Clinical Development of Histamine H_4 Receptor Antagonists

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Contents

Abstract

The discovery of the histamine H_4 receptor (H_4R) provided a new avenue for the exploration of the physiological role of histamine, as well as providing a new drug target for the development of novel antihistamines. The first step in this process was the identification of selective antagonists to help unravel the pharmacology of the H_4R relative to other histamine receptors. The discovery of the selective H_4R antagonist JNJ 7777120 was vital for showing a role for the H_4R in inflammation and pruritus. While this compound has been very successful as a tool for understanding the function of the receptor, it has drawbacks, including a short in vivo half-life and hypoadrenocorticism toxicity in rats and dogs, that prevented advancing it into clinical studies. Further research let to the discovery of JNJ 39758979, which, similar to JNJ 7777120, was a potent and selective H_4R antagonist and showed anti-inflammatory and anti-pruritic activity preclinically. JNJ 39758979 advanced into human clinical studies and showed efficacy in reducing experimental pruritus and in patients with atopic dermatitis. However, development of this compound was terminated due to the occurrence of drug-induced agranulocytosis. This was overcome by developing another H_4R

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antagonist with a different chemical structure, toreforant, that does not appear to have this side effect. Toreforant has been tested in clinical studies in patients with rheumatoid arthritis, asthma, or psoriasis. In conclusions there have been many H_4R antagonists reported in the literature, but only a few have been studied in humans underscoring the difficulty in finding ligands with all of the properties necessary for testing in the clinic. Nevertheless, the clinical data to date suggests that H_4R antagonists can be beneficial in treating atopic dermatitis and pruritus.

Keywords
Antihistamines • Atopic dermatitis • Inflammation • JNJ 39758979 • JNJ 7777120 • Pruritus • Rheumatoid arthritis • Toreforant

1 Introduction

The first reports of the identification of the histamine H_4 receptor (H_4R) were published in 2000–2001. It was the fourth member of the histamine receptor family and, along with the histamine H_1, H_2, and H_3 receptors, mediates the physiological functions of histamine (Panula et al. 2015). Discovery of this receptor provided a new avenue to explore histamine's biologic role and spurred basic research into the function of the receptor. This work has resulted in the testing of H_4R antagonists in the clinic (Table 1) and some data have recently emerged. In this review we will give a historical account of development of H_4R ligands at Janssen Research & Development, LLC.

The H_4R was discovered by identification of a genomic sequence that had the signature of a G-protein coupled receptor and was shown to bind histamine (Thurmond 2015). Profiling the activity of known histamine receptor ligands indicated that this receptor exhibited unique pharmacology and thus was named the histamine H_4 receptor. The initial pharmacological characterization of the receptor indicated that many previously characterized histamine H_3 receptor ligands, such as thioperamide, were also ligands for the H_4R. Thioperamide was initially described as a potent and selective histamine H_3 receptor antagonist, but the initial pharmacological characterization of the H_4R showed that it was also a potent H_4R antagonist (Arrang et al. 1987; Liu et al. 2001). This was not surprising given the high homology between the two receptors. Subsequently, 4-methylhistamine, which was known as a selective histamine H_2 receptor agonist, was shown to also be a potent H_4R agonist (Durant et al. 1975; Lim et al. 2005). While the availability of these ligands proved useful in some of the early characterization of the receptor (Buckland et al. 2003; Hofstra et al. 2003; Takeshita et al. 2003; Bell et al. 2004), it was clear that ligands selective for the H_4R would be needed to uncover its specific pharmacology.

Table 1 Clinical studies with H_4R antagonists

Indication	Compound	Results
Histamine-induced itch	JNJ 39758979	JNJ 39758979 reduced histamine-induced itch
Bronchial allergen challenge	ZPL-389	Not reported
Allergic rhinitis	UR-63325	Not reported
Atopic dermatitis	JNJ 39758979	Trend for efficacy in EASI. Nominally statistically significant reduction in pruritus
	ZPL-389	Nominally statistically significant reduction in EASI
Rheumatoid arthritis	Toreforant	Toreforant 100 mg/day showed reduction in DAS28 and in ACR response rates. Follow-up study at 3, 10 and 30 mg/day showed no efficacy
Asthma	Toreforant	Not reported
	JNJ 39758979	Not reported
Psoriasis	ZPL-389	Not reported
	Toreforant	Not reported

2 Early Selective H_4 Receptor Antagonists

In order to identify novel starting points for medicinal chemistry efforts to develop potent and selective H_4R ligands, a high throughput screen of a large compound library was conducted. The screen looked for compounds that could inhibit histamine binding to membranes expressing the human H_4R. This assay yielded several lead compounds including an indolylpiperazine (Fig. 1; Compound 1) that was a potent ligand for the H_4R with a K_i of 38 nM (Jablonowski et al. 2003). The subsequent medicinal chemistry effort focused on evaluation of various substituents on the indole core while maintaining the optimal *N*-methylpiperazine as the terminus. Small substituents in the 5 and 7-positions were well tolerated leading to many compounds with high affinity for the H_4R (Jablonowski et al. 2003). This work cumulated in the identification of JNJ 7777120 (Fig. 1) that had a K_i of 4.5 nM versus the human receptor and demonstrated functional antagonism with a pA_2 of 8.1 with at least 1,000-fold selectivity over the histamine H_1, H_2, or H_3 receptors and no cross-reactivity against 50 other targets (Thurmond et al. 2004). It was also a high affinity antagonist for the mouse and rat H_4R (Table 2). The proper characterization of the pharmacology of ligands in species besides human is absolutely crucial for interpreting preclinical data. This is especially important when dealing with data from preclinical animal models of human diseases where one must know the affinity, pharmacological action (agonist vs. antagonist), and compound levels in the species where the model is run. This information is essential in determining whether the effects seen in the animal model would also be seen in humans. In that same vein, the pharmacology also needs to be understood in the species being used

