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Summary of MID-NET® study: No. 2020-003

November 21, 2023

Study title

Evaluation of the risk of decreased neutrophil count in patients with antipsoriatics using MID-NET

Products investigated

Preparations shown below (hereinafter referred to as “anti-IL-17 antibody preparations”)

- Human anti-IL-17 receptor A monoclonal antibody preparation: Brodalumab (genetical recombination)
- Human anti-IL-17A monoclonal antibody preparation: Secukinumab (genetical recombination)
- Humanized anti-IL-17A monoclonal antibody preparation: Ixekizumab (genetical recombination)

Preparations shown below (hereinafter referred to as “anti-IL-23 antibody preparations”)

- Humanized anti-IL-23p19 monoclonal antibody preparation: Risankizumab (genetical recombination)
- Human anti-IL-12/23p40 monoclonal antibody preparation: Ustekinumab (genetical recombination)
- Human anti-IL-23p19 monoclonal antibody preparation: Guselkumab (genetical recombination)

Phosphodiesterase 4 (hereinafter referred to as “PDE4”) inhibitor shown below

- Apremilast

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Background

- Differences in the risks of decreased neutrophil count among the anti-IL-17 antibody preparations are not clarified, although decreased neutrophil count is included in the Clinically Significant Adverse Reactions section of information on PRECAUTIONS, etc. and decreased neutrophil count is listed as an important identified risk in the Risk Management Plan (hereinafter referred to as “RMP”) for anti-IL-17 antibody preparations.
- Regarding the information on PRECAUTIONS, etc. of anti-IL-23 antibody preparations, precaution against decreased neutrophile count is not in place for risankizumab (genetical recombination) and ustekinumab (genetical recombination) while the precaution is provided in the Other Adverse Reactions section for guselkumab (genetical recombination). Of note, for risankizumab (genetical recombination) and guselkumab (genetical recombination), decreased neutrophile count is listed as an important potential risk in the RMP.
- For apremilast, decreased neutrophil count is not included in the information on PRECAUTIONS, etc., nor is it listed as a risk in the RMP. Apremilast is a drug that increases intracellular cAMP concentration by inhibiting PDE4 and has the effect of regulating the expression of inflammatory cytokines including IL-17 and IL-23. An evaluation of apremilast as a benchmark would be also useful when assessing the risk of decreased neutrophile count for anti-IL-23 antibody preparations.
- In some cases, it would be difficult to evaluate the causal relationship between the suspected drug and the adverse drug reaction based on individual case reports due to the effects of other drugs, underlying diseases, etc. Therefore, an assessment based on other information including quantitative evaluation results comparing each preparation would be valuable. However, no related preceding studies have been reported.
- In this study, the risk of decreased neutrophil count after prescriptions of anti-IL-17 antibody preparations, anti-IL-23 antibody preparations, and apremilast in patients with psoriasis was examined.

Purpose of the study

<Primary purpose>

To evaluate the risk of decreased neutrophil count for anti-IL-17 antibody preparations, anti-

IL-23 antibody preparations, and apremilast by calculating incidences of decreased neutrophil count after prescriptions of each preparation in patients with psoriasis, in comparison to that for adalimumab (genetical recombination)[*1]

*1 Adalimumab (genetical recombination), a TNFα inhibitor, was used as a positive control for the following reasons: Adalimumab (genetical recombination) is a subcutaneous injection among the biological preparations for the treatment of psoriasis, as are the anti-IL-17 antibody preparations and the anti-IL-23 antibody preparations, and it is considered to have a clinical position close to them; its use in clinical settings is extensive; precautions for serious blood disorders including cytopenia are specified in the Clinically Significant Adverse Reactions section in the information on PRECAUTIONS, etc.

<Secondary purpose>

To evaluate multidirectionally the risk of decreased neutrophile count for anti-IL-23 antibody preparations in patients with psoriasis by comparing the incidences of decreased neutrophile count after prescriptions of anti-IL-23 antibody preparations with those after prescriptions of anti-IL-17 antibody preparations and apremilast[*2].

