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Development of an IL-31-Induced Pruritus Model in Cynomolgus Monkeys

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Abstract

Itching and scratching has evolved as an important protection mechanism against various threats to the skin. Pruritus is a severe itching condition most commonly associated with skin disorders such as atopic dermatitis (AD) or psoriasis. Recent clinical trials have demonstrated significant improvement of pruritus in patients with AD after administration of an anti-Interleukin-31 (IL-31) receptor antibody. In order to evaluate the efficacy of therapies intended to treat pruritic skin diseases, an IL-31 pruritus cynomolgus monkey model has been established. Cynomolgus monkeys were administered subcutaneous (SC), intradermal (ID), or intravenous (IV) injection(s) of cIL-31, ranging from 0.3 to 24 µg/kg. Pharmacological activity was monitored based on the number of scratching and self-grooming events over a 24-hour period. ID injections of cIL-31 in cynomolgus monkeys at doses of 6, 12, 19.5 and 24 µg/kg resulted in a consistent and robust systemic pharmacological response, as evidenced by a 3- to 6-fold increase from baseline. The pharmacological response was more pronounced between 0.5 and 1.5 hours post-dose and appeared to restore nearly to baseline levels by 24 hours post-dose. The IV route elicited a comparable scratching response to the highest ID levels tested but with smaller dose levels (0.3 to 1 µg/kg); SC provided the least useful data. Based on these observations, ID or IV injections of cIL-31 in cynomolgus monkey resulted in a consistent and robust model for future research and development of treatment strategies for atopic dermatitis and other pruritic skin diseases.

Background

Interleukin (IL)-31 is a cytokine that has been identified as a major player in a number of chronic inflammatory diseases, including atopic dermatitis. IL-31 is produced mainly by Th2 cells [1,2] and it signals via the IL-31 receptor A (IL-31RA) and oncostatin M receptor (OSMR) β heterodimer.[3,4] Overexpression or administration of interleukin 31 (IL-31) has been shown to induce a profound itch response in mice and dogs.[5] Nonetheless, because IL-31 and IL-31RA sequences have low homology between humans and mice (31% for IL-31 and 61% for IL-31RA[1]), it is difficult to extrapolate these rodent results directly to humans. Cynomolgus monkeys have sequence homology for IL-31 and IL-31RA with humans of 93% and 94%, respectively [6] and therefore was considered the species of choice to develop this model.

Methods

Seventy-four (74) cynomolgus monkeys were part of this model characterization and each animal received an injection of cIL-31 via the IDl, IV, or SC route.

An appropriate number of cIL-31 vials were removed from frozen storage and thawed at room temperature. The vials were gently inverted 10 to 20 times, then filtered through a 0.22 µm PVDF syringe filter into a sterile polypropylene container.

On each day of cIL-31 challenge administration, animals were monitored using the Noldus Media Recorder or Notocord Telemetry System for at least 1 hour prior to dosing, and for a duration of up to 24.25 hours post dosing, with defined intervals. Frequency of scratching and/or self-grooming events were documented, as well as the location and/or the duration of each event.

