ophthalmic diseases:
Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as:
- Allergic conjunctivitis
- Keratitis
- Allergic corneal marginal ulcers
- Herpes zoster ophthalmicus
- Iritis and iridocyclitis
- Chorioretinitis
- Anterior segment inflammation
- Diffuse posterior uveitis and choroiditis
- Optic neuritis
- Sympathetic ophthalmia

Respiratory diseases:
- Symptomatic sarcoidosis
- Loeffler's syndrome not manageable by other means

• Berylliosis • Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy. • Aspiration pneumonitis
Hematologic disorders: • Idiopathic thrombocytopenic purpura in adults • Secondary thrombocytopenia in adults • Acquired (autoimmune) hemolytic anemia • Eythroblastopenia (RBC anemia) • Congenital (erythroid) hypoplastic anemia
Neoplastic diseases: For palliative management of: • Leukemias and lymphomas in adults • Acute leukemia of childhood
Edematous states: To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.
Gastrointestinal diseases: To tide the patient over a critical period of the disease in: • Ulcerative colitis • Regional enteritis
Nervous system: Acute exacerbations of multiple sclerosis
Miscellaneous: Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy. Trichinosis with neurologic or myocardial involvement.

6. The use of any one of Claims 1 to 5, wherein the disease is phemphigus vulgaris.

7. The use of any one of Claims 1 to 4, wherein the BTK inhibitor is to be administered as a monotherapy.

8. The use of any one of Claims 1 to 5, wherein the BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosuppressive and/or antiinflammatory agent.

9. The use of any one of Claims 1 to 8, wherein the noncorticosteroidal immunosuppressive and/or antiinflammatory agent is an anti-CD20 antibody, anti-TNF antibody, anti-IL6 agent, anti-IL17 agent, or abatacept.

10. The use of any one of Claims 1 to 8, wherein the noncorticosteroidal immunosuppressive and/or antiinflammatory agent is rituximab, tositumomab, veltuzumab, obinutuzumab, Enbrel, or ofatumumab, or a biosimilar version thereof.

11. The use of any one of Claims 1 to 10 wherein the BTK inhibitor is chosen from:

(R,E)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile;

N-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)-pyrimidin-4-yl)amino)phenyl)acrylamide;

Ibrutinib (pharmacyclics);

AVL 263 and 293 (Avila Therapeutics, Celgene Corporation);

GDC-0834 (Genentech);

GDC0853 (Genentech);

BMS-488516 and 509744 (Bristol Myers Squibb);

CGI-1746 (Gilead Sciences);

CTA-056 (Genentech);

HY-11066 (also CTK417891);

ONO-4059 (Ono Pharmaceutical Co. Ltd), ONO-WG37 (Ono Pharmaceutical Co. Ltd);

PLS-123 (Peking Univ.);

RN486 (Hoffmann Las Roche);

HM71224 (Hanmi Pharmceutical Co. Ltd.); and

ACP-196 (also Acalabrutinib , Acerta Pharma BV) or a pharmaceutically acceptable salt thereof.

12. The use of any one of Claims 1 to 10 wherein the BTK inhibitor is chosen from:

ABT-105 or ABBV-105 (AbbVie),

AC0025 (ACEA Biosciences);

BGB3111(BeiGene), CC-292 (Celgene);

EBI-1266 (Eternity Bioscience);

MSC-2364447 (Merck Biopharma);

PF-06250112 and PF-303 (Pfizer);

RG7625 and RG7880 (Hoffmann La Roche);

SNS-062 (Sunesis), TP-4207 (Tolero Pharmaceuticals); and

X-022 (X-Chem); or a pharmaceutically acceptable salt thereof.