*2 Anti-IL-17 antibody preparations were used as positive controls. Although apremilast is not an established negative control, it was used as a comparator for interpretation, given that no apparent risk of decreased neutrophile count has been shown by clinical study results, etc. obtained before its marketing approval.

Reason to select MID-NET® for the study and data period

Reason to select : To perform evaluation with laboratory test results as an index

Data period : January 1, 2009 to March 31, 2021

Data from all healthcare organizations cooperating with MID-NET® (22 hospitals at 10 healthcare organizations) whose data were available throughout the target data period

Outline of method

- **Study Design**

  Cohort design

- **Study population**

  Patients who were newly prescribed any of the anti-IL-17 antibody preparations, anti-IL-23 antibody preparations, apremilast, and adalimumab (genetical recombination) during the data period and for whom a diagnosis of psoriasis-related disease had been recorded before the day of a new prescription were identified. A new prescription was

defined as a case where no anti-IL-17 antibody preparations, anti-IL-23 antibody preparations, apremilast, or adalimumab (genetical recombination) had been prescribed within 180 days before the first prescription during the data period. Of the identified patients, those described below were excluded: a) Patients who were prescribed more than 1 active ingredient of anti-IL-17 antibody preparations, anti-IL-23 antibody preparations, apremilast, adalimumab (genetical recombination), infliximab (genetical recombination) or certolizumab pegol (genetical recombination)[*3] at the day of a new prescription, b) patients who had a laboratory test result of neutrophil count less than 1 500/μL 1 to 90 days prior to the day of a new prescription, c) patients who received antineoplastic agent(s) or clozapine 1 to 90 days prior to the day of a new prescription. Patients who did not meet these exclusion criteria were included in the study population.

This study included 9 exposure groups (1) brodalumab group, 2) secukinumab group, 3) ixekizumab group, 4) risankizumab group, 5) ustekinumab group, 6) guselkumab group, 7) apremilast group, 8) anti-IL-17 antibody preparations group (an integrated group of group 1) to 3)), and 9) anti-IL-23 antibody preparations group (an integrated group of group 4) to 6))) as well as a comparator group (adalimumab group), in accordance with the active ingredient of the drug prescribed at the day of a new prescription.

*3 Infliximab (genetical recombination) and certolizumab pegol (genetical recombination), both of which are TNFα inhibitors, are biological preparations used for the treatment of psoriasis. They were specified for exclusion since it is possible that the risk of decreased neutrophile count is affected by them, given that precautions for serious blood disorders including cytopenia are listed in the Clinically Significant Adverse Reactions section in information on PRECAUTIONS, etc.

- Outcomes

  Decreased neutrophil count was defined as a neutrophil count less than 1 000/μL (equivalent to grade 3 or higher by Common Terminology Criteria for Adverse Events Version 5.0 (hereinafter referred to as “CTCAE”)).

- Follow-up period

  A follow-up period, during which occurrence of outcomes was identified, started at the day of a new prescription and ended at the earliest day of the following: a) The date of occurrence of outcomes, b) the date of completion of a prescription continuation period[*4],

c) the date of a prescription of infliximab (genetical recombination), certolizumab pegol (genetical recombination), or a drug belonging to a different group from the one prescribed on the day of a new prescription, d) the date of a prescription of antineoplastic agent(s) or clozapine, e) the date of the final medical record, or f) the end date of the data period.

*4 For injections (drugs other than apremilast), a prescription continuation period was defined as a connected period during which prescriptions were considered to be continuous in cases where the period between the end date of the preceding prescription period and the start date of the following prescription period was less than 30 days (hereinafter referred to as "gap period"). For apremilast, a prescription continuation period was defined as the period of the connected period during which prescriptions were considered to be continuous plus 28 days (hereinafter referred to as "grace period") taking into account the possible unused drugs. Of note, for injections for which self-administration is not approved, a prescription period was determined based on the prescription interval during the maintenance period under the approved dosage and administration. For injections for which self-administration is approved, a prescription period was determined based on the prescription interval during the maintenance period and the number of prescribed injections.

