

[NPL 3] Omori K et al., Situation on dialysis dermal pruritus - Search report on 2474 patients at 41 institutions in the Niigata prefecture -; Journal of the Japanese Society for Dialysis Therapy; 2001; 34:1469-77.

[NPL 4] Narita I et al. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. Kidney Int. 2006;69:1626-32

[NPL 5] Pisoni RL et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2006;21:3495-505

[NPL 6] Kimata N et al. Pruritus in hemodialysis patients: Results from the Japanese Dialysis Outcomes and Practice Patterns Study (JDOPPS). Hemodial Int 2014;18:657-67

[Summary]

[Technical Problem]

[0004]

The mechanism of uremic pruritus is still not exactly known, but possible involvement of IL-31 has been suggested (Gangemi S, Quartuccio S, Casciaro M, Trapani G, Minciullo PL, Imbalzano E. Interleukin 31 and skin diseases: A systematic review. Allergy Asthma Proc. 2017;38(6):401-8). Regarding IL-31 and pruritus in dialysis patients, it has been reported that maintenance hemodialysis patients with pruritus had higher serum IL-31 concentration than those without pruritus (Ko MJ et al. Interleukin-31 is associated with uremic pruritus in patients receiving hemodialysis. J Am Acad Dermatol. 2014;71:1151-9).

[0005]

IL-31 (interleukin-31) is a T-cell cytokine. It is known that dermatitis-like symptoms similar to pruritus or atopic dermatitis occur in transgenic mice overexpressing IL-31 (Nat Immunol (2004) 5, 752-760). It has also been found that the receptor to which IL-31 binds is a heterodimer of IL-31RA (interleukin-31 receptor A) and OSMR (oncostatin M receptor) (WO2004/003140), and IL-31 transduces signals into cells through this receptor.

[0006]

To date, IL-31 neutralizing antibodies and IL-31RA neutralizing antibodies as IL-31 antagonists have been reported (for example, WO2005/079566; WO2006/063864; WO2006/063865; WO2009/071696; WO2006/088855; WO2006/088955; WO2006/088956; WO2007/133816; WO2007/142325; WO2009/072598; WO2006/122079; WO2007/143231; WO2008/028192; WO2009/072604; WO2010/064697).

[0007]

However, there has been no report of experimental results showing that an IL-31 antagonist is effective in prevention and/or treatment of uremic pruritus.

[Solution to Problem]

[0007a]

In one aspect, the present disclosure refers to use of an IL-31 antagonist in the manufacture of a pharmaceutical composition for prevention and/or treatment of uremic pruritus, wherein the IL-31 antagonist is an anti-IL-31RA antibody, and wherein the anti-IL-31RA antibody comprises an H chain as set forth in SEQ ID NO: 9 and an L chain as set forth in SEQ ID NO: 10.

[0008]

In a non-limiting example, the present disclosure relates to the following:

[1] A pharmaceutical composition for prevention and/or treatment of uremic pruritus comprising an IL-31 antagonist as an active ingredient.

[2] The pharmaceutical composition of [1], wherein the IL-31 antagonist is administered to a subject with or potentially with uremic pruritus at 0.1 mg to 1000 mg/body/2 weeks, 0.1 mg to 1000 mg/body/4 weeks, or 0.1 mg to 1000 mg/body/8 weeks, repeatedly at the same dose and the same dosing interval.

[3] The pharmaceutical composition of [2], wherein the IL-31 antagonist is administered at 25 mg to 100 mg/body/4 weeks.

[4] The pharmaceutical composition of [2] or [3], wherein the IL-31 antagonist is administered at 50 to 100 mg/body/4 weeks.

[5] The pharmaceutical composition of any one of [1] to [4], wherein the IL-31 antagonist is administered to a subject with or potentially with uremic pruritus at 0.01 mg to 10 mg/kg/2 weeks, 0.01 mg to 10 mg/kg/4 weeks, or 0.01 mg to 10 mg/kg/8 weeks, repeatedly at the same dose and the same dosing interval.

[6] The pharmaceutical composition of [5], wherein the IL-31 antagonist is administered at 0.2 mg to 2 mg/kg/4 weeks.

[7] The pharmaceutical composition of any one of [1] to [6], wherein the IL-31 antagonist is administered to a subject with or potentially with uremic pruritus having a serum IL-31 concentration equal to or higher than a predetermined value.

[7-2] The pharmaceutical composition of any one of [1] to [7], which is for administration only to a subject that has been determined to be a responder to prevention and/or treatment with an IL-31 antagonist by a method for predicting the response of a subject to prevention and/or treatment with an IL-31 antagonist, the method comprising:

measuring IL-31 concentration in a serum obtained from a subject with or potentially with uremic pruritus;
and

determining the subject as a responder to prevention and/or treatment with an IL-31 antagonist if the IL-31 concentration is equal to or higher than a predetermined value.

