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REVIEW

Understanding and Minimising Injection-Site Pain Following Subcutaneous Administration of Biologics: A Narrative Review

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ABSTRACT

Injection-site pain (ISP) is a subjective side effect that is commonly reported with the subcutaneous administration of biological agents, yet it may only be a concern to some. Multiple factors related to the product formulation, such as pH, volume and excipients, and/or to the injection process have the potential to contribute to ISP, while patient-related factors, such as low body weight, gender and age, can make an individual more susceptible to experiencing ISP. While total elimination of ISP remains unlikely with any subcutaneously administered agent, it can be minimised by helping the patient to develop a confident and competent injection technique via robust and effective training. Careful management of patient expectations along with open discussion regarding the potential risk of ISP may serve to minimise treatment-related anxieties and, importantly, allow the patient to remain in control of his/her treatment. Other interventions to help minimise ISP include psychological interventions, allowing biologics to reach room temperature prior to injection, using the most suitable injection device for the individual patient and selecting an alternative drug formulation, when available. Productive patient–physician communication remains important in order to support and optimise treatment experience and adherence, while also providing the opportunity for patients to discuss any ISP-related issues.

Keywords: Biosimilar; Formulation; Injection process; Injection-site pain; Patient–physician communication; Subcutaneous; Training

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Key Summary Points

Injection-site pain (ISP) is a commonly reported subjective side effect with the subcutaneous (SC) administration of biological agents, yet it may only be a concern to some.

Multiple factors, including those related to product formulation (e.g. pH, volume, excipients, injection process) and to the patient (low body weight, gender and age) have the potential to contribute to ISP.

While total elimination of ISP remains unlikely, it can be minimised by helping the patient develop a competent injection technique and by lowering their treatment-related anxieties.

Other interventions to help minimise ISP include psychological interventions, allowing biologics to reach room temperature prior to injection, using the injection device most suitable for the individual patient and selecting an alternative drug formulation, when available.

Productive patient–physician communication remains important in order to support and optimise treatment experience and adherence, while also providing the opportunity for patients to discuss any ISP-related issues.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13034609.

INTRODUCTION

Biological agents have revolutionised treatment across a range of immune- and inflammatory-mediated diseases [1–4], and the efficacy and manageable side-effect profiles of these agents have led to them being recommended in treatment guidelines [5–9]. However, the use of intravenous (IV) infusions for these biologics involves invasive procedures that can be inconvenient for both patients and healthcare professionals alike [10]. Furthermore, such infusions require expensive healthcare resources and may be subject to capacity issues in overly stretched infusion clinics. Intramuscular (IM) injections are not commonly used due to limitations in injectable volume and typically cause more discomfort than subcutaneous (SC) injections [11]; however, it has been suggested that the IM route of administration is less immunogenic than the SC route [12]. The SC delivery of biologics has become a frequently used route of administration across many disease areas, including rheumatology, gastroenterology and dermatology [1, 10, 13, 14].

SC delivery has been shown to be a safe, efficacious and convenient dosing method that is particularly suitable for frequent treatment dosing, long-term regimens and patient self-administration [10, 15]. However, as with any injection, this mode of treatment administration can be associated with a subjective level of local pain and irritation from the needle puncture [16]; the chemical and physical properties of the biologic solution may also be contributing factors. Any pain and discomfort associated with injections may negatively affect medication adherence and overall patient experience.

In this review we explore factors that can influence injection-site pain (ISP) associated with the SC administration of biologics, as well as techniques to minimise this sensation. We focus on those agents for which biosimilars of differing formulations are currently available. This review is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors therefore ethical approval was not required.

Table 1 Factors contributing to subcutaneous injection-site pain

Product-related factors	Injection-related factors	Patient-related factors
• Formulation (ingredients, pH, buffers) [16, 17, 27, 28, 40]	• Injection speed [55–58]	• Low body weight [68]
• Delivery volume [15, 32–34]	• Fluid viscosity [55]	• Injection anxiety/'needle phobia' [69, 70]
• Needle gauge size [44]	• Injection angle/technique [59, 60]	• Pain catastrophising [72]
• Device type [49–54]	• Temperature of product [62, 63]	• Nocebo effect [73, 74]
	• Allergens [65, 66]	• Female gender [67]
	• Injection frequency [61]	• Fibromyalgia [67]
	• Injection site [35]	• Depression [67]
		• Severe rheumatoid arthritis [67]
		• Patient expectations [77, 78]
		• Patient movement (during injection) [87]

FACTORS CONTRIBUTING TO SC ISP

Factors contributing to SC ISP can be product-, injection- or patient-related (Table 1). In the following sections of this review, we discuss each of these factors in detail.