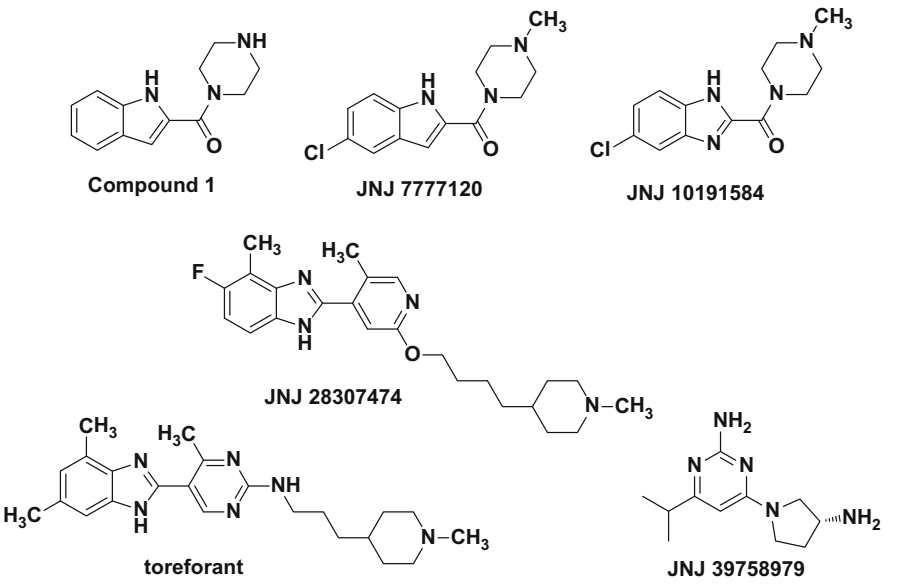

Fig. 1 Compound structures

Table 2 K_i (nM) at the various histamine receptors[a]

	JNJ 7777120	JNJ 10191584	JNJ 28307474	JNJ 39758979	Toreforant
Human H_4R	4.1	27	4.9	12.5	8.4
Mouse H_4R	4.6	55	109	5.3	307
Rat H_4R	2.6	97	87	188	9.3
Dog H_4R	79	630	62	>10,000	680
Monkey H_4R	32	199	ND	25	10.6
Human H_1R	>10,000	>10,000	2,501	>1,000	>10,000
Human H_2R	>1,000	>1,000	>1,000	>1,000	>1,000
Human H_3R	5,125	7,000	159	1,043	215

[a]*ND* not determined

for the toxicology studies required before testing in humans in order to make sure any potential safety issues are uncovered. For example, it would be inappropriate to use preclinical safety data to justify a human clinical study for a compound that is an antagonist in the toxicology species, but an agonist in humans.

As the first potent and selective H_4R antagonist, JNJ 7777120 has become one of the key standard ligands to define H_4R activity both in vitro and in vivo. In particular this ligand provided the first evidence that the H_4R was involved in inflammation in vivo. Based on the expression profile of the receptor, the activity of JNJ 7777120 was tested in a number of preclinical inflammation models to

elucidate its potential anti-inflammatory activity. One of the first models to show effects was a mouse peritonitis model. Zymosan, a toll-like receptor agonist, induces neutrophil influx within 4 h of being injected into the peritoneum. Pretreatment with JNJ 7777120 led to a reduction in the neutrophil influx, indicating an anti-inflammatory effect (Thurmond et al. 2004). Efficacy was also seen when chemokine (C-X-C motif) ligand-1 (CXCL1) or sodium urate crystals were used to induce peritonitis, but not when thioglycollate was used (Thurmond et al. 2004 and unpublished data). These results confirmed other results in peritonitis models with non-selective H_4R ligands (Takeshita et al. 2003). Anti-inflammatory efficacy was also seen in a 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced acute colitis model in rats. Here treatment with JNJ 7777120 led to a reduction in the colonic lesion area as well as reduced tissue myeloperoxidase and TNF-α levels (Varga et al. 2005). Since these initial observations, efficacy with JNJ 7777120 has subsequently been demonstrated in models of asthma, pulmonary fibrosis, pleurisy, dermatitis, anaphylaxis, pruritus, lipopolysaccharide (LPS)-induced inflammation, allergic rhinitis, allergic conjunctivitis, experimental allergic encephalomyelitis, and pain (Dunford et al. 2006, 2007; Smith et al. 2007; Nakano et al. 2009; Rossbach et al. 2009, 2011; Takahashi et al. 2009; Cowden et al. 2010a, b, 2013; Seike et al. 2010; Suwa et al. 2011; Beermann et al. 2012; Matsushita et al. 2012; Ohsawa and Hirasawa 2012; Ballerini et al. 2013; Somma et al. 2013; Ahmad et al. 2014, 2015; Mahapatra et al. 2014; Pini et al. 2014; Rosa et al. 2014; Lucarini et al. 2016; Wang et al. 2016).