13. The use of any one of Claims 1 to 10 wherein the BTK inhibitor is chosen from:

(R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

(R)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(S)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide;

(S)-7-(1-(but-2-ynoyl)piperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-(3-((2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)thieno[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide;

1-(3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-[1,2,4]triazolo[1,5-a]pyridin-8-yl)oxy)phenyl)prop-2-en-1-one;

(R)-6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7H-purin-8(9H)-one;

N-(2-((6-((5-(5-fluoro-2-(hydroxymethyl)-3-(4-oxo-6,7,8,9-tetrahydrobenzo[4,5]thieno[2,3-d]pyridazin-3(4H)-yl)phenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyridin-2-yl)amino)ethyl)acrylamide;

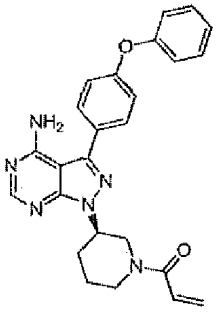
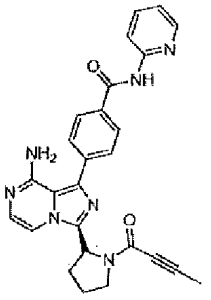
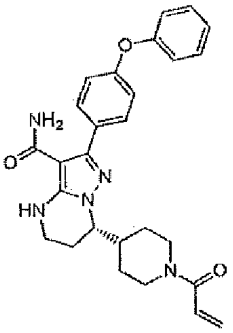
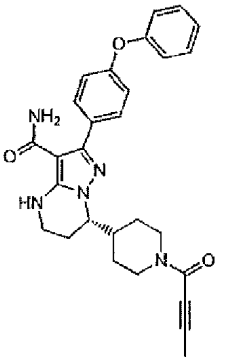
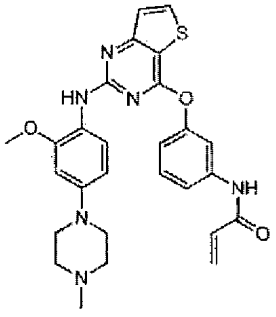
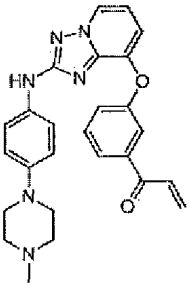
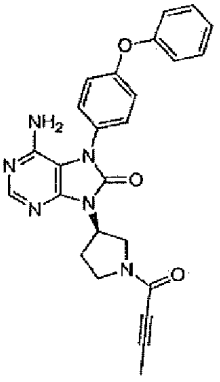
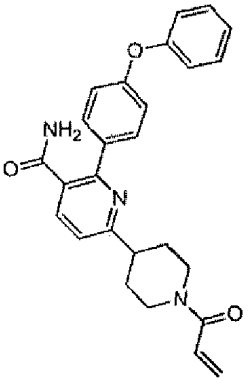
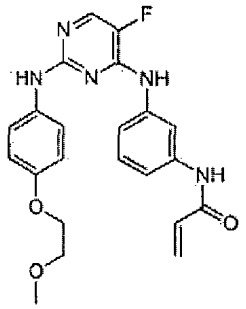
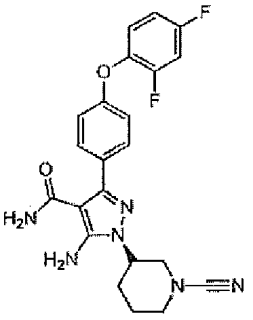
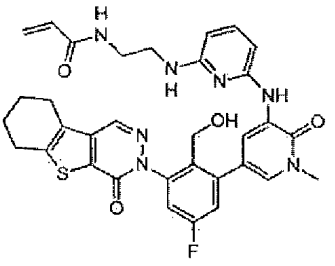
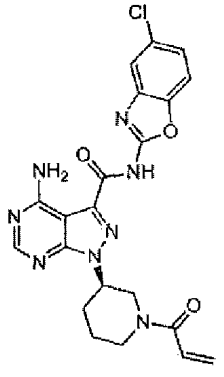
N-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

(S)-5-amino-1-(1-cyanopiperidin-3-yl)-3-(4-(2,4-difluorophenoxy)phenyl)-1H-pyrazole-4-carboxamide;

6-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)nicotinamide; and

(R)-1-(1-acryloylpiperidin-3-yl)-4-amino-N-(5-chlorobenzo[d]oxazol-2-yl)-1H-pyrazolo[3,4-d]pyrimidine-3-carboxamide; or a pharmaceutically acceptable salt thereof.

14. The use of any one of Claims 1 to 10, wherein the BTK inhibitor is chosen from:


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; or a pharmaceutically acceptable salt thereof.

15. The use of any one of Claims 1 to 13, wherein the BTK inhibitor is to be administered in a pharmaceutical composition.