Product-Related Factors Contributing to SC ISP

Product-related factors vary widely between biologics, but also between different approved products containing the same active ingredient, such as a reference product and a biosimilar. The formulation of a biologic affects (amongst others) the pH, osmolality (the osmotic pressure of the drug solution), its excipients, and the administered volume. Different formulations of biologics administered subcutaneously (SC biologics) can impact on patient experience and preference, as shown by Klement and Arndt [17] who reported that ISP could be evoked by the unphysiological osmolality or pH of their formulation [17]. As a number of biosimilar biologics are now available for clinical use, with many more in the pipeline, the varying formulations of biosimilars also need to be considered. For example, the diversity of product-related factors across available originator and biosimilar formulations of the anti-tumour necrosis factors (anti-TNF) adalimumab and etanercept is shown in Table 2. Of note, available data for etanercept and adalimumab biosimilars demonstrate similar levels of ISP between the originator agents and their biosimilars in patients with psoriasis, psoriatic arthritis and rheumatoid arthritis (and healthy volunteers) [18–21]. In addition, Krishnan et al. [22] demonstrated that patient perception of ISP was lower with an adalimumab biosimilar than with the originator agent, with results attributed to the different excipients in the biosimilar formulation [22]. Of note, any variations in ISP between originator and biosimilar biologics do not appear to reflect any differences in immunogenicity between these agents [23], with biosimilars reported to be effective and well tolerated in maintaining complete remission after the switch from the originator agent [24, 25].

pH

Bunke et al. [26] suggested that the difference between the physiological pH of the tissue at

Table 2 Variability in product-related factors contributing to injection-site pain across available references for and biosimilar formulations of a) adalimumab and b) etanercept

a)

Product-related factors contributing to SC ISP	Humira (concentrated) (adalimumab) [90]	Humira (classic) (adalimumab) [90]	Imraldi (SB5) [91]	Amgevita (ABP 501) [92]	Idacio (MSB11022) [93]	Hulio (FKB327) [94]	Hyrimoz (GP2017) [95]
Citrate	No	Yes	Yes	No	Yes	No	Yes
Needle gauge	AI: 29 PFS: 29	AI: 27 PFS: 27	AI: 29 PFS: 29	AI: 27 PFS: 29	PFS: 29 PFP: 29	PFS: 29 PFP: 29	PFS: 27 PFP: 27
Latex	No	Yes	No	Yes	No	No	Yes
pH	5.2[a]	5.2	5.2	5.2	5.2	5.2	5.2
Volume (mL) for 40 mg injection	0.4	0.8	0.8	0.8	0.8	0.8	0.8
Complete formulation	• Mannitol • Polysorbate 80 • Water for injection	• Mannitol • Polysorbate 80 • Citric acid monohydrate • Disodium phosphate dihydrate • Sodium chloride • Sodium citrate • Sodium dihydrogen phosphate dihydrate • Sodium hydroxide (for pH adjustment) • Water for injection	• Sorbitol • Polysorbate 20 • Citric acid monohydrate • Histidine • Histidine hydrochloride monohydrate • Sodium citrate • Water for injection	• Sucrose • Polysorbate 80 • Glacial acetic acid • Sodium hydroxide (for pH adjustment) • Water for injection	• Mannitol • Polysorbate 80 • Citric acid monohydrate • Disodium phosphate dihydrate • Sodium chloride • Sodium citrate • Sodium dihydrogen phosphate dihydrate • Sodium hydroxide (for pH adjustment) • Water for injection	• Sorbitol (E420) • Polysorbate 80 • Methionine • Monosodium glutamate • Hydrochloric acid (for pH adjustment) • Water for injection	• Mannitol • Polysorbate 80 • Adipic acid • Citric acid monohydrate • Sodium chloride • Hydrochloric acid (for pH adjustment) • Sodium hydroxide (for pH adjustment) • Water for injection