- **Analyses and methods**

[Primary analysis]

For the 9 exposure groups, crude hazard ratios and adjusted hazard ratios weighted by the inverse of the propensity score in comparison to the adalimumab group were estimated using the Cox proportional hazards model. Of note, propensity scores were estimated using a logistic regression model for each combination of the exposure group and comparator group.

[Secondary analysis]

For the anti-IL-23 antibody preparations group, crude hazard ratios and adjusted hazard ratios weighted by the inverse of the propensity score in comparison to the anti-IL-17 antibody preparations group and the apremilast group were estimated using the Cox proportional hazards model.

[Sensitivity analysis]

To confirm the robustness of the primary and secondary analysis, adjusted hazard ratios were estimated for the primary and secondary analysis when the conditions were changed as described below:

- Sensitivity analysis 1: The outcome definition was changed to a neutrophil count less than 500/μL (equivalent to grade 4 by CTCAE).
- Sensitivity analysis 2: The outcome definition was changed to a neutrophil count

less than 1 500/μL (equivalent to grade 2 or higher by CTCAE).

- Sensitivity analysis 3: The study population was limited to patients whose neutrophil counts were within the standard range of 2 000/μL to 7 500/μL from 1 to 90 days prior to the day of a new prescription.
- Sensitivity analysis 4: The study population was limited to patients whose neutrophil counts were within the standard range of 2 000/μL to 7 500/μL from 1 to 90 days prior to the day of a new prescription, and the outcome definition was changed to a neutrophil count less than 1 500/μL.
- Sensitivity analysis 5: The gap period and grace period were changed to twice the conditions of the primary analysis.

[Additional analysis]

Since the number of outcome occurrences in the comparator group was 0 in the primary analysis (outcome definition: a neutrophil count less than 1 000/μL), adjusted hazard ratios were estimated for the outcome definition of a neutrophil count less than 1 500/μL under the modified conditions such as doubling the gap period and grace period so that the risk of decreased neutrophil count can be investigated multidirectionally.

Outline of results

■ **Study population**

- A total of 1 371 patients were identified who were newly prescribed anti-IL-17 antibody preparations, anti-IL-23 antibody preparations, apremilast or adalimumab (genetical recombination) during the data period and for whom a diagnosis record of psoriasis-related disease was found before the day of a new prescription, with 1 309 patients out of them not meeting the exclusion criteria.
- The number of patients in each group and the distribution of age and sex are summarized in Table 1 shown below.

Table 1. Number of patients and distribution of patients' age and sex

	Number of patients	Average age (standard deviation)	Number of male patients (%)
Adalimumab group	293	51.5 (13.2)	189 (64.5)
Brodalumab group	33	54.0 (14.9)	21 (63.6)
Secukinumab group	115	57.4 (15.2)	61 (53.0)
Ixekizumab group	41	54.2 (14.3)	28 (68.3)
Risankizumab group	22	58.5 (17.7)	12 (54.5)
Ustekinumab group	195	53.3 (15.5)	124 (63.6)
Guselkumab group	70	55.1 (13.4)	39 (55.7)
Apremilast group	540	59.7 (15.7)	327 (60.6)
Anti-IL-17 antibody preparations group	189	56.1 (15.0)	110 (58.2)
Anti-IL-23 antibody preparations group	287	54.1 (15.2)	175 (61.0)

- Even after weighting by the inverse of the propensity score, imbalances in patient background factors (adjustment factors used for estimating propensity scores) with an absolute standardized difference greater than 0.20 compared to the adalimumab group were observed for the brodalumab group, ixekizumab group, and risankizumab groups of the 9 exposure groups.

Risk of decreased neutrophil count

- The results of the primary analysis are shown in Table 2. Hazard ratios could not be estimated for each exposure group since no occurrence of outcomes was observed in the comparator adalimumab group.
- As a result of the secondary analysis, the adjusted hazard ratio for the anti-IL-23 antibody preparations group was 0.40 (95% confidence interval (CI) 0.02−7.60) in comparison to the anti-IL-17 antibody preparations group, and 0.43 (95% CI 0.02 −11.63) in comparison to the apremilast group.
- The results of the sensitivity analysis 2, in which the outcome definition was changed to a neutrophil count less than 1 500/μL, are shown in Table 3. Hazard ratios could not be estimated for the brodalumab group, ixekizumab group, and risankizumab group, since no occurrence of outcomes was observed. For the other groups, no significant increase in risk compared to the adalimumab group was observed.
- The results for the anti-IL-23 antibody preparations were as described below. Of note,

the number of patients subject to the sensitivity analyses 3 and 4, in which the study population differs from that in the primary and secondary analysis, was 190 in the anti-IL-23 antibody preparations group, 193 in the adalimumab group, 115 in the anti-IL-17 antibody preparations group, and 201 in the apremilast group.

