Clinical evaluation of a novel microneedle device for intradermal delivery of an influenza vaccine: Are all delivery methods the same?

Yotam Levin a,*, Efrat Kochba a, Richard Kenney b,1

a NanoPass Technologies Ltd., 3 Gdala Meir Street, Nes Ziona 7403648, Israel
b Crucell Holland B.V., Archimedesweg 4, 2333 CN Leiden, The Netherlands

1. Introduction

Even with decades of efforts to improve influenza vaccination, influenza virus infection remains an annual cause of substantial illness and mortality, associated with pronounced clinical, logistical, and policy-making challenges to healthcare organizations globally. Immunization rates are disappointing within the public sector [1] and even for healthcare workers [2]. This continues despite major governmental efforts and the fact that vaccination remains the best global strategy for reducing influenza morbidity and mortality [3,4]. Annual strain matching remainsmediocre at times and overall effectiveness rates, whenever tested, appear moderate [5]. One of the major issues for vaccine developers continues to be the timely production of the influenza vaccine in large volumes. Improving its immunogenicity, especially in low-responder populations like the elderly, the immunocompromised, and young children, remains a high developmental priority [6].

Multiple approaches are being evaluated to achieve better influenza vaccine immunogenicity and reduce the dose required for vaccination. Intradermal delivery has been proposed as a means of dose sparing in adults [7–9], children [10], and infants [11], as well as in the elderly [12]. Studies have demonstrated mixed results using the intradermal route, with some showing potentially inferior results compared to full dose IM delivery [13], whereas others show equivalence or non-inferiority [9,14] and a few show superior immunogenicity [14,15]. While there are multiple differences between the studies with respect to the populations, vaccine products, and study designs, it appears that one of the dominant factors might be the device in use. Several studies have been reported where conventional needles are used with the Mantoux technique [9,12], which is neither easy to perform nor reliable at providing consistently shallow injections [16]. More recent studies have used novel technologies that incorporate mini- (<1 mm) and micro-(<1 mm) needle approaches. A recent Phase II clinical study comparing the mininneedle technology delivering partial doses of a seasonal influenza vaccine demonstrated superior immunogenicity to the full-dose conventional IM injection for the influenza A strains [14], yet these needles tend to deliver the antigens well below the superficial dermis and epidermis. Most of the dendritic cells (DCs) that migrate from the bone marrow into the skin reside in this superficial space and perform the dual role of immune surveillance and antigen presentation [17]. Intradermal techniques
theoretical need to target these specialized epidermal cells to provide improved immunogenicity.

We report a clinical trial directly evaluating two methods of intradermal delivery: the century-old Mantoux technique using a conventional needle [18], compared to a novel microneedle device (MicronJetTM, NanoPass Technologies Ltd, Israel). The MicronJetTM contains highly precise silicon needles that are only 0.45 mm long and are manufactured using semiconductor technology to deliver vaccine specifically to the epidermis and shallow dermis. We report here additional results from a Phase II clinical study comparing the safety and immunogenicity of various doses of the virosomal-influenza vaccine and by different routes of administration [19].

2. Materials and Methods

In order to evaluate the feasibility of using this novel microneedle device we included a treatment arm of 1/5th (3 μg hemagglutinin [HA]/strain in 0.1 mL) of the standard virosomal influenza vaccine (Crucell Switzerland AG [Crucell]), delivered intradermally (ID) via the MicronJetTM device (Group C). This was compared with the full dose (15 μg HA/strain in 0.5 mL) Inflexal® V (Crucell) commercial vaccine delivered intramuscularly (IM) that provided a positive control (Group B), and with reduced doses of the virosomal influenza vaccine (Crucell) delivered ID in 0.1 mL volumes using the conventional Mantoux technique with a 25 G 16 mm (5/8 in.) length needle (3 μg, 4.5 μg or 6 μg HA/strain in Groups A1, A2, and A3, respectively). The study was conducted under cGMP in a Phase I Unit in Basel, Switzerland between September and November 2007 and was sponsored by Crucell (http://www.controlled-trials.com/ISRCTN33950739). All injections were performed by a single experienced nurse and given into the deltoid muscle or the adjacent skin. Table 1 summarizes the vaccine formulations and study groups. The vaccine used was the 2007/2008-season virosomal adjuvanted influenza vaccine, containing purified viral surface antigens of A/Solomon Islands/3/2006 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, and B/Malaysia/2506/2004-like virus, as recommended by the WHO and EMA/CHMP.