Table 2 continued

b)

Product-related factors contributing to SC ISP	Enbrel (etanercept) [96]	Benepali (SB4) [97]	Erelzi (GP2015) [98]	Nepexto (YLB113) [99]
Citrate	No	No	Yes	Yes
Needle gauge	PFP: 27 PFS: 27	PFP: 27 PFS: 27	PFP: 27 PFS: 27	PFP: 27 PFS: 27
Latex	Yes	No	No	No
pH	6.3	6.2	6.3	6.3
Volume (mL) for 50 mg injections	1.0	0.98	1.0	1.0
Complete formulation	• Mannitol • Sucrose • Trometamol • Sodium phosphate monobasic dihydrate • Sodium phosphate dibasic dihydrate • Sodium chloride • L-arginine hydrochloride • Water for injection	• Sucrose • Sodium dihydrogen phosphate monohydrate • Disodium hydrogen phosphate heptahydrate • Sodium chloride • Water for injection	• Sucrose • Citric acid anhydrous • Sodium citrate dihydrate • Sodium chloride • L-lysine hydrochloride • Sodium hydroxide (for pH adjustment) • Hydrochloric acid (for pH adjustment) • Water for injection	• Glycine • Sucrose • Sodium citrate • Sodium dihydrogen phosphate dihydrate • Sodium chloride • Water for injection

AI autoinjector, *ISP* Injection-site pain, *PFP* prefilled pen, *PFS* prefilled syringe, *SC* subcutaneous, *SPC* Summary of Product Characteristics

[a] Based on US Food and Drug Administration (FDA) principal investigators' data; the classic formulation is based on 2014 FDA Product Information

the injection site and that, for example, of a more acidic formulation increases the number of hydrogen ions upon infiltration [26]. Hydrogen ions activate nociceptors, which is thought to be the reason for the sensation of pain upon injection of a formulation that has a non-physiological pH. Thus, a biologic agent should ideally have a pH close to physiological pH to minimise pain, irritation and tissue damage. Of note, highly similar versions of approved branded biologics, termed 'biosimilars', usually have the same pH as their originator product.

Buffers

Buffers, such as citrate and phosphates, are frequently added to parenteral formulations to optimise solubility and stability by adjusting the pH. However, conflicting data have been reported for ISP associated with buffer use. For example, the use of citrate to buffer adalimumab solutions has been related to a higher sensation of ISP in some studies [27, 28]. Rosembert et al. reported that patients switching from originator adalimumab to biosimilar adalimumab were more likely to report injection-site problems if the biosimilar was buffered with citrate versus citrate-free buffer [29]. In contrast, a recent report from the UK National Health Service (NHS) based on 6 months' usage of adalimumab biosimilars in 35,000 patients reported injection-site discomfort across products regardless of citrate content [30]. To our knowledge, there are no published reports of

increased ISP for etanercept (anti-TNF) SC formulations containing citrate versus those without. In addition, while it has been suggested that citrate concentration might affect pain sensation, there is no clear evidence to support this statement [31]. Cohen et al. reported decreased ISP (lower mean pain scores) with a phosphate-free etanercept formulation compared with an earlier phosphate-containing formulation in patients with rheumatoid arthritis and psoriatic arthritis, with the largest pain reductions observed among patients who reported the highest pain with the prior phosphate-containing formulation [16].

Volume

Higher volumes of injection are typically associated with increased patient discomfort and sometimes pain at the site of administration, with less ISP reported where reduced volume is possible [15, 32–34]. The injection volume for a biologic generally ranges from 0.4–2.0 mL although it is typically restricted to $\leq$ 1.5 mL to prevent injection pain, leakage and tissue distortion [15, 35].