- A tendency of decreased risks in comparison to the adalimumab group was shown in the analyses where the outcome was defined as a neutrophil count less than 1 500/μL (sensitivity analysis 2, 4, and the additional analyses).
- Of the sensitivity analyses of the secondary analyses as well as the additional analyses in comparison to the anti-IL-17 antibody preparations group, all the analyses except for the sensitivity analysis 1 showed a tendency to decrease risks in a similar manner to the corresponding secondary analysis. In the sensitivity analysis 1 (outcome definition: a neutrophil count less than 500/μL), no occurrence of outcomes was observed in the anti-IL-17 antibody preparations group and hazard ratios could not be estimated.
- Of the sensitivity analyses of the secondary analyses as well as the additional analyses in comparison to the apremilast group, the sensitivity analysis 3, 4, 5 and some of the additional analyses showed a tendency to decrease risks in a similar manner to the corresponding secondary analysis (the adjusted hazard ratio of 0.33 (95% CI 0.01−9.07) for the sensitivity analysis 3, 0.48 (95% CI 0.03−6.67) for the sensitivity analysis 4, and 0.52 (95% CI 0.02−11.57) for the sensitivity analysis 5), while the sensitivity analysis 2 and some of the additional analyses showed a tendency to increase risks contrary to the corresponding secondary analysis (the adjusted hazard ratio of 3.88 (95% CI 0.62−24.48) for the sensitivity analysis 2). In the sensitivity analysis 1 (outcome definition: a neutrophil count less than 500/μL), no occurrence of outcomes was observed in the apremilast group and hazard ratios could not be estimated.

Table 2. Occurrence of decreased neutrophil count (less than 1 000/μL)

	Number of patients	Follow-up period (person-year)	Number of outcome occurrences*	Crude hazard ratio (95% CI)	Adjusted hazard ratio† (95% CI)
Adalimumab group	293	445.3	0	reference	reference
Brodalumab group	33	45.4	0	Incalculable	Incalculable
Secukinumab group	115	153.8	< 10	Incalculable	Incalculable
Ixekizumab group	41	59.3	0	Incalculable	Incalculable
Risankizumab group	22	15.0	0	Incalculable	Incalculable
Ustekinumab group	195	496.4	< 10	Incalculable	Incalculable
Guselkumab group	70	73.0	0	Incalculable	Incalculable
Apremilast group	540	399.9	< 10	Incalculable	Incalculable
Anti-IL-17 antibody preparations group	189	271.6	< 10	Incalculable	Incalculable
Anti-IL-23 antibody preparations group	287	607.8	< 10	Incalculable	Incalculable

* Data are masked so that the number of patients (less than 10) cannot be identified according to the MID-NET® publication criteria.

Table 3. Occurrence of decreased neutrophil count (less than 1 500/μL)

	Number of patients	Follow-up period (person-year)	Number of outcome occurrences*	Crude hazard ratio (95% CI)	Adjusted hazard ratio† (95% CI)
Adalimumab group	293	425.5	10	reference	reference
Brodalumab group	33	45.4	0	Incalculable	Incalculable
Secukinumab group	115	147.3	< 10	1.50 (0.55–4.10)	1.10 (0.37–3.24)
Ixekizumab group	41	59.3	0	Incalculable	Incalculable
Risankizumab group	22	15.0	0	Incalculable	Incalculable
Ustekinumab group	195	495.0	< 10	0.29 (0.08–1.03)	0.61 (0.16–2.31)
Guselkumab group	70	69.6	< 10	2.28 (0.78–6.70)	1.28 (0.35–4.68)
Apremilast group	540	399.9	< 10	0.26 (0.07–1.04)	0.26 (0.06–1.09)
Anti-IL-17 antibody preparations group	189	265.0	< 10	0.84 (0.31–2.30)	0.77 (0.27–2.17)
Anti-IL-23 antibody preparations group	287	603.0	< 10	0.63 (0.25–1.59)	0.76 (0.28–2.06)

* Data are masked so that the number of patients (less than 10) cannot be identified according to the MID-NET® publication criteria.