Subjects were randomized to receive a single low dose ID vaccination (Groups A1 [N=56], A2 [N=56] or A3 [N=56]) using the Mantoux technique or a full-dose IM vaccination (Group B [N=56]) using a standard needle. A fifth group was added after randomization and given a single low dose ID vaccination with the MicronJetTM device (Group C [N=56]). Groups of this size provide the ability to distinguish about a 2-fold difference in comparing immunogenicity results. Antibody titers were measured using hemagglutination-inhibition (HI) assays according to standard methods at Crucell [19] at baseline and 21 days after vaccination; HI analysis was done using standard EMEA definitions [20]. Safety was assessed using a solicited adverse event checklist and a 4-day diary. Comparisons between groups were performed in the according-to-protocol (ATP) population based on t-test, F-test.

Figure 1. GMT fold increase. Significant p-values are noted compared to Group A1 (for the A/Solomon Islands [H1N1] and B/Malaysia strains) and compared to Group B (for the A/Wisconsin [H3N2] strain) (horizontal line indicates EMEA criteria threshold).
Table 2

<table>
<thead>
<tr>
<th>Seroconversion</th>
<th>A1 (ID 3 µg) [N=55]</th>
<th>A2 (ID 4.5 µg) [N=53]</th>
<th>A3 (ID 6 µg) [N=55]</th>
<th>B (IM 15 µg) [N=54]</th>
<th>C (ID-M) 3 µg* [N=54]</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>A/Solomon Islands</td>
<td>47 (85.5)</td>
<td>44 (83.0)</td>
<td>46 (83.6)</td>
<td>47 (87.0)</td>
<td>49 (90.7)</td>
</tr>
<tr>
<td>A/Wisconsin</td>
<td>33 (60.0)</td>
<td>38 (71.7)</td>
<td>43 (78.2)</td>
<td>38 (70.4)</td>
<td>47 (87.0)*</td>
</tr>
<tr>
<td>B/Malaysia</td>
<td>28 (50.9)</td>
<td>36 (67.9)</td>
<td>33 (60.0)</td>
<td>44 (79.6)*</td>
<td>40 (74.1)</td>
</tr>
<tr>
<td>Seroprotection</td>
<td>pre (% pre) post (% post)</td>
<td>pre (% pre) post (% post)</td>
<td>pre (% pre) post (% post)</td>
<td>pre (% pre) post (% post)</td>
<td>pre (% pre) post (% post)</td>
</tr>
<tr>
<td>A/Solomon Islands</td>
<td>20 (36.4)</td>
<td>19 (35.8)</td>
<td>16 (29.1)</td>
<td>19 (35.2)</td>
<td>16 (29.6)</td>
</tr>
<tr>
<td>A/Wisconsin</td>
<td>53 (96.4)</td>
<td>51 (96.2)</td>
<td>49 (89.1)</td>
<td>52 (96.3)</td>
<td>52 (96.3)</td>
</tr>
<tr>
<td>B/Malaysia</td>
<td>11 (20.0)</td>
<td>5 (9.4)</td>
<td>5 (9.1)</td>
<td>7 (13.0)</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td>GMT</td>
<td>(pre) post fold increase</td>
<td>(pre) post fold increase</td>
<td>(pre) post fold increase</td>
<td>(pre) post fold increase</td>
<td>(pre) post fold increase</td>
</tr>
<tr>
<td>A/Solomon Islands</td>
<td>(27.4) 1034.3</td>
<td>(25.4) 1788.3</td>
<td>(16.4) 765.3</td>
<td>(20.9) 1180.4</td>
<td>(22.8) 1924.6</td>
</tr>
<tr>
<td>A/Wisconsin</td>
<td>(52.9) 1182.8</td>
<td>(45.2) 1293.0*</td>
<td>(34.0) 1324.1*</td>
<td>(40.9) 691.8</td>
<td>(38.3) 1529.2*</td>
</tr>
<tr>
<td>B/Malaysia</td>
<td>(10.5) 72.8</td>
<td>(9.0) 149.9</td>
<td>(8.0) 91.4</td>
<td>(8.5) 152.9*</td>
<td>(6.4) 183.0*</td>
</tr>
<tr>
<td>6.9</td>
<td>16.7*</td>
<td>11.4</td>
<td>18.0**</td>
<td>28.5***</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05 compared to A1.
* p < 0.01 compared to A1.
* $p < 0.05$ compared to A3.
* $p < 0.01$ compared to A3.
* $p < 0.05$ compared to B.
* $p < 0.01$ compared to B.

or, $X^2$-test, whenever applicable, and expressed as p-values of the investigated contrast. The analysis of HI antibodies was performed on log$_{10}$-transformed data; adverse events (secondary endpoints) are reported descriptively.