Keeping in mind an important principle of pharmacology, it was important to not misinterpret the function of the H_4R based on the activity on a single ligand since the full specificity of that ligand may be unknown (see, for example, thioperamide specificity prior to the discovery of the H_4R) or, alternatively, its activity as an antagonist versus agonist may vary depending on conditions. One way to support the findings with a purported antagonist like JNJ 7777120 was to show that H_4R-deficient mice have a similar phenotype in the model of question. Indeed this has been shown for mouse asthma, dermatitis, LPS-induced inflammation, colitis, experimental allergic encephalomyelitis, and pruritus models, which supports the conclusions that the effects seen in vivo with JNJ 7777120 are due to antagonism of the H_4R (Dunford et al. 2006, 2007; Cowden et al. 2010b, 2013; del Rio et al. 2012; Schirmer et al. 2015). Another way to support selectivity is to show similar effects with different H_4R antagonists. To this end the results seen with JNJ 7777120 have been replicated by other compounds in models of colitis, asthma, dermatitis, pain, and pruritus (Varga et al. 2005; Dunford et al. 2006, 2007; Coruzzi et al. 2007; Altenbach et al. 2008; Cowart et al. 2008; Liu et al. 2008; Cowden et al. 2010b, 2014; Hsieh et al. 2010; Shin et al. 2012; Savall et al. 2014; Thurmond et al. 2014).

While JNJ 7777120 is an excellent pharmacological tool for helping dissect the role of the H_4R in several disease states, it has limitations that preclude its development as a drug. One of these is that it is rapidly metabolized in vivo and therefore the pharmacokinetics are not appropriate for an oral human therapeutic or even for dosing in long-term animal models; even short term models may require very high doses or multiple dosing regimens. JNJ 7777120 has an oral

bioavailability of ~30% in rats and 100% in dogs with a half-life of ~3 h in both species (Thurmond et al. 2004). In mice the half-life was around 1–2 h. The compound appears to work best in acute challenge models such as the mouse asthma, pruritus, and atopic dermatitis models. However, in more chronic models where continuous inhibition of the receptor is likely required, JNJ 7777120 is less effective. One example of such a model is the mouse collagen-induced arthritis model where JNJ 7777120 has not been shown to be efficacious, but other H_4R antagonists have (Cowden et al. 2014).

One of the main metabolites of JNJ 7777120 is demethylation of the piperazine. However, this is also important for potency of the compound since removing the methyl group reduces the affinity for the human H_4R to 25 nM (Engelhardt et al. 2012). One strategy for improving metabolic stability was to modify the core indole of the molecule including replacing the pyrrole ring of the indole carboxamides for imidazole (Venable et al. 2005). This led to a series of potent and selective compounds that had similar properties with their indole counterparts, however, their metabolic profiles differed. One of these compounds was JNJ 10191584 (Fig. 1), which shared all of the structural features of JNJ 7777120 except that the C(3) CH group was replaced with a nitrogen atom. Like JNJ 7777120, this compound was a potent and selective H_4R antagonist with a K_i of 26 nM (Table 2) (Venable et al. 2005). It also behaves in a similar fashion to JNJ 7777120 in models of asthma and colitis (Table 3) (Varga et al. 2005; Dunford et al. 2006). This compound exhibited no improvement in pharmacokinetics in rats or mice (half-life ~1 h), but the human in vitro data suggested that it would have better human exposure compared to JNJ 7777120.

With the improved human pharmacokinetic predictions, preclinical toxicity studies were initiated with JNJ 10191584. Dose range finding studies were carried out in rats and dogs. In rats (5 animals of each sex per group) doses of 0, 100, 250, 500, 1,000 mg/kg/day, divided b.i.d, were given for 5 days. The main findings were dose dependent decreases in serum sodium and chloride, increases in serum potassium, and decreased sodium:potassium ratios (Table 4). In dogs (1 animal of

Table 3 Activity in preclinical disease models[a]

	KO	JNJ 7777120	JNJ 10191584	JNJ 28307474	JNJ 39758979	Toreforant
Asthma	Y	Y	Y	Y	Y	Y
LPS-induced inflammation	Y	Y	NT	Y	Y	Y
Dermatitis	Y	Y	NT	Y	Y	Y
Collagen-induced arthritis	Y	N	NT	Y	Y	Y
Neuropathic pain	NT	Y	NT	NT	Y	N
Colitis	NT	Y	Y	NT	NT	NT
Histamine-induced pruritus	Y	Y	NT	Y	Y	N

[a]*Y* activity seen, *N* tested but no activity, *NT* not tested, *KO* H_4R-deficient mice