Other Excipients

The use of some excipients to support product stability, such as polysorbates, glutamate and serum, have also been associated with ISP and injection-site reactions in some studies [36–38]. Singh et al. reported a patient who developed erythematous injection-site reactions following administration of a monoclonal antibody formulation containing polysorbates, with subsequent skin testing confirming that the patient was reacting to this excipient [38]. The SC injection of polysorbate 20 was reported to be less painful than polysorbate 80 by patients with chronic kidney disease treated with SC epoetin-β or darbepoetin-α [39, 40]. Polysorbates appear to activate complement and have the potential to cause a range of acute hypersensitivity and systemic immunostimulation reactions. Gazerani et al. were the first to report glutamate-evoked pain, vasomotor responses, and pinprick hyperalgesia in human volunteers following SC injection of glutamate solution, with some responses being significantly greater in women than in men [36]. Finally, formulations of interferon (IFN)β-1a without the inclusion of foetal bovine serum or human serum albumin as excipients were associated with lower levels of ISP compared with the standard IFNβ-1b formulation containing those excipients in IFNβ-treatment-naïve patients with relapsing–remitting multiple sclerosis [37].

In addition to excipients, the propensity for any preservatives contained within the biologic solution to potentially cause ISP also needs to be considered. Regarding preservatives required in multiple-dose biologic preparations, m-cresol appears to be related to more ISP than benzyl alcohol or phenol [41]. While injectable products should be formulated as isotonic solutions (approx. osmolality 300 mOsm/kg), it is common clinical practice to administer hypertonic solutions to reduce the total volume injected [42, 43]. However, the solution osmolality of the biologic agent should be < 600 mOsm/kg in order to minimise ISP.

Needle

The frequency of a painful needle insertion has been directly correlated with needle diameter [44]. Thus, short (4–8 mm) and thin-wall needles, conveniently lubricated and with sharp tips, are generally used to minimise pain and improve patient comfort during SC administration of the dose [44–48]. While all needles are sharp, anecdotal evidence suggests that some needles are deemed to be 'sharper' or 'more blunt' by some patients, which may impact on ISP.

Device Type

Preference for the type of device used to administer SC injections can vary from patient to patient, with options including pre-filled syringes (PFS) and autoinjectors such as pre-filled pens (PFP). For those patients who are fearful of needles, an autoinjector allows injections to be self-administered without the needle being seen [35]. Any reported ISP with these devices varies from being generally comparative to being reduced with autoinjector/PFS devices [49–54]. Ghil et al. [49] demonstrated that patients using an autoinjector pen to deliver the

adalimumab biosimilar SB5 were less likely to report ISP compared with those using the PFS, although both devices were well tolerated and overall impressions of the injection process were comparable [49]. In contrast, von Richter et al. [54] reported comparable and low levels of ISP with the etanercept biosimilar GP2015 when administered via a PFS or an autoinjector [54].

Injection Process-Related Factors Contributing to SC ISP

Injection Speed and Fluid Viscosity

Injection speed and fluid viscosity may play a role in ISP. Studies evaluating the effect of injection speed on ISP have reported inconsistent findings [55–58]. Chan et al. demonstrated that a SC heparin injection lasting 30 s caused less ISP than one lasting 10 s in stroke patients, while Dias et al. reported that a SC injection of a viscous placebo buffer characteristic of a high-concentration antibody formulation over a period of 10 min caused less ISP in healthy volunteers than the same volume administered over 1 min [56, 57]. In contrast, studies by Heise et al. and Berteau et al. reported no correlation between injection speed and ISP [55, 58]. Of note, Berteau et al. reported that fluid viscosity had a significant effect on ISP, with SC injections of high viscosity (15–20 centipoise [cP]) placebo solution being less painful than those of medium (8–10 cP) or low (1 cP) viscosity [55].

Injection Angle/Technique

Injection angle may affect perceived ISP [59, 60]. PFSs are typically administered at an angle of 45° or 90° using the skin pinch technique to achieve the optimal deposition for SC injections, while autoinjector pens are best administered at a 90° angle to the skin. Failure to achieve the proper injection depth can result in ISP and adversely affect the bioavailability of the administered agent.

Frequency of Injection

Frequency of injection can also impact pain perception. Both patients and physicians have expressed a significant preference for regimens requiring less frequent administration of biologics (dosing once every 8 weeks preferred to once every 2 or 4 weeks for patients with asthma]) and for SC over IV injection [61].

