The Impact of COVID-19 on Dermatology Clinical Trials

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TO THE EDITOR

The demands of social distancing during the novel coronavirus 2019 (COVID-19) pandemic have upended standard healthcare workflows through travel limitations, site closures, and interruptions of medication supply chains (U.S. Food & Drug Administration, 2020). These changes have impacted the conduct of highly choreographed clinical trials, which require timely visits and assessments to maintain scientific validity in evaluating the safety and efficacy of new medications (European Medicines Agency, 2020; U.S. Food & Drug Administration, 2020).

In response to the logistic and economic uncertainties of the current times, some clinical trials have been suspended or will not begin as originally planned because of the global pandemic (Ledford, 2020). We aimed to investigate the impact of the COVID-19 outbreak on dermatology-related clinical trials by examining the publicly available clinical trials data.

Methods

We queried ClinicalTrials.gov, a global repository of privately and publicly funded clinical studies, to identify the clinical trials related to dermatologic conditions using the search terms dermatologic diseases, skin diseases, and skin disorders from 1 April 2019 to 31 May 2020. For interventional trials listed as withdrawn, suspended, or terminated, the date the trial listing was last updated was used as a proxy for when the trial’s status was changed. We excluded trials that were not related to dermatology, listed as completed, had not posted updates, or had not been verified by ClinicalTrials.gov within the past 2 years. We also excluded trials that had been withdrawn, terminated, or suspended before 1 March 2019.

Information on the trial’s name, related condition(s), estimated enrollment, last update, and current status (suspended, withdrawn, terminated, active not recruiting, recruiting, and enrolling by invitation) were collected. Active, not recruiting trials include ongoing studies with participants who are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled. For any trials suspended in March, April, or May 2020, we reviewed any listed reasons for trial closures and documented if this reason was specifically attributed to COVID-19.

Although we were unable to ascertain the total number of ongoing dermatology trials in 2019, we performed a sensitivity analysis using chi-square analysis to determine the minimum number of ongoing trials required in 2019 to ensure that the change in the proportion of trial suspensions, terminations, and withdrawals in March—May 2019 was different than the proportion of trial suspensions, terminations, and withdrawals in March—May 2020 (defined as P < 0.05).

Results

We identified 1,010 active (not recruiting), recruiting, and enrolling by invitation trials for dermatologic conditions, with an estimated enrollment of 284,881 patients. In total, 293 (29%) of trials were listed as active (not recruiting) with an enrollment of 121,310 patients. In addition, 92 of 1,010 trials (9.1% of the ongoing dermatology-related clinical trials) had been suspended, withdrawn, or terminated. Over half of the suspensions, terminations, and withdrawals occurred in March, April, and May of 2020 (n = 57 of 92, 62%; Figure 1), with an estimated enrollment of 7,141 patients (7,141 of 292,022; 2.4% of all the patients enrolled in the dermatology trials). There were 17, 21, and 7 excess dermatology trial suspensions, terminations, and withdrawals that occurred in March, April, and May of 2020, respectively, as compared with March, April, and May of 2019 (Table 1).

Among the affected trials, 5,607 patients (79%) were enrolled in 32 trials (56%) listed as suspended specifically because of the COVID-19 pandemic. The most common COVID-19 trial suspensions were for atopic dermatitis (n = 7), psoriasis (n = 7), and hidradenitis suppurativa (n = 5). Most (63%, 20 of 32) of the COVID-19 affected trials were phase 2 and 3 trials. A total of 44% (14 of 32) of the COVID-19—affect ed trials had an estimated enrollment of more than 100 patients.

Our sensitivity analysis revealed that the proportion of trial suspensions, withdrawals, and terminations in March, April, and May of 2020 (N = 57) was significantly more than the proportion of trial suspensions, withdrawals, and terminations occurring in March, April, and May of 2019 (N = 12, P < 0.05). Assuming that the number of active, not recruiting, recruiting, and enrolling trials (e.g., ongoing trials) in 2019 did not fall below 398 (61% less than the number of ongoing trials in 2020).

Discussion

We observed an increase in the suspension, withdrawal, and termination of clinical trials for dermatologic conditions during the initial months of the COVID-19 pandemic, many of which were attributed specifically to the coronavirus outbreak. These changes
have substantial implications on the currently enrolled patients, as clinical trials provide patients with skin disorder treatments that can significantly improve their clinical outcomes and QOL (Torre and Shahriari, 2017). The reverberations of clinical trial closures will not only affect patients during the pandemic but will also extend well beyond this timeframe. Halting clinical trials, which serve as the basis for regulatory approval of new treatments (U.S. Food & Drug Administration, 2019), can create considerable delays in drug development.