Table 4 Rat serum electrolytes in a 5 day oral toxicity study with JNJ 10191584

Dose mg/kg/day divided b.i.d.	Male				Female			
	Na	Cl	K	Na:K[a]	Na	Cl	K	Na:K
0	147.4	99.60	6.434	22.8	144.6	100.12	7.070	20.4
100	146.0	99.18	7.374	19.8	143.2	98.48	7.096	20.2
250	145.3	99.20	6.952	20.9	143.6	98.04	7.330	19.6
500	144.2	97.92	7.066	20.4	141.1	96.48	7.35	19.2
1,000	141.6	96.52	8.488	16.7	139.9	92.88	7.840	17.8

Five animals of each sex per group
[a]*Na:K* serum sodium to potassium ratio

each sex per group) doses of 0, 20, 100, 200, 300 mg/kg/day, divided b.i.d., were given for 5 days. As with rats decreased serum sodium and chloride levels and elevated serum potassium values were evident in the high dose animals with a lower sodium:potassium ratio relative to control group animals (Table 5). In the dog, histopathology of the adrenal gland revealed diffuse necrosis of the zona glomerulosa (Fig. 2). No histopathologic lesions were apparent in the adrenal glands of rats. This characteristic pattern of serum electrolyte effects and lowered sodium: potassium ratios is consistent with hypoadrenocorticism (Klein and Peterson 2010). In the dog this was corroborated by the striking necrosis of the adrenal gland zona glomerulosa, the anatomic region of the adrenal gland where aldosterone is synthesized. The mineralocorticoid, aldosterone, is critical for maintaining serum electrolyte balance and decreased sodium:potassium ratios are a hallmark of aldosterone deficiency. The adrenal gland is an unusual target organ for xenobiotic toxicity. In this case, because the serum electrolyte changes were seen in two species, developed rapidly over 5 days of treatment, and could result in life threatening serum electrolyte perturbations in human subjects, the development of JNJ 10191584 was terminated. Subsequent testing of JNJ 7777120 indicated that it too caused comparable serum electrolyte effects in rats. However, as noted above, the structures of JNJ 10191584 and JNJ 7777120 are very similar and therefore it was unclear whether these effects were due to H_4R antagonism or to the compound structures. To address this, an H_4R antagonist was needed from a different structural class.

A review of the initial compound screening results revealed another potential chemotype that led to the discovery of JNJ 28307474 (Fig. 1). This class of pyridinyl benzimidazoles is structurally distinct from the indole chemotypes, but does maintain a basic amine (piperidine) that is important for the interaction with the H_4R. From a pharmacological perspective it was similar to JNJ 7777120 with a high affinity for the human H_4R (Table 2), however, it was less potent at the mouse H_4R and did have some affinity for the human H_3 receptor (Cowden et al. 2010b). As for JNJ 7777120, this compound showed activity in mouse models of asthma, atopic dermatitis, LPS-induced inflammation, and itch (Table 3) (Cowden et al. 2010b, 2013; Dunford, unpublished data). In contrast to JNJ 7777120, JNJ 28307474 demonstrated activity in the mouse collagen-induced arthritis model,

Table 5 Dog serum electrolytes in a 5 day oral toxicity study with JNJ 10191584

Dose mg/kg/day divided b.i.d.	Male				Female			
	Na	Cl	K	Na:K[a]	Na	Cl	K	Na:K
0	142.9	109.3	4.52	31.6	144.1	109.7	4.30	33.5
20	143.2	110.3	4.29	33.4	145.0	110.8	4.43	32.7
100	143.4	111.6	4.28	33.5	143.5	109.5	4.59	31.3
200	139.0	109.0	4.44	31.3	144.6	110.5	4.73	30.6
300	140.7	108.7	4.64	30.3	136.9	104.6	4.83	28.3

One animal of each sex per group
[a]*Na:K* serum sodium to potassium ratio

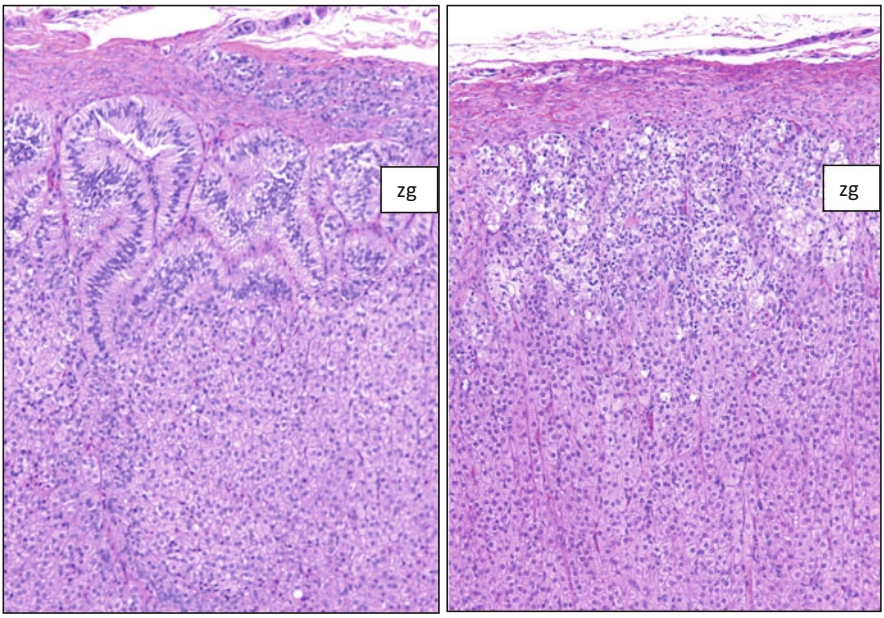

Fig. 2 Photomicrograph showing adrenal changes in a dog treated with JNJ 10191584. Adrenal glands of dog treated with vehicle (*left*) or 300 mg/kg/day JNJ10191584 (*right*). The normal canine zona glomerulosa (zg) is comprised of tall, organized epithelial cells with prominent eosinophilic cytoplasm and basally oriented nuclei. In the treated adrenal gland on the right the zona glomerulosa is diffusely necrotic