[7-3] The pharmaceutical composition of any one of [1] to [7], which is for administration only to a subject that has been determined to be a responder to prevention and/or treatment with an IL-31 antagonist by a method for predicting the response of a subject to prevention and/or treatment with an IL-31 antagonist, the method comprising:

[CLAIMS]

[Claim 1]

Use of an IL-31 antagonist in the manufacture of a pharmaceutical composition for prevention and/or treatment of uremic pruritus, wherein the IL-31 antagonist is an anti-IL-31RA antibody, and wherein the anti-IL-31RA antibody comprises an H chain as set forth in SEQ ID NO: 9 and an L chain as set forth in SEQ ID NO: 10.

[Claim 2]

The use of claim 1, wherein the IL-31 antagonist is to be administered to a subject with or potentially with uremic pruritus at 0.1 mg to 1000 mg/body/2 weeks, 0.1 mg to 1000 mg/body/4 weeks, or 0.1 mg to 1000 mg/body/8 weeks, repeatedly at the same dose and the same dosing interval.

[Claim 3]

The use of claim 2, wherein the IL-31 antagonist is to be administered at 25 mg to 100 mg/body/4 weeks.

[Claim 4]

The use of claim 3, wherein the IL-31 antagonist is to be administered at 50 mg to 100 mg/body/4 weeks.

[Claim 5]

The use of claim 4, wherein the IL-31 antagonist is to be administered at 50 mg to 75 mg/body/4 weeks.

[Claim 6]

The use of claim 3, wherein the IL-31 antagonist is to be administered at 30 mg/body/4 weeks.

[Claim 7]

The use of claim 1, wherein the IL-31 antagonist is to be administered to a subject with or potentially with uremic pruritus at an initial dose of 60 mg/body and at a continued dose of 30 mg/body/4 weeks, the dosing interval between the initial dose and the first continued dose being 4 weeks.

[Claim 8]

The use of claim 1, wherein the IL-31 antagonist is to be administered to a subject with or potentially with uremic pruritus at 0.01 mg to 10 mg/kg/2 weeks, 0.01 mg to 10 mg/kg/4 weeks, or 0.01 mg to 10 mg/kg/8 weeks, repeatedly at the same dose and the same dosing interval.

[Claim 9]

The use of claim 8, wherein the IL-31 antagonist is to be administered at 0.1

mg to 3 mg/kg/4weeks.

[Claim 10]

The use of claim 8, wherein the IL-31 antagonist is to be administered at 0.2 mg to 2 mg/kg/4 weeks.

[Claim 11]

The use of claim 9, wherein the IL-31 antagonist is to be administered at 0.125 mg/kg/4 weeks.

[Claim 12]

The use of claim 9, wherein the IL-31 antagonist is to be administered at 0.5 mg/kg/4 weeks.

[Claim 13]

The use of claim 10, wherein the IL-31 antagonist is to be administered at 2 mg/kg/4 weeks.

[Claim 14]

The use of any one of claims 1 to 13, wherein the IL-31 antagonist is to be administered to a subject with or potentially with uremic pruritus having a serum IL-31 concentration equal to or higher than a predetermined value.

[Claim 15]

The use of claim 14, wherein the predetermined value is measured using ultrasensitive enzyme-linked immunosorbent assay.

[Claim 16]

The use of any one of claims 1 to 15, wherein the pharmaceutical composition is for administration only to a subject that has been determined to be a responder to prevention and/or treatment with an IL-31 antagonist by a method for predicting the response of a subject to prevention and/or treatment with an IL-31 antagonist, the method comprising: measuring IL-31 concentration in a serum obtained from a subject with or potentially with uremic pruritus; and determining the subject as a responder to prevention and/or treatment with an IL-31 antagonist if the IL-31 concentration is equal to or higher than a predetermined value.

[Claim 17]

The use of any one of claims 1 to 15, wherein the pharmaceutical composition is for administration only to a subject that has been determined to be a responder to prevention and/or treatment with an IL-31 antagonist by a method for predicting the response of a subject to prevention and/or treatment with an IL-31 antagonist, the method comprising: determining a subject with or potentially with uremic pruritus whose serum IL-31 concentration has been measured as a responder to prevention

and/or treatment with an IL-31 antagonist if the IL-31 concentration is equal to or higher than a predetermined value.

[Claim 18]

The use of any one of claims 1 to 17, wherein the uremic pruritus has been treated by a systemic or topical therapy excluding nalfurafine hydrochloride, and the treatment has not been sufficiently effective.

[Claim 19]

The use of claim 18, wherein the systemic therapy is a treatment with an antihistamine agent or an antiallergic agent, and the topical therapy is a treatment with a moisturizing agent or a steroid.

[Claim 20]

The use of any one of claims 1 to 19, wherein the uremic pruritus is caused by IL-31 signaling.

[Claim 21]

The use of any one of claims 1 to 20, wherein the pharmaceutical composition is for improvement of sleep disturbance caused by uremic pruritus.

[Claim 22]

The use of claim 21, wherein the improvement of sleep disturbance is the increase in time from falling asleep to awakening, and/or the decrease in sleep latency (time from going to bed to falling asleep).

[Claim 23]

The use of claim 1, wherein the antibody does not exhibit cross-reactivity with IL-31RA from any of mouse, rat, and rabbit.