† Weighted by the inverse of the propensity score. The propensity score was estimated by using adjustment factors shown below. Adjustment factors: Sex, age, disease type of psoriasis, neutrophil count at baseline, previous treatment with infliximab (genetical recombination) or certolizumab pegol (genetical recombination), complications that may increase the risk of outcome occurrence (severe renal impairment, autoimmune diseases excluding psoriasis, deficiency of vitamin B_{12} or folic acid, aplastic anaemia, hepatic cirrhosis or hypersplenism), complications that may decrease the risk of outcome occurrence (phaeochromocytoma or Cushing's syndrome), concomitant drugs that may increase the risk of outcome occurrence (antivirals, anti-thyroid drugs, phenothiazine antipsychotics, ticlopidine,

salazosulfapyridine, ST combination preparations, H_2 receptor antagonists, interferon preparations, allopurinol, ritodrine, aprindine, valsartan, carbamazepine, glycopeptide antibiotics, carbapenem antibiotics, levofloxacin, proton pump inhibitors, edaravone, hangekobokuto, diaphenylsulfone, methotrexate), concomitant drugs that may decrease the risk of outcome occurrence (corticosteroids, lithium carbonate)

■ **Discussion based on the results**

- Based on the following points regarding the results for anti-IL-23 antibody preparations group, the study results do not suggest that the anti-IL-23 preparations have risks of decreased neutrophil count.
  - ➢ For the comparisons against the adalimumab group, the results of the sensitivity and additional analyses, where the outcome was defined as a neutrophil count less than 1 500/μL, showed a consistent tendency to decrease risks.
  - ➢ For comparisons against the anti-IL-17 antibody preparations group, the results of the secondary analyses, as well as the corresponding sensitivity and additional analyses, showed a consistent tendency to decrease risks.
  - ➢ For the comparisons against the apremilast group, the results of the secondary analyses, as well as the corresponding sensitivity and additional analyses, did not show a consistent tendency to increase risks.
- Based on the following points, distinct differences in the risks could not be confirmed among the anti-IL-23 antibody preparations and among the anti-IL-17 antibody preparations.
  - ➢ Although the adjusted hazard ratios in comparison to the adalimumab group for the ustekinumab group and the guselkumab group among the anti-IL-23 antibody preparations showed a different tendency to each other, the results were based on a limited number of patients leading to the wide 95% CIs.
  - ➢ Since no occurrence of outcomes was observed in the risankizumab group among the anti-IL-23 antibody preparations and in the brodalumab group and the ixekizumab group among the anti-IL-17 antibody preparations, hazard ratios could not be estimated for those groups. Of note, the propensity score-weighted adjustment for confounding was difficult in those groups.
- It should be noted that there are certain limitations including the limited number of patients in this study and the possibility that comparability is not ensured for apremilast since apremilast, which is not a biological preparation, has a different clinical

positioning[*5] and that other potential confounders (e.g., general condition of patients and detailed treatment history of psoriasis, etc.) may have affected the results. In addition, it should be also noted that adjusted hazard ratios should be carefully interpreted taking into account the 95% CIs, etc. and that the point estimates of each exposure group shown in this study do not necessarily indicate the magnitude of correlations of the risk of decreased neutrophile count for each exposure group, since propensity scores were estimated for each combination of an exposure group and a comparator group and comparability among exposure groups was not ensured.

*5 It is described in “Japanese guidance for use of biologics for psoriasis (the 2022 version)” (The Japanese Journal of Dermatology. 2022; 132: 2271−96) that systemic therapy including administration of apremilast should be considered at first, in general, concerning the use of biological preparations for psoriasis vulgaris.