most likely due to the better half-life in the mouse compared to JNJ 7777120 that lacked this activity (half-life ~4–5 h). Importantly, no adrenal gland or associated toxicities were observed with JNJ 28307474 in rat and dog, supporting the conclusion that the findings seen with JNJ 10191584 and JNJ 7777120 were chemotype driven and not class effects related to the H_4R. However, a major drawback with

JNJ 28307474 was its inhibition of human ether-à-go-go-related gene (hERG) channel activity in vitro with an IC_{50} ~ 200 nM. This translated into in vivo QT-interval prolongation in both dogs (~10–15% increase) and monkeys (~30% increase). Prolongation of the QT-interval in humans can lead to serious arrhythmias and Torsade de Pointes. Therefore, this safety issue, and more specifically the lack of an estimated therapeutic window, led to the termination of the development of the compound.

3 Clinical Activity of JNJ 39758979

Once again a potential safety issue prompted the search for a different pharmacophore. Screening hits identified a tricyclic pyrimidine series as potential H_4R antagonists and led to the development of a series of both tricyclic and monocyclic aminopyrimidine antagonists (Savall et al. 2011). Out of this series emerged JNJ 39758979 (Fig. 1), one of the first H_4R antagonists to enter the clinic (Savall et al. 2014; Thurmond et al. 2014). JNJ 39758979 is a potent and selective H_4R antagonist with a K_i of 12.5 nM at the human H_4R (Table 2) and at least 80-fold lower affinity for the human histamine H_1, H_2, and H_3 receptors (Thurmond et al. 2014). Importantly, in contrast to JNJ 28307474, there was no inhibition of the human ether-à-go-go-related gene (hERG)-mediated K^+ current in transfected cells at concentrations up to 10 μM and no indication of cardiovascular effects in vivo (Savall et al. 2014). JNJ 39758979 exhibited excellent exposure, bioavailability, and half-life in mouse, rats, and dogs and this translated into excellent human pharmacokinetic properties (Savall et al. 2014; Thurmond et al. 2014). Consistent with other H_4R antagonists, JNJ 39758979 exhibited efficacy in preclinical models of asthma, dermatitis, pruritus, LPS-induced inflammation, and arthritis (Table 3) (Savall et al. 2014; Thurmond et al. 2014).

Preclinical safety testing indicated no issues that would preclude testing in humans (Thurmond et al. 2014). As with JNJ 28307474, no adrenal gland or associated toxicities were observed in any toxicology species tested, confirming that the findings with the previous compounds were related to their chemotype. Therefore, a phase 1 safety study was conducted with JNJ 39758979 in healthy human volunteers starting in September 2008. In the phase 1 study the only tolerability or safety issue noted was dose-dependent nausea thought to be due to local irritation, since it was reduced with an enteric coated formulation. The compound also exhibited excellent oral exposure with a long half-life. A pharmacodynamics assay was used to show that the compound inhibited the H_4R in vivo. This assay exploited the fact that when histamine is added to eosinophils a shape change is induced that can be detected by fluorescence activated cell sorting (FACS). Therefore, in the clinic blood was drawn from subjects after dosing with JNJ 39758979 and histamine was added. The inhibition of the eosinophil shape change was evidence that the compound was bound to the receptor and blocked its activation. Therefore, the dose-dependent inhibition of histamine-induced

eosinophil shape change observed suggested that JNJ 39758979 antagonized the H_4R in vivo.

H_4R antagonists have shown efficacy in several preclinical models of human disease and thus there were several possible avenues to explore in the clinic. One area of particular interest was pruritus since it has long been linked to histamine. In mice several different H_4R antagonists have been shown to inhibit scratching induced by histamine (Bell et al. 2004; Dunford et al. 2007; Cowart et al. 2008; Liu et al. 2008; Yamaura et al. 2009; Koenig et al. 2010; Shin et al. 2012; Savall et al. 2014). JNJ 39758979 given orally was efficacious in reducing histamine-mediated pruritus starting at doses of 5 mg/kg and higher, thus providing the rationale for testing the compound in humans (Savall et al. 2014). Histamine-induced pruritus in humans has been used for decades to study and compare the effect of antihistamines that target the histamine H_1 receptor. Injection of histamine into the skin of humans causes a perception of pruritus (i.e., the desire to scratch) within minutes of application. Mice also respond to the pruritic effects of histamine and therefore novel mechanisms can be tested in this model in mice and then directly translated into humans.