3. Results

A total of 280 subjects were enrolled, of which 279 concluded the study. Baseline demographics between the five groups were well matched, except that Group C was slightly younger (mean of 34.1 years old) compared to the two oldest groups A1 and A3 (39.5 and 39.6 years old, respectively). No deaths or serious adverse events were reported. The local symptom of post-vaccination pain in the 4 days following vaccination was more common in the IM Group B (38.8%) than in the ID Group C using the MicronJet$^\text{TM}$ device (10.9%), whereas induration was more common in Group C (50.9%) than Group B (16.7%) and erythema was more common in the ID groups (61.8%, 52.8%, 74.5%, and 89.1% in Groups A1, A2, A3, and C, respectively). Other local and systemic symptoms were reported in similar frequency in both groups.

Immunogenicity (Fig. 1 and Table 2) was higher in the 3 µg ID group using the MicronJet$^\text{TM}$ needle (Group C) compared to the ID groups using the conventional Mantoux needle (Groups A1, A2, and A3) and the IM group (Group B). Group C had a higher GMT fold increase for the A/Solomon Islands (H1N1) and the B/Malaysia strains compared to Group A1 (p = 0.048 and p < 0.001, respectively), a higher A/Wisconsin (H3N2) increase compared to Group B (p = 0.047), and a higher B/Malaysia increase compared to Group A3 (p = 0.004). Groups A2 and B also had a higher increase for the B/Malaysia strain compared to Group A1 (p = 0.006 and 0.003, respectively). All other GMT increases appeared to be equivalent between the various groups. No dose-response curve was identified in the conventional ID delivery arms [19]. Importantly, IM delivery of the full vaccine dose did not show higher immunogenicity than the 1/5th dose ID delivery group using the MicronJet$^\text{TM}$ device.

Serovaccination rates for the three strains ranged from 50.9% to 85.5% in the ID groups using the conventional needle with 3, 4.5, or 6 µg per strain (Groups A1, A2, or A3, respectively), from 70.4% to 87.0% in Group B (IM 15 µg), and from 74.1% to 90.7% in Group C (ID 3 µg using the MicronJet$^\text{TM}$ device). Group C had a significantly higher serovaccination rate than Group A1 for the H3N2 and B strains (p = 0.002 and 0.018, respectively). After ID vaccination by conventional needle (Groups A1, A3, or A3), subjects had seroprotection rates of 65.5% to 98.2%. Seroprotection rates following intramuscular vaccination (Group B) ranged from 85.1% to 96.3%. After intradermal vaccination with the MicronJet$^\text{TM}$ device (Group C), subjects had seroprotection rates of 83.3% to 98.1%. The response in Group C was somewhat greater than the response in Group A1 for the B/Malaysia strain (p = 0.048).

4. Discussion

This study was designed to gather information on whether a reduced ID dose of Inflexal$^\text{®}$ V could achieve comparable results to IM full dose administration in healthy adults. As the group dosed with the MicronJet$^\text{TM}$ device was added at the same study site soon after randomization, the groups are comparable and in addition were dosed with the same vaccine, so comparisons with the original groups can provide useful insights. Inflexal$^\text{®}$ V administered ID at reduced doses or IM at the full dose fulfilled the individual annual relicensure parameters set by EMEA for influenza vaccines [20] in all study groups, except that seroprotection in ID Group A1, which was dosed at 3 µg using a conventional needle, was below the EMEA threshold for the B strain. Intradermal vaccination using the MicronJet$^\text{TM}$ device induced significantly higher antibody
responses than a comparable dose injected with the Mantoux technique using a conventional needle for the H1N1 and B strains.

This study suggests that the immunogenicity of seasonal influenza vaccine may be dependent on the administration route (ID vs. IM) and delivery device, in addition to the effect of the vaccine dose and influenza strain in any individual year. The benefits seen with the MicronJet™ device could be due to the precise delivery of the influenza vaccine primarily to the superficial dermis, where DCs are abundant, compared to deeper intradermal delivery. Injections in this study were performed by a highly experienced nurse in a professional Phase I unit; the authors hypothesize that the differences could be further pronounced in larger (Phase III) or field studies, when multiple users having varied levels of experience and expertise are performing the injections. Further data is required to evaluate the differences between delivery methods in similar studies, and particularly for low-responder populations such as the elderly and the very young.

Acknowledgments

This clinical study was sponsored by Crucell and was supported with devices and training by NanoPass Technologies. The authors would like to thank Dr. Georgi Shukarev and Dr. Valérie Kunzi, Clinical Development & Medical Affairs Managers, as well as Dr. Jaco Klap, Sr. Statistician, from Crucell in assisting with this study and reviewing the manuscript.

Conflict of interest statement: Drs. Levin and Kochba are employed by and have a financial interest in NanoPass Technologies. Dr Kenney was employed by and had a financial interest in Crucell.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.03.024.

References