Reduced injection site pain with succinate buffer based adalimumab injection (SUFFER Study): An observational study

# Background

Pain due to subcutaneous injections often leads to patient incompliance. Advances in formulation of injection are targeted at developing injectables, which can cause minimal discomfort. Injection associated discomfort includes local site pain, erythema, edema, hematoma and pruritus. Subcutaneous injections are more painful than any other types. The cause of local injection pain owing to the formulation is unknown; however, it is thought to occur due to any of the following reasons: injection volume, speed of injection, osmolality, pH, anatomical region of injection site, size and quality of injection needle, presence of irritating substances, individual patient characteristics, frequency of administration, and temperature of the solution.1 Buffers are ideally used in injectable formulations to prevent the pH-associated degradation of the active ingredient(s) and improve the stability of the product. The choice of buffers includes citrates, carbonates, acetates, histidine, sodium bicarbonate and phosphates. Citrate buffers, the most widely studied buffer has been shown to be associated with more pain than histidine buffer, phosphate buffer, or isotonic saline.2–5 *In vitro* comparison of myotoxicity of different buffers showed that isotonic succinate buffers were associated with the low myotoxicity vs. citrate buffers.6 Adalimumab (Humira) is a citrate buffer based formulation. Navarro-Millán et al. reported that significant proportion of patients injected with adalimumab (Humira) injection experienced injection/infusion-site burning and stinging than those injected with etanercept. The plausible reason was ascertained to the potential differences in the pH (adalimumab pH=5.2; etanercept pH=6.3) or the inactive ingredients used to maintain the pH.7

# Study objective

Since citrate buffer based formulation has been associated with pain and discomfort at injection site, we wanted to evaluate the pain associated with adalimumab (Exemptia™), which is formulated using succinate buffer.

# Study design

We conducted a prospective (questionnaire-based) study in patients treated with adalimumab (Exemptia™) injection for various rheumatological conditions (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis). Adalimumab (Exemptia™) injection is formulated with succinate buffer.

# Materials and method

Patients aged 12 years and above <70 years suffering from rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA) taking adalimumab (Exemptia™) injection were included in the study. We collected data (N=92) with respect to pain at the site of injection and injection site reaction with the aid of a questionnaire. Data was collected from 500 patients over 6 months and most of them completed at least 3 cycles of injection. Primary objective is pain at the site of injection within 24 h of injection. Pain was assessed using the verbal pain intensity scale provided by National Initiative on Pain Control™ (NIPC™).8

# Results

Patients included in this study were aged between 13 and 65 years (mean 39.72 ±14.42 years); 367 of them were men and 133 were women (Table 1).

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| **Table 1. Patient distribution and age in the study** |
| **Indication** | **Ankylosing spondylitis** | **Juvenile idiopathic arthritis** | **Psoriatic arthritis** | **Rheumatoid arthritis** |
| Females (N) | 74 | 9 | 3 | 43 |
| Males (N) | 291 | 3 | 20 | 50 |
| Average age in females (years ±SD) | 32.8 (10.43) | 16.56(5.66) | 54.66(16.78) | 45.72(10.91) |
| Average age in males (years ±SD) | 38.85(13.76) | 16.33(7.51) | 53.85(9.92) | 49.44(14.48) |
| SD, standard deviation |

Majority of the patients received injections in the abdomen (N=490) while eight received it in the thigh. We excluded seven patients from the analysis because they were not treated for rheumatologic conditions. We assessed the pain following the use of succinate buffer injection of adalimumab (Exemptia™) injection in 492 patients with rheumatoid arthritis (RA; N=93), ankylosing spondylitis (AS; N=365), juvenile idiopathic arthritis (N=12), and psoriatic arthritis (N=23). Majority of the patients (83.12%) reported ‘no pain’ (Figure 1). On the verbal pain intensity scale, more than 90% of the patients reported ‘no pain’ or ‘mild pain’. None of the patients reported ‘extreme pain’ or ‘worst possible pain’. One patient with ankylosing spondylitis reported ‘severe pain’ (Table 2).

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| Table 2. Distribution of patients with different rheumatological conditions across the verbal pain intensity scale  |
| **Verbal pain intensity scale** | **Ankylosing spondylitis (N)** | **Juvenile idiopathic arthritis (N)** | **Psoriatic arthritis (N)** | **Rheumatoid arthritis (N)** | **Total number of patients** | **Percentage of patients** |
| No pain | 312 | 9 | 21 | 67 | 409 | 83.12 |
| Mild pain | 35 | 3 | 2 | 22 | 62 | 12.6 |
| Moderate pain | 17 | 0 | 0 | 4 | 21 | 4.26 |
| Severe pain | 1 | 0 | 0 | 0 | 1 | 0.2 |
| Very severe pain  | 0 | 0 | 0 | 0 | 0 | 0 |
| Worst possible pain | 0 | 0 | 0 | 0 | 0 | 0 |
| Total (N) | 365 | 12 | 23 | 93 | 493 |  |

# Conclusion

In our study, use of succinate buffer adalimumab (Exemptia™) injection was associated with no pain or mild pain. The outcome of this pilot study needs to be confirmed with a larger control-group trial.

# References

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