A clinical study was conducted to test the effect of JNJ 39758989 on pruritus in humans. Subjects were given a single dose of either JNJ 39758979, cetirizine (an histamine H_1 receptor antagonist), or placebo (Kollmeier et al. 2014). The use of JNJ 39758979 and cetirizine could definitively determine the relative roles for the histamine H_1 receptor and H_4R since the former only has affinity for the H_4R with no affinity for the histamine H_1 receptor and the later only exhibits histamine H_1 receptor antagonist activity with no affinity for the H_4R (Lim et al. 2005; Savall et al. 2014). Subjects were challenged with an intradermal injection of histamine one day before compound administration, to assess the baseline response, and then again 2 and 6 h after taking a dose of compound. At each of these times the subjects were asked to rate the itching sensation over a 10-min period. As predicted from the mouse model, JNJ 39758979 was able to significantly inhibit the pruritus induced by histamine to a similar extent as the positive control, cetirizine (Kollmeier et al. 2014). Of interest, JNJ 39758979 did not block the histamine-induced wheal response, although it was inhibited by cetirizine. This result was also predicted by the preclinical animal models where JNJ 7777120 was not able to block histamine-induced edema formation, whereas a histamine H_1 receptor antagonist was effective (Thurmond et al. 2004). Therefore, the specificity of JNJ 39758979 for the H_4R versus the histamine H_1 receptor was confirmed in vivo in humans. This clinical study proved a role for the H_4R in histamine-induced pruritus in humans and suggests that antagonists of the receptor may be efficacious in pruritic conditions driven by histamine such as urticaria.

Atopic dermatitis is a disease where pruritus can be the most troubling symptom. However, histamine was not thought to be involved since antihistamines that target the histamine H_1 receptor are not effective in managing the pruritus or the overall disease (Thurmond et al. 2015). The fact that the H_4R is involved in mediating histamine-induced pruritus in humans provided rationale for reinvestigating the role of histamine in atopic dermatitis. In addition to this, H_4R antagonists have

shown activity against pruritus in a number of mouse preclinical models of dermatitis (Rossbach et al. 2009; Cowden et al. 2010b; Suwa et al. 2011; Ohsawa and Hirasawa 2012). Further rationale was provided by the efficacy of H_4R antagonists on inflammatory parameters in these mouse models. In particular, JNJ 7777120, JNJ 28307474, and JNJ 39758979 have all been shown to reduce inflammation in an FITC-mediated model that has a phenotype similar to atopic dermatitis in that it is Th2 driven and leads to the accumulation of eosinophils and mast cells at the site of inflammation (Cowden et al. 2010b; Thurmond et al. 2014). H_4R-deficient mice also had a reduction in inflammation in this model similar to what was seen with the antagonists (Cowden et al. 2010b). Efficacy with H_4R antagonist has also been observed in other chronic allergic dermatitis models (Seike et al. 2010; Matsushita et al. 2012; Ohsawa and Hirasawa 2012; Mahapatra et al. 2014).

With this rationale, a clinical study was conducted to test efficacy of JNJ 39758979 in atopic dermatitis patients (Murata et al. 2015). Two dose levels of JNJ 39758979, 100 and 300 mg/day, were compared to placebo. These doses were selected because they were the highest tolerated doses in the phase 1 studies and provided through exposures well above those needed for efficacy in mouse models, 170 nM (38 ng/mL). The study was terminated early due to safety reasons (see below), and thus only 50 of the planned 105 patients reached the primary endpoint at 6 weeks. Nevertheless, the post-hoc results indicated that JNJ 39758979 appeared to have efficacy in atopic dermatitis. The primary endpoint for the study was a change in the Eczema Area and Severity Index (EASI) (Hanifin et al. 2001) compared to placebo. This index measures several parameters related to the skin lesions associated with atopic dermatitis including erythema, infiltration/population, excoriation, and lichenification. Both the 100 and 300 mg arms of the study exhibited numerical improvements in EASI compared to placebo starting at week 1; however, the results were not statistically significant with the caveat that the sample size was very small. These results suggest that H_4R antagonists can be effective in treating atopic dermatitis. As confirmation of the results seen with JNJ 39758979, another H_4R antagonist, ZPL-389, was recently shown to also be effective in patients with atopic dermatitis. In this case the reductions in EASI compared to placebo were nominally statistically significant (Werfel et al. 2016).

As mentioned above, itch is one of the characteristic symptoms of atopic dermatitis (Williams 2005). JNJ 39758979 was able to reduce pruritus in atopic dermatitis patients in the clinical study (Murata et al. 2015). There is no standard way to assess pruritus in the clinic, however, one of the most commonly used methods is a numerical rating scale where patients are asked to rate their itch on 0–10 scale. In the clinical study with JNJ 39758979 this was administered by electronic devices twice a day (morning for pruritus overnight and evening for pruritus during the day) for both the severity and duration of itch. For both of these parameters, patients taking JNJ 39758979 reported lower scores than those on placebo and the results reached nominal statistical significance for the 300 mg group. The improvement in the severity of itch was of similar magnitude to that seen with dulipumab (Thaci et al. 2015). Similar effects were seen by using other daily tools including a pruritus categorical response scale and a pruritus

interference numeric rating scale. Even more impressive were results obtained when a subject's global impression of change was used. In this case at each visit (roughly every 1–2 weeks) subjects were asked to rate their pruritus intensity and duration compared to the beginning of the study. At week 6 between 70 and 90% of the patients on JNJ 39758979 reported that the intensity was less and the duration of itch was shorter compared to what was observed at the beginning of the study, whereas only 30–40% of the patients on placebo reported improvements in these parameters. All of these results were nominally statistically significant.