Barriers to the treatment and timely assessment of trial enrollees may also threaten the integrity of clinical trials data and limit their interpretation (McDermott and Newman, 2020). Furthermore, the financial impact of trial closures and reassignment of study personnel may alter the available infrastructure for future trials. Additional studies are necessary to investigate the impact of trial closures on both trial integrity and infrastructure.

The results of our study must be interpreted within the context of our study design. Our sensitivity analysis was simple and unadjusted. Although ClinicalTrials.gov requires responsible parties to update their records within 30 days of a change to an individual site and overall recruitment status (ClinicalTrials.gov, 2020), it is possible that some sponsors do not change the status of their studies in a timely manner (Tse et al., 2018). In addition, a multisite trial’s overall recruitment status may have remained unchanged if only a subset of its sites experienced closures. Our study may therefore underestimate the number of trials affected.

Although our data show a spike in trial suspensions, withdrawals, and terminations over the past 3 months, longitudinal data are required to determine the complete scope of the impact of COVID-19 on the dermatology trials. Until then, the development and dissemination of best practices to maintain patient safety and trial integrity are essential in maintaining the progress of therapeutic development within dermatology.

Table 1. Excess Trial Suspensions, Withdrawals, and Terminations in March–May 2019 Relative to Suspensions, Withdrawals, and Terminations in March–May 2020

<table>
<thead>
<tr>
<th>Month</th>
<th>March</th>
<th>April</th>
<th>May</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2019</td>
<td>2</td>
<td>90</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>March 2020</td>
<td>19</td>
<td>1,545</td>
<td>28</td>
<td>4,680</td>
</tr>
<tr>
<td>Excess</td>
<td>17</td>
<td>1,455</td>
<td>21</td>
<td>4,680</td>
</tr>
</tbody>
</table>

Figure 1. Trials for dermatologic conditions that were suspended, withdrawn, or terminated between 1 April 2019 and 31 May 2020. Suspended trials: the study has stopped early but may start again. Terminated trials: the study has stopped early and will not start again. Participants are no longer being examined or treated. Withdrawn trials: the study stopped early, before enrolling its first participant.
MRGPRX2 Activation Causes Increased Skin Reactivity in Patients with Chronic Spontaneous Urticaria


TO THE EDITOR

Previous studies showed that injection of basic secretagogues such as substance P, compound 48/80, and vasoactive intestinal peptide induced exaggerated responses in the skin of patients with chronic spontaneous urticaria (CSU) versus those of healthy controls through an unknown G protein–coupled receptor (Borici-Mazi et al., 1999; Bédard et al., 1986; Smith et al., 1992). The human receptor for these secretagogues has been identified as MRGPRX2, and in vitro work has shown that MRGPRX2 can activate mast cells (MCs) through a diverse range of drug ligands such as the neuromuscular blocking drug, atracurium, and a bradykinin B2 receptor antagonist, icatibant (McNeil et al., 2015). Further in vitro studies have provided evidence of MRGPRX2 drug ligand activation in cell lines and animal models, but no human experiments have been performed (Che et al., 2018; Navinés-Ferrer et al., 2018; Roy et al., 2019). With the recent discovery that MRGPRX2 protein expression is increased in the MC taken from skin biopsies of patients with severe CSU (Fujisawa et al., 2014), we examined whether subjects with milder CSU would show a heightened in vivo functional skin response when tested with MRGPRX2 drug ligands compared with healthy controls. This study is a demonstration of an increased functional skin response supporting MRGPRX2-increased protein expression in patients with CSU. We further demonstrate that drug-induced MC activation requires MRGPRX2 using knockout LAD2 cells and is not occurring through IgE pathways.

We conducted the study at the Johns Hopkins Asthma and Allergy Center (Baltimore, MD) after approval by the Institutional Review Board. After written informed consent, healthy subjects and subjects with mild CSU between the ages of 18 and 65 years underwent serial intradermal skin titration testing with two MRGPRX2 drug ligands, icatibant (0.01–100 μg/ml, 7×10⁻³–76 μM, physiologic range 974 ± 280 ng/ml [Shire Pharmaceuticals, Lakewood, NJ]) and atracurium (0.001–10 μg/ml, 8×10⁻⁴–8 μM, physiologic range ~100–3,000 ng/ml [Hospira, Lake Forest, IL]) and saline control (Hospira) as well as histamine (0.01–100 μg/ml, COVID-19 (coronavirus) pandemic, version 3. https://ec.europa.eu/health/sites/health/files/files/ eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf, 2020 (accessed 6 May 2020).


Tse T, Fain KM, Zarin DA. How to avoid common problems when using ClinicalTrials.gov in research: 10 issues to consider. BMJ 2018;361: k1452.


Abbreviations: CSU, chronic spontaneous urticaria; MC, mast cell

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