Results

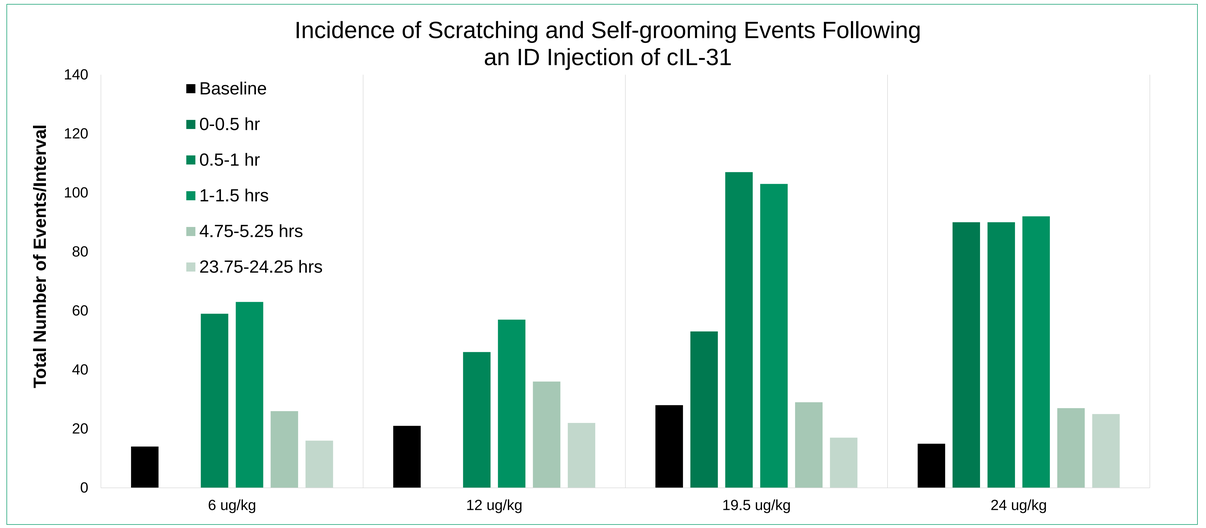

Figure 1. incidence of events over an approximate period of 24 hours following an intradermal injection of cIL-31

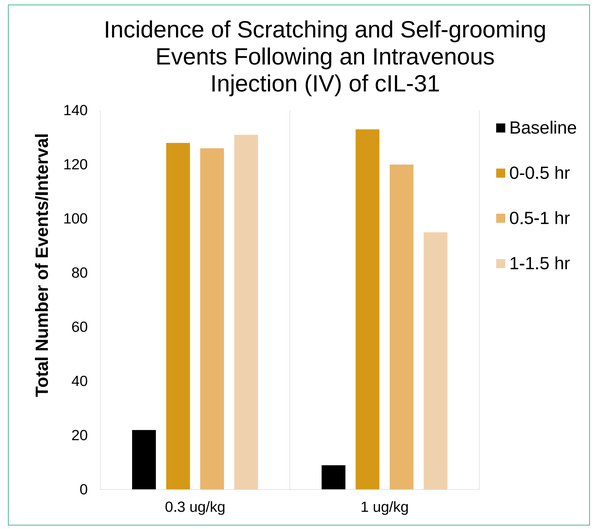

Figure 2. incidence of events over a period of 1.5 hour following an intravenous injection of cIL-31

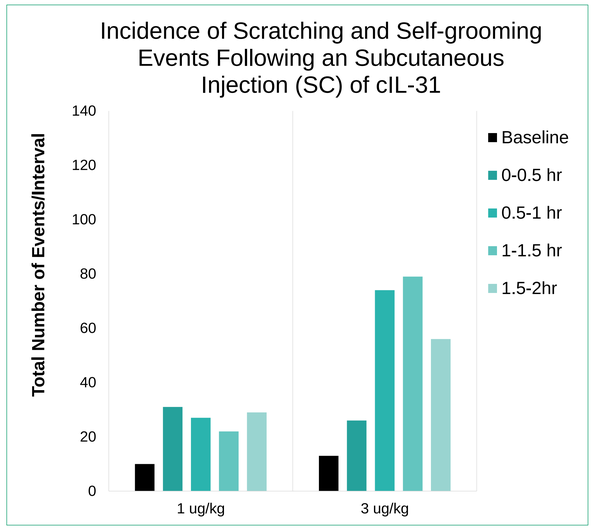

Figure 3. incidence of events over a period of 2 hours following a subcutaneous injection of cIL-31

The challenge agent resulted in a dose-related increase in the average scratching and self-grooming responses in all animals. The pharmacological response was more pronounced between 0.5 and 1.5 hours post cIL-31 administration for the ID and SC routes and immediately post injection when using the IV route. Based on the location documented (data not shown), the overall scratching/grooming events appeared to reflect a more systemic response to the cIL-31, rather than being limited to a local reaction. The effect restored nearly to baseline levels by 24 hours post-dose.

Intradermal:

While there was some levels of inter-animal variability in the severity of the pruritic response to cIL-31, the 24 µg/kg ID dose resulted in the most consistent and robust response, as evidenced by the total number of events that were increased by 3- to 6-fold from baseline.

N = 12 at 6 µg/kg; **N = 8** at 12 µg/kg; **N = 16** at 19.5 µg/kg; **N = 31** at 24 µg/kg

Intravenous:

The IV route elicited a comparable scratching response to the highest ID dose level tested but with much smaller doses (0.3 to 1 µg/kg).

N = 1 at 0.3 µg/kg; **N = 4** at 1 µg/kg

Subcutaneous:

SC injections resulted in a variable number of events over time. More animals will be required to properly characterize the pruritis response using this route of administration.

N = 1 at 1 µg/kg; **N = 1** at 3 µg/kg

Conclusion

In conclusion, ID or IV injections of cIL-31 in cynomolgus monkeys were considered suitable routes of administration to induce a consistent and robust pruritis response for future research and development of treatment strategies for atopic dermatitis and other pruritic skin diseases.

References

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Acknowledgments

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