Of potential interest is that the time course for improvement of EASI is similar to that of pruritus. One hypothesis is that H_4R antagonists would directly block the transmission of the pruritic signal. This is most likely the case for histamine-induced itch. If this was true for atopic dermatitis, then one would predict that the onset of pruritus relief would be rapid. However, it appears that it takes several weeks and parallels the improvement in inflammation. This suggests that the mechanism for the anti-pruritic effect of H_4R antagonists in atopic dermatitis may be a result of the anti-inflammatory effects and not a direct effect on pruritic signals. Overall, the pruritus results combined with the effects on the skin lesions suggest that H_4R antagonists may be promising future drugs for the treatment of atopic dermatitis.

While other H_4R antagonists may eventually be available for the treatment of atopic dermatitis, the development of JNJ 39758979 was terminated. In the atopic dermatitis study two patients receiving the 300 mg dose of JNJ 39758979 developed agranulocytosis (Murata et al. 2015). Agranulocytosis is a severe form of neutropenia where the absolute neutrophil count drops to less than 0.5×10^9/L. Fortunately, both patients recovered once they stopped taking JNJ 39758979. Drug-induced agranulocytosis is a rare, idiosyncratic disorder that has been reported for a number of different drugs (Andersohn et al. 2007). The reduction in neutrophils is thought to be the result of either apoptosis of neutrophils themselves, activation of immune mechanisms to target neutrophils, or disruption of myelopoiesis. While the exact mechanisms leading to these effects are unknown, the current hypothesis is that reactive intermediate(s) of the drug play an important role in the pathogenesis (Tesfa et al. 2009). These reactive intermediates can be formed via the normal metabolic pathways for the drug or, as is the putative case for clozapine, the generation of reactive intermediate(s) can result from reactions with compounds produced by activated neutrophils. Therefore, the most likely cause for the agranulocytosis seen with JNJ 39758979 is the formation of reactive intermediate(s). One reactive metabolite of JNJ 39758979 has been identified, but the actual identity of the species leading to agranulocytosis is unknown and may only be present in tissues (Murata et al. 2015).

Agranulocytosis could also occur by mechanism-based disruption of myelopoiesis. One report has shown the H_4R is expressed on murine and human progenitor cells and in vitro data from this paper indicate that agonists of the receptor reduce growth factor-induced cell cycle progression that leads to decreased myeloid, erythroid, and lymphoid colony formation (Petit-Bertron et al. 2009). To determine if JNJ 39758979 had such an effect, the impact of JNJ 39758979 on

human myeloid colony formation was studied in vitro (Thurmond and Dunford, unpublished data). Briefly, human bone marrow derived hematopoietic progenitor cells were cultured in methylcellulose-based media containing the appropriate recombinant cytokines to differentiate the stem cells to myeloid colony forming units and their granulocyte or macrophage sub-sets. Mature hematopoietic colonies were assessed and scored. No effects on human myelopoiesis were detected with JNJ 39758979 in vitro up to a highest concentration of 30 μM. In addition such effects on myelopoiesis should be detectable in preclinical toxicology studies unless they were human specific. However, neutrophil levels and neutrophil turnover were normal in H_4R-deficient mice and in rat and monkey toxicity studies, as well as there being no signs of bone marrow abnormalities or toxicity. These results support the conclusion that the compound is unlikely to have any direct inhibitory effects on myelopoiesis and the most likely explanation for the agranulocytosis observed with JNJ 39758979 is the formation of reactive species, consistent with the current thinking of the mechanisms by which other drugs cause agranulocytosis.

4 The Development of Toreforant

Since the formation of reactive intermediates is related to the structure of the compound, the best way to mitigate this would be to develop compounds with structural differences that are metabolized differently. The best example of this is clozapine that has a warning in its label for the occurrence of agranulocytosis with an estimated yearly incidence rate of 1.3%. However, the drug olanzapine, which is closely related structurally, causes little, if any, agranulocytosis (Naumann et al. 1999). Fortunately, a second H_4R antagonist, toreforant (pronunciation – tor ef' oh rant), was being developed in parallel. This molecule was structurally distinct from JNJ 39758979 (Fig. 1). This compound is derived from the pyridinyl benzimidazole series represented by JNJ28307474, with key modifications leading to the replacement of the core pyridine with an aminopyrimidine. Overall the pharmacology of toreforant was similar to JNJ 39758979 and previous H_4R antagonists (Table 2). One notable exception is that the affinity for the mouse H_4R is reduced compared to JNJ 7777120 and JNJ 39758979 and thus high doses are needed for efficacy in mouse disease models. That being said, the compound has efficacy in mouse models of asthma, dermatitis, and arthritis similar to that of JNJ 39758979 (Table 3) (Thurmond et al. 2017). However, one difference is that toreforant had no activity against histamine-induced scratching in mice, even at very high doses (Thurmond et al. 2017). This may be due to the fact that toreforant does not cross the blood–brain barrier, due to being a substrate for P-glycoprotein, and central nervous system activity may be required to block histamine-induced itch in mice.