Injection Site

Repeated use of the same injection site has the potential to increase both irritation and ISP, suggesting the need to rotate injection sites [35]. Injections administered in the thigh are reported as being more painful than identical ones in the abdomen, possibly due to the presence of less adipose tissue on the thighs [34, 58] However, small average differences in pain ratings do not appear to lead to a statistical difference in the acceptance of the injection pain [34].

Temperature of Biologic Solution

The temperature of the biologic solution to be injected can affect the sensation of pain, given that most biologics are stored at 2–8 °C. It is important to let the product reach room temperature prior to injecting [62, 63].

Hypersensitivity

In some individuals ISP may be related to hypersensitivity which most often occurs within 10 min to 4 h post-injection (deemed 'immediate') or within 24–48 h ('delayed') [35, 64]. Latex hypersensitivity to injection devices for biologic therapies are rare but have been reported [65, 66]. Zbehlik and Brown suggested that increasingly severe reactions could potentially occur in the setting of a latex allergy and highlighted a general lack of knowledge among providers and nurses regarding this contraindication to therapy [66]. Any hypersensitivity following an injection should be appropriately treated, the cause identified and a suitable allergen-free formulation selected for subsequent use.

ISP FROM THE PATIENT'S PERSPECTIVE (PATIENT-RELATED ISP)

While many patients experience ISP with SC injections, it may only cause a concern for

some. This difference may be related to the reduced intensity of ISP reported with repeated administrations, which allows some patients to become more tolerant to the overall injection experience [22, 50]. Curtis et al. reported that neither time on biologic therapy (≤ 6 vs. > 6 months or < 12 vs. ≥ 12 months) nor patient age appeared to significantly affect the likelihood of ISP with subcutaneously administered biologics [67]. However, patient factors, such as female gender, low body weight and the presence of fibromyalgia, depression or severe rheumatoid arthritis, have been independently associated with a significantly increased likelihood of experiencing greater ISP following SC injection [67, 68].

Concerns over the self-injection procedure can lead to injection anxiety in up to 20% of individuals, and some patients may also have reduced confidence in being able to carry out the procedure correctly [69, 70]. Some patients may have individual reasons for discomfort with subcutaneously administered medications, such as needle phobia [71]. However, Curtis et al. reported that SC injection of biologics by a healthcare professional was associated with an increased risk of ISP compared with self-administration [67].

Pain catastrophising has been conceptualised as a negative cognitive-affective response to anticipated or actual pain and is one of the psychosocial factors that can influence the experience and reporting of pain [72]. Age, gender and disease duration do not appear to influence the strong associations between pain catastrophising and patient-reported outcomes. The nocebo effect, a non-pharmacological effect causing a negative subjective outcome on treatment, which cannot be objectivised, may also increase the patient perception of ISP in some patients [73, 74]. While the nocebo effect is a well-documented phenomenon, it is often disregarded even though it has the potential to impact patient outcomes across multiple therapeutic areas. Importantly, some patients may lack the terminology to independently express certain influential aspects of their therapeutic experience, such as ISP [75]. When patients were prompted with a choice of predefined reasons for discontinuing subcutaneously administered anti-TNF treatments, concerns about the injection experience replaced safety issues as the second most common answer.

CHALLENGES IN ASSESSING ISP

Pain, including ISP, is a complex perceptual phenomenon and a subjective experience and, consequently, it is difficult to describe and accurately measure [76]. There is no simple measure that can objectively record how much pain an individual patient is experiencing. Thus, physicians are only able to indirectly assess the intensity of an individual's pain using subjective verbal responses, overt behaviour (including facial expressions) and/or physiological correlates of the patient. A common way to classify pain is to use severity as a linear dimension which is measured on categorical scales (e.g. 'Mild', 'Moderate' and 'Severe'), numerical rating scales (e.g. 0 = 'No pain' to 10 = 'Worst pain possible'), visual analogue scales (VAS) (a point along a 10-cm line) or via adjectival descriptors. The timing of pain assessment for ISP using VAS is typically immediately before, immediately after, 5–10 min after and 30 min after the injection [37]. Although many studies have attempted to establish a minimal clinically important difference or minimal clinically important change in pain VAS scores, the estimates vary widely based on the source of pain, chronicity and disease [16]. A commonly used cut-off for mild pain is a score of ≤ 3.0 on the VAS, although patient response can vary depending upon how a question regarding ISP is phrased and/or the patient may be unable to discriminate reliably between the points on a scale [76]. In addition, it is important to recognise that although intensity and descriptive characteristics are critical features of pain that require attention, they are not sufficiently broad features to provide an adequate classification of the experience of even acute pain.

Limited clinical data (along with the varying use of blinded and non-blinded study designs) make it difficult to fully determine the factors influencing ISP. In addition, it is difficult to assess and compare ISP between studies and/or

biologics given that many differing terms are used, which may include ISP, such as the 'all-encompassing' umbrella term of 'injection-site reactions', as opposed to more distinct ISP-related terms such as 'injection-site burning and stinging' [67]. In addition, not all injection-site reactions are painful, and not all occurrences of ISP may be reported as an injection-site reaction. The reporting of pain is also influenced by a number of interpersonal variables, including cultural background, previous pain experience, patient personality and levels of attention and emotion [76]. Reporting of ISP is also typically higher when a patient is specifically asked about his/her injection experience than when medical records are reviewed [67]. Table 3 shows the wide variation in ISP with the SC administration of the same biologic, different biologics and non-biologic agents, highlighting the difficulty in consistent reporting and demonstrating that ISP occurs regardless of the mechanism of action of the treatment.

WHAT CAN BE DONE TO MINIMISE ISP?

While the complete elimination of ISP with any subcutaneously administered agent remains unlikely, it is important that it be minimised for the sake of adherence to therapy and patient outcomes [75, 77, 78].

Patient Training

First and foremost, this can be achieved by providing effective patient training to ensure a confident, competent and consistent injection technique. Patient training should ideally be carried out face-to-face with a competent trainer (physician/nurse) to ensure any necessary corrections to the injection technique can be made at an early stage. The physician/nurse should take this opportunity to fully explain the risk of ISP and carefully manage any patient expectations. Patients should also be encouraged to utilise social networking services and refer to the internet for additional support with their injection technique, particularly in situations where clinical services may be limited due to the ongoing coronavirus disease 2019 (COVID-19) pandemic. Robust training of the injection technique may also serve to support the psychological wellbeing of the individual, minimise treatment-related anxieties and, importantly, allow the patient to remain in control of his/her treatment [79, 80].

Psychological Intervention

There are no published studies of simple psychological interventions for ISP in adults, although some evidence from studies on other needle procedures show a benefit from breathing strategies and neutral signaling of the start of the procedure [81].

Choice of Treatment Device

As a poor drug administration technique can cause more ISP, the treatment device selected should take into consideration any dexterity limitations/problems on an individual patient-by-patient basis [82]. For example, a device may need to be used by a patient suffering from arthritic pain and swelling of the hands. Devices with hidden needles, such as PFPs, may possibly reduce needle phobia, although ease of use appears to vary between PFSs and PFPs [50, 83]. Physicians should consider the use of improved formulations of a specific biologic agent to reduce the risk of ISP. A reduced administration volume and/or the removal of excipients, such as citrate, glutamate and phosphate, might reduce the perception of pain and associated pre-administration anxiety, leading to a positive impact on patients' convenience and adherence [22, 27, 34].

Pre- and Post-Injection Techniques

Pre- and post-injection techniques can be also used to minimise ISP. The use of topical analgesics has been shown to reduce ISP both immediately and 5 min after an injection [84, 85]. In addition, the use of an ice pack or coolant may help to numb the site prior to the injection and reduce ISP [59, 60, 86]. As most

Table 3 Examples of ISP variability across biologic agent disease area when administered subcutaneously