JNJ 7777120 has been shown to have activity in a variety of pain models including models of inflammatory pain, neuropathic pain, pain associated with osteoarthritis, and post-operative pain and this may be related to similar mechanisms that mediate the anti-pruritic effects (Coruzzi et al. 2007; Altenbach et al. 2008; Cowart et al. 2008; Hsieh et al. 2010). Both JNJ 39758979 and toreforant

have been tested in a rat spinal nerve ligation model. At 50 mg/kg p.o. JNJ 39758979 yielded a 50% reduction in pain responses (Thurmond et al. 2017). Efficacy was also been seen in a rat mild thermal injury model. In contrast toreforant did not show efficacy in either model despite having more affinity for the rat H_4R than JNJ 39758979 (Thurmond et al. 2017). As with the pruritus model this could be related to the lack of CNS penetration for toreforant. However, it should be noted that the presence of the H_4R in the brain is controversial (Panula et al. 2015; Schneider and Seifert 2016).

While histamine has mainly been associated with allergic, Th2-type conditions, there is emerging evidence that it, and the cells that produce it, may be important in autoimmune diseases like rheumatoid arthritis (RA) (Zhang et al. 2006). Increases in histamine levels have been reported in the plasma and synovial fluid of RA patients and, in addition, mast cells appear to be increased in synovial fluid (Crisp 1984; Godfrey et al. 1984; Frewin et al. 1986; Tetlow and Woolley 1995, 1996; Gotis-Graham and McNeil 1997; Gotis-Graham et al. 1998). The H_4R appears to be expressed in synovial cells from subjects with RA (Ikawa et al. 2005). Preclinically H_4R-deficient mice or mice treated with H_4R antagonists showed reduced symptoms and inflammation in models of RA (Cowden et al. 2013; Savall et al. 2014). Toreforant shows a similar effect in reducing disease score in a mouse model of arthritis (Thurmond et al. 2017).

With this rationale in hand, two studies with toreforant were conducted in patients with RA (Thurmond et al. 2016). The first study was a phase 2a study comparing 100 mg/day toreforant to placebo in RA patients on stable doses of methotrexate who still exhibited disease activity. This study was planned to enroll approximately 90 subjects (2:1 active:placebo randomization) and for them to be treated for 12 weeks. However, the study was terminated early due to what at the time was an unexplained death in a patient who received toreforant. It was later determined that the cause of death was secondary hemophagocytic lymphohistiocytosis, an immune activation syndrome, and unlikely to be related to toreforant, although the relation cannot be ruled out entirely. Due to the early termination, only 36 subjects completed the study and the efficacy analysis was post-hoc. Nevertheless, it appeared that subjects taking toreforant had improvements in signs and symptoms associated with RA (Thurmond et al. 2016). A follow-up study was conducted in the same patient population, but this time assessing 3, 10, and 30 mg/day doses of toreforant over 6 months (Thurmond et al. 2016). The top dose of toreforant was lowered compared to the phase 2a study based on preclinical efficacy models predicting that trough values of 6 ng/mL would be necessary for efficacy and the 30 mg dose yields a trough value significantly above this, 104 ng/mL. In addition, QT prolongation was observed in subjects at doses above 100 mg, making long-term development of the 100 mg dose problematic (Thurmond et al. 2017). In contrast to what was seen in the phase 2a study, no efficacy was observed for toreforant on any efficacy parameter in RA patients (Thurmond et al. 2016). Given the disparity between the results it is unclear as to whether the lack of efficacy in the second study was due to the lower doses used or misleading results from the first study due to the early termination. Overall, it is still unclear whether H_4R antagonists will have efficacy in RA.

5 Concluding Remarks

In conclusion, the first reports of clinical data with H_4R antagonists have appeared over the past couple of years; however, as evidenced by the history with the Janssen H_4R program, the path to the clinic has not been a smooth one. In the process of developing compounds that target the H_4R, thousands of compounds have been made that are ligands for the receptor; however, very few of them have all of the properties needed to advance into clinical testing. This is not unique for the H_4R, as finding ligands and inhibitors for drug targets is just a starting point and the real difficulty lies in finding a compound with the right properties to make it a useful therapeutic. Fortunately for the H_4R, compounds like JNJ 39758979 and toreforant exhibited profiles that allowed clinical testing and so the role of the H_4R in human diseases can be explored. Clinical work with these compounds have shown the clear potential for the use of H_4R antagonists in the treatment of pruritus and atopic dermatitis and it may not be long before drugs that target the H_4R are available for the treatment of such conditions. However, the efficacy in rheumatoid arthritis is still not clear and results from other studies conducted in allergen challenge models, asthma, and psoriasis have yet to be reported. In conclusion, there has been much progress in identifying useful ligands for the H_4R, understanding its role in preclinical models and early success in clinical studies. However, the next frontier will be to detail out the full therapeutic potential of H_4R antagonists and the full spectrum of human diseases where the H_4R plays a role.

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