Biologic agent	Type of agent	Indication	Study duration (weeks)	ISP, % (*n*/*N*) or reporting rate (*n*/*N*)	References
Studies					
Adalimumab	Anti-TNF	Psoriasis	12	6.7 (3/45)	Gordon et al. [100]
Adalimumab	Anti-TNF	RA	24	11.3 (36/318)	Furst et al. [101]
Adalimumab	Anti-TNF	CD	56	1.9 (5/261)	Colombel et al. [102]
Galcanezumab	Humanised mAb (CGRP)	Chronic headache	12	11.1 (13/117)	Dodick et al. [103]
Glatiramer acetate	Immunomodulator	RRMS	16	56.5 (61/108)[b]	Wolinsky et al. [104]
Insulin	Hormone	Diabetes	0.14 (1 day)	16.5 (13/79)	Zijlstra et al. [34]
Mepolizumab	Humanised mAb (IL-5)	Asthma	8	64 (36/56)	Bel et al. [105]
Spontaneous reports					
Adalimumab[a]	Anti-TNF	Psoriasis	ns	3650/15637	Grace et al. [106]
Etanercept[a]	Anti-TNF	Psoriasis	ns	23/141	Grace et al. [106]
Ixekizumab[a]	Humanised mAb (IL-17)	Psoriasis	ns	350/1771	Grace et al. [106]
Secukinumab[a]	Humanised mAb (IL-17)	Psoriasis	ns	166/654	Grace et al. [106]
Ustekinumab[a]	Humanised mAb (IL-12/IL-23)	Psoriasis	ns	6/8	Grace et al. [106]

CD Crohn's disease, *CGRP* calcitonin gene-related peptide, *IL* interleukin, *mAb* monoclonal antibody, *ns* not specified, *RA* rheumatoid arthritis, *RRMS* relapsing–remitting multiple sclerosis, *TNF* tumour necrosis factor

[a] Spontaneous reporting of ISP in post-marketing databases

[b] ISP reported as part of injection-site reaction (annualised event rate of 55.3% reported for ISP)

biologics are stored at 2–8 °C, they should be warmed to room temperature for about 30–45 min prior to administration in order to avoid any pain associated with the injection of a cold solution [62, 63]. However, given that the warming process can vary between agents, the physician or nurse should refer to the package inserts for specific information on the length of time that the agent can remain at room temperature prior to injection and whether the medication should remain inside the carton during warming. It is important to note that direct heat sources should not be used to warm biologic agents due to the risk of protein denaturation which would render them ineffective.

Patient Movement and Muscle Stiffness

Attempts to minimise patient movement and muscle stiffness, which are often associated with higher anxiety levels, during the SC injection process may help to lessen any ISP given that body movement and anxiety have correlated with verbal pain intensity ratings [87]. The development of a 'ritualised' routine for when, where and how to inject can help

patients' control of the process, improve confidence and reduce injection-associated anxiety [88]. As injections administered in the thigh are reported to be more painful than those administered in the abdomen [58], patients with ISP issues should be directed to administer injections in the abdomen. Rotating sites with each injection may also help to minimise irritation and ISP.

MANAGING PATIENT EXPECTATIONS

Patient expectations of potential ISP with any given SC biologic need to be carefully managed given that adherence to these agents can be influenced by ISP and skin perception, with misconceptions of SC routes of administration negatively impacting treatment adherence [77, 78]. Bolge et al. reported that up to one-fifth of patients who cited injection problems as their primary reason for treatment discontinuation did not choose to discuss these issues with their physician [75]; such findings highlight the importance of establishing productive patient–physician communication in order to optimise treatment adherence. Patients should be fully informed of any potential for ISP and reassured that they can discuss this with their healthcare provider. Physician/support services should provide patient education on the injection process, disease and treatment, and encourage patients to ask about, and therefore resolve, any problems with self-injection [75, 89].

SUMMARY

Injection-site pain is a commonly reported, yet subjective, side effect associated with the SC administration of drugs, including biologic agents. Multiple factors have the potential to contribute to ISP, some of which are related to the product formulation and/or injection process, while several patient-related factors may also make an individual more susceptible to experiencing ISP. It is important to understand that the complete elimination of ISP remains unlikely with any subcutaneously administered agent, including biologics. However, ISP can be minimised by providing effective initial patient training (face-to-face and online/digital) to ensure a confident and competent injection technique, while also serving to support the psychological wellbeing of the individual and minimising treatment-related anxieties. From the patient perspective, simple techniques, such as allowing the product to reach room temperature prior to administration, is a simple way to reduce ISP. In contrast, the physician should focus on managing patient expectations of the overall pre- and post-injection experience, along with the suitability of alternative formulations and optimal choice of treatment device on an individual patient basis. As many patients may not choose to discuss ISP issues with their physician, it remains important to establish productive patient–physician communication in order to support and optimise treatment adherence.

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